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Towards an improved estimation of the burden of bacterial foodborne diseases

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Towards an improved estimation of the burden of bacterial foodborne diseases

Front cover: A meat merchant in Morocco (2009). Improper storage of meat is a major risk factor for foodborne diseases.

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Nobody knows if anyone pays any attention (C.J.L. Murray).

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List of Abbreviations

ACF	Autocorrelation Function
AHI	Annual Household Income
AIC	Akaike's Information Criterion
ARIMA	Autoregressive Integrated Moving Average
BCoDE	Burden of Communicable Disease in Europe
CB	Capacity Building
CNS	Central Nervous System
CrI	Credible Interval
CRP	C-Reactive Protein
DALY	Disability-Adjusted Life Year
DFLE	Disability-Free Life Expectancy
DLM	Dynamic Linear Model
DW	Disability Weight
EDCD	Epidemiology and Disease Control Division
EEA	European Economic Area
EFSA	European Food Safety Authority
EL	Educational Level
EQ5D	EuroQol 5 Dimensions questionnaire
ETEC	Enterotoxigenic *Escherichia coli*
EU	European Union
FASFC	Federal Agency for the Safety of Food Chain
FBD	Foodborne Disease
FERG	Foodborne Disease Burden Epidemiology Reference Group
GBD	Global Burden of Disease

GE	Gastroenteritis
GBS	Guillain-Barré Syndrome
GHE	Global Health Estimates
HLE	Health Life Expectancy
HLY	Healthy Life Years
HMIS	Health Management Information System
HRQoL	Health-Related Quality of Life
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IHME	Institute for Health Metrics and Evaluation
KTE	Knowledge Transfer and Exchange
LOESS	Locally Weighted Scatterplot Smoothing regression model
MHI	Monthly Household Income
OR	Odds Ratio
PACF	Partial Autocorrelation Function
PC	Paired Comparison
PHE	Population Health Equivalence
QALY	Quality-Adjusted Life Years
QoL	Quality of Life
SD	Standard Deviation
SMPH	Summary Measure of Population Health
SNL	Sentinel Network of Laboratories
STL	Seasonal-Trend-Loess
TTO	Time Trade-Off
UI	Uncertainty Interval
URF	Underreporting factor
VAS	Visual Analogue Scale
WHO	World Health Organization
WIV-ISP	Belgian Scientific Institute for Public Health

YLD	Years Lived with Disability
YLL	Years of Life Lost due to mortality

1

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, et al. (2014) Calculating Disability-Adjusted Life Years to quantify burden of disease. *International Journal of Public Health*.

Devleesschauwer B, Havelaar AH, **Maertens de Noordhout C**, Haagsma JA, Praet N, Dorny P, et al. (2014) Daly calculation in practice: A stepwise approach. *International Journal of Public Health* 59:571-4.

Speybroeck N, **Maertens de Noordhout C**, Devleesschauwer B (2015). Comment les nombres rendent vos aliments plus sûrs. *Le Soir*.

1.1 What is a foodborne disease?

Everyone has the right to safe, sufficient and nutritious food, and to be in good health [1, 2]. Moreover, a safe food supply supports and stimulates economic development because it promotes agriculture, trade and tourism.

The Codex Alimentarius Commission defines foodborne diseases (FBDs) as diseases transmitted through consumption of contaminated food, including a broad group of illnesses caused by viral, parasitic, chemical and bacterial agents. FBDs occur commonly throughout the world and the contamination of food can occur at any stage of the farm-to-fork chain and result from environmental contamination, including pollution of water, soil or air [3].

Gastroenteritis (GE) is the most common consequence of FBDs and can lead to mild symptoms which don't require medical treatment, but can also produce more severe complications leading to life-long sequelae and even death. Consequences of the exposure to contaminated food depend, amongst other things, on the capacity of the host to generate an immune reaction. Indeed, GE is more severe and more frequent in at risk people such as pregnant women, the very young and very old people or immunocompromised patients [4].

Salmonella spp., *Campylobacter* spp. and pathogenic *Escherichia coli* are among the most common bacteria to cause FBD. Infection with *Listeria monocytogenes*, through infrequent, is often severe and has a high case-fatality ratio [4].

In humans campylobacteriosis is mainly caused in by the Gram-negative bacteria *Campylobacter jejuni* and *Campylobacter coli*. *Campylobacter* species grow best at 37°C to 42°C and transmission to humans is most often associated with the improper handling or consumption of undercooked poultry products, contaminated during slaughter and carcass processing. *Campylobacter* species need to grow at lower-than atmospheric oxygen concentrations and can be killed easily by drying, heating, acidic conditions and disinfectants [5]. The main symptomatic outcome generally lasting from two to ten days, is mild or self-limiting GE but *Campylobacter* can also lead to complications such as Guillain-Barré Syndrome (GBS) affecting the nerves of the body and starting several weeks after the diarrheal illness, reactive arthritis which is a form of inflammatory arthritis that develops in response to an infection in another part of the body and inflammatory bowel disease (IBD) [5].

Salmonellosis in humans, is caused by the Gram-negative non-typhoidal *Salmonella enterica* bacteria which can grow at temperature within the range 7-48°C but is also able

to survive for extended periods in chilled and frozen foods with our without oxygen and over a range of pH values from 3.7-9.5. *Salmonella* is not especially resistant to sanitisers used in the food industry, but is able to survive if cleaning is inadequate. *Salmonella enterica* originates from animal reservoirs and can spread to humans through consumption of contaminated foods such as eggs, raw pig meat, turkey and chicken. Transmission can also occur through direct contact with infected animals or their environment and directly between humans. The most common symptoms of human salmonellosis, generally starting 6 to 72 hours after exposure, include fever, diarrhea and abdominal cramps, but if the bloodstream is infected, septicemia and even death are possible outcome. The illness usually lasts 4-7 days and healthy people recover without treatment. In at risk people, invasive salmonellosis can also cause reactive arthritis and life-long consequences such as IBD [6]. Antimicrobial therapy is therefore considered mainly for patients who are severely ill, i.e. those with severe diarrhea, high fever, or manifestations of extra-intestinal infection and for gastroenteritis caused by *Salmonella* species in persons at increased risk of invasive disease.

Listeriosis is caused by *Listeria monocytogenes*, a Gram-positive ubiquitous bacterium that was first recognized as a foodborne pathogen in the early 1980s [7]. Subsequently, there have been major foodborne outbreaks of listeriosis making *L. monocytogenes* a significant foodborne pathogen. Unlike most other foodborne pathogens, *L. monocytogenes* can grow in food with relatively low moisture content and at a high salt concentration. Most importantly, *L. monocytogenes* grows at refrigeration temperatures, in contrast to many other foodborne pathogens. This ability to persist and multiply in the food environment makes *L. monocytogenes* particularly difficult to control [8]. Clinical listeriosis mainly occurs in certain "at risk" groups: pregnant women, elderly persons, immunocompromised people, unborn babies and neonates (through vertical transmission from the mother to the child or more rarely at birth by ascending colonization from the vagina) [9]. *L. monocytogenes* infections in healthy people may cause febrile gastroenteritis, which is usually mild and self-limiting. Mainly in patients with impaired cell-mediated immunity, listeriosis leads to severe illnesses including septicemia, meningitis or encephalitis and herewith producing lifelong consequences and even death [10–12]. Infection during pregnancy may result in spontaneous abortions or stillbirths [13]. Preterm birth is also a common consequence of listeriosis in pregnant women [14, 15].

The risk of contamination by foodborne agents can be reduced by applying simple principles, such as cooking raw meat, separation of raw and cooked foods, preservation of food to appropriate temperatures, and washing hands and food during meal preparation [16]. However in many countries people are not aware of food safety principles. In 2014 it was

reported that only 10% of the Belgian population handled raw eggs and meat properly, and that less than half of the population defrosted meat, poultry or fish safely [17]. In 2014 in the UK, the Kitchen Life study revealed that food safety was not a top priority in households or was simply misunderstood. The study also demonstrated that food safety behaviour was mainly based on "common sense", rather than on expert recommendations [18]. Majowicz and Green also demonstrated that food safety knowledge is low among high school students and young adults in Ontario, Canada [19, 20].

In addition to consumer and industry awareness, food safety also requires political support. Governments have to be on guard against the potential daily hazards and need to implement a strategy "from farm to fork", involving different stakeholders in the food chain. Indeed, the food production chain is long, requiring multidisciplinary participation. The main steps of the food production chain are production, processing, distribution and preparation [21]. Production refers to the plants growing and animals raising for food production purposes, and may include production of plants and animals in the wild. During the production, pesticide spraying can spread norovirus to vegetables or poultry can be exposed to water containing animal feces [22]. After the production step comes the processing step, depending on the type of food. For vegetables or fruits this may involve a simple cleaning and sorting, for milk a pasteurisation and for animals, slaughter. Meat can also be smoked, frozen, cooked and mixed with other foods. During the processing, water or ice can contaminate foods used to wash and pack foods, or pathogens from the intestines of the slaughtered animal can infect the final meat. The third step in the "farm to fork" process is the distribution: food is transported from farms or processing plants to the consumer. This step may involve transporting the food just once, from a farm to the local farmers' market, or it may comprise many stages, e.g. when food is exported to another country. During this step, fresh produce can be contaminated by an unclean truck or because it is left on a loading dock for too long in warm weather. Finally, the last step in the food safety chain is the preparation, i.e. the processing of food for consumption. This stage can occur for example in the kitchen of a home, a restaurant or a school. During the preparation, people can contaminate food if they do not wash their hands carefully after using the toilet or if they use the same knife to cut raw vegetables and meat. Storage is also an important factor as well for the survival of some pathogens such as *L. monocytogenes* growing at refrigeration temperatures. Food can be mishandled many times along the food production chain which can increase the risk of outbreaks and sporadic diseases. Reheating or boiling does not always guarantee safe food because some pathogens develop toxins that are not eliminated by heating [21].

1.2 What is burden of disease?

The main objective of public health policy is to promote and protect population health [23]. This requires evidence and data on the health status of the population. The impact of a disease on population health is often referred as the "burden of a 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. Information on the disease burden is crucial for decision-makers who work within the health arena. In order to make relevant decisions, develop strategies and initiate appropriate priorities, policy needs to be informed about the size of health problems in the population, the groups that are particularly at risk, and the trends in the health state over time. The disease burden can be described by a variety of indicators, because public health is a multifactorial phenomenon with many facets and different ways to measure it [24]. 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) [25].

The concept of SMPH was introduced with the development of healthy life expectancy in the 1960s [26] and had the advantage of combining both the level of - and change in - well being. It was seen as a particularly appropriate measure of health in older populations in which mortality rates were decreasing. It was noticed that despite these decreasing mortality rates, an extended life does not automatically equal an extension of healthy life. SMPH where further developed in the 1980s and two major groups of SMPH emerged. The first group was composed of so called Health Life Expectancy (HLE) and included metrics such as Disability-Free Life Expectancy (DFLE). Measures of HLE have been used to track and explain changes in population health. For example in 1999 Hayward and Heron demonstrated that in the US, native Americans lived longer but in worse health than the non-Hispanic white population [27]. The second group of SMPH includes health measures such as Disability-Adjusted Life Year (DALY) and Quality-Adjusted Life Years (QALY).

QALY combines mortality and morbidity and was developed by health economists and psychologists. QALYs are mainly used in the economic evaluation of alternative health care interventions. In cost-effectiveness, analyses QALY allows comparing health interventions by calculating the QALYs gained resulting from positive intervention effects. One QALY can be translated as one year lived in perfect health. To calculate QALYs "utilities" are needed. Utilities allow to quantify Quality of Life in the QALY concept and are a measure of preference that people assign to health outcomes. Utilities range

from death (0) and a state of perfect health (1). In some situations, the lower bound can be negative, and is therefore considered worst possible health state [28, 29].

In this thesis we will use the DALY, developed as the metric of choice for the Global Burden of Disease (GBD) project in the early 1990s [30].

The DALYs are SMPH used in the GBD studies, each presenting a comprehensive assessment of the worldwide health impact of disease, injury or risk factors [30–34]. In addition, several national and regional DALY estimates were used to express and monitor local health status, to set priorities within the local health sector and to compare the impact of a health problems between regions [35–37].

The DALY measures the burden of a disease, i.e. it aggregates the total health loss at the population level into a single metric by summarizing:
1.1) years lived with disability (YLD), and 1.2) years of life lost (YLL). YLD represents the healthy time lost while living with a disease and YLL represents the time lost through premature mortality.

YLDs, the morbidity part of the DALYs, are calculated as follows when using an incidence-based approach:

$$\text{YLD} = \text{Number of incident cases} \times \text{Duration till remission or death} \times \text{Disability Weight} \tag{1.1}$$

Using the prevalence approach, YLDs are calculated as follows:

$$\text{YLD} = \text{Number of prevalent cases} \times \text{Disability Weight} \tag{1.2}$$

Disability Weights (DWs) are an important component of YLDs. A DW of 0 is equivalent to full health, whereas a DW equal to 1 is equivalent to death. The DW is meant to capture the severity of functional limitations in different domains of health, but not the welfare or social welfare loss associated with a given health state [38–41]. The value of a DW can be derived from the valuations of a panel of judges (any population group, e.g., experts, patients, lay people) stated towards a set of hypothetical health states expressing the relative undesirability of the health state [25, 42]. There are three main types of health state valuation methods: 1) trade-off methods such as the time trade-off, or the person trade-off; 2) discrete choice experiments and 3) scales such as the Rating or Visual Analogue Scale or a combination thereof [43].

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

$$\text{YLL} = \text{Number of deaths} \times \text{Remaining life expectancy at the age of death} \tag{1.3}$$

DALYs are then simply the sum of the YLDs and YLLs:

$$\text{DALY} = \text{YLD} + \text{YLL} \tag{1.4}$$

The basic formula for YLDs and YLLs can also be extended by applying social weighting functions, meaning that not all life years lost will be valued equally. This concept is however not universally accepted [44, 45]. There are two types of social weighting functions: age-weighting and time-discounting. Age-weighting assumes that value of life depends on age, meaning that a higher weight is attributed to the healthy life years lived in the socially more important life span between 5 and 56. Time-discounting years of healthy life lived in the future, at a common rate of 3%, prevents policy makers from saving resources for a future program, instead of investing in ongoing, but less effective, interventions programs [46].

1.3 Without data, there is no action

FBDs are a growing global public health concern because of developments such as rapid urbanization and the emergence of antibiotic resistance. Changing consumer habits and global warming further affect food safety risks. Foodborne illnesses, like campylobacteriosis can peak during the summer months because of increasing fly activities which have been shown to carry *Campylobacter* and can potentially infect both humans and animals [47, 48]. In addition, outside activities occur more often in summer and more people cook outside where safety controls, that a kitchen provides, i.e. thermostat controlled cooking, refrigeration, and washing facilities are not always available. An increasingly important part of our food supply is from foreign countries which makes new food risks appear. The traceability of foods has therefore become more complex. Finding the origin of a food contamination event can be very complicated, as the ingredients used in many processed and ready-to-eat foods can come from a wide range of countries with different foodborne hazards and risks. Globalization can make of a localized problem a problem of international magnitude in a very short time. For example between May and July 2011 in Germany, an *Escherichia coli* outbreak affected more than 3,950 people and caused 53 deaths. An epidemiological study demonstrated that fenugreek sprouts were the source of this contamination. The contaminated batch was imported from Egypt, was

sprouted in Germany, had been widely distributed and finally infected people from 16 countries, among them the Canada and the United States. In addition to the impact on public health, this outbreak cost more than a billion euros to the global food industry [49].

Since the Bovine Spongiform Encephalopathy crisis at the end of 1980s [50] and the dioxin crisis in 1999 [51], food safety became a priority for Europe. The European Union became aware that every European citizen needs to have access to safe food of the highest standard and drew attention to the need to create mutual principles and requirements concerning food and feed law at Union level. The European Commission created an integrated approach to food safety from "farm to table" and in 2002 the European Parliament and the Council adopted Regulation No 178/2002 laying down the general principles and requirements of food law. Subsequently, the European Food Safety Authority (EFSA) was set up as a source of scientific advice and communication on risks associated with the food chain [52]. In Belgium in 1983, the Belgian Sentinel Network of Laboratories (SNL) was created in order to monitor trends in infectious diseases and in 2000, the Federal Agency for the Safety of the Food Chain (FASFC) was created to ensure maximum safety for the consumer [53].

Despite this effort, there are still many cases of bacterial foodborne infections such as, *Salmonella* and *Campylobacter* infections in Europe. The WHO effort to quantify the burden of diseases, demonstrated a lack of data related to foodborne diseases in every country [4]. Even though every Belgian person is potentially exposed to foodborne diseases, their real public health impact in Belgium is incompletely known. The Belgian Scientific Institute for Public Health (WIV-ISP) collects data on laboratory-confirmed cases of most of the foodborne pathogens. Positive results of stool culture can also be collected by laboratories participating in the sentinel laboratory network. About 60% of Belgian laboratories are participating in this sentinel system [54]. The TIAC ("Toxi-Infection Alimentaire Collective") working group that is organized and presided by the WIV-ISP also ensures the monitoring of FBDs in participating in the analysis of epidemiological trends. This group performs aetiologic research related to foodborne infections as well. Data on foodborne diseases are published yearly by WIV-ISP, but so far their burden has not yet been expressed in terms of DALYs. In addition, most of the FBDs are not notifiable, leading to underestimation and under-recognition of the impact of these diseases on public health. Correct information on health problems is important for public health and for citizens alike.

The thesis at hand will address the lack of knowledge of FBD burden in the world and in Belgium, and explore methods to better estimate the burden of FBDs, making

foodborne burden of disease estimates a strong pillar for policy makers aiming to protect and improve population health.

2 Objectives

The main objective of this thesis is two-fold:

- **To contribute to assessing the burden of bacterial foodborne disease**
  We will achieve this objective by calculating the global burden of listeriosis through a systematic review and meta-analysis in **Chapter 3** and by calculating the burden of salmonellosis, listeriosis and campylobacteriosis in Belgium from 2012 to 2020 in **Chapter 4**.

- **To investigate methods to improve burden of bacterial foodborne disease estimates**
  To achieve this goal, we will perform an in depth investigation of incidence data needed to assess YLDs by describing comorbidities and factors associated to death and central nervous system infections in non-perinatal listeriosis in **Chapter 5**. Then we will perform methodological studies on disability weights being crucial parameters to assess YLDs caused by foodborne diseases. In **Chapter 6**, we will propose a new set of disability weights for infectious diseases in Europe and in **Chapter 7**, we will evaluate differences in health valuation across the population. In **Chapter 8** we will develop an approach to map utilities to disability weights.

These specific objectives have been chosen because of their scientific interest described in the **Introduction** but also because this work has been connected with two international projects: 1)"The Global Burden of Foodborne Diseases" supported by the WHO [55] and 2)"The Burden of Communicable Disease in Europe (BCoDE)" with the European Center for Disease Prevention and Control (ECDC) [56]. The involvement of this project in such initiatives shows the high level of importance of gaining more insight into foodborne diseases.

3

The global burden of listeriosis: a systematic review and meta-analysis

Adapted from

Maertens de Noordhout C, Devleesschauwer B, Angulo FJ, Verbeke G, Haagsma J, Kirk M, et al. The global burden of listeriosis: a systematic review and meta-analysis (2014). *Lancet infectious diseases*. 1073-82.

3.1 Introduction

Listeriosis is caused by *Listeria monocytogenes*, a Gram-positive ubiquitous bacterium that was first recognized as a foodborne pathogen in the early 1980s [7]. Subsequently, there have been major foodborne outbreaks of listeriosis making *L. monocytogenes* a significant foodborne pathogen. Unlike most other foodborne pathogens, *L. monocytogenes* can grow in food with relatively low moisture content and with a high salt concentration. Most importantly, *L. monocytogenes* grows at refrigeration temperatures, in contrast to many other foodborne pathogens. This ability to persist and multiply in the food environment makes *L. monocytogenes* particularly difficult to control [8].

Clinical listeriosis mainly occurs in certain "at risk" groups: pregnant women, elderly persons, immunocompromised people, unborn babies and neonates (through a vertical transmission from the mother or more rarely at birth by ascending colonization from the vagina) [9]. *L. monocytogenes* infections in healthy individuals may cause febrile gastroenteritis, which is usually mild and self-limiting. Mainly in patients with impaired cell-mediated immunity, listeriosis leads to severe illnesses including, septicemia, meningitis or encephalitis and herewith producing lifelong consequences and even death [10–12]. Infection during pregnancy may result in spontaneous abortions or stillbirths [13]. Preterm birth is also a common consequence of listeriosis in pregnant women [14, 15].

Most cases of listeriosis are sporadic and have been reported in high-income countries, where the incidence is relatively low but with a high fatality rate [57]. Important outbreaks also occurred, e.g., recently in 2011 the USA, an outbreak of listeriosis in Colorado from cantaloups resulted in 146 persons infected and 30 deaths making it the second deadliest recorded U.S. outbreak since the Centers for Disease Control and Prevention began tracking outbreaks in the 1970s [58–60].

Listeriosis frequently results in hospitalization in intensive care, which makes *L. monocytogenes* the third most costly foodborne pathogen in the United States per case in 2010 after *Clostridium botulinum* and *Vibrio vulnificus* [61]. Ivanek and colleagues estimated that in the US the annual cost of *L. monocytogenes* was $2.3 to $22 billion, and the annual benefit of Listeria food safety measures was $0.01 to $2.4 billion [62].

Only a few countries have evaluated the listeriosis burden in terms of Disability-Adjusted Life Years (DALYs) [63–65], and a global estimation of the burden of listeriosis has never been conducted. However, DALYs can be used to compare diseases and conditions and thereby help policy makers allocate limited resources. To understand the global burden of foodborne diseases, including listeriosis, the World Health Organization (WHO)

therefore established an advisory body, the Foodborne Disease Epidemiology Reference Group (FERG) [66]. The aim of the present study was to estimate the annual global number of human illnesses, deaths and DALYs due to listeriosis to contribute to the FERG initiative. We synthesized existing information and knowledge through a systematic literature review and meta-analysis, which was incorporated in the calculations of the disease burden.

3.2 Materials and Methods

3.2.1 Search strategy and selection criteria

A systematic review was conducted to identify all relevant information about the global burden of listeriosis. We searched PubMed, WHOLIS, Sciverse Scopus, CAB astracts (BIDS), OpenGrey and Conference proceedings citation index (Web of knowledge) for references published between January 1, 1990 and May 21, 2012. No language restrictions were set. Papers in languages that were not mastered by the authors were translated by native speakers. For one report in Malaysian, no native speakers could be identified, and Google Translate was used (http://translate.google.com). The search terms were developed in line with the Medical Subject Headings thesaurus by conducting a combination of test searches and via collaboration between independent researchers and knowledge users. Search terms were designed to capture a range of terms and outcomes associated with listeriosis (Appendix 1 - *Available upon request to C. Maertens*). Further details on the databases and Boolean operators that were checked are summarized in Appendix 2 (*Available upon request to C. Maertens*). In addition, for each of the member states of WHO for which no incidence data were found, national surveillance data were reviewed where available via national websites. The national websites and surveillance data were found through a Google search in French, Dutch, English or the official language of the country using Google Translate if no website was found. Search terms are summarized in Appendix 2. Countries, for which no websites or no national surveillance data were found, were contacted by mailing the ministry of health or other health professionals. Finally, for each of the WHO sub-regions for which no incidence data were found, the WHO Collaborating Centre for Foodborne Listeriosis was consulted to assist in filing remaining data gaps. After deleting duplicates, titles, abstracts or entire articles were screened for exclusion criteria. The screening was conducted independently by two researchers (CMN, BD). Any disagreement about eligibility between reviewers was solved by a third expert (NS). Data were extracted from included papers by the same two reviewers using a data extraction form reviewed by experts (Appendix 3 (*Available upon request to C. Maertens*))

and incidence data older than 1990 were excluded from the analysis. Bibliographies of included documents were hand-searched for additional references. The PRISMA guidelines for reporting systematic reviews were followed.

3.2.2 Listeriosis disease model

For a quantitative assessment of the listeriosis disease burden, we constructed a disease model for perinatal and non-perinatal listeriosis, based on identified qualitative information about pathological and clinical symptoms, and the availability of quantitative data [67]. This model permitted the quantification of the global burden of listeriosis, expressed in DALYs (Figure 3.1) [68].

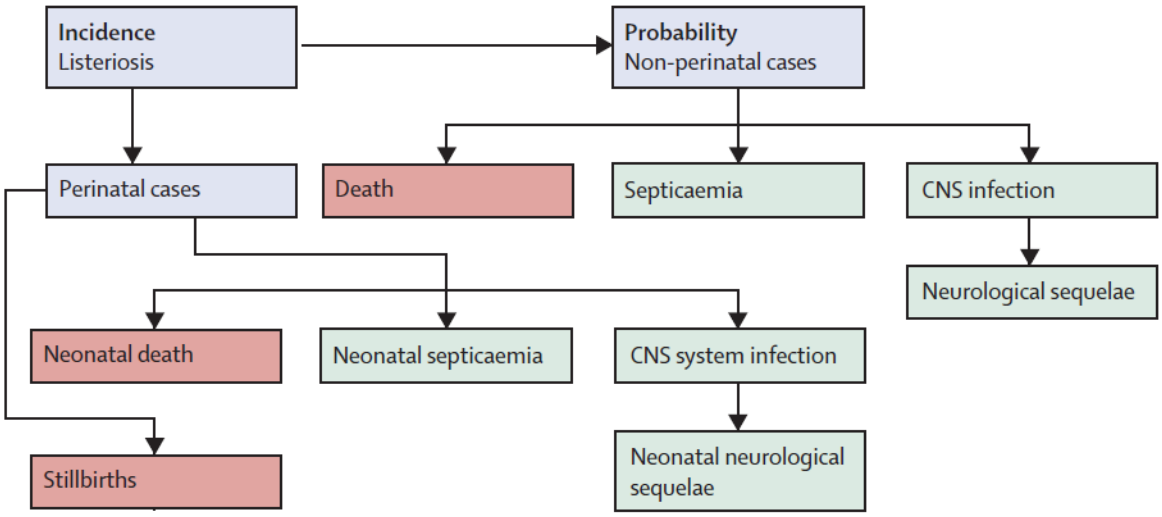


Figure 3.1: Outcome tree for perinatal and non-perinatal listeriosis.
Each block represents a node in the computational disease mode, while arrows represent transition probabilities between nodes. Pink boxes contribute Years of Life Lost caused by premature death (YLLs), green boxes contribute Years Lived with Disability (YLDs) and grey boxes have no contribution to the DALYs. In addition to this baseline model, a scenario analysis was performed in which stillbirths were excluded from the burden estimates.

A case of listeriosis was defined as isolation of *L. monocytogenes* from a normally sterile site (e.g., blood or cerebrospinal fluid) or from products of conception (e.g., placental or fetal tissue) and septicemia referred to severe sepsis. Perinatal cases were defined as materno-fetal cases including pregnancy-associated cases and cases in newborns during the first month of life. A materno-fetal infection was counted as one case. Stillbirths were defined as a death in a fetus between 24 and 41 weeks of gestation. Because of the controversy regarding the inclusion of stillbirths in disease burden estimates [69], we also performed a scenario analysis in which we excluded stillbirths from the burden estimates.

3.2.3 Statistical analyses

Multiple imputation of missing country-specific incidences

A multilevel random effects model was developed to impute missing country-level incidence values [70]. In this model, the number of cases y_{ijk} in each study k from country j belonging to WHO subregion i was assumed to follow a Poisson distribution with parameter $\lambda_{ijk} = \Theta_{ijk} n_{ijk}/100,000$, with Θ_{ijk} the listeriosis incidence per 100,000 and n_{ijk} the study-specific population size. Furthermore, the natural logarithm of the incidence per 100,000 was modelled as the sum of a global intercept α_0, a region-specific random effect t_i, a country-specific random effect u_{ij} and a study-specific random effect v_{ijk}:

$$log_{\Theta_{ijk}} = \alpha_0 + t_i + u_{ij} + v_{ijk}$$

For the random effects, independent Normal distributions with means zero and variances $(\sigma_t^2, \sigma_u^2, \sigma_v^2)'$ were assumed. The multilevel random effects model was implemented in a Bayesian framework, using a $Normal(\mu = 0, \sigma^2 = 10,000)$ prior distribution for the global intercept α_0, and a $Uniform(min = 0, max = 10)$ prior distribution for each of the random effect standard errors $(\sigma_t, \sigma_u, \sigma_v)'$. The analysis was conducted in WinBUGS 1.4.3 [71].

Incidence values for countries with no data were imputed based on the posterior predictive distributions from the multilevel random effects model. For countries in a WHO sub-region where none of the countries had data, the log-incidence was imputed as multiple random draws from a Normal distribution with mean equal to the global intercept α_0, and variance equal to the sum of the between-region variance σ_t^2 and the between-country variance σ_u^2. For countries in a WHO sub-region where at least one of the other countries had data, the log-incidence was imputed as multiple random draws from a Normal distribution with mean equal to the sum of the global intercept α_0 and the region-specific random effect t_i, and variance equal to the between-country variance σ_u^2. In other words, these imputations corresponded to the predicted distribution for, respectively, an average country within an average WHO sub-region and an average country within the concerned WHO sub-region. These analyses were performed in R 3.0.1 (R Core Team, 2013). Finally, note that for countries with available incidence data no imputations were performed. The incidence data used in the further analyses are thus a combination of actual data and imputed estimates.

Meta-analysis of transition probabilities

Values for the transition probabilities listed in Figure 3.1 extracted from the studies identified in the systematic review were combined into a single estimate with corresponding uncertainty interval using a random effects meta-regression model. For each study, an indicator variable was assigned reflecting the study quality, with 0 = prospective cohort studies, multiplier study, case-based notifiable study, and 1 = notifiable outbreaks or other (e.g. case-control study). This indicator was included as a fixed effect in the meta-regression model. The analyses were performed in R 3.0.1 (R Core Team, 2013) using the metafor package (Viechtbauer, 2010).

Disability Weights

Health outcomes for perinatal and non-perinatal listeriosis were death, septicemia, central nervous system (CNS) infection, and neurological sequelae following a CNS infection. Disability Weights (DWs) for septicemia, CNS infection, and neurological sequelae were derived from DWs for various health states in the Global Burden of Disease (GBD) 2010 study (Table 3.1) [38].

For septicemia, we used the GBD2010 DW for severe acute episode of infectious disease. For CNS infection we used a combination of four GBD2010 DWs: (1) severe acute episode of infectious disease, (2) severe intellectual disability, (3) average of the DWs severe epilepsy and treated epilepsy with recent seizures, and (4) moderate motor impairment. For neurological sequelae, we used a combination of three GBD2010 DWs: (1) average of the 10 DWs for hearing loss, (2) average of the 5 DWs for vision loss, (3) average of the 4 DWs for stroke with long-term consequences. To create DWs for CNS infection and neurological sequelae, we conducted an expert elicitation of eight members of the Belgian Association of Neurology via a web-based questionnaire; members were asked to estimate the probability of occurrence of each health state, or combinations of each health states, following perinatal or non-perinatal listeriosis. The DWs for the combinations of health states were determined using a described multiplicative method [72]. The Las Vegas method was applied, in which experts were asked to distribute “100 points” over the different possible outcomes and combinations [73]. Per expert, a weighted overall DW was obtained by combining the individual DWs and the assigned probabilities. Finally, a bootstrap analysis was performed on these weighted DWs to derive the 95% confidence intervals to account for the between-expert variability.

Table 3.1: Disability weights used to calculate the global burden of listeriosis

Listeriosis Outcome	GBD 2010 health state	Disability Weight	95% Confidence Interval
Perinatal or non-perinatal septicemia			
	(A) Infectious disease: acute episode (severe). **Disability Weight used for septicemia**	0.210*	0.139–0.298
Perinatal or non-perinatal central nervous system infection			
	(A) Infectious disease: acute episode (severe)	0.210*	
	(B) Intellectual disability (severe)	0.126*	
	(C) Epilepsy (severe and treated, with recent seizures)	0.488#*	
	(D) Motor impairment (moderate)	0.076*	
	(A) and (B)	0.340◊	
	(A) and (C)	0.540◊	
	(A) and (D)	0.270◊	
	(B) and (C)	0.553◊	
	(B) and (D)	0.192◊	
	(C) and (D)	0.527◊	
	(A) and (B) and (C)	0.646◊	
	(A) and (B) and (D)	0.362◊	
	(B) and (C) and (D)	0.626◊	
	(A) and (B) and (C) and (D)	0.673◊	
	Disability Weight used for CNS infection	0.426d	0.368-0.474 dd
Perinatal or non-perinatal neurological sequelae			
	(A) Hearing loss	0.047#*	
	(B) Vision loss	0.087#*	
	(C) Stroke: long-term consequences	0.303#*	
	(A) and (B)	0.130◊	
	(B) and (C)	0.364◊	
	(A) and (C)	0.336◊	
	(A) and (B) and (C)	0.394◊	
	Disability Weight used for neurological sequelae	0.292d	0.272-0.316 dd

= Averaged Disability Weight; * = GBD 2010 (Salomon et al., 2013); ◊ = Multiplicative methodology; d = Using expert elicitation; dd = Bootstrap analysis.

DALY calculation

DALYs were calculated according to the standard formulas [68, 74], without age weighting and time discounting. Life expectancies were based on the Coale-Demeny model life table West [75]. No sex distinction was applied. Parameter uncertainty was taken into account by Monte Carlo simulations of the input parameters based on 10,000 samples. To facilitate comparisons of our results with others studies, scenario analyses were performed in which DALYs were calculated based on a 3% discount rate, with and without age weighting [76]. We did not correct for co-morbidity. We used a duration of 7 days for septicemia, 182 days for central nervous system infection and 7 years for neurological sequelae [63]. The DALY calculations were conducted in R 3.0.1 (R Core Team, 2013), using the DALY package version 1.2.0 (Devleesschauwer and colleagues, 2013). The global maps were generated with the rworldmap package (South and colleagues, 2011).

3.3 Results

The systematic review identified 11,722 studies, of which 87 were included in the quantitative analysis (Figure 3.2, Appendix 4 and 5 (*Available upon request to C. Maertens*)). Incidence data were available from 43 articles and for seven of the 14 WHO sub-regions. The WHO Collaborating Center for Foodborne Listeriosis did not provide additional incidence data. In AMRO A, incidence data were available for two out of three countries, in EURO A for 23 out of 27 countries, in WPRO A for four out of five countries, in AMRO B, for one out of 26 countries, in EURO B for eight out of 16 countries, in WPRO B for one out of 22 countries and in EURO C for six out of nine countries.

For 75% of the studies included in the different meta-analyses a good study quality weight of zero was assigned.

We were unable to identify any useful incidence data for Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo, Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania Zambia, Zimbabwe, Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru, Bahrain, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates, Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, South Sudan, Sudan, Yemen, Indonesia, Sri Lanka, Thailand,

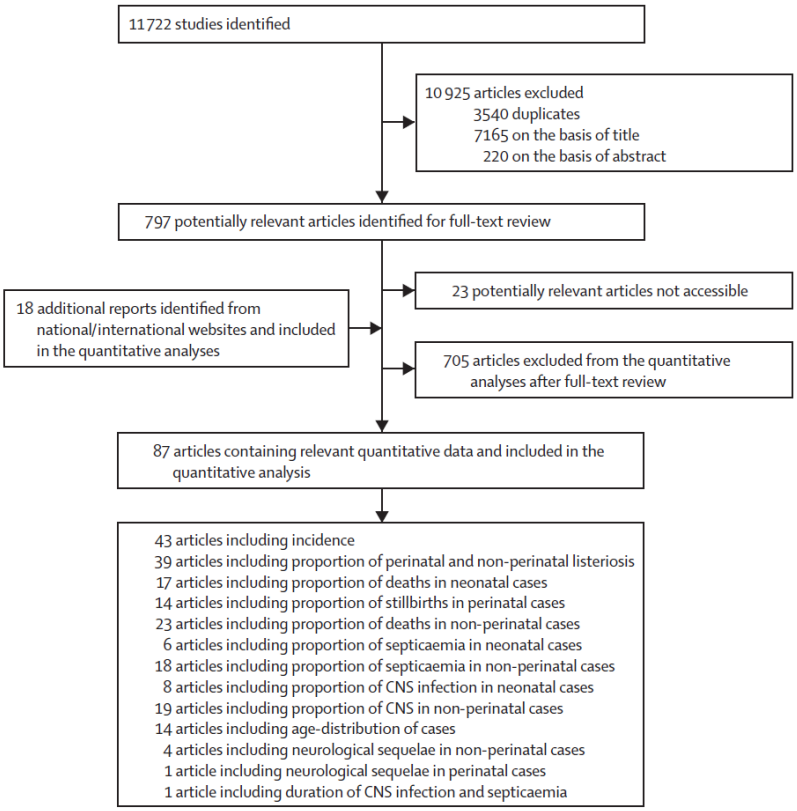


Figure 3.2: Study selection

Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal, Timor Leste. These countries correspond to a total population of 3,320,865,627 and 48% of the 2010 worldwide population.

We estimated that *L. monocytogenes* caused 23,150 illnesses worldwide in 2010 (95% Credible Interval [CrI]: 6,061-91,247) based on the 2010 population of 6,860,035,412. The highest estimated listeriosis incidence rate was in AMRO B (Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela) with 0.469 cases per 100,000 per year (95% CrI: 0.019-2.046), while the lowest estimated incidence was in the EURO B WHO sub-region (Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Montenegro, Poland, Romania, Serbia, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan) with 0.042 cases per 100,000 per year (95% CrI: 0.022-0.091). We also estimated that listeriosis lead to 5,463 deaths (95% CrI: 1,401-21,497) globally in 2010 (Table 3.2).

Table 3.2: Summary of listeriosis cases and deaths caused by listeriosis in 2010 by WHO sub-region

WHO Sub-regions[1]	Incident cases net values		Incident cases rates(per 100,000)		Deaths net values		Deaths rates (per 100,000)	
	Mean	CrI95%	Mean	CrI95%	Mean	CrI95%	Mean	CrI95%
AFR D	1,711	0-9,760	0.433	0.000-2.470	404	0-2,322	0.102	0.000-0.588
AFR E	1,913	0-10,912	0.433	0.000-2.470	451	0-2,596	0.102	0.000-0.588
AMR A	1,330	910-2,104	0.374	0.256-0.592	314	207-508	0.088	0.058-0.143
AMR B	2,298	92-10,023	0.469	0.019-2.046	544	22-2,386	0.111	0.004-0.487
AMR D	362	0-2,066	0.433	0.000-2.470	85	0-491	0.102	0.000-0.588
EMR B	715	0-4,079	0.433	0.000-2.470	169	0-970	0.102	0.000-0.588
EMR D	1,851	0-10,560	0.433	0.000-2.470	437	0-2,512	0.102	0.000-0.588
EUR A	1,491	1,238-1,765	0.342	0.284-0.405	352	277-436	0.081	0.063-0.100
EUR B	96	49-206	0.042	0.022-0.091	23	11-49	0.01	0.005-0.022
EUR C	209	86-593	0.089	0.037-0.253	49	20-140	0.021	0.008-0.060
SEAR B	1,428	0-8,146	0.433	0.000-2.470	337	0-1,938	0.102	0.000-0.588
SEAR D	6,399	0-36,505	0.433	0.000-2.470	1,510	0-8,684	0.102	0.000-0.588
WPR A	205	137-290	0.129	0.087-0.183	48	31-70	0.03	0.020-0.044
WPR B	3,141	1,986-6,887	0.192	0.121-0.420	741	447-1,632	0.045	0.027-0.100
Global total	**23,150**	**6,061-91,247**	**0.337**	**0.088-1.330**	**5,463**	**1,401-21,497**	**0.08**	**0.020-0.313**

[1] AFRO D: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo. AFRO E: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania Zambia, Zimbabwe. AMRO A: Canada, Cuba, United States of America. AMRO B: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela. AMRO D: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru. EMRO B: Bahrain, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates. EMRO D: Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, South Sudan, Sudan, Yemen. EURO A: Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany,

Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom. EURO B: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Montenegro, Poland, Romania, Serbia, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan. EURO C: Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine. SEARO B: Indonesia, Sri Lanka, Thailand. SEARO D: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal, Timor Leste. WPRO A: Australia, Brunei Darussalam, Japan, New Zealand, Singapore. WPRO B: Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia , Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam. Sub-regions: AFRO=Africa; AMRO=Americas; EMRO=Eastern Mediterranean; EURO=Europe; SEARO=South-East Asia; WPRO=Western Pacific; A: very low child, very low adult mortality; B Low child, low adult mortality; C: Low child, high adult mortality; D: High child, high adult mortality; E: High child, very high adult mortality.

We estimated 2% of non-perinatal cases to be 1 to 4 years of age, 4% 5-14 years, 10% 15-34 years, 6% 35-44 years, 7% 45-54 years, 13% 55-64 years, 20% 65-74 years, 20% 75-84 years and 18% $>$ 85 years.

Of all listeriosis cases, 20.7% ($\pm$1.7%) were perinatal infections, while 79.3% ($\pm$2.0%) were non-perinatal. Septicemia was the most common outcome in perinatal cases, occurring in 30.7% ($\pm$9.3%) of infected neonates. In total, 15.2% ($\pm$2.1%) of infected neonates developed central nervous system infections, of which 43.8% ($\pm$12.0%) showed neurological sequelae. Among all perinatal cases, 9.2% ($\pm$1.7%) resulted in neonatal deaths (among live births) and 5.7% ($\pm$1.9%) resulted in stillbirths, for an overall case fatality of 14.9%. Of all non-perinatal listeriosis cases, 61.6% ($\pm$2.2%) resulted in septicemia and 30.7% ($\pm$2.0%) resulted in central nervous system infections. Among the non-perinatal cases affected by CNS infection, 13.7% ($\pm$5.5%) developed neurological sequelae. In total, 25.9% ($\pm$2.1%) of the non-perinatal cases resulted in death.

Based on the expert elicitations and bootstrap analysis, a DW of 0.426 (95% Confidence Interval [CI]: 0.368-0.474) was obtained for CNS infection and 0.292 (95% CI: 0.272-0.316) for neurological sequelae (Table 3.1). In 2010, we estimated that listeriosis resulted in 172,823 DALYs (95% CrI: 44,079-676,465) and 2.519 DALYs per 100,000 persons (95% CrI: 0.643-9.861). YLLs accounted for 98% of the total DALYs. The highest burden occurred in AMRO B, where listeriosis resulted in 3.512 DALYs per 100,000 persons (95% CrI: 0.140-15.532). The lowest rate was in EURO B, with an estimated 0.311 DALYs per 100,000 persons (95% CrI: 0.155-0.673).

Table 3.3: Summary of listeriosis burden in 2010 by WHO sub-region

WHO Sub-regions[1]	Years Lived with Disability (net values)		Years of Life Lost (net values)		Disability-Adjusted Life Years (net values)	
	Mean	CrI95%	Mean	CrI95%	Mean	CrI95%
AFRO D	263	0-1,533	12,504	1-71,215	12,767	1-72,726
AFRO E	294	0-1,714	13,984	1-79,641	14,278	1-81,331
AMRO A	204	112-367	9,730	6,358-15,882	9,934	6,496-16,215
AMRO B	354	13-1,602	16,846	672-74,350	17,200	686-76,070
AMRO D	56	0-325	2,647	0-15,075	2,703	0-15,395
EMRO B	110	0-641	5,226	0-29,763	5,336	0-30,395
EMRO D	284	0-1,659	13,530	1-77,053	13,814	1-78,688
EURO A	229	146-344	10,903	8,464-13,723	11,132	8,656-13,991
EURO B	15	7-33	703	351-1,523	718	359-1,553
EURO C	32	11-95	1,526	609-4,362	1,558	621-4,447
SEARO B	219	0-1,279	10,437	1-59,539	10,656	1-60,701
SEARO D	983	0-5,734	46,769	3-266,357	47,752	3-272,009
WPRO A	31	18-52	1,497	967-2,188	1,528	988-2,233
WPRO B	482	244-1,117	22,965	13,739-50,696	23,447	14,059-51,688
Global total	**3,556**	**815-14,542**	**169,267**	**43,106-661,907**	**172,823**	**44,079-676,465**

[1] See Table 3.2

The scenario analysis showed that the inclusion of stillbirths increased the average DALYs total by 14.7% (Table 3.4) (Figure 3.3 and 3.4).

Table 3.4: Global burden of listeriosis, with and without the inclusion of stillbirths

	Years Lived with Disability (rate per 100,000)		**Years of Life Lost (rate per 100,000)**		**Disability-Adjusted Life Years (rate per 100,000)**	
	Mean	**CrI95%**	**Mean**	**CrI95%**	**Mean**	**CrI95%**
Without stillbirths	0.052	0.012-0.212	2.145	0.547-8.447	2.197	0.560-8.621
With stillbirths	0.052	0.012-0.212	2.467	0.628-9.649	2.519	0.643-9.861

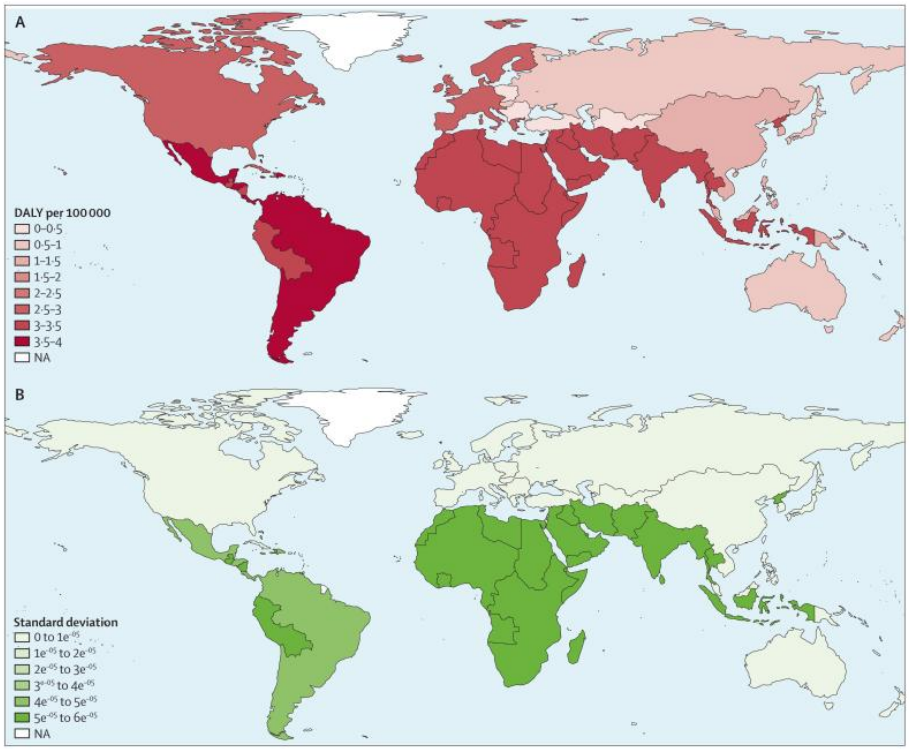


Figure 3.3: Disability-Adjusted Life Years (DALYs) per 100,000 people for listeriosis (with stillbirths) by WHO sub-region

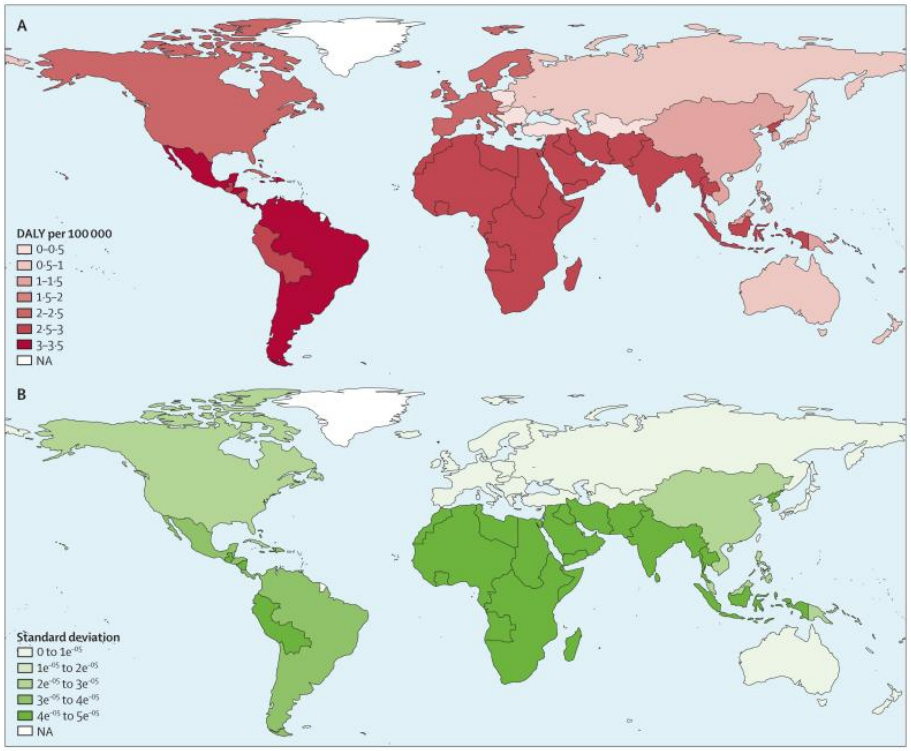


Figure 3.4: Disability-Adjusted Life Years (DALYs) per 100,000 people for listeriosis (without stillbirths) by WHO sub-region.

3.4 Discussion

This study provides the first estimates of the global burden of listeriosis and allows the relative burden of listeriosis to be put in perspective. We estimated that in 2010 *L. monocytogenes* caused 23,150 cases (95% CrI: 6,061-91,247), 5,463 deaths (95% CrI: 1,401-21,497), 172,823 DALYs (95% CrI: 44,079-676,465) and 7.466 DALYs by case (95% CrI: 6.386-8.676) globally.

Compared to other foodborne pathogens, *L. monocytogenes* causes fewer infections than non-typhoidal *Salmonella* (93.8 million cases; 95% CI: 61.8-131.6 million cases) [77], *Salmonella* serotype Typhi (21.7 million cases) [78] or *Toxoplasma gondii* (190,100 cases) [79]; *L. monocytogenes* causes a similar number of infections as *Echinococcus multilocularis* (18,235 cases; 95% CI:11,900-28,200 cases) [80]. *Listeria monocytogenes* also caused fewer deaths than *S.* Typhi (216,500 deaths) [78] or non-typhoidal *Salmonella* (155,000 deaths; 95% CI: 39,000-303,000 deaths) [77]. The number of DALYs due to listeriosis was lower than that of congenital toxoplasmosis (1.20 million DALYs) [79] but in line with that of echinococcosis (144,000 DALYs; 95% CrI: 69,000-286,000 DALYs) [23]. However, compared to these other diseases, listeriosis is mainly foodborne and is a major problem for the food industry, as it is a pathogen that is difficult to control in the production environment.

Havelaar and colleagues estimated that listeriosis caused 0.58 DALYs per 100,000 inhabitants in 2009 in the Netherlands. We estimated a higher rate, 2.555 DALYs per 100,000 persons (95% CrI: 1.987-3.211) in EURO A, but we used updated DWs to generate DALYs and included stillbirths in the burden calculation. Cressey and colleagues estimated that listeriosis caused 217 DALYs in New-Zealand in 2007 ($\sim$ 5.24 DALYs per 100,000 inhabitants) [64, 65]. We estimated a lower rate, 0.963 DALYs per 100,000 persons (95% CrI: 0.623-1.408), because we included the lower incidence reported in Japan in WPRO A and a 3% discount rate in DALYs calculation. In Greece, it was estimated that listeriosis caused 4.1 YLLs (95% CrI: 0.45-9.7) per 1 million inhabitants in an average year and that DALYs due to listeriosis were mainly determined by the YLLs [81]. We similarly found that the YLLs accounted for the highest part of the total DALYs but we estimated a higher YLL per million population (25.03 YLLs per 1 million population; 95% CrI: 19.43-31.50) because we included stillbirths.

We found that including stillbirths in the DALY calculations for listeriosis increased the global burden by 14.7%. In contrast, despite substantial interest in the number of intrapartum fetal deaths, stillbirths are not included in the disease burden estimates in the Global Burden of Disease 2010 work [23]. Bhutta and colleagues estimated that world-

wide, 2.65 million stillbirths occur yearly, of which 98% occur in low and middle income countries [82]. In 2011, Frøen and colleagues launched an initiative to spotlight stillbirths; this study contributes to this goal [83].

This study proposes a multilevel meta-analysis model for imputing missing country-specific incidences, taking into account the variability at the study, country and WHO subregion levels. To our knowledge, such a multiple imputation model has not yet been applied in other global burden of disease studies. Indeed, other studies applied simple imputation techniques, e.g., by imputing the median value of the same or a neighboring region (e.g., Resnikoff and colleagues, 2004), [84] which ignores the variability in the data, and thus the uncertainty in the imputations. Our multiple imputation methodology could further be extended by including a correction for underreporting, provided that a realistic model were available for the amount of underreporting, and for the variability in underreporting within and between regions.

The current study uncovered important data gaps. Most importantly, we were unable to identify incidence data for the AFRO, EMRO and SEARO WHO regions. We therefore had to rely on multiple data sources and assumptions to produce global estimations. The major assumption of our imputation model is that missing data were "missing at random", meaning that the unobserved values were not associated with the probability of being missing [85]. In our case, this assumption implied that, within each sub-region, countries with data provided unbiased information on those without data, and that, across sub-regions, sub-regions with data provided unbiased information on those without data. We recognize that the latter assumption may be problematic, as we could only retrieve data from high and middle income sub-regions. However, in absence of any information on the systematic difference in listeriosis incidence rates across sub-regions, it is virtually impossible to account for this, unless arbitrary assumptions were to be made, which cannot be checked with observed data, and which may highly affect the final results. Data from these sub-regions are therefore urgently required. This lack of data, and thus our large uncertainty, was reflected in the large credible intervals for these sub-regions.

Our model did not take into account the food habits (storage) or practices of importation that could be different between countries. We also did not correct for underreporting as such because this information was only available for some countries in EURO A and AMRO A WHO sub-regions, is typically low ($\sim$ 1.1) [86] and impossible to estimate for the other countries with the available data. We think that using multipliers for underreporting that are derived from studies in others countries, raises questions regarding the comparability of multipliers and health care systems of countries. However, most of the

studies included in the different meta-analyses got a good study quality weight score of zero; this would mean that most data points somehow accounted for underreporting.

Moreover incidence data about listeriosis could vary depending on the surveillance system of the country (passive or active, case mandatory reported or not) and on the definition of case based on isolation of bacteria or detected by PCR/immunological test. Additionally, gastrointestinal listeriosis exists and has been proven to be linked with septicemia and CNS infections [87]. By excluding gastrointestinal listeriosis from our calculations, we have underestimated the burden of listeriosis. However, we believe that this underestimation is probably minor, as acute gastroenteritis is typically less severe than the outcomes of invasive listeriosis considered in our analyses, and as the listeriosis burden appears to be dominated by the fatal outcomes. Nevertheless, we acknowledge the importance of recognizing and correctly managing such cases to avoid invasive forms of listeriosis.

Given the limited data in some regions, we did not take into account the trends of increasing or decreasing listeriosis incidence that could have occurred in some countries. In the USA, Voetsch and colleagues have estimated that compared to 1996-1998, the incidence of listeriosis had declined by about 37% by 2001 [88]. In Europe, the number of listeriosis cases slowly increased in the period 2008-2012 [89] and in Australia, the notification rate of listeriosis has remained stable over the years 1991-2000 [90].

We also did not include all possible sequelae in our outcome tree designed to calculate DALYs, because some were deemed rare or mild, or because there was not enough data. Listeriosis can also lead to other atypical forms, such as skin infections, pneumonia or peritonitis [91–93].

We also did not correct our estimates for co-morbidities; non-perinatal listeriosis cases are often linked with co-morbidities as cancer or diabetes. Some authors, such as Havelaar and colleagues, [65] corrected the number of DALYs for co-morbidities by reducing the life expectancy of non-perinatal listeriosis cases.

For some health outcomes such as neurological sequelae caused by CNS infection we found few references, making these proportions to be interpreted carefully. No DWs were available for the CNS infections and neurological sequelae, and had to be elicited through eight experts in CNS infection. More optimal DWs should be designed in future.

Finally, the probabilities of developing symptoms and the case fatality ratios were considered constant across the world. More data, particularly from developing countries,

are needed to take into account regional differences in clinical outcome of listeriosis.

3.5 Conclusion

This study is the first attempt to quantify the global burden of listeriosis, and will allow listeriosis to be included in international prioritization exercises. Nevertheless, because of the limited data on listeriosis incidence, there remains large uncertainty about the real impact of listeriosis worldwide. We encourage further studies, particularly in the AFRO, EMRO and SEARO WHO regions, to increase efforts to generate and share local data about listeriosis incidence [94][36]. As additional data becomes available, an update of this review should be repeated.

In the next chapter we will focus on obtaining burden of listeriosis estimates for Belgium. We will further compute DALYs estimates for two other major bacterial foodborne diseases in Belgium: campylobacteriosis and salmonellosis.

4

Current and future burden of foodborne diseases in Belgium: a time series analysis

Adapted from

Maertens de Noordhout C, Devleesschauwer B, Haagsma JA, Havelaar HA, Bertrand S, Vandenberg O, Quoilin S, Brandt PT, Speybroeck N. Current and future burden of salmonellosis, campylobacteriosis and listeriosis in Belgium: a time series analysis. *Under Review*

4.1 Introduction

Salmonellosis in humans is caused by non-typhoidal *Salmonella enterica* bacteria, which originate from animal reservoirs and can spread to humans through contaminated foods such as eggs and raw meat from pigs and chickens, but also through non-food pathways. The most common symptoms of human salmonellosis include fever, diarrhea and abdominal cramps but if the bacterium infects the bloodstream, it can cause septicemia and even death. Irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and reactive arthritis may also be consequences of the infection. For 2010, the World Health Organization (WHO) estimated that non-typhoidal salmonellosis caused 8 Disability-Adjusted Life Years (DALYs)/100,000 inhabitants (95% Uncertainty Interval [UI]: 5-14) in the WHO European region [4, 95].

Campylobacteriosis is a foodborne disease mainly caused in humans by the gram-negative bacteria *Campylobacter jejuni* and *Campylobacter coli*. Transmission to humans is most often associated with the handling and consumption of poultry meat, contaminated during slaughter and carcass processing. The main symptomatic outcome of the disease is mild or self-limiting gastroenteritis, but in immunocompromised people *Campylobacter* can lead to immunoreactive complications such as Guillain-Barré Syndrome (GBS) or reactive arthritis [95, 96]. It was estimated that in 2010, *Campylobacter* caused 96 million foodborne illnesses worldwide (95% UI: 51-177 millions), being the highest number of confirmed foodborne bacterial infections worldwide. In 2010, foodborne campylobacteriosis caused 9 DALYs/100,000 inhabitants (95% UI: 6-13) in the WHO European region [4].

Listeriosis is caused by the Gram-positive bacterium, *Listeria monocytogenes*, which can grow at refrigeration temperatures, in contrast to many other foodborne pathogens. This ability to persist and multiply in the food environment makes *L. monocytogenes* particularly difficult to control [7]. *L. monocytogenes* infections in healthy individuals may cause febrile gastroenteritis, which is usually mild and self-limiting but in patients with impaired cell-mediated immunity listeriosis can lead to severe illnesses including septicemia, meningitis or encephalitis, producing lifelong consequences and even death. Infection during pregnancy may result in spontaneous abortions or stillbirths. Estimations indicated that in 2010 listeriosis caused two DALYs/100,000 inhabitants (95% UI: 1-2) in the WHO European region [4, 97].

Even though every Belgian person is potentially exposed to *Salmonella*, *Campylobacter* and *Listeria*, their real public health impact in Belgium is incomplete. Simple hygiene

rules to avoid food contamination is poor among Belgian residents. In 2014, a report indicated that only 10% of the Belgian population properly handled raw eggs and meat, and that less than half of the population defrosted meat, poultry or fish safely [17].

The DALY metric that quantifies the burden of a disease as the number of healthy life years lost due to morbidity and mortality emerged internationally as the most used summary measure of population health. Its use facilitates the comparison of the relative impact of diseases and risk factors and the monitoring of public health over time [25, 68]. Estimations of the burden of non-communicable diseases or injury in Belgium using the DALY metric were reported [37, 98, 99] but no such study exists yet for the burden of communicable diseases while its applicability has been demonstrated for other European countries [65, 81, 100]. If data on the trends in the state of public health over time are important to plan public health interventions [101], the use of DALYs has to be considered as a crucial additional information on disease burden for policy makers to make relevant decisions and set appropriate priorities. Globally nor in Belgium, the future burden of foodborne diseases has ever been predicted, despite a changing, aging population, and life expectancy may influence the burden of the bacterial foodborne diseases in the future years. The use of time series analyses, mainly used in economics, may be relevant for studying trends and future trends of foodborne diseases.

This study tries to address the aforementioned gaps by providing estimates of the current and future numbers of *Salmonella*, *Campylobacter* and *Listeria* cases, and the resulting DALYs in Belgium from 2012 to 2020 using time series analyses. This study will generate valuable information for decision-makers and researchers, and may be a starting point for other burden of foodborne diseases studies in Belgium.

4.2 Materials and Methods

4.2.1 Data

The Belgian Scientific Institute for Public Health (WIV-ISP) collects data on laboratory-confirmed salmonellosis, campylobacteriosis and listeriosis cases in Belgium. National Reference Centre for *Salmonella* spp. and *Listeria* spp. of the WIV-ISP is receiving strains from Belgian laboratories in order to type them or define their profile for resistance against antibiotics [102]. Positive results of stool culture for *Campylobacter* spp. are collected by laboratories participating to the sentinel laboratory network. Belgian Sentinel Network of Laboratories (SNL) were created in 1983 in order to monitor trends in infectious diseases. About 60% of Belgian laboratories are participating to this sen-

tinel system [54]. The number of cases per month were available from January 2001 to December 2012 for salmonellosis, from 1993 to 2013 for campylobacteriosis and from 2011 to 2013 for listeriosis. More recent data were not available because there is some delay between data collection and publication of the data by WIV-ISP.

4.2.2 Salmonellosis model

Visual inspection of the time series of the Salmonella time series (Figure 4.2) showed that there was a downward trend in the time series after 2005 and strong seasonality. Both the Shapiro and Jarque-Berqua tests rejected the normality of the Salmonella time series distribution ($p < 0.001$). Autocorrelation and partial autocorrelation plots (Appendix 1) indicated that the data were highly autocorrelated and seasonal. This led to the need for a non-linear, non-Gaussian time series model.

Collard et al. [103] had already reported a dramatic drop in salmonellosis cases in Belgium from 2005 onwards. They noted that in 2003, as part of the European Union policy, Belgium adopted changes in the breeder-flock poultry monitoring and control program, with a possible influence on the *Salmonella* transmission and control. Since 2003, a mandated monitoring, and vaccination programs were put in place. Vaccination against *S. enteritidis* is mandatory and vaccination against *S. typhimurium* became strongly recommended. *Salmonella* positive flocks were logistically slaughtered within the month. The effects of these policy changes, could not be dated exactly, meaning that the time series was not easy to segment into forecastable sub-series and that the data exhibited possible non-stationarity or unstable behavior [104], therefore requiring the need of a change-point model. We selected the Bai and Perron [105, 106] change-point model for autoregressive time series models allowing for structural changes in the parameters. The time series' partial and autocorrelation functions (PACF and ACF) related to the latter model (Appendix 2) resulted in stationarity, suggesting that the change-point model could explain the intense changes in the dynamics, levels, and trends in the data. The model identified the number and location (in time) of the breakpoints. Since in a regression context adding more breakpoints will always result in lower errors, a Bayesian information criterion was used for final model selection, ensuring the selection of a model with an optimal set of breakpoints [105]. The choice of the number and location of the lagged values used in the model was made such that the residuals of the final regression were white noise, or serially uncorrelated.

The final model with serially uncorrelated residuals for the *Salmonella* series S_t had the form:

$$S_t = c + \Phi_{1j} S_{t-1} + \Phi_{2j} S_{t-2} + \Phi_{12j} S_{t-12} + (\beta_j t)/T + \epsilon_t$$

where the sub-samples for the m breakpoints are defined by the indices at time t,

$$t = t_{j-1} + 1, ..., t_j,\ j = 1, ..., m + 1$$

This regression had m sets of regression coefficients for the $m+1$ subsets of the data. The lagged S_t terms captured the first and second order and seasonal autoregressive effects. The c and $\Phi_{1j}, \Phi_{2j}, \Phi_{12j}$ are the intercept and autoregressive terms for the effects of the lagged values at times $t-1$, $t-2$, and $t-12$. These autoregressive terms captured the lagged effects of the previous two months and the seasonal correlation across the same month the previous year. The normalized trend term $\beta_j t$ was allowed to vary across the regimes allowing determining if the trend increased or decreased over the data.

4.2.3 Campylobacteriosis model

The campylobacteriosis time series consisted of monthly number of cases from December 1993 to December 2013. As for salmonellosis, we first investigated the distributional properties of the data. The ACF and PACF for the campylobacteriosis time series were supportive of strong seasonality, as well as low order autocorrelation since there were significant spikes at the low order lags (1-4 in the PACF plot) (Appendix 3). A time-varying behavior, was indicated by shifts in the trend over time (leftmost panel of the ACF figure in Appendix 3), suggesting that a dynamic linear model (DLM) was appropriate. A DLM nests as special cases the autoregressive integrated moving average (ARIMA) and change-point models. While ARIMA models may be appropriate for fitting these data, such models would forecast poorly since assuming constant parameters. Further, for the data at hand, ARIMA models resulted in coefficients indicating borderline non-stationarity. The trend in these data had a stochastic drift and varied locally, increasing at an earlier stage in the sample and at the end, but relatively constant in between. The DLM dealt with all these potential issues, estimated the time-varying trend, and recognized that there were parameter stability issues around the seasonal component of the data. The DLM was made up of separate components for the drift, trend, and cyclical components of the time series. With a DLM these separate components can be filtered out of the data resulting in a forecasting model with fixed, and time-varying parameters. As Figure 4.4 shows, the seasonal component of the data was not constant over time, and the seasonal variation is lowest in the more recent years. Second, there is a strong upward

trend in the data, as the trend ranges from 400 to nearly 800 cases per year and fluctuates over time, further supporting the choice of a time-varying parameter model like a DLM.

The DLM at hand, contains three components: a stochastic linear trend, a time-varying set of deterministic dummy variables for the seasonal component, and a first order autoregression. The linear trend allowed for capturing the changing trend seen in Figure 4.4. The seasonal terms captured the time-varying seasonality in Figure 4.4. Finally, the autoregression captured the serial correlation reported in Appendix 3. The resulting model was fitted via maximum likelihood methods.

In DLMs, there are two main objects of interest, i.e. trend and seasonal components, being computed recursively with one-step ahead updates using the Kalman filter. This approach employs the information at time t (and only this information) to make a prediction at time t+1. Alternatively, one can look at the smoothed values, conditionally on the full sample. Figure 4.5 presents these components graphically. The top panel of the figure shows the data and the filtered and smoothed trend estimates. Here one sees that the model captures the time-varying and local nature of the trend, as was documented in the discussion of Figure 4.4. The middle panel of Figure 4.5 gives the time-varying seasonal component. The general seasonal pattern is the same, but the magnitudes of the seasonality changed over time. The last panel of Figure 4.5 shows the residuals. Ljung-Box tests for serial correlation failed to reject the null hypothesis of no serial correlation at multiple lag lengths (lag 1, p=0.53; lag 2, p=0.55; lag 12, p=0.31).

Since this model had white noise residuals and captured the main trend, cyclical features, and seasonality of the data, it was considered a good candidate for forecasting the number of campylobacteriosis cases in Belgium.

4.2.4 Listeriosis model

The listeriosis time series counted monthly cases from January 2011 to December 2013. This was a relatively short time series so a comparison of both a dynamic or time series model and a static prediction were in order. The short time span of 36 months, made it harder to obtain good estimates of seasonal or other dynamic patterns. Figure 4.7 displays the listeriosis time series. As previously demonstrated by pathogenesis researches [107], the testing for serial correlation in the series via ACFs (Appendix 4) showed no significant serial correlation in the time series. The lack of significance for serial correlation via ACF tests did not mean that there was no serial correlation in the count series. To better investigate the serial correlation aspects, a series of Poisson autoregressive (PAR(p)) models were fitted to the data. In 2001, Brandt and Williams proposed this model as an autore-

gressive lagged count model that used the previous p observations as predictors of the current observation in a non-linear state-space form [108]. The main choice in employing the model is the order of the lag, the integer value of p. In this analysis, values of p from one to four were tested. The best fitting model was chosen based on the statistical significance of the estimated autoregressive coefficients is a PAR(2) model.

Predictions from this model were made by simulation using direct forecasting via the mean prediction function from Brandt and Williams [108].

A simulation of 1,000 forecast paths was employed for the three developed models to generate mean forecasts and to compute a confidence region for them.

4.2.5 DALY calculations

The burden of salmonellosis, campylobacteriosis and listeriosis was evaluated in terms of DALYs. DALYs were calculated according to the standard formulas [109], without age weighting and time discounting. Standard expected years of life lost were based on the GBD 2010 model life table, while Belgian life tables were used for estimating lifelong durations of sequelae. We calculated DALYs in 2012, based on observed number of cases and DALYs in 2014 and 2020, based on the number of cases estimated by the three models developed above. The incidence calculations were based on a Belgian population of 11,161,642 inhabitants in 2012, 11,226,322 inhabitants in 2014 and prediction of 11,364,047 inhabitants in 2020 from United Nations estimations assuming a medium fertility [110]. We did not correct for co-morbidity. We corrected reported cases for underreporting of campylobacteriosis and of salmonellosis cases in Belgium, using the underreporting factors (URF) developed for Belgium, i.e., 3.5 (95% UI: 0.3-11.3) for salmonellosis and 10.5 (95% UI: 3.2-26.5) for campylobacteriosis [111]. We did not correct the listeriosis time series for underreporting as the severity of the cases was assumed to imply perfect reporting.

The DALY calculations were conducted in R 3.1.1, using the FERG package [112]. Uncertainty was propagated using 1,000 Monte Carlo simulations, and results were presented as the mean and 95% UI of the resulting uncertainty distributions.

4.2.6 Outcome tree

In addition to acute illnesses, foodborne diseases can also lead to long-term consequences, which sometime impose a heavy burden on public health. To estimate the full burden caused by a pathogen, all health outcomes of the infection have to be considered in the so-called “outcome tree”. This involves the visualization of all health outcomes and their

possible transitions in a flow chart. We used outcome trees and transition probabilities suggested by the European Centre for Disease Prevention and Control (ECDC) [113] for campylobacteriosis, salmonellosis and listeriosis (Figure 4.1). The proportion of perinatal listeriosis was from Maertens de Noordhout et al. [97] and perinatal cases were defined as materno-fetal cases including pregnancy-associated cases and cases in newborns during the first month of life. A materno-fetal infection was counted as one case in the time series. We adopted durations and DWs proposed by ECDC [113].

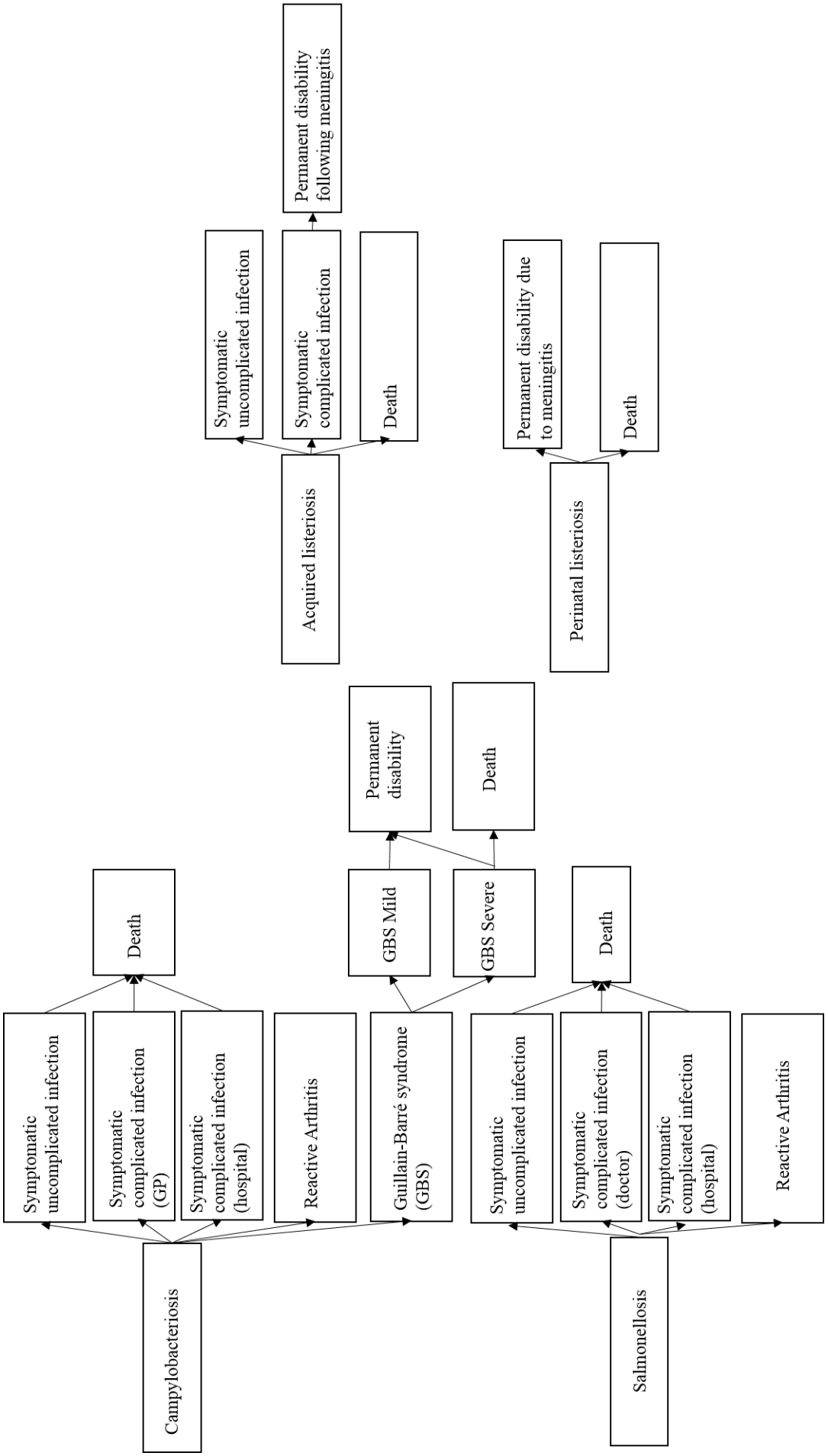


Figure 4.1: Outcome trees used for DALY calculations of campylobacteriosis, salmonellosis and listeriosis (acquired and perinatal)

4.3 Results

4.3.1 Salmonellosis

Fitting up to a five breakpoint model (m=5), the optimal BIC was produced for a two breaks model. The estimated breaks were in December 2003 and in November 2005, consistent with the results reported in Collard et al. [103]. Table 4.1 shows the estimated parameters over each of the periods.

Table 4.1: Bai-Perron changepoint regression estimates for salmonellosis, with standard errors in parentheses and p-values in square brackets

Coefficient	2001(1)-2003(11)	2003(12)-2005(10)	2005(11)-2012(12)
Intercept	144.35	626.36	44.56
	(-51.94)	(-114.7)	(-50.39)
	[0.006]	[<0.001]	[0.378]
ϕ_{1j}	1.197	0.059	0.666
	(-0.104)	(-0.193)	(-0.137)
	[<0.001]	[0.759]	[<0.001]
ϕ_{2j}	-0.831	0.047	-0.238
	(-0.076)	(-0.13)	(-0.12)
	[<0.001]	[0.717]	[0.049]
ϕ_{12j}	0.322	0.539	0.361
	(-0.081)	(-0.077)	(-0.093)
	[<0.001]	[<0.001]	[<0.001]
β_j	2106.07	-2261.68	14.54
	(-456.2)	(-375.7)	(-44.9)
	[<0.001]	[<0.001]	[0.747]
Standard Error	73.99		
R^2	0.986		

We observed a strong autoregressive model with seasonality with relatively more salmonellosis cases from June to August than in other months, and a statistically significant positive trend ($p < 0.001$) during the period January 2001 to November 2003. The dynamics of the second period, from December 2003 to October 2005, was different compared to the dynamics in the first period. The first two autoregressive lags were not significant, but there was a strong seasonal component ($p < 0.001$). The trend became negative in this period, meaning that the number of cases decreased, reflecting the poultry vaccination. During this second period, the estimated trend coefficient was negative and larger in absolute value than the upward trend of the first period. In the last period from November

2005 to December 2012, a new equilibrium was reached after the drop brought by the changes in vaccination and hygiene policies. There was no statistically significant intercept or trend. Instead, the autoregressive dynamics dominated the process.

The seasonality gets much weaker in the third segment of the changepoint model and explained why the seasonality is much reduced in the prediction. It has a much stronger AR(1) and AR(2) component that osscillate in the third period and smooth out to a long run equilibrium.

Figure 4.2 presents the in-sample fit, as well as a 96 month (8 year) forecast through the end of 2020. The time series is well fitted by this model (Appendix 5), and the forecast shows a continued decline to the long-run means of the post-2005 process. Figure 4.2 also includes simulated one standard deviation error bands. The 2012 average number of confirmed cases per month was 264 (SD 86), and the final equilibrium prediction for 2020 was 212 cases (SD 87) per month.

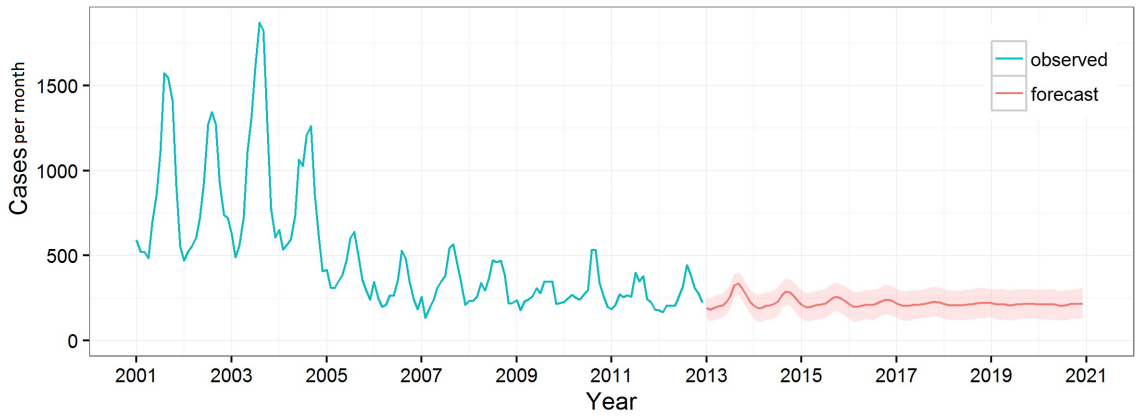


Figure 4.2: Monthly confirmed *Salmonella* cases and forecasts through 2020. Forecasts are red lines. Red areas are simulated one standard deviation error bands

Notice that in the aggregated data used in the analysis, the trend is dominated by *Salmonella Enteritidis*, with numbers decreasing to very low levels, whereas the number of cases caused by *Salmonella Typhimurium* and other *Salmonella* species remained constant across the series (Figure 4.3).

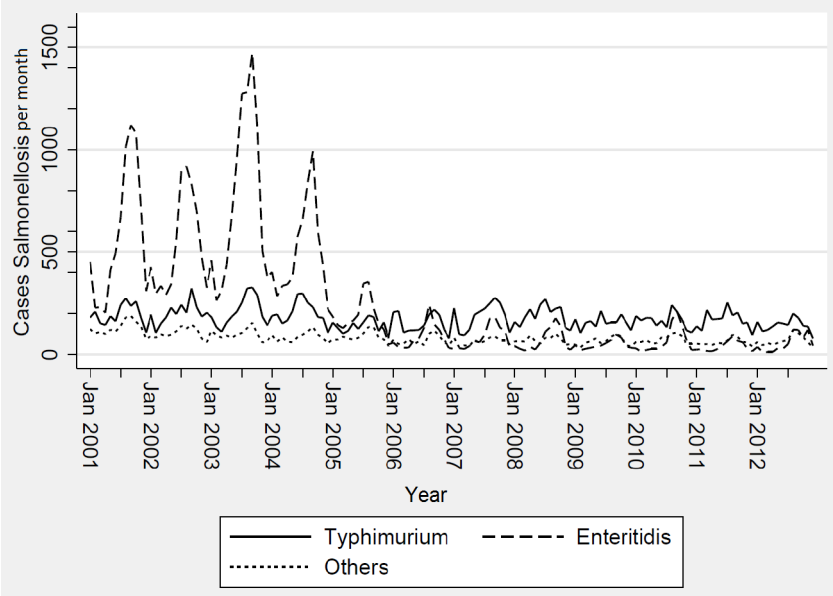


Figure 4.3: Monthly confirmed *Salmonella* cases by species

We estimated that in 2012, salmonellosis caused 102 DALYs (95% UI: 8-376) or 0.9 DALYs/100.000 population (95% UI: 0.07-3). Based on our forecast model, the burden in 2020 would drop to 82 DALYs (95% UI: 6-310) or 0.7 DALYs/100,000 population (95% UI: 0.05-3) (Table 4.3).

4.3.2 Campylobacteriosis

Figure 4.6 shows the Campylobacteriosis forecasts through 2020. The green lines are the observed *Campylobacter* data, and the red are the forecasts and one standard deviation confidence region. The upward trend was extrapolated from the earlier analysis in Figure 4.5. The seasonal component is seen in the middle panel of Figure 4.5. The average monthly number of campylobacteriosis confirmed cases was 633 (SD 81) in 2012, with the predictions showing an upward trend until 2020 to an average of 1081 (SD 311) cases per month. The predictions showed that the campylobacteriosis cases will exceed their previous peak of 1005 cases in August 2000 in May 2019.

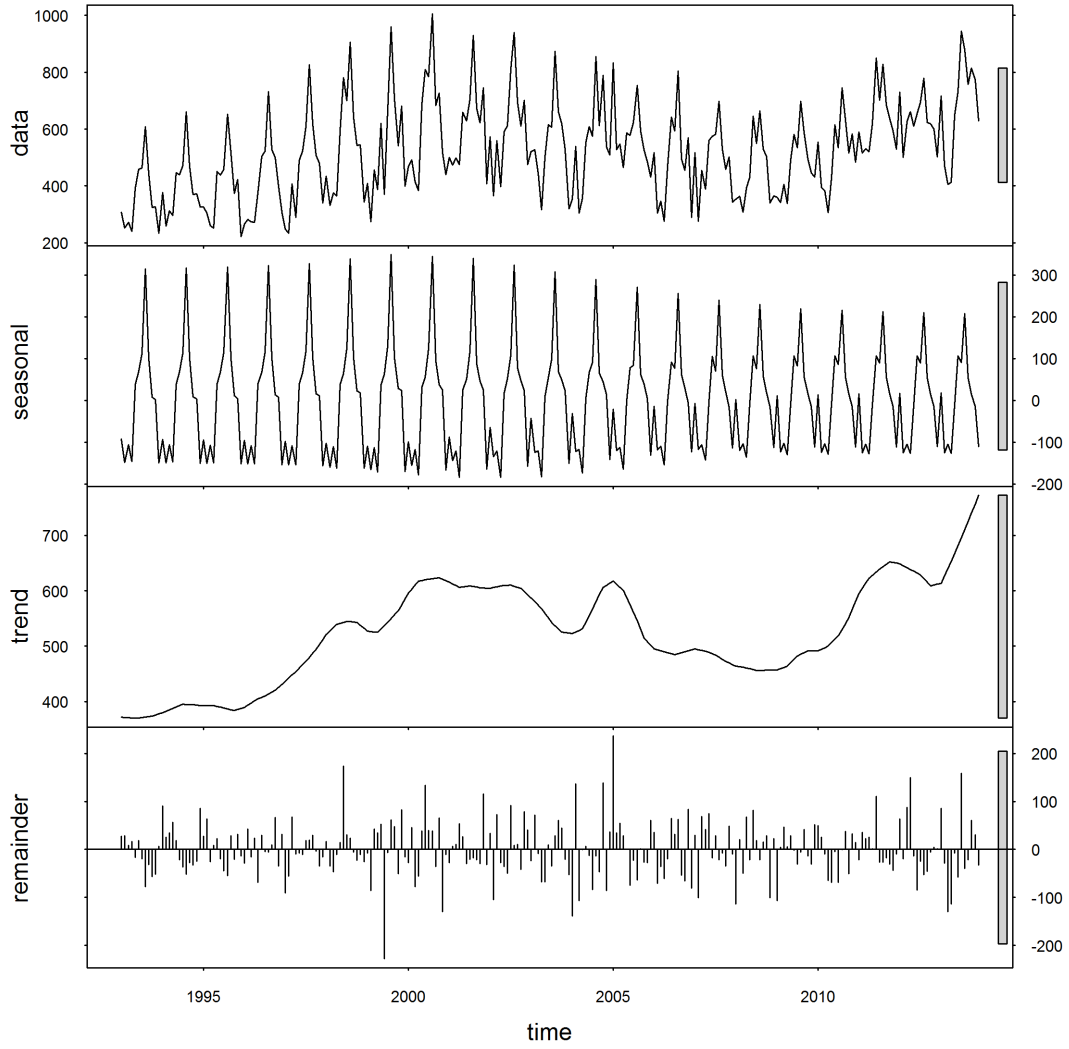


Figure 4.4: Seasonal-trend-loess (STL) decomposition of the monthly Belgian *Campylobacter* data, 1993-2013

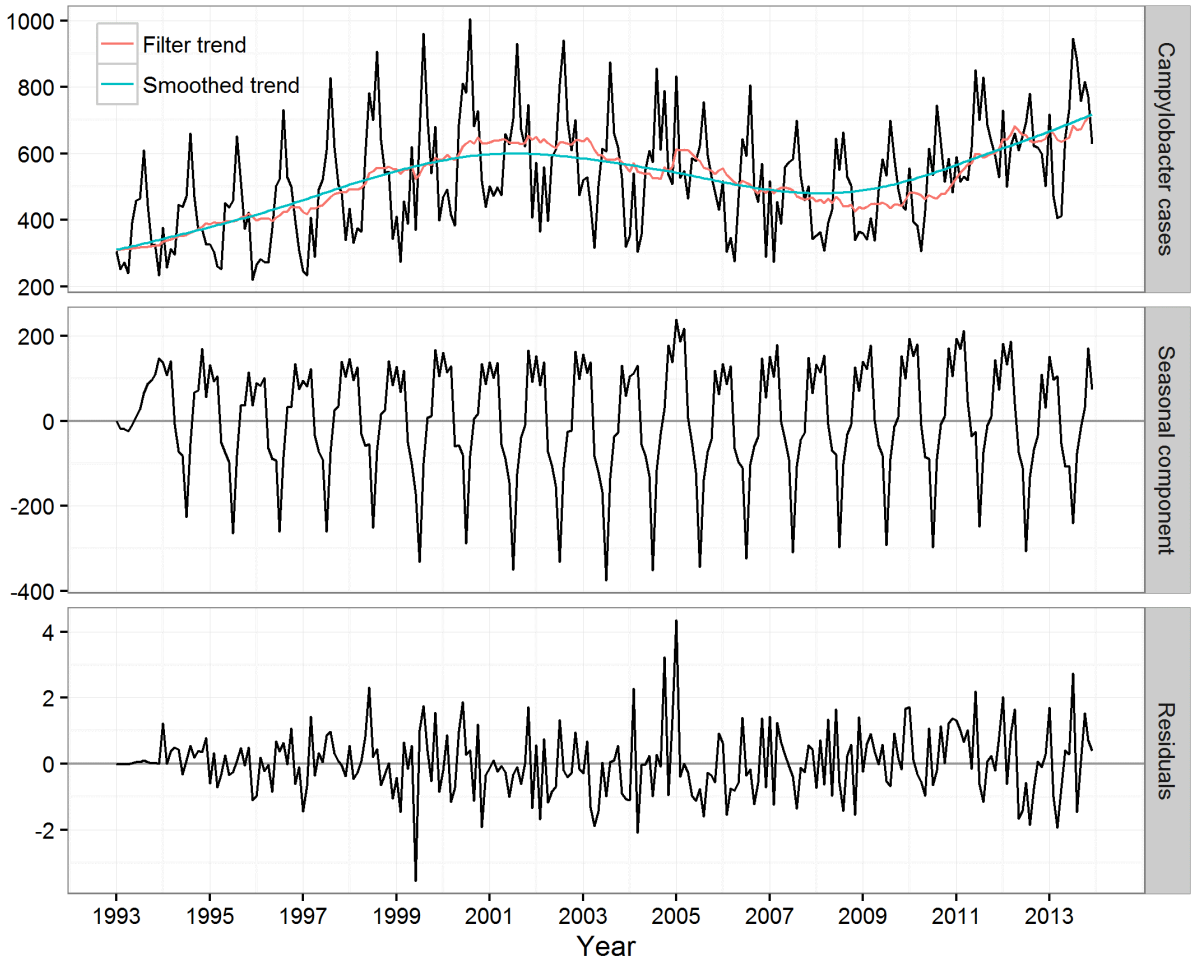


Figure 4.5: Fitted DLM and decomposition for the Belgian *Campylobacter* series, 2001-2013

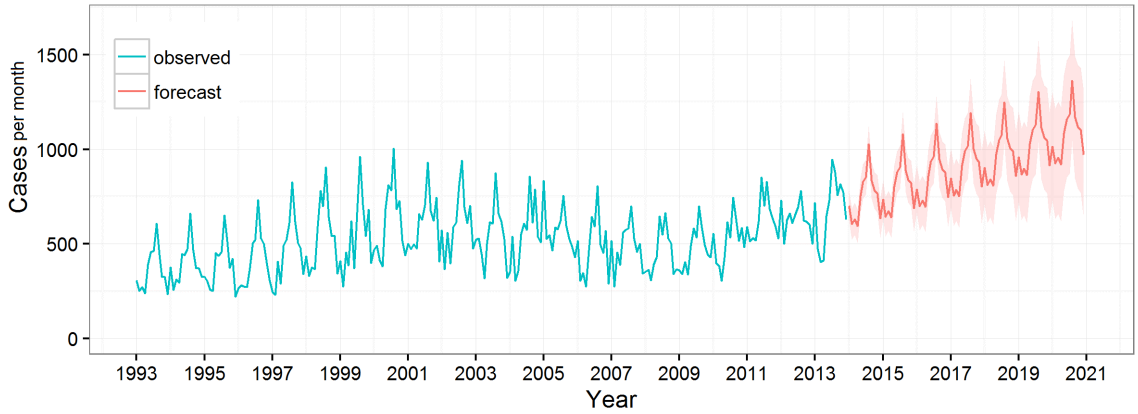


Figure 4.6: Monthly *Campylobacter* data and forecasts through 2020. Forecasts are red line. Red areas are simulated one standard deviation error bands

We estimated that campylobacteriosis caused 1,019 DALYs (95% UI: 137-3,181) or 9 DALYs/100,000 inhabitants (95% UI: 1-29) in 2012, which would increase to 1,736 DALYs (95% UI: 178-5,874) or 15 DALYs/100,000 inhabitants (95% UI: 2-52) in 2020. In 2012, 63% of the burden was caused by years of life lost (Table 4.3).

4.3.3 Listeriosis

Table 4.2 shows the estimated coefficients and fit for this model. The Wald test for comparison with a static Poisson regression had a value of 15.46 with a p-value less than 0.001, indicating that this model is preferred over a standard Poisson regression model. The estimated autoregressive parameters for this model, λ_1 and λ_2 were negative, meaning there were fewer predicted listeriosis cases after they were observed. The mean forecast is 74 cases (SD 6.1) in 2014 or 6 new additional cases per month (SD 2.6) in 2014 (Figure 4.7).

Table 4.2: PAR(2) estimates for listeriosis time series

Coefficient	Estimate	Standard Error	Z-score
λ_1	-0.28	0.13	-2.17
λ_2	-0.24	0.15	-1.67
Intercept	1.83	0.06	32.11

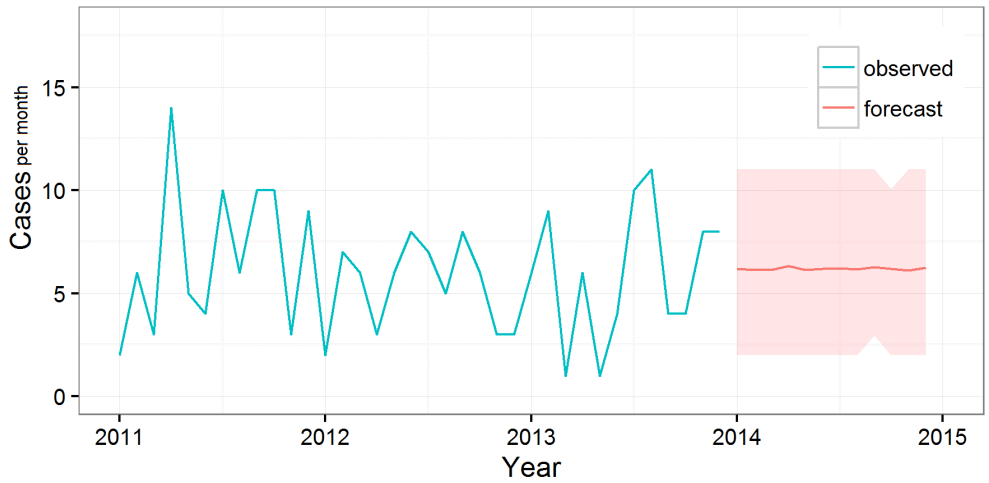


Figure 4.7: Monthly *Listeria* confirmed cases and forecasts through 2020. Forecasts are red line. Red areas are simulated one standard deviation error bands

Acquired listeriosis caused 208 DALYs (95% UI: 192-226) or 2 DALYs/100,000 inhabitants (95% UI: 1-2) in 2012 and was predicted to cause 252 DALYs (95% UI: 200-307) or 2 DALYs/100,000 inhabitants (95% UI: 2-3) in 2014. Perinatal listeriosis caused 269 DALYs (95% UI: 208-347) or 2 DALYs/100,000 inhabitants (95% UI: 2-3) in 2012 and

was estimated to cause 258 DALYs (95% UI: 204-322) or 2 DALYs/100,000 inhabitants (95% UI: 2-3) in 2014. Most of the burden is caused by mortality (Table 4.3).

Table 4.3: Current and future Disability-Adjusted Life Years for salmonellosis, campylobacteriosis and listeriosis in Belgium

Burden of salmonellosis, campylobacteriosis and listeriosis in 2012 in Belgium

Pathogen		Years Lived with Disability (net values)		Years of Life Lost (net values)		Disability-Adjusted Life Years (net values)	
		Mean	**95% UI**	**Mean**	**95% UI**	**Mean**	**95% UI**
Non-typhoidal *Salmonella enterica**		44	4-162	58	2-238	102	8-376
Campylobacter spp.*		379	67-1,295	640	44-2,023	1,019	137-3,181
Listeria Monocytogenes							
	Acquired	14	2-29	193	185-200	208	192-226
	Perinatal	56	7-115	213	185-248	269	208-347
Non-typhoidal *Salmonella enterica***		13	7-24	17	2-33	30	10-54
Campylobacter spp.**		37	14-101	62	7-121	98	23-203

Burden of salmonellosis, campylobacteriosis in 2020 and of listeriosis in 2014 in Belgium

Pathogen		Years Lived with Disability (net values)		Years of Life Lost (net values)		Disability-Adjusted Life Years (net values)	
		Mean	**95% UI**	**Mean**	**95% UI**	**Mean**	**95% UI**
Non-typhoidal *Salmonella enterica**		35	3-132	47	2-182	82	6-310
Campylobacter spp.*		651	89-2,381	1,085	59-3,555	1,736	178-5,874
Listeria Monocytogenes							
	Acquired	17	2-36	235	191-282	252	200-307
	Perinatal	54	6-107	204	188-223	258	204-322
Non-typhoidal *Salmonella enterica***		10	5-20	14	1-29	24	7-46
Campylobacter spp.**		63	16-205	104	8-252	167	28-394

* with correction for underreporting of 3.5 [95% UI 0.34-11.3] for samonellosis and 11.5 [95% UI 3.2-26.5] for campylobacteriosis; ** without underreporting correction

4.4 Discussion

Using time series analysis we estimated that in Belgium the burden of salmonellosis and listeriosis would remain stable between 2014 and 2020, but that the burden of campylobacteriosis would increase by a factor of almost 2 by 2020.

A time series analysis is an appropriate methodology to help reveal or clarify trends of foodborne illnesses, to forecast future cases and to test the impact of interventions on the burden of foodborne diseases. Time series models could complement the public health surveillance of foodborne diseases [114, 115], and could also be used to identify irregularities in disease incidence [116, 117]. Model application can also result in more efficient and cost-effective control strategies [118].

We used a Bai and Perron [105, 106] two breakpoints regression model to design and forecast salmonellosis time series taking into account the multiple changes in *Salmonella* spp. transmission and control. Despite some authors already predicted future DALYs of non-foodborne diseases using a demographic dynamics model [119], or of future YLDs caused by *Salmonella* spp. infection using the prediction of future temperature changes [120] or examined seasonal and secular trends of enteric diseases using spatio-temporal analysis [121], this study is, to our knowledge, the first that used and developed segmented regressions to predict foodborne diseases and that predicted salmonellosis cases and DALYs. We estimated that salmonellosis caused 0.9 DALYs/100,000 population (95% UI: 0.07-3) in 2012. This is less than the estimations of the WHO, that estimated that salmonellosis resulted in 8 DALYs/100,000 inhabitants (95% UI: 5-14) in 2010 in the WHO European region [4], less than in Denmark where salmonellosis resulted in 7 DALYs/100,000 inhabitants (95% UI: 5-10) in 2012 [100], less than in Germany in 2007 where salmonellosis resulted in 23 DALYs/100,000 inhabitants (95% UI: 18-30) [122] and less than in The Netherlands where van Lier et al. estimated that salmonellosis resulted in 8 DALYs/100,000 (95% UI: 4-17) inhabitants in 2011 [123]. These major differences are caused by differences in the outcome trees used. Indeed, IBS and IBD are not included in the new outcome trees developed by ECDC because they concluded that there was not enough evidence that salmonellosis resulted in IBS and IBD [113]. The differences can also be explained by the fact we adjusted the salmonellosis incidence for underreporting using an URF developed by Havelaar et al. [111] to compare the burden due to salmonellosis with the burden caused by other diseases, such as listeriosis. The URF developed by Havelaar et al. for salmonellosis is particularly low for Belgium (3.5). Indeed, the URFs used in Danish (7.2) [100], German (8.7) [122] or Netherlands (18) studies were higher than for Belgium, which could also explain why the DALYs resulted of salmonellosis in-

fection is lower in Belgium than in these European countries. There is a need to develop more precise URFs for the Belgian population because the uncertainty in the URFs of salmonellosis remains high.

We used a DLM to predict that the number of *Campylobacter* DALYs and cases would almost double by 2020. We used DLM because the high variation observed in the time series. This variation can be partly explained by the improvement of the identification and data collection techniques over time. This is the first time that DLM models were used to predict foodborne diseases cases and DALYs. Weizent et al. also concluded that decomposition models, like DLM, are more appropriate models for forecasting campylobacteriosis risk in the US than regression or Box-Jenkins autoregressive integrated moving averages models [124]. Nobre et al. applied DLM models for malaria and hepatitis A data, and concluded that DLM models were adequate tools for use in epidemiological surveillance [125]. We estimated that campylobacteriosis caused 9 DALYs/100,000 inhabitants (95% UI: 1-29) in 2012. This is equal to the estimations of WHO for EURO region (9 DALYs/100,000 population (95% UI: 6-13)) and taking into account the 95% UI, not different than the estimations of van Lier et al. for the Netherlands in 2011 (20 DALYs/100,000 population (95% UI: 8-41)) [123] and of Pires for Denmark in 2012 (28 DALYs/100,000 population (95% UI: 25-33)) [100].

We developed a Poisson autoregressive model for listeriosis cases given the short time series. This is the first time severe listeriosis burden has been estimated in Belgium. We estimated that acquired listeriosis caused 4 DALYs/100,000 inhabitants (95% UI: 3-4), both in 2012 and in 2014. Perinatal listeriosis was estimate to cause 2 DALYs/100,000 inhabitants (95% UI: 2-3) in 2012 and in 2014. These results are in line with those of Maertens de Noordhout et al. [97] who estimated that listeriosis caused 3 DALYs/100,000 (95% UI: 2-3) people in 2010 in WHO European sub-region A, which includes Belgium. However listeriosis estimations could have been underestimated because we did not correct for underreporting as the severity of the cases was assumed to imply perfect reporting. Some listeriosis cases could be uncomplicated, especially in healthy people, and have not been totally reported.

A major limitation of prediction models is that they implicitly assume that the environment will stay stable. Changes in knowledge about safe food handling, physician testing practices, new interventions in the public or animal health domain, or future outbreaks, could all violate this assumption, but are impossible to predict [126]. The precision of our time series models could be further improved by including relevant covariates that were not available for the Belgium estimations. For instance, inclusion of the data source, of

incidence of the infection in animals, prevalence in food or consumption of proton-pump inhibitors, which can increase the risk of *Campylobacter* spp., *Salmonella* spp. or *Listeria* spp. infection [127, 128] could be included in the model to decrease the uncertainty of the predictions. When available, more recent data could also be included in our analysis. Including additional data will require a re-evaluation of the selected prediction model, mainly for listeriosis for which little data was available, but will decrease the uncertainty in our estimations.

Finally, we did use projected life expectancies for sequelae with a lifelong duration but we used the same transition probabilities and age distribution of cases in the DALY calculations for the projected DALYs as for the estimations in 2012. Of course, these parameters would be influenced by many factors as new treatment, improving in the management of foodborne diseases, aging of the population [119] or climate changing [129].

4.5 Conclusion

Assuming a constant environment, e.g. no change in policy and control or breeding practices, the incidence of salmonellosis and listeriosis will remain stable in Belgium, while the incidence of campylobacteriosis may almost double until 2020. New actions are urgently needed to reduce the risk of food contamination with *Campylobacter* spp. This study is a starting point for other studies that project future burden of disease of other foodborne pathogens.

In the next chapter we will start exploring how to improve burden estimates of bacterial FBDs for Belgium and globally, and investigate comorbidities and sequelae related to listeriosis.

Appendix

Appendix 1: Autocorrelation and partial autocorrelation analysis for salmonellosis time series

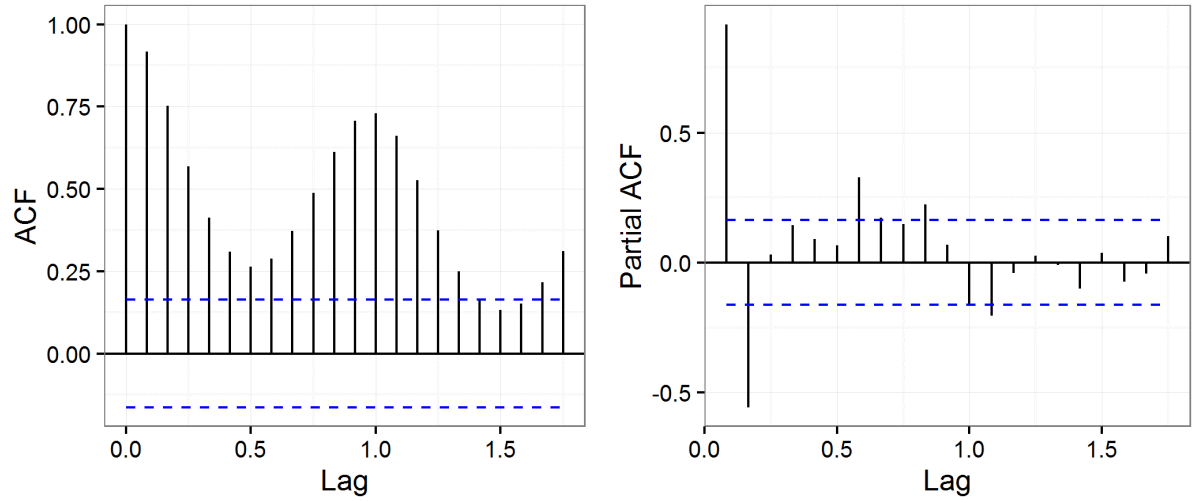


Figure 4.8: Autocorrelation and partial autocorrelation plots for salmonellosis time series (2011-2012)

Appendix 2: Autocorrelation and partial autocorrelation analysis for salmonellosis time series before and after November 2004

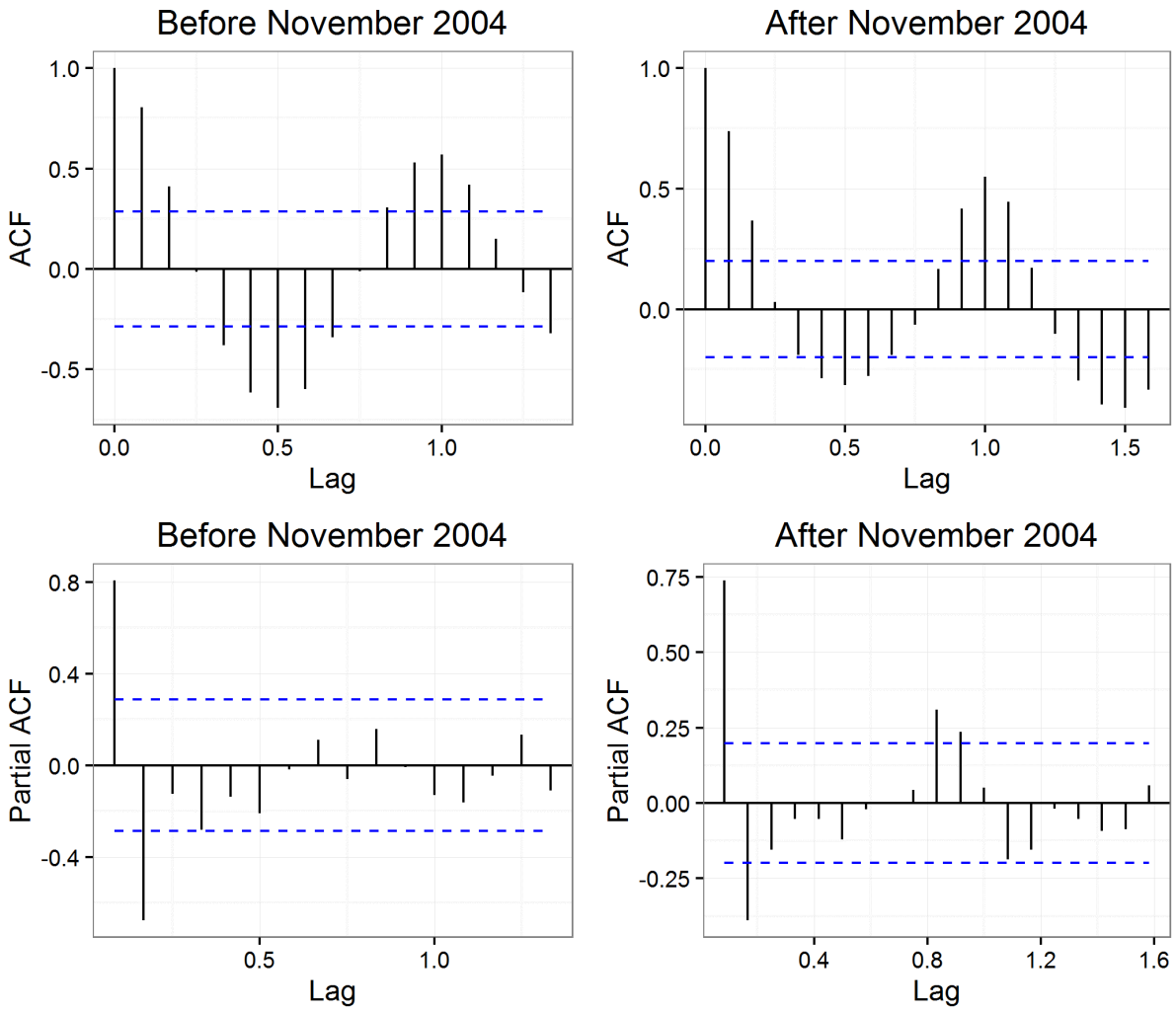


Figure 4.9: Autocorrelation and partial autocorrelation plots for salmonellosis time series before and after November 2004

Appendix 3: Autocorrelation and partial autocorrelation analysis for campylobacteriosis time series

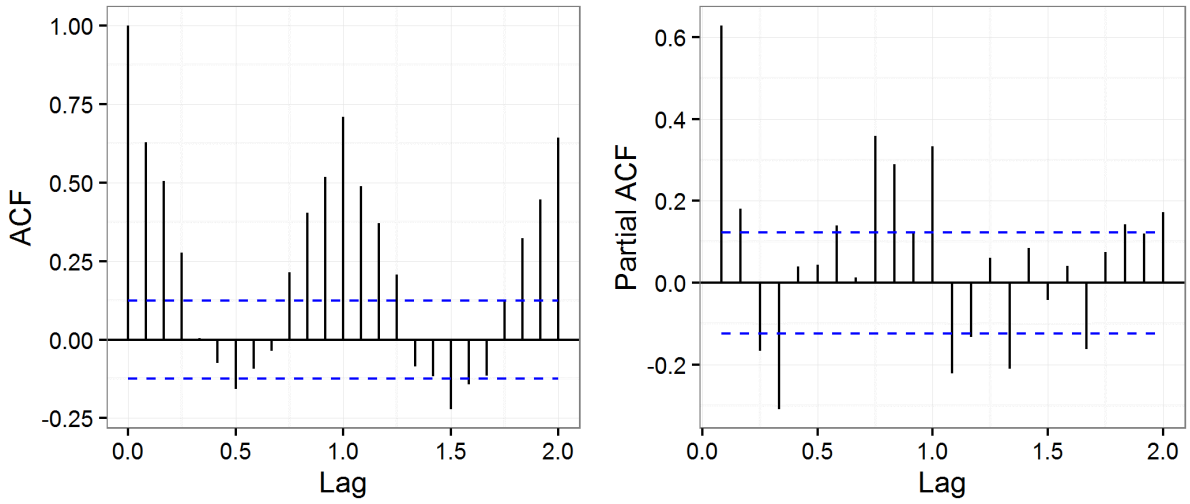


Figure 4.10: Autocorrelation and partial autocorrelation plots for campylobacteriosis time series

Appendix 4: Autocorrelation and partial autocorrelation analysis for listeriosis time series

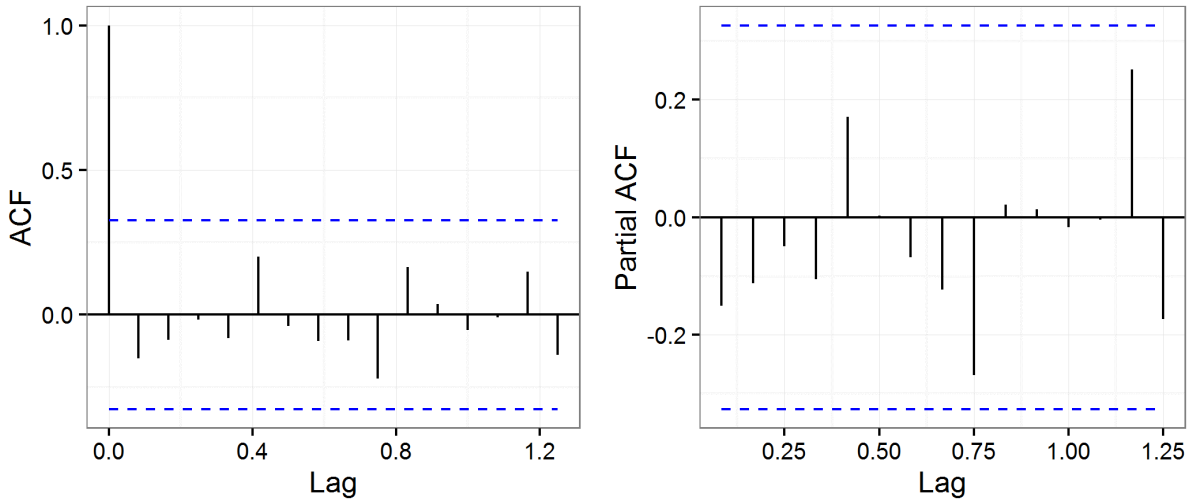


Figure 4.11: Autocorrelation and partial autocorrelation plots for listeriosis time series

Appendix 5: Salmonellosis time-series

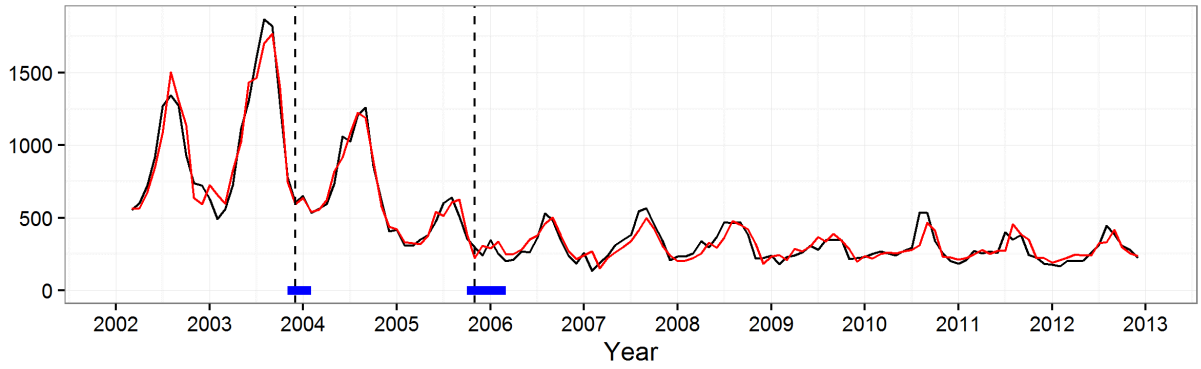


Figure 4.12: Observed salmonellosis time-series (black line) and modelled time series (red line)

5

Comorbidities and factors associated with non-perinatal listeriosis

Adapted from

Maertens de Noordhout C, Devleesschauwer B, Maertens de Noordhout A, Blocher J, Haagsma JA, Havelaar AH, Speybroeck N (2016) Comorbidities and factors associated with central nervous system infections and death in non-perinatal listeriosis: a clinical case series. *BMC Infectious Disease*. 16:256.

5.1 Introduction

Listeriosis is caused by *Listeria monocytogenes*, a Gram-positive bacterium that was first described by Murray et al. in rabbits and guinea pigs in 1926 [130]. The bacterium is typically widespread in nature but the main sources of infection are mainly dairy and ready-to-eat foods [131]. *L. monocytogenes* is a high concern for the food industry because it has the capacity to survive and grow in harsh conditions such as wide pH ranges, high salt concentrations and at refrigeration temperatures [132].

Listeriosis is a rare disease showing a high case-fatality ratio. It was estimated that in 2010, listeriosis caused 23,150 illnesses (95% Credible Interval [CrI]: 6,061-91,247) and 5,463 deaths (95% CrI: 1,401-21,497) worldwide, resulting in 172,823 Disability-Adjusted Life Years (DALYs) (95% CrI: 42,079-679,465) [97].

Listeriosis mainly affects at risk groups such as pregnant women, the elderly, and patients affected by comorbidities such as cancer or transplantation [11]. Comorbidity can be defined as the presence of any clinical condition which qualifies for formal classification as a disease additional to listeriosis. Three types of comorbidities can be distinguished: 1) unrelated (diseases/conditions happening by chance on the same patient); 2) indirectly related (diseases/conditions with common risk factors while pathophysiology is unrelated); and 3) directly related (when pathophysiology shows that one condition can be regarded as natural consequence or parallel manifestation of the other condition) [133].

Listeriosis typically affects patients with underlying diseases and can cause severe symptoms such as sepsis or central nervous system (CNS) infections, possibly leading to lifelong consequences or death [11, 12]. It is therefore important to identify high risk populations and identify risk factors linked with CNS infections and death caused by listeriosis.

The aims of our study were 1) to identify and quantify the comorbidities underlying listeriosis cases, 2) to describe the factors associated to death and CNS infections and 3) and to describe and quantify the neurological sequelae associated to non-perinatal listeriosis.

5.2 Materials and Methods

5.2.1 Data collection

We collected information about listeriosis cases in two Belgian university hospitals: "Le centre hospitalier universitaire" (CHU) in Liège in the period 2003-2013 and "Les cliniques universitaires saint Luc" (UCL) in Brussels in the period 1978-2014 (April). We collected retrospective data through computerized, paper or microfilmed medical records. We extracted general information (date of hospital and discharge admission), information on the patients characteristics (age, gender, weight, height), information on medical and surgical antecedents, characteristics of the patient at admission, blood and cerebrospinal fluid culture characteristics at admission, treatment received against listeriosis, outcome of listeriosis and information about follow-up.

The listeriosis cases were detected by laboratories included in each hospital and listeriosis was defined when *Listeria monocytogenes* was isolated from a sterile site (blood, cerebrospinal fluid or aortic wall).

5.2.2 Statistical analyses

We evaluated the association between death during hospitalization and CNS infections, and various potential risk factors based on literature review, i.e., age at hospital admission, presence of a severe cardiovascular disease, antibiotic monotherapy, gender, blood pressure, diabetes mellitus, immunosuppressive therapy, cancer, alcoholism, renal disease, HIV infection, hepatic disease, auto-immune disease, immunocompromised status, neutrophil and lymphocyte count in blood, C-Reactive Protein (CRP), creatinine, and blood platelets, using univariable logistic regression analyses. All covariates with a p-value <0.10 were subsequently included in a multivariable logistic regression model. The two final models were chosen based on the Likelihood Ratio Test using a backward inclusion methodology, testing for the significance of elimination of the variable at each stage. We only retained significant variables in the final models. For death we started with a full model including antibiotic monotherapy, age at admission, hepatic disease, severe cardiovascular disease, renal disease and transplantation. For CNS infection we started with a full model including antibiotic monotherapy, immunosuppressive therapy and renal disease.

We performed a t-test for equal variances to compare mean age in antibiotic bi-therapy and antibiotic monotherapy groups.

We applied a Mann-Whitney test to compare time until antibiotic therapy between CNS infection cases and non CNS infection cases. We performed the analyses with SPSS 22.0.

5.3 Results

We identified 16 non-perinatal listeriosis cases in CHU and 105 listeriosis cases in UCL. Fifty-seven cases were excluded from the analysis (33 were not isolated from a sterile site, 16 medical records were unavailable because too old, 2 were duplicates, 6 were perinatal cases) (Figure 5.1).

Among the remaining 64 cases, 34 patients were male (53%) and the median age was 62 years (Interquartile interval 53-72) (Figure 5.2).

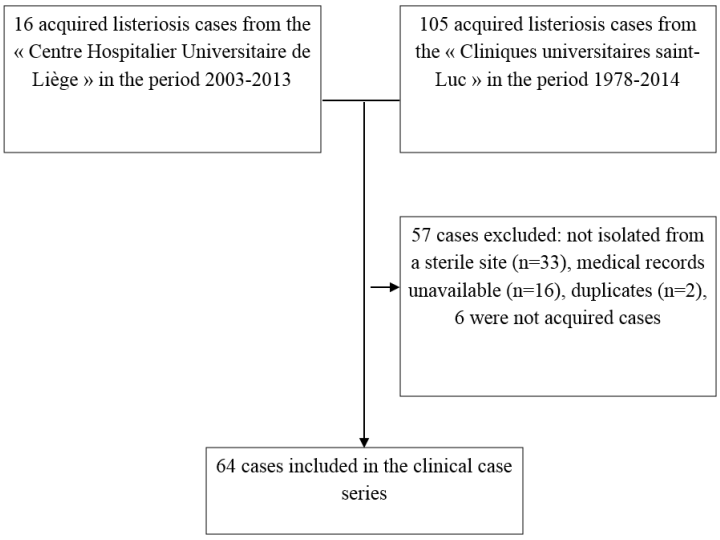


Figure 5.1: Selection of the listeriosis cases

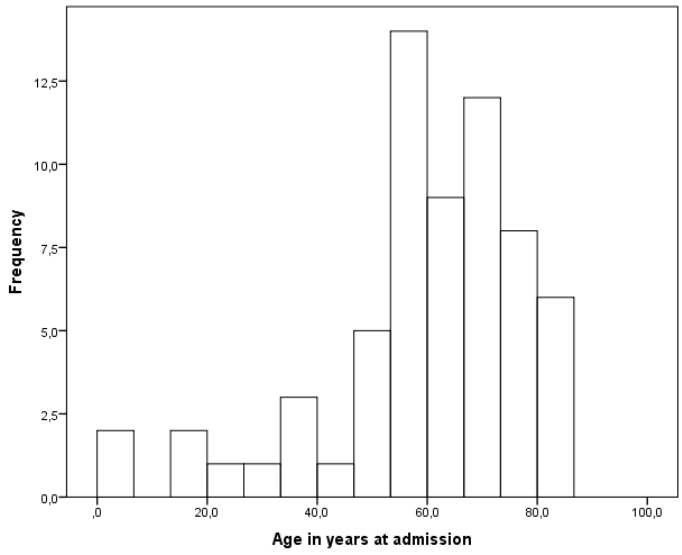


Figure 5.2: Age distribution of the patients with non-perinatal listeriosis (n=64)

All patients, except one, were hospitalized. The median duration of hospitalization was 22 days (range: 2-187) (Figure 5.3). The exact source of contamination was never identified, only one patient reported having eaten camembert but the contamination of the cheese was not analyzed. Thirteen patients (20%) were previously hospitalized within the four weeks of hospital admission, which could suggest a nosocomial infection.

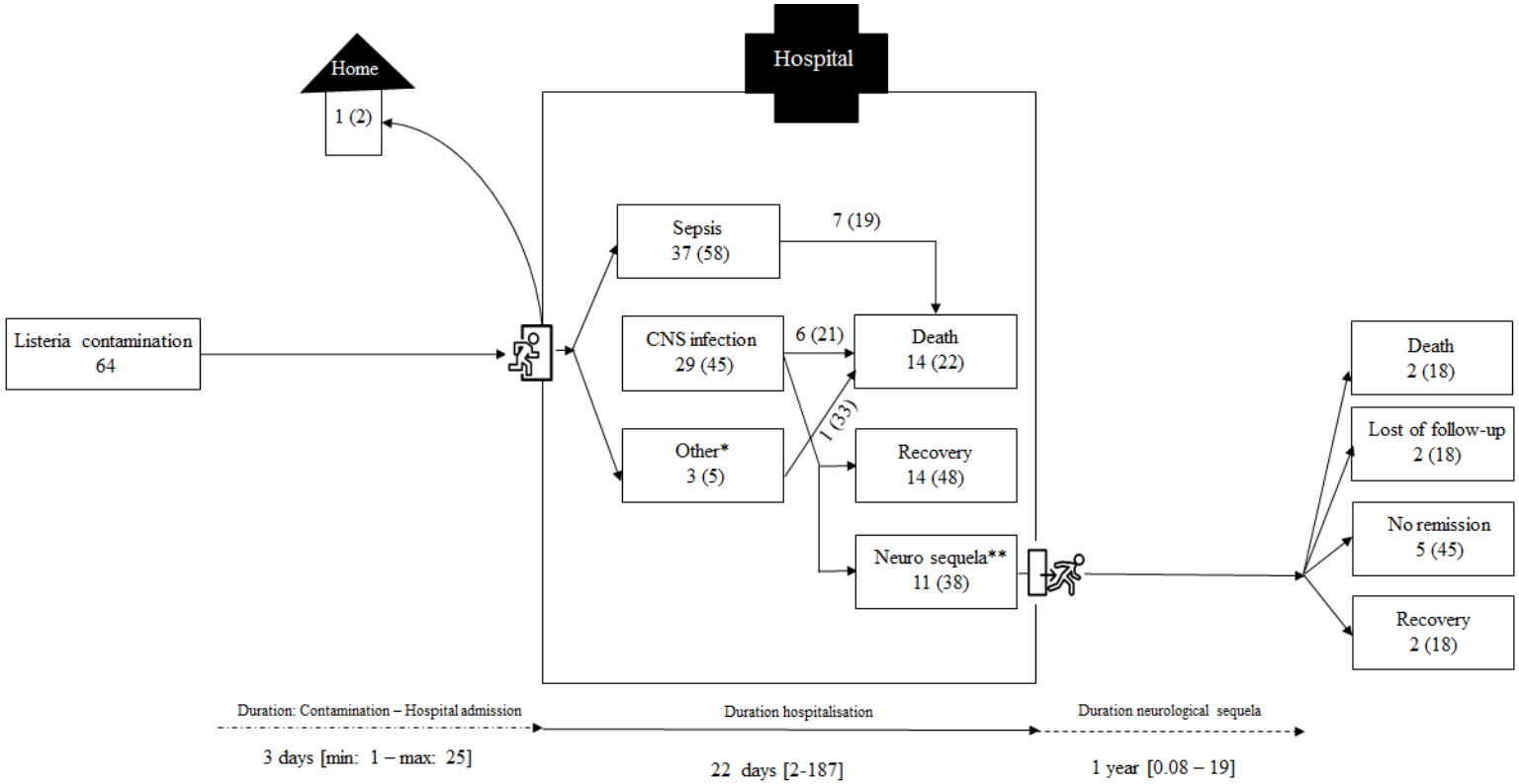


Figure 5.3: Patients follow-up after positive listeria culture

* Peritonitis, endocarditis, infrarenal abdominal aortic aneurysm. ** 1) bilateral hearing loss, 2) discrete dysarthria and mild instability in Romberg (test used to investigate the ataxia. A positive Romberg test suggests that the ataxia is sensory in nature) and in walking on a straight line, 3) slight diplopia (a trochlear nerve palsy), 4) memory loss and forgetfulness (damage of the mammillary body and fornix), 5) dystonia (difficulty in opening jaw), 6) persistence of an impaired general condition with small steps walk and brachypsychie, 7) discrete right dysdiadochokinesia, hypoesthesia in the territory V2, V3 to and an ataxic walk with deviation to the right side, 8) right hemibody motor deficit with Babinski sign , 9) dysarthria, 10) deep sensitivity deficit of the left arm and left leg and 11) mild paresis of the right upper and lower limb.

5.3.1 Clinical data

We found that among the 64 people affected by acquired listeriosis, most frequent comorbidities were ongoing immunosuppressive treatment (53%), cancer (34%), severe cardiovascular disease (30%) and renal disease (27%). 84% of the patients were affected by at least one comorbidity (Table 5.1). One patient was 3 months pregnant at admission.

Table 5.1: Comorbidities and factors associated with listeriosis cases (n=64)

Comorbidity	N	%
Immunosuppressive therapy	34	53.1
Cancer	22	34.4
Severe cardiovascular disease	19	29.7
Renal disease	17	26.6
Transplantation*	12	18.8
Hepatic disease	11	17.2
No recognized comorbidities	10	15.6
Diabetes mellitus	8	12.5
HIV	6	9.4
Auto-immune disease	5	7.8
Alcoholism	3	4.7
Pregnancy	1	1.6

* Kidney (6), heart (5), liver (1)

The immunosuppressive treatments were anti-rejection treatment (n=13, 32%), chemotherapy (n=11, 27%), radiotherapy (n=1, 2%), corticosteroids (n=13, 32%), infliximab (n=2, 5%). The encountered cancers were colon (n=3, 14%), liver (n=3, 14%), breast (n=3, 14%), lung (n=2, 10%), leukemia (n=5, 24%), myeloma (n=1, 5%), lymphoma (n=3, 14%) and melanoma (n=1, 5%). The severe cardiovascular diseases (n=19) were heart transplantation, heart transplantation followed by a triple bypass of the transplanted heart followed by high blood pressure, heart transplantation followed by multiple myocardial infractions and high blood pressure, double heart transplanted, heart transplantation, angina pectoris and high blood pressure treated with cardiac bypass, angina pectoris, ischemic heart disease followed by a heart transplantation and followed by an aortic bypass, myocardial infarction caused by a ischemic heart disease, myocardial infarction

followed by cardiac decompensation, obstructive hypertrophic heart disease and essential hypertension treated by pacemaker, obstructive hypertrophic cardiomyopathy, cardiac decompensation, cardiac decompensation treated by pacemaker, cardiac decompensation treated by bypass but remaining high blood pressure, aortic insufficiency, aortic dissection and high blood pressure, aortic insufficiency, aortic insufficiency.

The renal diseases were kidney transplantation (n=6, 35%), chronic renal disease (n=7, 41%), polycystic kidney (n=1, 6%), end stage renal (dialysis) disease (n=2, 12%), Raynaud disease with cystic kidney (n=1, 6%). The hepatic diseases were congestive hepatopathy (n=2, 20%), chronic hepatitis (n=1, 10%), hepatitis C (n=4, 40%), liver transplantation (n=1, 10%), liver cancer (n=2, 20%).

Sixty-four percent of the patients were immunocompromised by treatment, cancer or HIV.

Nine patients (14%) did not suffer from any comorbidity. Among these patients the median age was 41.5 (range: 1.3–75.1), 7 patients (78%) had CNS infection, 6 (67%) had neurological sequelae at hospital discharge. One died 19 years after hospital discharge.

Among all cases, the most frequent symptoms at admission were fever ($> 38°C$) (77%), diarrhea (23%) and vomiting (13%). For 20 patients, the median duration between appearance of symptoms and admission at hospital was 3 days (range: 1–25). Two patients were infected during their hospitalization after 26 and 11 days respectively (Figure 5.3). The first patient was a man hospitalized for a heart transplantation and the second was a woman hospitalized for a breast implant removal.

L. monocytogenes caused a central nervous system infection in 29 patients (45%). Twenty-seven neurological cases were confirmed by positive CSF culture and two by neuroimaging. The mean CSF protein level was 252.6 (sd 227.8) mg/L, the median CSF lymphocytes percentage was 40 (range: 2–88) and the median CSF monocytes percentage was 6 (range: 5.5–6).

Among the neurological cases, the classical triad for meningitis of neck stiffness, fever and altered mental status were present among eight (28%) of cases. In addition, 14 (48%) had headaches, five (17%) seizures, six (21%) were aphasic, six (21%) showed hemiparesis, seven (24%) had cranial nerve palsies, four (14%) had nystagmus, five (17%) suffered from dysarthria and seven (24%) had limb and gait ataxia.

The initial reported listeriosis manifestations were: sepsis for 37 (58%) patients, en-

docarditis for one (2%), peritonitis for one (2%), infrarenal abdominal aortic aneurysm for one (2%), meningitis for 14 (22%), meningo-encephalitis for ten (19%) and rhombo-encephalitis for one (2%). One patient suffered from both brain abscess and rhombo-encephalitis (2%), one patient suffered from both brain abscess and meningo-encephalitis (2%), one patient suffered from both brain abscess and encephalitis (2%) and one patient suffered from both brain abscess and meningitis (2%). Five patients (8%) suffered from both meningitis and sepsis, four patients of meningo-encephalitis and sepsis (6%), one of encephalitis and sepsis (2%). For one patient who suffered of sepsis, *L. monocytogenes* was also isolated from his hip prosthesis joint (Figure 5.3).

In total 56 patients (92%) received a parenteral antibiotic therapy during hospitalization. Among the 56 patients, 59% received a bi-therapy for against listeriosis, mostly ampicillin and with gentamycin. We did not find any significant association between age at admission and the administration of parenteral antibiotic bi-therapy (p=0.738). Four neurological cases (14%) received a neurosurgical therapy: three external ventricular derivations of the cerebral fluid and one ventriculostomy. No patient who developed brain abscesses was operated.

If we assume that antibiotic therapy was implemented at admission, we did not find significant difference of time until antibiotic therapy between CNS infection cases (median 3.5 days, min-max 1–8 days) and non CNS infection cases (median 3 days, min–max 0–25) (U Mann-Whitney 53, p=0.943).

The patient with endocarditis was initially treated against Candida (fluconazole). Then after he underwent an explanation of the left aorto-femoral prosthesis and of the left crossed femoral prosthesis and an implementation of a homograft left axillary-femoral. The patient died during hospitalization.

The patient with a *L. monocytogenes* aneurysm was successfully operated for a replacement of the abdominal aorta (cadaveric allograft) during the hospitalization.

The patient for whom *L. monocytogenes* was isolated from the hip prosthesis joint was successfully treated with parenteral gentamycin associated with a surgical scrub of the hip prosthesis.

During hospitalization 14 patients (22%) died, among whom 6 (38%) had a CNS infection. Listeriosis was linked to all death at hospital.

5.3.2 Factors associated with CNS infections and death

In the univariate analysis, the factors associated with neurological listeriosis were antibiotic monotherapy (OR=0.31, 95% CI 0.10–0.93, p=0.036) and the presence of a renal disease (OR=0.27 , 95% CI 0.08–0.95, p=0.042) (Table 5.2). Both variables were retained by the multivariable model (presence of a renal disease (OR=0.18, 95% CI 0.04–0.79, p=0.020), antibiotic monotherapy (OR=0.28, 95% CI 0.09–0.92, p=0.04).

Table 5.2: Comorbidities and factors associated with neurological listeriosis - *Univariate logistic analysis*

	Neurological listeriosis (n=29)		Not Neurological listeriosis (n=35)			
	N	**%**	**N**	**%**	**OR**	**95%CI**
Monotherapy (n=57)	11	42.3	23	71.9	0.31	0.10-0.93**
Male	14	48.3	20	57.1	0.70	0.26-1.88
Saint Luc hospital	23	79.3	29	82.9	0.79	0.27-2.79
Diabetes mellitus	2	6.9	6	17.1	0.36	0.07-1.93
Immunosuppressive therapy	12	41.4	22	62.9	0.42	0.15-1.14
Cancer	11	37.9	11	31.4	1.33	0.47-3.76
Alcoholism	1	3.4	2	5.7	0.59	0.05-6.85
Renal disease	4	13.8	13	37.1	0.27	0.08-0.95**
HIV infection	2	6.9	4	11.4	0.57	0.10-3.38
Transplantation	3	10.3	9	25.7	0.33	0.08-1.37
Severe cardiovascular disease	6	20.7	13	37.1	0.44	0.14-1.37
Hepatic disease	3	10.3	8	22.9	0.40	0.09-1.63
Auto-immune disease	1	3.4	4	11.4	0.28	0.03-2.63
Immunocompromised status	16	55.2	25	71.4	0.49	0.18-1.38
	Mean	**SD**	**Mean**	**SD**	**OR**	**95 % CI**
Age in years at admission	57.6	19.5	60.6	19.1	0.99	0.97-1.02
BMI (n=33)	23.6	5.6	24.8	5.3	0.96	0.83-1.10
Systole at admission (mmHg) (n=55)	129.2	32.9	123.3	30.2	1.01	0.99-1.03
Diastole at admission (mmHg)	75.0	12.1	70.8	19.1	1.02	0.98-1.05
% neutrophil in blood at admission (n=41)	74.1	25.3	74.0	19.1	1.00	0.97-1.03
% lymphocytes in blood at admission (n=37)	15.5	17.6	14.0	9.3	1.01	0.96-1.06
CRP mg/dl at admission (n=47)	31.9	33.5	34.2	18.3	0.10	0.99-1.01
Creatinine in blood at admission mg/L (n=60)	2.8	3.0	4.6	9.9	0.96	0.86-1.06
Blood platelets at admission /L (10^3) (n=56)	209.8	95.4	254.8	372.0	1.00	0.99-1.00
	Median	**Range**	**Median**	**Range**	**OR**	**95 % CI**
% neutrophil in CSF (n=20)	71.5	35.0-94.0	79.0	8.5-94.6	1.00	0.96-1.04
% lymphocytes in CSF (n=8)	40.0	2.0-88				
Glucose in CSF (mg/dL)(n=10)	31.0	0.4-74.0				
Protein in CSF (mg/L) (n=14)	164.5	27.0-732.0				
Admission year	1998	1983-2013	2006	1978-2014	0.95	0.90-1.02

** p-value < 0.05

In the univariate analysis, the factors associated with death during the hospitalization were the presence of a severe cardiovascular disease (OR=4.73, 95% CI 1.35–16.54, p=0.015), the presence of a hepatic disease (OR=4.07, 95% CI 1.02–16.30, p=0.047) and

the presence of a renal disease (OR=4.0, 95% CI 1.14–14.05, p=0.031) (Table 5.3). At a multivariable level and based on the likelihood ratio test only the presence of a severe cardio-vascular disease (OR=4.73, 95% CI 1.35–16.54, p=0.015) was significant.

Table 5.3: Comorbidities and factors associated with death at hospital - *Univariate logistic analysis*

	Death (n=14)		**Alive (n=50)**			
	N	**%**	**N**	**%**	**OR**	**95 % CI**
CNS infection	6	42.3	23	46.0	0.88	0.27-2.91
Monotherapy (n=57)	7	77.8	27	56.3	2.72	0.51-14.49
Male	9	64.3	25	50.0	1.80	0.53-6.13
Saint Luc hospital	12	86.0	40	80.0	1.50	0.29-7.81
Diabetes mellitus	2	14.3	6	12.0	1.22	0.22-6.85
Immunosuppressive therapy	8	57.1	26	52.0	1.23	0.37-1.07
Cancer	7	50.0	15	30.0	2.33	0.70-7.82
Alcoholism	0	0.0	3	6.0		
Renal disease	7	50.0	10	20.0	4.00	1.14-14.48**
HIV infection	1	7.1	5	10.0	0.69	0.07-6.46
Transplantation	5	35.7	7	14.0	3.41	0.88-13.22
Severe cardiovascular disease	8	57.1	11	22.0	4.73	1.35-16.54**
Hepatic disease	5	35.7	6	12.0	4.07	1.02-16.30**
Auto-immune disease	0	0.0	5	10.0	/	/
Immunocompromised status	11	78.6	30	60.0	2.44	0.61-9.88
	Mean	**SD**	**Mean**	**SD**	**OR**	**95 % CI**
Age in years at admission	67.9	9.9	56.8	20.5	1.04	0.98-1.09
BMI (n=33)	25.4	3.0	24.0	5.8	1.05	0.90-1.23
Systole at admission (mmHg) (n=55)	116.7	20.6	127.5	32.8	0.99	0.97-1.01
Diastole at admission (mmHg)	68.7	10.5	73.3	17.5	0.98	0.94-1.03
% neutrophil in blood at admission (n=41)	69.7	30.8	75.1	18.9	0.99	0.96-1.02
% lymphocytes in blood at admission (n=37)	11.7	9.5	15.2	13.7	0.97	0.89-1.06
CRP mg/dl at admission (n=47)	55.1	110.5	28.1	32.3	1.01	0.96-1.02
Creatinine in blood at admission mg/L (n=60)	7.1	15.5	3.0	3.6	1.06	0.97-1.16
Blood platelets at admission /L (10^3)(n=56)	170.7	86.3	248.9	314.5	0.98	0.99-1.01
% neutrophil in CSF (n=20)	83.8	11.5	67.4	23.8	1.06	0.94-1.19
	Median	**Range**	**Median**	**Range**	**OR**	**95 % CI**
Admission year	2004	1984-2013	2003	1978-2014	1.01	0.95-1.07

** p-value < 0.05

5.3.3 Neurological sequelae

Among the surviving patients, eleven (22%) suffered from at least one sequela at discharge. The median age of patients affected by neurological sequelae was 51.1 (range 83.1) years. Among these patients, six (54%) did not suffer of any recognized comorbidity but all suffered of CNS infection. One of the two children included in the study suffered of neurological sequelae.

The neurological sequelae were: bilateral hearing loss, discrete dysarthria and mild instability in Romberg (test used to investigate the ataxia. A positive Romberg test suggests that the ataxia is sensory in nature) and in walking on a straight line, slight diplopia (a trochlear nerve palsy), memory loss and forgetfulness (damage of the mammillary body and fornix), dystonia (difficulty in opening jaw), persistence of an impaired general condition with small steps walk and brachypsychie, discrete right dysdiadochokinesia, hypoesthesia in the territory V2, V3 to and an ataxic walk with deviation to the right side, right hemibody motor deficit with Babinski sign, dysarthria, deep sensory deficit of the left arm and left leg and mild paresis of the right upper and lower limb.

Among these eleven patients, two were lost to follow-up, two died (of a ischemic heart disease and of an unknown cause) after 3 and 19 years of follow-up and five still suffered from their neurological sequelae at the last contact with neurologist (median follow-up: 1 [range: 0.08–19] years) (Figure 5.3).

5.4 Discussion

Among the 64 patients, 84% suffered from an underlying disease. The main comorbidities affecting non-perinatal listeriosis cases were cancer, renal and severe cardio-vascular diseases and undergoing immunosuppressive therapy. In total, 19% of the patients included in the clinical case series were transplanted and one patient was infected only six days after the cardiac transplantation. In all cases, the source of infection was unknown. However 20% of the patients were previously hospitalized for 4 weeks before admission which could suggest that the infection was nosocomial. The incubation time of *L. monocytogenes* is very variable which makes the identification of the source of infection difficult [134].

Despite most non-perinatal listeriosis cases are people with comorbid conditions, the study also indicated that neurological listeriosis can affect people without (known) underlying diseases and very young immunocompetent children. Other recent case reports also revealed that listeriosis can affect very young children and that an appropriate treatment

at the onset, based on intravenous ampicillin in the first line therapy, can avoid the spread of the infection in the patient [135–137].

To our knowledge this is the first study identifying factors associated with death and CNS infection. We identified that people who received a parenteral antibiotic monotherapy suffered a CNS infection less frequently than people who received a combination therapy (ampicillin and an aminoglycoside). An explanation could be that patients with neurological listeriosis have more severe initial clinical symptoms and therefore received more often broad-spectrum antibiotic therapy at admission. Although combination therapy is often promoted in patients older than 50 years, we did not find any significant association between age at admission and the administration of parenteral antibiotic monotherapy [138]. Time until antibiotic therapy is started could also be a significant factor of CNS infection. We collected information on time of appearance of symptoms for 20 patients. If we assume that antibiotic therapy was implemented at admission, we did not find significant difference of time until antibiotic therapy between CNS infection cases and non CNS infection cases.

We also identified that patients with a renal disease suffered less frequently (OR=0.18, p=0.020) from a CNS infection. One explanation could be that people suffering from a chronic renal disease (n=7) receive a prophylactic antibiotic therapy that may protect against CNS infection. We also found that severe cardiovascular (OR=4.72, p=0.015) disease was the main factor associated with death caused by listeriosis. However, given the small sample size of our study, these estimates should be interpreted with caution and in the context of any other available information [139].

Moreover an acute severe illness (e.g. cardiovascular diseases) was a strong risk factor for mortality at the hospital.

In a public health context our findings could improve listeriosis burden estimations because we present rare data on type and duration of sequelae caused by CNS infections associated with listeriosis, both crucial parameters in the calculation of the number of years lived with disability, one of the two components included in the DALY calculation [68, 109]. We also think that these results could be a starting point for future burden of listeriosis studies aiming to take comorbidities into account. Ignoring comorbidities, as is the case in many burden of disease studies, could overestimate the overall disease burden [12], especially in the context of an ageing population. Correcting for comorbidities could be relevant to support policy intervention strategies. Strategies for the estimation of the prevalence and severity of multimorbid conditions do exist [140]. However, these

strategies typically assume independence between the occurrence of different diseases and symptoms. Our estimates show that this is not true for listeriosis and its comorbidities.

The main limitation of our study may be that it is not necessarily representative of all non-perinatal listeriosis cases in Belgium, as the data came from two Belgian university hospitals. Both hospitals were located in Brussels and the Walloon region, excluding Flanders. However, "Les Cliniques Universitaires saint Luc", counting 979 beds, is the third biggest hospital in Belgium and "Le Centre Hospitalier Universitaire", counting 595 beds, is the second biggest hospital in the Walloon region. The two hospitals are also affiliated with a university and probably received most severe listeriosis cases. Finally, we expect that patients suffering of a CNS infection will be frequently transferred to a university hospital because of the need of intensive care making the representativeness of our sample reasonable.

Another weakness of our study may be the retrospective design and the long observation duration (> 40 years). However, listeriosis is a rare disease making the use of a prospective study design difficult. A retrospective design and long observation duration allowed us to collect a study population sufficiently large to perform a parametric statistical analysis. Moreover, we did not identify a significant effect of year at hospital admission on death and on CNS infection. The broad categories of comorbidities allowing statistical analysis could also be a limitation for clinicians and public health professionals to easily focus on a specific disease or health condition. To remedy this, we described each case included in disease groups (e.g. severe cardiovascular diseases) in detail.

5.5 Conclusion

In a public health context our study could improve burden of listeriosis estimations because we proposed rare data on type and duration of sequelae caused by CNS infection associated with listeriosis, both crucial parameters in the calculation of the number of healthy life years lost by a disability, one of the two components included in the DALY calculation. Our results could also be an initial contribution to future burden of listeriosis studies aiming to take into account multi-morbidity in summary measure of population health. Additional data on neurological sequelae and comorbidities underlying listeriosis collected through other retrospective studies could be added to the data at hand to improve our estimations.

In the next chapter we will continue exploring how to improve burden estimates of

bacterial FBDs. We will develop a new set of disability weights for infectious diseases based on European participants.

6

Assessing DWs based on the responses of 30,660 people from four European countries

Adapted from

Haagsma JA, **Maertens de Noordhout C**, Polinder S, Vos T, Havelaar HA, Cassini A, Devleesschauwer B, Kretzschmar M, Speybroeck N, Salomon JA (2015). Assessing disability weights based on the responses of 30,660 people from four European countries. *Population Health Metrics*.

6.1 Introduction

Priority-setting for health care policies and research is informed increasingly by burden of disease and injury studies, because these studies provide knowledge on the size of health problems and the potential benefit of proposed interventions and policies directed against these problems [74, 141]. Burden of disease can be expressed in disability-adjusted fife years (DALYs), a summary measure of population health that captures health losses associated with mortality and with different non-fatal outcomes of diseases and injuries in a single figure [25, 68, 109]. The DALY methodology was developed in the 1990s for the Global Burden of Disease (GBD) study [25, 30, 46, 142, 143] and has since been used in many other disease burden studies (e.g. [35, 144–148]) as well as in cost-utility studies (e.g. [149–151]).

DALYs are calculated by adding years of life lost (YLLs) and years lived with disability (YLDs). YLLs represent the life years lost due to premature death and are calculated for any cause by multiplying the number of deaths by a standardized expectation of remaining life years at the age of death. YLDs represent the life years lost due to disability, adjusted for the severity of the disability. YLDs are computed for a given health outcome by multiplying the prevalence of that outcome by a disability weight that has a value between 0 (equivalent to full health) and 1 (equivalent to death).

For the 1996 revision of the GBD a large set of global disability weights was derived in a group exercise in which a panel of health experts assessed conditions using a range of techniques, and the scale was determined largely by responses to two different variants of a measurement method called the person trade-off [25, 46]. This approach has been criticized, particularly regarding aspects such as the health construct, measurement techniques, and panel composition [152–154]. Because of a need to improve the approach and a need for disability weights that reflect the views of the global population, a new approach to measuring disability weights was developed for the GBD 2010 study [38, 155]. This study used a conceptually less difficult measurement technique to elicit health state valuations (paired comparisons instead of the person trade-off). Health state descriptions focused primarily on the impact of a condition on functional health status. The study collected responses from 30,230 people in 167 countries. For five countries (Bangladesh, Indonesia, Peru, Tanzania, and the United States of America) household sample surveys were used, with samples designed to be representative of the population in a particular geographical area (or in the case of the USA, nationally representative). An important finding of the GBD 2010 disability weights study was that comparative assessments of different disabling sequelae, as revealed in paired comparisons, are similar in samples

that vary with respect to cultural, educational, environmental, and demographic circumstances [38]. The GBD 2010 disability weights study has been criticized regarding the estimated weights for certain conditions, such as vision loss, and for the interpretation of evidence on the level of international agreement in paired comparison responses [156, 157].

For some purposes in which the need for standardization and global comparison is not primary, it is useful to have disability weights that reflect the particular views of a specific population under study, for example in a national burden of disease study [158]. The present study was initiated as part of a study on the burden of communicable diseases in the European Union/ European Economic Area (EEA) countries [67, 159], which motivates an interest in disability weights from European population samples. The GBD 2010 disability weights study did include respondents from European countries; however, these respondents were not representative for these European countries, as they participated in an open access web-based survey rather than in nationally representative sample surveys. This raises a question as to whether the current GBD 2010 disability weights are suitable for national burden of disease studies in European countries. The objectives of the present study were: 1) To assess the feasibility of replicating the GBD 2010 disability weights measurement study in a set of four nationally representative sample surveys in European countries using web-based surveys; 2) To estimate disability weights for Europe for a set of 255 health states, including 43 new health states and; 3) To evaluate consistency in comparative assessments of disability across selected European countries.

6.2 Materials and Methods

6.2.1 Study design

For the assessment of a set of disability weights for Europe we replicated the online survey protocol used in the GBD 2010 disability weights measurement study [38].

6.2.2 Health states and description

In total 255 health states were evaluated. These health states can be subdivided into four categories: original GBD 2010 health states (n=172) [38], new health states (n=43), modified GBD 2010 health states (n=33), and health states that were included for experimental purposes but were not part of the European disability weights study (n=7).

Regarding the original GBD 2010 health states, we selected all health states associated with infectious diseases, injuries, and vision and hearing loss of primary interest for the new European study on communicable disease and supplemented these health states with

a further subset of GBD 2010 health states selected to have some representation from each of the other health state categories (e.g., cancer, cardiovascular and circulatory disease, diabetes, digestive and genitourinary disease, chronic respiratory disease, musculoskeletal disorders, neurological disorders, and other).

For the 43 new health states lay descriptions were constructed following the same general design principles used in GBD 2010. The descriptions have a word limit of 50 words or less and were constructed through an iterative process. The brief lay descriptions are intended to highlight the major functional consequences and symptoms associated with the health state using simple, non-clinical vocabulary. Disease experts and health professionals were consulted to ensure that the descriptions were appropriate and reflective of the common manifestations of the disabling sequela in question. For the 33 modified health states the description of the health states of original GBD health states were amended because they were found to be lacking in consistency or in content [38, 156]. For instance, in the case of spinal cord injury, incontinence was added to the description. Both the original and modified health state descriptions were evaluated in this study in order to facilitate direct comparison. The health state descriptions that were evaluated in this study are included in appendix (*Available upon request to C. Maertens*).

6.2.3 Health state valuation

To elicit health state valuations for the 255 health states, two valuation techniques were used: paired comparison (PC) and population health equivalence (PHE). All of the 255 health states were evaluated with the PC technique, and a subset of 28 states were evaluated with PHE questions. Paired (sometimes called "pairwise") comparison is an ordinal measurement method. With this method, persons in two alternative health states are presented, and respondents have to decide whom they regard as being healthier. PHE questions ask for a retrospective assessment that compares two hypothetical health programs. The first health program prevented 1,000 people from getting an illness that causes rapid death; the second health program prevented 1,500, 2,000, 3,000, 5,000, or 10,000 (dependent on the bid that was selected randomly for each question) people from getting an illness that is not fatal but causes the lifelong health problems of one of the selected health states. The respondents are asked to choose which health program they think produced the greater overall population health benefit.

The 28 health states that were evaluated here were a subset of the 30 health states evaluated with the PHE in the GBD 2010 disability weights study.

6.2.4 Panel of participants

The panel consisted of members of the general public aged 18 to 65 years from four European countries, namely Hungary, Italy, the Netherlands, and Sweden. We selected these four countries because they are believed to be representative of four regions of Europe (Eastern, Southern, Central, and Northern Europe) with regards to age, sex, and educational level. We used existing large internet panels in the selected European countries. By selecting panel members with certain characteristics (in our case: age, sex, and educational level) from the existing large panels, the panel of participants for this study could be composed in such a way that the respondents were representative of the population aged 18 to 65 in the selected countries. The procedure to invite panelists to fill in the questionnaire differed between the Netherlands and the other three countries. In the Netherlands panelists were invited via individual emails. In the three other countries a link to the questionnaire was placed on a website. Subsequently, the relevant respondents were selected based on their characteristics as assessed in the questionnaire. Because of this, the specific number of panelists that were invited to fill in the questionnaire in Hungary, Italy, and Sweden is not known, and the response rate could not be calculated for these countries.

6.2.5 Data collection

The GBD 2010 disability weights study consisted of two main components: a) a face-to-face or telephone survey based on a subset of the sequelae (household survey) and b) a web-based survey based on the full set of sequelae. In the current study we used the GBD 2010 web-based survey instrument.

Three versions of the web-based survey were developed. The number and framing of the PC questions differed per version. Each version included questions regarding the demographics of the respondent (age, sex, educational and income level, and disease experience) and three PHE and PC questions. The first version of the questionnaire included 15 PC questions with a chronic framing, the second version included 15 PC questions with a temporary framing, and the third version included five PC questions with a chronic framing to accommodate PHE questions. Chronic framing means that the participants are asked to consider the situation that the described health state will last for the rest of a person's life. Temporary framing means that the participant is asked to consider that the health state will last for one week.

The survey and description of health states were translated from English into Dutch, Hungarian, Italian, and Swedish using translation software and subsequently translated

back into English. The translations were verified independently by bilingual native speakers.

In the period 23 September to 11 November 2013 the disability weight survey was administered via the internet. The survey versions and health states were randomly assigned to the respondents following a randomization algorithm. First, the algorithm randomly allocated the survey version, based on the lowest percentage of respondents at that moment for each version. After the version was allocated, the algorithm selected the health states based on the minimum number of allocations that the health state had at that moment, i.e., the probability of selection was inversely proportional to number of allocations that health state at that moment.

6.2.6 Data analysis

Analyses were performed with R (version 3.0.2) [160] and SPSS (version 21). The PC data were analyzed through probit regression, following the approach used in GBD 2010 [38]. Coefficients from the probit regression were compared across the four European countries in order to assess variation in the comparative assessments of different disabilities, as expressed in paired comparisons. To examine the feasibility of using the PHE rescaling method from the GBD 2010, we evaluated the PHE data in terms of the probabilities of choosing the alternative program over the first program by health state and by bid, as well as by educational level. This analysis thus focused on "sensitivity to scope" in the PHE [161], i.e., the degree to which bid probabilities are dependent on the number of people benefiting from the program, as the conceptual model for analyzing PHE data presumes, as well as responsiveness to variation in the severity of the different outcomes under consideration, i.e., the degree to which bid probabilities are sensitive to the nature of the health outcomes affected by the two programs in each comparison. As an alternative rescaling procedure, we ran a non-parametric regression model (loess) of the probit regression coefficients against the logit-transformed disability weights from GBD 2010. Based on this loess fit, we then predicted logit transformed disability weights for each of the probit coefficients, including the ones that were not matched to a GBD 2010 health state. Finally, we applied an inverse logit transformation at the draw level to these predicted disability weights. Uncertainty intervals around the mean disability weights were estimated through a Monte Carlo simulation approach. First, 200 samples of the paired comparison coefficients were generated based on their probit estimated mean and standard deviation. These samples were then used to produce 200 loess fits, as described above. Based on each loess fit, 200 samples were generated for each of the disability weights, yielding a total of 40,000 samples per disability weight. Uncertainty intervals

around the mean disability weights were derived as the 2.5^{th} and 97.5^{th} percentile of the corresponding distribution of sampled weights.

6.3 Results

6.3.1 Respondents

A total of 30,660 respondents filled in the questionnaire. Approximately half of the respondents were male. The average age was 42.3 (SD 13.1). 76% of the respondents had a low or medium educational level and the majority (84.9%) had a low to medium income level. Table 6.1 shows the characteristics of the respondents. The response rate in the Netherlands was 63.1%. The response rates of the other countries could not be calculated.

Table 6.1: Characteristics of the 30,600 participants

Sex		
	Male	48.0%
Age (years)		
	18-34	31.2%
	35-49	35.1%
	50-65	33.7%
Educational level		
	Low	29.8%
	Medium	45.7%
	High	24.6%
Income level		
	Low	39.5%
	Medium	45.4%
	High	15.1%
Country		
	Hungary	19.8%
	Italy	26.3%
	Netherlands	26.2%
	Sweden	27.8%

6.3.2 Paired comparison

Figure 6.1 shows a heat map of the paired comparison response probabilities for the 255 x 255 possible paired comparisons. Each cell in the heat map indicates the response proba-

bility for one pair of states. The colors of the heat map correspond to the probability that the first health state in a pair comparison is chosen as the healthier outcome. Figure 6.1 shows a relatively smooth transition in colors from high to low probabilities between the upper left and lower right corner, indicating a small amount of measurement error and high internal consistency.

Of the respondents, 6.9% were given the same pair in the first and 15th paired comparison question, and of these 51% were presented in the same order and 49% in reversed order. This deliberate repetition allows assessment of test-retest reliability of PC responses. Overall, the probability of choosing the same health state was slightly higher if the two health states were presented in the same order (probability of choosing the same health state: 0.75) compared to reversed order (probability of choosing the same health state: 0.73). This is above the probability of chance agreement (0.50). The probabilities that respondents from Hungary (n=414), Italy (n=564), the Netherlands (n=553), and Sweden (n=573) chose the same health state in the retest were 0.78, 0.72, 0.73, and 0.75, respectively.

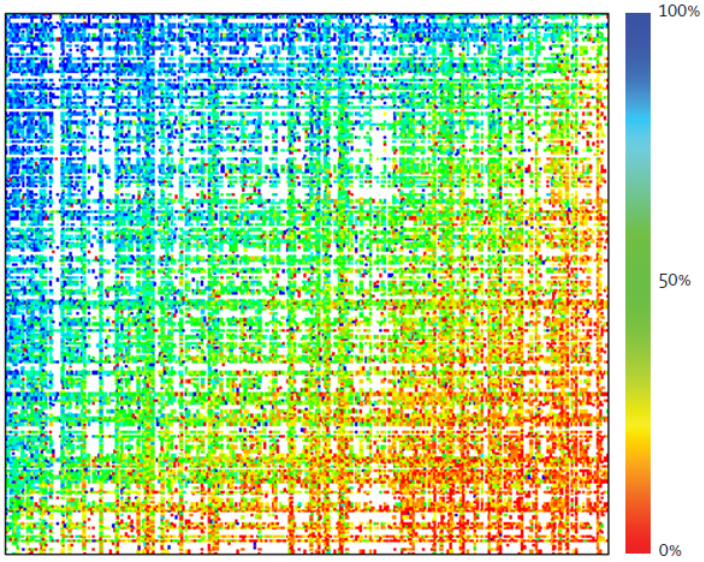


Figure 6.1: Response probabilities for paired comparisons.
Red corresponds to probabilities that are 0.25 or lower. Blue corresponds to probabilities that are 0.75 or higher. Green, yellow, and orange correspond to probabilities between 0.25 and 0.75. A smooth transition in colors from high to low probabilities between the upper left and lower right corners indicates a small amount of measurement error and high internal consistency, whereas a completely random assortment of colors would indicate a high amount of measurement error and low internal consistency. It should be noted that not every possible 255 x 255 pair was evaluated with the pairwise comparison. This is indicated by the white spaces in the figure.

Comparison of the regression results on the paired comparison responses for each country with those run on the pooled data showed high linear correlations in all four cases (Pearson's correlation coefficients between 0.855 and 0.978; $p < 0.001$; see Table 6.2).

Table 6.2: Pearson's correlation coefficients for country-specific and pooled probit regression analyses of paired comparison responses

	Hungary	Italy	Sweden	Pooled
Netherlands	0.867*	0.855*	0.894*	0.941*
Hungary	-	0.944*	0.929*	0.966*
Italy		-	0.935*	0.967*
Sweden			-	0.978*

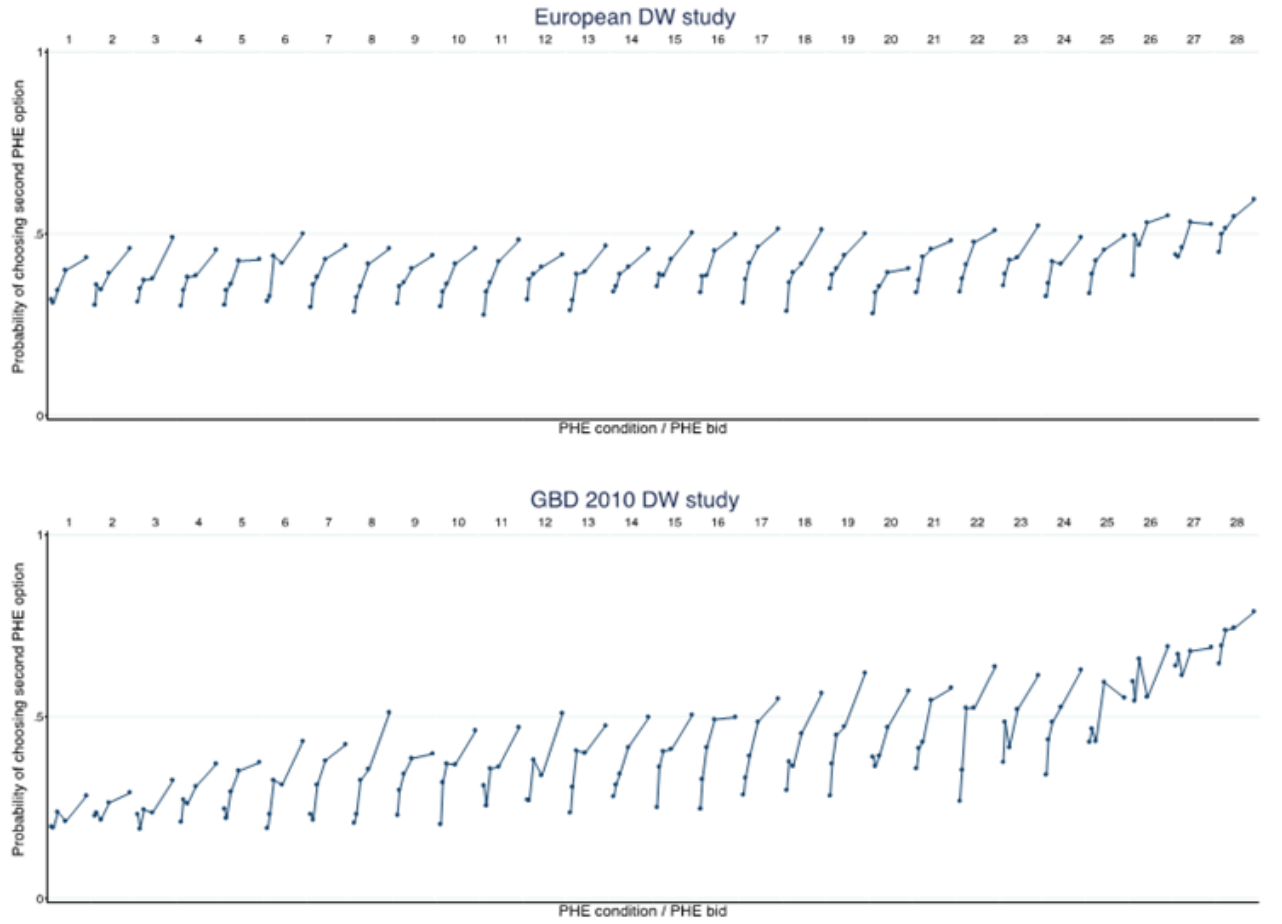
*correlation is significant at the 0.01 level

Population health equivalence

With the PHE a choice has to be made between two hypothetical health programs. We found that the probability of choosing the second health program option was higher as the bid increased (i.e., when the number of beneficiaries was greater), as expected. However, the span of probabilities between the lowest bid value (with 1,500 beneficiaries) and the highest bid value (with 10,000 beneficiaries) was generally lower than expected and varied by educational level on the PHE responses. On average, the differences between the probabilities of choosing the second health program at the highest versus the lowest bid values were 0.12, 0.16, and 0.19 for the lower, middle, and higher educational level, respectively.

The responsiveness to variation in the severity of the different outcomes under consideration was also lower than expected. While the 28 health states could be ranked according to the probabilities of choosing the second program (which prevented a specified number of cases of each outcome), there was relatively little variation across the range of health outcomes with quite distinct profiles of severity. Figure 6.2 shows the probabilities of choosing the second program at each bid value for each of the 28 health states that were evaluated with the PHE. For comparison, a similar graph of the PHE data from the GBD 2010 disability weights measurement study is presented. The graphs show that the GBD 2010 PHE data had better discrimination by bid (higher sensitivity to scope), illustrated by longer lines between the bids within one health state, as well as a better discrimination by health state (better responsiveness to variation in the severity of the different outcomes), illustrated by a steeper gradient across health states, moving from left to right. These results suggest that the PHE responses in the present study were

subject to high levels of measurement error; consequently, the feasibility of using discrete choice formulation in general population web-based sample surveys may be questioned.



1: Asthma, 2: Hearing loss (moderate), 3: Asthma (partially controlled), 4: COPD and other chronic respiratory disease (mild), 5: Distance vision (moderate), 6: Muskuloskeletal problems (lower limbs, mild), 7: Angina pectoris (moderate), 8: Hearing loss (complete), 9: Diabetic neuropathy, 10: Dementia (mild), 11: Anemia (moderate), 12: Anxiety disorders (moderate), 13: Amputation of finger(s), excluding thumb (long term, with treatment), 14: Acute myocardial infarction (days 3-28), 15: Stroke (long-term consequences, moderate), 16: Traumatic brain injury (long-term consequences, moderate (with ou without treatment), 17: Motor impairment (moderate), 18: Cancer diagnosis and primary therapy, 19: Major depressive disorder (moderate episode), 20: Decompensated cirrhosis of the liver, 21: Distance vision (severe impairment), 22: Parkinson's disease (moderate), 23: Anxiety disorders (severe), 24: COPD and other chronic respiratory disease (severe), 25: Dementia (moderate), 26: Multiple sclerosis (severe), 27: Stroke (long-term consequences, severe plus cognition problems) and 28: Spinal cord lesion at neck level (treated).

Figure 6.2: Analysis of the population health equivalence answers.
Probability of choosing the second program at each bid value for each of the 28 health states that were evaluated with the population health equivalence questions, in the present study (top panel) compared to results in the GBD 2010 study (bottom panel). Each line represents one health state and each dot represents a bid within one health state.

Disability weights

Given the evident lack of feasibility of the discrete choice PHE in this sample, a non-parametric regression approach was used as an alternative rescaling procedure to locate results onto the 0-to-1 disability weight scale. The R-squared from that regression was

0.801, based on 172 health states that were in both studies. The resulting disability weights and 95% uncertainty interval (UI) are shown in table 6.3 (original GBD 2010 health states, new health states, and modified GBD 2010 health states). Distance vision mild impairment and mild anemia shared the lowest disability weight (0.004) and severe multiple sclerosis had the highest disability weight (0.677).

The results show that the disability weights are ranked logically; lowest disability weights were attributed to mild health states, such as mild hearing impairment (disability weight 0.005) and mild acute infectious disease (disability weight 0.007), and highest disability weights were attributed to severe health states, such as the terminal phase of cancer or chronic kidney disease without medication (disability weight 0.588) and untreated spinal cord lesion below neck level (disability weight 0.648). This is illustrated by increasing disability weights by level of severity within specific types of diseases. For example, mild diarrhea (disability weight 0.073) is rated lower than moderate diarrhea (disability weight 0.149) and severe diarrhea (disability weight 0.239).

6.3.3 Comparison to GBD disability weights

For 141 (82.0%) of the 172 health states that were included in the European and GBD studies, the point estimate of the European disability weight fell within the 95% UI of the GBD 2010 disability weights. For 17 (10.1%) health states the European disability weights were higher than the upper bound, and for 11 (6.5%) health states the European disability weights were lower than the lower bound of the 95% UI from the GBD 2010 study.

In absolute terms, differences between GBD and European disability weights ranged from -0.165 (HIV, cases, symptomatic, pre-AIDS; GBD 2010 disability weight=0.186, European disability weight=0.351) to 0.185 (fracture of pelvis, short term; GBD 2010 disability weight=0.390, European disability weight=0.205). The relative difference ranged from 0% to 61%, with the highest relative differences generally appearing in cases of low disability weights (asthma controlled GBD 2010 disability weight=0.009, European disability weight=0.015; fractures treated, long term GBD 2010 disability weight=0.003, European disability weight=0.005).

6.4 Discussion

This study aimed to assess disability weights for 255 health states. The resulting disability weights were ranked logically; the lowest disability weights were attributed to mild health

states and the highest disability weights to severe health states. Furthermore, the results pointed to a high level of overall agreement in paired comparison responses across four countries, as indicated by high linear correlations in country-specific results from probit regression analyses.

6.4.1 Strengths of the current study

Thus far, the largest European disability weights study, published in 2003, included 232 respondents [162]. Apart from a lower number of health states, different valuation techniques and sample size, the study of Schwarzinger et al. utilized a different panel composition, namely health professionals rather than a population panel [162]. Since burden of disease studies are used primarily as a tool for decision-making on resource allocation at a population level, it has been recommended to incorporate the views of the general public to inform decision-making in a democratic society [38, 158]. However, the majority of previously performed disability weight studies asked health professionals to value health states. Studies that included both medical experts and members of the general public showed significant differences between disability weights derived from these two groups [163–165].

6.4.2 Web-based survey

A limitation of this study is that we used a web-based survey to collect the data. Internet users tend to be more highly educated and younger than the general EU population [166]. We have tried to mitigate these limitations by using existing large internet panels in the selected European countries. By selecting panel members with certain characteristics (in our case, age, sex, and educational level) from the existing large panel, the panel of participants for this study could be composed in such a way that it was representative of the population aged 18 to 65 years in the selected countries. Our panel did not include participants older than 65 years. For the age groups over age 65 it was too difficult to find enough participants. The GBD 2010 disability weights study did include respondents aged 65 and older (approximately 5% of the total sample).

6.4.3 Population health equivalence

Based on responses to population health equivalence questions, as expected, the probability of choosing the second health program option was higher with increasing bid (i.e., a higher number people that are prevented from getting a certain illness). However, the differences between the choice probabilities with the highest (10,000 people prevented from getting a certain illness) and lowest bids (1,500 people prevented from getting that illness)

were small. The relatively small difference is consistent with large numbers of respondents answering randomly, which will drive all aggregate-level response probabilities toward 50% and thus dilute differences across types of outcomes (either defined by different numbers of beneficiaries or different severity of the health state under consideration). The spans in response probabilities between the low and high bids were smallest among those with lower education. In the GBD study, the PHE was included in the web-based survey as well [38]. However, the educational level of the respondents of the GBD study was much higher (93% with a higher education) compared to our study (25% with a higher education), and respondents to the GBD survey were a self-selected group who were evidently interested enough in the content of the survey to participate voluntarily. This may have resulted in greater attention to the question and care in weighing the responses, both of which are likely to have improved the signal-to-noise ratio in the responses. We conclude from the results in the present study that the discrete choice formulation of the PHE may not be suitable for use in a general population survey administered by the internet.

6.4.4 Disability weights

The ranking of certain conditions seems counterintuitive. For instance, the disability weight for profound intellectual disability is lower than the disability weight for back pain. A possible explanation for this may be that brief lay descriptions were used to describe the major functional consequences and symptoms associated with the health state and that the disease label, indicating the cause of the health state, was removed from the description. The latter was a deliberate choice, because the disease label may elicit bias for stigmatized conditions [38]. However, previous studies showed that including certain disease information in health state descriptions yields different values [167]. A second explanation may be the framing of the paired comparison. In the pairwise comparison respondents are asked to judge the level of health of the health states and this may lead to bias if respondents consider some health states as not being associated with "being ill" [156].

For future health state valuation studies that use a similar design and a similar panel composition it is important to consider different techniques to anchor estimates from paired comparisons onto the disability weight scale, such as the time trade-off or the standard gamble. However, each of these existing techniques to measure health state preferences suffers from limitations that hamper their application in a study design where a web-based survey is used to collect health state valuations from a panel that consists of members of the general public. Alternatively, the disability weights may be recalibrated post-hoc by health professionals. Health professionals are argued to have the ability to

make careful comparative judgments. However, an argument against the use of a panel composed of health professionals is that the disability weights will not entirely reflect the views of the global population, as has been recommended.

6.4.5 Agreement between European disability weights and GBD 2010 disability weights

Given the lack of feasibility of the discrete choice PHE in this sample, an alternative rescaling procedure was applied based on non-parametric regression. It is important to note that as a result, this study does not include new information on tradeoffs between nonfatal and fatal outcomes, which are central to the rescaling of results to a unique 0-to-1 disability weights scale. We therefore emphasize that comparison of disability weights between this study and GBD 2010 should be understood as reflecting variation in comparative evaluations of different functional outcomes (as manifest in responses to paired comparison questions) rather than a complete assessment of differences in the valuation of nonfatal versus fatal health outcomes.

6.4.6 Cultural differences

Similar to the GBD 2010 disability weights measurement study, our study aspired to quantify health loss as opposed to welfare loss [38]. Previous studies have shown that there are clear cultural differences in the ways people perceive health problems and how such problems affect their lives [168–172]. This was endorsed by Ustun et al., who found significant differences in ranking of health states between 14 countries [165]. Furthermore, the findings from Jelsma et al. suggest that the effect of cultural differences on health state valuations may be stronger among lay people compared to health professionals [164]. However, in the largest disability weights study thus far, Salomon et al. found that comparative paired comparisons of different functional outcomes produced similar results in samples that varied with respect to cultural, educational, environmental, and demographic circumstances [38]. The current study also found a high degree of consistency between countries, though it should be noted that all of the countries in our study were high-income European settings, so we caution against over-generalization of the significance of the findings. Apart from cultural differences, other differences between high- and low-income settings may also influence how people weigh different health outcomes. For example, we might hypothesize that diseases and injuries rated as less severe by experts in a high-income country could be rated as more burdensome by people in low-income settings. Further research is needed to gain greater insight into the effects of cultural differences on disability weights, particularly in low-income settings.

6.5 Conclusion

Limitations notwithstanding, this study provided an opportunity to expand the evidence base on disability weights derived from the GBD disability weights measurement study, since PC assessments of health outcomes in this study resulted in estimates that were highly correlated across four European countries. Furthermore, the European disability weights study provided the opportunity to expand the set of health outcomes that will be covered in the burden of communicable disease study in the European Union/EEA countries and the next revision of the GBD.

In the next chapter we will continue exploring how to improve burden estimates of bacterial FBDs. We will evaluate if population characteristics have an impact on health valuation and therefore have to be taken into account in the selection of study populations of future studies aiming to assess DWs related to infectious diseases.

Table 6.3: Estimated disability weights with 95% uncertainty intervals (UI)

Category*	Health state definition	Mean DW	2.50% UI DW	97.50% UI DW
Infectious diseases				
Original	Infectious disease, acute episode, mild	0.007	0.005	0.01
Original	Infectious disease, acute episode, moderate	0.051	0.039	0.06
Original	Infectious disease, acute episode, severe	0.125	0.104	0.152
Original	Infectious disease, post-acute consequences (fatigue, emotional lability, insomnia)	0.217	0.179	0.251
Original	Diarrhea, mild	0.073	0.061	0.092
Original	Diarrhea, moderate	0.149	0.12	0.182
Original	Diarrhea, severe	0.239	0.202	0.285
Original	Epididymo-orchitis	0.176	0.143	0.208
Original	HIV cases, symptomatic, pre-AIDS	0.351	0.299	0.394
Original	HIV/AIDS cases, receiving ARV treatment	0.108	0.089	0.132
Original	AIDS cases, not receiving ARV treatment	0.574	0.518	0.635
Original	Ear pain	0.015	0.011	0.019
Original	Tuberculosis, not HIV infected	0.308	0.264	0.353
Original	Tuberculosis, HIV infected	0.383	0.345	0.435
Original	Tuberculosis of vertebrae	0.287	0.245	0.332
New	Subacute sclerosing panencephalitis – phase 1	0.088	0.07	0.108
New	Thrombocytopenic purpura	0.167	0.134	0.201
New	Lymphogranuloma Venereum - local infection	0.07	0.057	0.087
New	Subacute sclerosing panencephalitis – phase 2	0.276	0.235	0.323
New	Subacute sclerosing panencephalitis – phase 3	0.543	0.481	0.606
Cancer				
Original	Cancer, diagnosis and primary therapy	0.265	0.222	0.303
Original	Cancer, metastatic	0.358	0.317	0.417
Original	Stoma	0.125	0.104	0.155

Original	Terminal phase, with medication (for cancers, end-stage kidney/liver disease)	0.515	0.459	0.572
Original	Terminal phase, without medication (for cancers, end-stage kidney/liver disease)	0.588	0.524	0.65
Cardiovascular and circulatory disease				
Original	Acute myocardial infarction, days 3-28	0.098	0.08	0.121
Original	Angina pectoris, moderate	0.103	0.089	0.128
Original	Cardiac conduction disorders and cardiac dysrhythmias	0.295	0.258	0.343
Original	Heart failure, mild	0.052	0.041	0.063
Original	Heart failure, moderate	0.07	0.057	0.085
Original	Heart failure, severe	0.173	0.14	0.205
Original	Stroke, long-term consequences, moderate	0.075	0.059	0.093
Original	Stroke, long-term consequences, severe plus cognition problems	0.58	0.519	0.639
Diabetes, digestive, and genitourinary disease				
Original	Diabetic neuropathy	0.165	0.134	0.199
Original	Chronic kidney disease (stage 4)	0.108	0.09	0.132
Original	End-stage renal disease, on dialysis	0.487	0.432	0.544
Original	End-stage renal disease, with kidney transplant	0.03	0.023	0.037
Original	Decompensated cirrhosis of the liver	0.163	0.136	0.194
Original	Crohn's disease or ulcerative colitis	0.221	0.184	0.26
Original	Infertility, primary	0.008	0.005	0.01
Original	Infertility, secondary	0.007	0.005	0.01
New	Heart burn & reflux "GERD"	0.038	0.029	0.046
New	Constipation	0.075	0.061	0.092
New	Vaginal discharge	0.018	0.013	0.022
New	Dyspareunia	0.022	0.017	0.027
New	Irritable bowel syndrome	0.062	0.05	0.077
New	Stress incontinence	0.032	0.024	0.038

Chronic respiratory diseases				
Original	Asthma, controlled	0.02	0.015	0.024
Original	Asthma, partially controlled	0.045	0.035	0.055
Original	COPD and other chronic respiratory problems, mild	0.025	0.019	0.031
Original	COPD and other chronic respiratory problems, moderate	0.284	0.242	0.329
Original	COPD and other chronic respiratory problems, severe	0.418	0.367	0.468
Mental, behavioural, and substance abuse disorder				
New	Harmful alcohol use	0.106	0.087	0.132
New	Alcohol use disorder, very mild	0.154	0.123	0.187
Original	Alcohol use disorder, mild	0.209	0.175	0.247
Original	Alcohol use disorder, moderate	0.357	0.309	0.41
Original	Alcohol use disorder, severe	0.5	0.457	0.567
New	Cannabis dependence, mild	0.043	0.033	0.052
Original	Cannabis dependence	0.191	0.147	0.235
New	Amphetamine dependence, mild	0.088	0.072	0.11
Original	Amphetamine dependence	0.474	0.417	0.531
New	Cocaine dependence, mild	0.131	0.107	0.163
Original	Cocaine dependence	0.493	0.444	0.549
New	Opioid dependence, mild	0.365	0.314	0.417
Original	Heroin and other opioid dependence	0.624	0.553	0.707
Original	Anxiety disorders, mild	0.045	0.035	0.054
Original	Anxiety disorders, moderate	0.119	0.098	0.15
Original	Anxiety disorders, severe	0.422	0.372	0.475
Modified	Major depressive disorder, mild episode	0.129	0.102	0.154
Original	Major depressive disorder, moderate episode	0.294	0.248	0.341
Original	Major depressive disorder, severe episode	0.571	0.509	0.635
Modified	Intellectual disability, borderline	0.014	0.01	0.017

Modified	Intellectual disability, mild	0.053	0.041	0.065
Modified	Intellectual disability, moderate	0.123	0.097	0.152
Modified	Intellectual disability, severe	0.141	0.112	0.174
Modified	Intellectual disability, profound	0.213	0.177	0.255
New	Borderline personality disorder	0.193	0.16	0.228
New	Somatoform disorder	0.144	0.116	0.174
Hearing and vision loss				
Modified	Hearing loss, mild	0.011	0.007	0.014
Modified	Hearing loss, moderate	0.037	0.028	0.045
Modified	Hearing loss, severe	0.152	0.125	0.187
Modified	Hearing loss, profound	0.235	0.197	0.274
Modified	Hearing loss, mild, with ringing	0.027	0.021	0.034
Modified	Hearing loss, moderate, with ringing	0.07	0.056	0.087
Modified	Hearing loss, severe, with ringing	0.274	0.231	0.318
Modified	Hearing loss, profound, with ringing	0.242	0.204	0.288
Modified	Hearing loss, complete, with ringing	0.313	0.268	0.361
Original	Unilateral hearing loss	0.008	0.005	0.012
Original	Near vision impairment	0.012	0.008	0.015
Original	Distance vision, mild impairment	0.004	0.002	0.005
Original	Distance vision, moderate impairment	0.034	0.027	0.042
Original	Distance vision, severe impairment	0.158	0.13	0.193
Modified	Distance vision blindness	0.173	0.145	0.213
Musculoskeletal disorders				
Original	Back pain, acute, with leg pain	0.275	0.237	0.324
Original	Back pain, acute, without leg pain	0.298	0.254	0.343
Original	Back pain, chronic, with leg pain	0.395	0.345	0.45
Original	Back pain, chronic, without leg pain	0.365	0.322	0.413
New	Low back pain, mild	0.024	0.018	0.03
New	Low back pain, moderate	0.06	0.05	0.074
Original	Neck pain, acute, mild	0.062	0.05	0.075

Original	Neck pain, acute, severe	0.224	0.19	0.268
Original	Neck pain, chronic, mild	0.111	0.089	0.136
New	Neck pain, moderate	0.056	0.044	0.067
Original	Neck pain, chronic, severe	0.311	0.263	0.359
Original	Musculoskeletal problems, lower limbs, mild	0.027	0.021	0.032
Original	Musculoskeletal problems, lower limbs, moderate	0.094	0.08	0.12
Original	Musculoskeletal problems, lower limbs, severe	0.134	0.11	0.165
Original	Musculoskeletal problems, upper limbs, mild	0.041	0.032	0.05
Original	Musculoskeletal problems, upper limbs, moderate	0.138	0.114	0.167
Original	Musculoskeletal problems, generalized, moderate	0.344	0.3	0.391
Original	Musculoskeletal problems, generalized, severe	0.518	0.457	0.576
New	Osteomyelitis	0.053	0.041	0.065
New	Shoulder lesions	0.016	0.012	0.02
Injuries				
Modified	Amputation of finger(s), excluding thumb	0.007	0.005	0.009
Original	Amputation of thumb (long term)	0.015	0.011	0.018
New	Amputation of one upper limb (long term, without treatment)	0.105	0.085	0.128
Modified	Amputation of one upper limb (with treatment)	0.048	0.037	0.057
Modified	Amputation of both upper limbs (long term, with treatment)	0.121	0.097	0.153
Modified	Amputation of both upper limbs (long term, without treatment)	0.392	0.344	0.451
Modified	Amputation of one lower limb (long term, with treatment)	0.041	0.031	0.049
Original	Amputation of one lower limb (long term, without treatment)	0.188	0.153	0.225

Modified	Amputation of both lower limbs (long term, with treatment)	0.088	0.071	0.107
Modified	Amputation of both lower limbs (long term, without treatment)	0.427	0.381	0.484
Original	Amputation of toe	0.007	0.005	0.009
Original	Burns, <20% total burned surface area without lower airway burns (short term, with or without treatment)	0.154	0.125	0.189
Original	Burns, <20% total burned surface area or <10% total burned surface area if head/neck or hands/wrist involved (long term, with or without treatment)	0.019	0.014	0.024
Original	Burns, ≥20% total burned surface area (short term, with or without treatment)	0.262	0.218	0.303
Original	Burns, ≥20% total burned surface area or ≥10% total burned surface area if head/neck or hands/wrist involved (long term, with treatment)	0.161	0.131	0.195
Original	Burns, ≥20% total burned surface area or ≥10% total burned surface area if head/neck or hands/wrist involved (long term, without treatment)	0.424	0.372	0.478
Original	Crush injury (short or long term, with or without treatment)	0.138	0.112	0.169
Original	Dislocation of hip (long term, with or without treatment)	0.018	0.014	0.023
Original	Dislocation of knee (long term, with or without treatment)	0.112	0.094	0.141
Original	Dislocation of shoulder (long term, with or without treatment)	0.041	0.033	0.051
Original	Other injuries of muscle and tendon (includes sprains, strains and dislocations other than shoulder, knee, hip)	0.009	0.007	0.012

Original	Drowning and nonfatal submersion (short or long term, with or without treatment)	0.24	0.197	0.286
Original	Fracture of clavicle, scapula or humerus (short or long term, with or without treatment)	0.038	0.029	0.045
Modified	Fracture of face bone (short or long term with or without treatment)	0.038	0.031	0.044
Original	Fracture of foot bones (short term, with or without treatment)	0.027	0.021	0.033
Original	Fracture of foot bones (long term, without treatment)	0.026	0.019	0.032
Original	Fracture of hand (short term, with or without treatment)	0.01	0.007	0.013
Original	Fracture of hand (long term, without treatment)	0.02	0.015	0.026
Original	Fracture of neck of femur (short term, with or without treatment)	0.228	0.193	0.275
Original	Fracture of neck of femur (long term, with treatment)	0.057	0.045	0.068
Original	Fracture of neck of femur (long term, without treatment)	0.44	0.391	0.493
Original	Fracture of patella, tibia or fibula or ankle (short term, with or without treatment)	0.044	0.034	0.053
Original	Fracture of patella, tibia or fibula or ankle (long term, with or without treatment)	0.051	0.04	0.062
Original	Fracture of pelvis (short term)	0.205	0.171	0.243
Original	Fracture of pelvis (long term)	0.158	0.127	0.194
Original	Fracture of radius or ulna (short term, with or without treatment)	0.03	0.024	0.037
Original	Fracture of radius or ulna (long term, without treatment)	0.052	0.042	0.063
Original	Fracture of skull (short or long term, with or without treatment)	0.083	0.066	0.103

Original	Fracture of sternum and/or fracture of one or two ribs (short term, with or without treatment)	0.185	0.161	0.21
Original	Fracture of vertebral column (short or long term, with or without treatment)	0.101	0.084	0.124
Original	Fracture, other than femoral neck (short term, with or without treatment)	0.08	0.064	0.097
Original	Fracture, other than femoral neck (long term, without treatment)	0.042	0.032	0.051
Original	Fractures, treated (long term)	0.005	0.004	0.008
Original	Injured nerves (short term)	0.126	0.104	0.156
Original	Injured nerves (long term)	0.074	0.059	0.088
Original	Injury to eyes (short term)	0.06	0.048	0.072
New	Concussion	0.104	0.085	0.126
Original	Traumatic brain injury, long-term consequences, minor (with or without treatment)	0.089	0.072	0.109
Original	Traumatic brain injury, long-term consequences, moderate (with or without treatment)	0.214	0.18	0.252
Original	Severe traumatic brain injury, short term (with or without treatment)	0.192	0.151	0.228
Original	Traumatic brain injury, long-term consequences, severe (with or without treatment)	0.604	0.539	0.674
Original	Open wound (short term, with or without treatment)	0.007	0.005	0.01
Original	Poisoning (short term with or without treatment)	0.17	0.139	0.202
Original	Severe chest injury (short term, with or without treatment)	0.377	0.333	0.434
Original	Severe chest injury (long term, with or without treatment)	0.047	0.036	0.056

Modified	Spinal cord lesion below neck level (treated)	0.298	0.256	0.349
Modified	Spinal cord lesion below neck level (untreated)	0.619	0.553	0.696
Modified	Spinal cord lesion at neck level (treated)	0.52	0.465	0.581
Modified	Spinal cord lesion at neck level (untreated)	0.648	0.578	0.728
Neurological disorders				
Original	Dementia, mild	0.059	0.048	0.073
Original	Dementia, moderate	0.434	0.38	0.481
New	Encephalopathy - moderate	0.41	0.358	0.47
New	Encephalopathy - severe	0.447	0.391	0.501
New	Epilepsy, seizures >= once a month	0.488	0.432	0.546
New	Epilepsy, seizures 1-11 per year	0.255	0.215	0.294
Original	Epilepsy, severe	0.562	0.505	0.631
Original	Epilepsy, treated, with recent seizures	0.335	0.294	0.388
Original	Multiple sclerosis, mild	0.16	0.128	0.195
Original	Multiple sclerosis, moderate	0.469	0.417	0.531
Original	Multiple sclerosis, severe	0.677	0.594	0.757
Original	Parkinson's disease, mild	0.016	0.012	0.022
Original	Parkinson's disease, moderate	0.239	0.205	0.286
Original	Parkinson's disease, severe	0.53	0.477	0.59
New	Trigeminal neuralgia	0.068	0.056	0.084
New	Vertigo and balance disorder (Menière, labyrinthitis)	0.097	0.079	0.119
Other				
Original	Abdominopelvic problem, mild	0.018	0.013	0.022
Original	Abdominopelvic problem, moderate	0.123	0.1	0.15
Original	Abdominopelvic problem, severe	0.31	0.262	0.355
New	Allergic rhinitis (hay fever)	0.006	0.004	0.009
New	Anal fissure/abscess/fistula	0.082	0.066	0.1
Original	Anemia, mild	0.004	0.003	0.006
Original	Anemia, moderate	0.045	0.035	0.054

Original	Anemia, severe	0.118	0.098	0.145
New	Carpal tunnel syndrome	0.039	0.031	0.047
Original	Conjunctivitis without corneal scar	0.015	0.011	0.019
Modified	Generic uncomplicated disease: anxiety about diagnosis	0.021	0.015	0.026
Original	Generic uncomplicated disease: worry and daily medication	0.07	0.057	0.088
New	Haemorrhoids	0.109	0.085	0.133
New	Hyperthyroidism	0.144	0.115	0.176
New	Hypothyroidism	0.022	0.017	0.028
New	Insomnia	0.023	0.017	0.028
New	Intensive care unit admission	0.655	0.579	0.727
New	Invasive device/drain	0.163	0.131	0.198
Original	Motor impairment, mild	0.011	0.008	0.014
Original	Motor impairment, moderate	0.053	0.042	0.064
Original	Motor impairment, severe	0.421	0.377	0.477
Modified	Motor plus cognitive impairments, mild	0.044	0.035	0.053
Modified	Motor plus cognitive impairments, moderate	0.185	0.154	0.223
Modified	Motor plus cognitive impairments, severe	0.494	0.438	0.557
New	Sleep apnoea	0.036	0.027	0.044
New	Varicose veins	0.02	0.016	0.025

*Original = original GBD 2010 health states [38]; New = new health states; Modified = modified GBD 2010 health states

7

Disability weights for infectious diseases: comparison across respondent characteristics

Adapted from

Maertens de Noordhout C, Devleesschauwer B, Salomon JA, Turner H, Cassini A, Colzani E, Speybroeck N, Polinder S, Kretzschmar ME, Havelaar HA, Haagsma JA. Disability weights for infectious diseases in four European countries: comparison between countries and across respondent characteristics. *Under Review*

7.1 Introduction

The Global Burden of Disease (GBD) studies, which started in the early 1990s, presented an important set of comparative findings on the impact of different diseases, injuries and risk factors on population health [30, 173]. One of the most important results of these initiatives has been the introduction of the disability-adjusted life year (DALY), a new measure of overall disease burden, reflecting the number of healthy life years lost due to illness, disability or early death. This metric accounts for both premature mortality, expressed as years of life lost (YLLs), and time spent in states of reduced health, expressed as years lived with disability (YLDs). One of the main advantages of the DALY is that it allows for a quantitative comparison of the population health impact of diseases, injuries and risk factors. An essential parameter to calculate YLDs is the disability weight (DW), representing the severity of health loss associated with illness or disability. The DW is a value on a scale from zero to one: a DW of 0 means that a health state is equivalent to full health, whereas a DW equal to 1 means that a health state is equivalent to death. The value of a DW can be derived from the valuations of a panel of judges (any population group, e.g., experts, patients, lay people) stated toward a set of hypothetical health states expressing the relative undesirability of the health state [25, 42]. There are three main types of health state valuation methods: 1) trade-off methods such as the time trade-off, and the person trade-off; 2) discrete choice experiments and 3) scales such as the Rating or Visual Analogue Scale or a combination of these [43].

In 2012, an update of the GBD study was performed, including a new set of DWs for 220 unique health states [38]. To assess the DWs, the GBD 2010 study proposed a new ordinal health state valuation methodology based on paired comparisons questions, a type of discrete choice question, and a new population health equivalence technique, a type of trade-off method, to anchor DWs to the scale (from zero to one) aiming to address criticisms of previous approaches [174–176]. With paired comparisons two descriptions of hypothetical health states are presented to respondents who have to decide which they regard as being healthier.

In 2008, the European Centre for Disease Prevention and Control (ECDC) launched an initiative to estimate the current and future burden of communicable disease in the European Union (EU) and European Economic Area (EEA) countries using DALYs [159]. A list of 32 infectious diseases and six healthcare associated infections was selected and for each of these infectious diseases outcome trees were developed to define the different health states related to these diseases and the related DWs to evaluate in subsequent calculations [56, 159].

For the purpose of the burden of communicable disease in Europe, the set of DWs developed for the GBD 2010 study [38] had a number of limitations. The set of DWs was derived from a household survey based on responses from the general population of five non-European countries (Tanzania, Bangladesh, Indonesia, Peru and USA) and from an open-access web-survey study performed in 167 countries with most of the participants from North America and Australia. This web-survey study was available in English, Spanish and Mandarin, whereas German (16%) is the most spoken language in Europe followed by English (13%), Italian (13%) and French (12%) [177]. Consequently the DWs were not based on the values representative of socio-demographic groups of the EU/EEA population [158]. Moreover, DWs for 84 health states related to infectious diseases did not exist at all. Therefore ECDC, the Institute for Health Metrics and Evaluation, the Erasmus University and others started a collaboration to assess new DWs. They performed a web-based survey in Hungary, the Netherlands, Sweden and Italy [39] because these four countries were considered geographically representative of the EU/EEA Member States.

The results of this study showed a high degree of agreement between the GBD 2010 and the European study. However, the putative differences in DWs between respondent characteristics with respect to their ranking of infectious diseases were not assessed. If significant differences in health valuation exist between participants, they may have to be taken into account in the selection of study populations of future studies aiming to assess DWs related to infectious diseases or in the translation of study results to the general population. The objective of the current study is therefore to compare DWs between the four European countries and across respondents' characteristics.

7.2 Materials and Methods

7.2.1 Study design and participants

We performed a web-based survey between September and November 2013 in Hungary, the Netherlands, Sweden and Italy [39]. These four countries were considered geographically representative of the EU/EEA Member States. The eligible study population was aged from 18 to 65 years. The participants were recruited through existing large panels of people available through the Growth From Knowledge (GFK) Company for participating in online surveys and were composed in such a way that they were representative of the general populations aged 18-65 years of the countries with regards to age, sex, educational and income level.

7.2.2 Outcome trees

In addition to acute illnesses, infections can also lead to long-term consequences, e.g., hearing loss as a consequence of meningitis.

To estimate the full burden caused by an infection, all health outcomes caused by the infection have to be estimated [112, 159]. This process, which relates all outcomes to their infectious causes results in an "outcome tree" or a "disease model" [109], representing all health outcomes that are causally related to a hazard, their possible transition and transition probabilities in a flow chart. For example, an outcome tree for symptomatic non-typhoidal salmonellosis may have four health outcomes for which DWs are needed (excluding death for which the DW equals 1 and recovery to full health for which the DW equals 0), namely uncomplicated diarrheal illness, complicated diarrheal illness for which patient consulted a general practitioner, complicated diarrheal illness for which patient was hospitalized, and reactive arthritis [67].

In total, 32 infectious diseases and six healthcare-associated infections were included in the burden of communicable disease in Europe study. These 32 infectious diseases and six healthcare-associated infections had 74 unique health states for which DWs were evaluated in this study [67].

7.2.3 Procedures

We adapted the questionnaire developed by Salomon et al. [38] by including additional questions about disease experience and by changing income and educational categories to fit the situation in the four countries. For disease experience status we asked if the participant suffered from a disease or the consequences of an injury (yes/no answer). We used existing health state descriptions developed by Salomon et al. [38] for 74 health states related to infectious diseases. For 13 additional infectious disease related health states we developed new health state descriptions through expert consultation. Three different versions of the questionnaire were designed. The first version was composed of 15 paired comparison questions on life-long health states, the second version included 15 paired comparison questions on temporary (lasting for one week) health states and the third version included 5 PWC questions with a chronic framing to a to accommodate population health equivalence (PHE) questions. PHE questions, which allow to anchor the final DWs from 0 to 1, were finally not used in the European DW study. Each version was composed of four different parts. Two parts included questions about demographics of the participant (age, sex, educational and income level and disease experience), while the two remaining parts included paired comparison and population health equivalence

questions (Appendix-*Available upon request to C. Maertens*).

The income levels were country-specific, meaning that they were calculated based on the average national income of each European country. In Sweden low income level was defined as an annual household income (AHI) equal or lower than 349 000 SEK (36 528 euros), medium income level as an AHI that ranged between 349 000 SEK (36 528 euros), and 872 000 SEK (91 267 euros) and high income level as an AHI higher than 872 000 SEK (91 267 euros). In the Netherlands low income level was defined as an AHI equal or lower than 29 000 euros, medium income level as an AHI that ranged between 29 000 euros and 72 000 euros and high income level as an AHI higher than 72 000 euros. In Italy low income level was defined as an AHI equal or lower than 21 000 euros, medium income level as an AHI that ranged between 21 000 euros and 53 000 euros and high income level as an AHI higher than 53 000 euros. In Hungary low income level was defined as a monthly household income (MHI) equal or lower than 180 000 Ft (580 euros), medium income level as an MHI between 180 000 Ft (580 euros) and 230 000 Ft (756 euros) and high income level as an MHI higher than 230 000 Ft (756 euros).

Educational levels were also country-specific. In the Netherlands low educational level (EL) was defined as an EL equals or lower than "vocational school". Medium EL was defined as an EL between "higher secondary education (general education)" and "higher vocational school" and a high EL was defined as equal as or higher than "University, college or higher learning". In Hungary low EL was specified as an EL equal or lower than "Unfinished secondary school". Medium EL was identified as an EL between "Vocational secondary school, vocational school" and "Unfinished higher level school (college or university)" and a high EL was defined as an EL equal or higher than "College degree". In Italy low EL was defined as an EL equals or lower than "Lower secondary education (general education)". Medium EL was defined as an EL between "Secondary Education: Vocational or Technical education 2-3 years education" and "Post-secondary, non-tertiary education-vocational training" and high EL as an EL equal or higher than "University Diploma (old system degree courses), first level vocational or technical degree-three years cycle)". In Sweden, low EL was identified as an EL equals or lower than "Nine-year compulsory school". Medium EL was defined as an EL between "upper secondary school" and "College of health sciences" and high EL as an EL equal or higher than "University, college or higher learning".

A third part of the questionnaire included pairwise comparison questions, in which respondents were presented with two descriptions of hypothetical people, each living in a particular health state, and then asked which person they regarded as being healthier. The

questions involved temporary or chronic health states. Chronic health state was defined as a state that will be lifelong and temporary health state as a state that will last one week. Finally, the last part of the questionnaire was dedicated to the population health equivalence, a question aiming to elicit tradeoffs between mortality and nonfatal health states. The questionnaires and health states were translated from English to Hungarian, Dutch, Swedish and Italian and then checked by an independent native speaker.

The questionnaire was assigned to participants through a computer algorithm. The algorithm first attributed the study version (chronic or temporary) with the lowest percentage of participants at the time of assignment. Then after the version was allocated, the algorithm selected the health states to include in the questionnaire based on the minimum number of allocations that the health state had at that moment.

7.2.4 Statistical analysis

To assess the representativeness of our study population, we applied chi-squared tests to compare age groups (18-34 years, 35-49 years and 50-65 years), sex and educational distribution of the study with the national populations. Because income levels were categorized, we assigned the midpoint of each income category to all respondents in that category, which we compared with mean household income values from Eurostat [178].

To investigate the differences between health states, we ran probit regression analyses on the choice responses. The first health state of the pair had a value of 1, the second health state of the pair had a value of -1 and those not in the pair had a value of 0. The resulting probit regression coefficients for each health state expressed the relative differences in valuation of the health state on an arbitrary scale. To project the results from the probit regression model on a DW scale ranging from zero to one, we ran a locally weighted scatterplot smoothing regression model (loess) of the probit regression coefficients versus the logit transformed GBD2010 DWs [39]. We then predicted logit transformed DWs for each of the probit coefficients from the loess fit. To change the scale and obtain values ranging between 0 and 1 we applied an inverse logistic transformation of these predicted DWs. We estimated uncertainty around the mean DWs through a bootstrap procedure. We first generated 200 samples of the pairwise coefficients using their probit estimated mean and standard deviation. We then used the generated samples to calculate 200 loess fits. We generated 200 samples for each of the DWs using loess fit, producing 40 000 bootstrap samples for each DW. We finally calculated uncertainty intervals (UI) as the 2.5^{th} and 97.5^{th} percentile of the corresponding distribution of bootstrapped samples intervals for the DW. These analyses were performed using the overall database of 255 health states

available in Haagsma et al. [39]. We hereby extracted the 74 probit coefficients and DWs of the health states relating to infectious diseases, which were the primary focus of this study.

We performed the same analysis of the responses across countries, sex, age, disease experience status, income and education level and within countries by sex, age, disease experience status, income and education level.

The Spearman correlation coefficient was also used to evaluate the relation of both the probit coefficients between countries, age groups, sex, disease experience status, educational and income level.

To evaluate the effect of participant's characteristics, we also estimated difference between two health states in models with interactions that allow each country, or each population subgroups (age, sex, disease experience status, income and education level) to have its own set of distinct values, assuming that the difference between the two state values was normally distributed. We then compared models using Akaike's Information Criterion (AIC).

We interpreted a p-value < 0.05 as significant. Analyses were done with R (version 3.0.2) and using speedglm package [179].

7.3 Results

7.3.1 Characteristics of respondents

Overall, 30,660 respondents completed the DW survey of which 6053 participants (20%) were from Hungary, 8054 (26%) from Italy, 8005 (26%) from the Netherlands and 8548 (28%) from Sweden.

The average age was 41.5 years (standard deviation [sd] 13.3) in Hungary, 41.7 years in Italy (sd 12.3), 44.1 years in the Netherlands (sd 12.9) and 41.9 years in Sweden (sd 13.7). Approximately half of the respondents were male in each of the four countries.

The majority of the respondents had a medium educational level in Hungary (49%), Italy (48%) and Sweden (51%) but while in the Netherlands the level of education of the participants was more equally distributed (low: 35%, medium: 35% and high: 30%).

Most of the respondents had a low income level in Italy (47%), medium income level in the Netherlands (56%) and Sweden (50%) and high income level in Hungary (47%)

(Table 7.2).

Approximately one in three respondents reported that they were suffering of a disease or of the consequences of an injury in Hungary (34%), the Netherlands (29%) and Sweden (35%) and one in five respondents in Italy (18%) (Table 7.2).

Comparison of the study population with data from Eurostat showed that the study population was representative of the national populations in the four countries in terms of sex distribution, age distribution and educational levels [180]. For income levels we observed that, except in Sweden, mean income of the respondents was higher than in the general population (Table 7.2).

7.3.2 Probit regression models

We observed that all models, except the model including disease experience status (model 3) (AIC=417.722), had lower AIC than the model without covariate (AIC=417.572). We also observed that the model including country as covariate had the lowest AIC (411.142), the next lowest being the based on age (AIC=416.94), then on educational level (AIC=417.178), on sex (AIC=417.271) and finally on disease experience status (AIC=417.722). That means that probit model including country as covariate was the best model because AIC represents the loss of information caused by using models to represent the process generating the actual data. We did not compare the AIC for the model including income level as covariate with the other models because it included less data because of the missing answers (Table 7.1).

Table 7.1: AIC of seven probit models, including a null model and six models containing one covariate, i.e., country, sex, age, disease experience status, income level, or educational level

	Probit models	AIC
1)	Null model	417.572
2)	Country	411.142
3)	Disease experience status	417.722
4)	Sex	417.271
5)	Educational level	417.178
6)	Income level	NA*
7)	Age	416.940

* Not available: AIC not calculated because it included less data than the other models.

Table 7.2: Description of the study population

	Total (n=30660)	Hungary (n=6053)	Hungarian pop. (%)*	p-valueΔ	Italy (n=8054)	Italian pop. (%)*	p-valueΔ	Netherlands (n=8005)	Dutch pop.	p-valueΔ (%)*	Sweden (n=8548)	Swedish pop. (%)*	p-valueΔ
Sex													
Men	14719(48.0%)	2889(47.7%)	47.6	0.999	3886(48.2%)	48.4	0.999	3842(48.0%)	49.5	0.943	4102(48.0%)	49.9	0.902
Age													
18-34 years	9574(31.2%)	2047(33.8%)	34.1	0.993	2522(31.3%)	30.2	0.982	2148(26.8%)	33.3	0.584	2857(33.4%)	36.5	0.869
35-49 years	10753(35.1%)	2026(33.5%)	34		2983(37.0%)	38.1		2883(36.0%)	34.3		2861(33.5%)	33.4	
50-65 years	10333(33.7%)	1980(32.7%)	31.9		2549(31.6%)	31.7		2974(37.2%)	32.4		2830(33.1%)	30.1	
Educational level													
Low	9125(29.8%)	2344(38.7%)	80.9	0.242	2668(33.1%)	86.1	0.49	2801(35.0%)	71.4	0.95	1312(15.3%)	69.9	0.546
Medium	14000(45.7%)	2976(49.2%)			3896(48.4%)			2804(35.0%)			4324(50.6%)		
High	7535(24.6%)	733(12.1%)	19.1		1490(18.5%)	13.9		2400(30.0%)	28.6		2912(34.1%)	30.1	
Income level (n=23950)													
Low	9458(39.4%)	1301(30.0%)			3177(47.2%)			2053(35.3%)			2927(41.4%)		
Medium	10879(45.4%)	1016(23.4%)			3083(45.8%)			3271(56.3%)			3509(49.7%)		
High	3613(15.1%)	2026(46.6%)			472(7.0%)			484(8.3%)			631(8.9%)		
Mean [SD] (euros)		6778 [3276]	5469		25764 [17723]	18997		39839 [23850]	23802		23404 [12541]	27728	
Disease experience													
Yes	8900(29.0%)	2085(34.4%)	NA		1448(18.0%)	NA		2337(29.2%)	NA		3026(35.4%)	NA	

*According to Eurostat [181] (2013 population). Δ = Chi-squared test. NA = Not Available

7.3.3 Probit regression coefficients-correlation coefficients

Between country

Overall, we found a lower correlation of the probit coefficients between country than between age-groups, educational and income levels, sex and disease experience status (Figure 7.1).

The highest linear correlation of the probit coefficients was found between Italy and Hungary ($r_s = 0.95$, $p < 0.01$) and the lowest correlation was observed between Hungary and the Netherlands ($r_s = 0.89$, $p < 0.01$)(Figure 7.1).

The correlation of the probit coefficients was high between age groups (range r_s : 0.98-0.99, $p < 0.01$), educational levels (range r_s : 0.98-0.99, $p < 0.01$), sex ($r_s = 0.99$, $p < 0.01$) and disease experience status ($r_s = 0.99$, $p < 0.01$) and lower for income levels (range r_s : 0.97-0.99, $p < 0.01$)

Within country

We observed a higher correlation of the probit coefficients by age-groups in the Netherlands (range r_s : 0.97-0.98, $p < 0.01$) than in Hungary (range r_s : 0.95-0.96, $p < 0.01$), Italy (range r_s : 0.95-0.97, $p < 0.01$) or Sweden (range r_s: 0.96-0.97, $p < 0.01$). In all countries, the highest correlation was observed between 35-49 years and 50-65 years groups. In every country, except for the Netherlands, the lowest observed correlation was between 18-34 years and 50-64 years. In the Netherlands, the lowest observed correlation was between 18-34 years and 35-49 years groups ($r_s = 0.97$, $p < 0.01$).

We observed roughly the same pattern for educational levels. The correlation of the coefficients was higher in the Netherlands (range r_s : 0.97-0.98, $p < 0.01$) than in Hungary (range r_s : 0.94-0.98, $p < 0.01$), Italy (range r_s : 0.94-0.96, $p < 0.01$) and Sweden (range r_s : 0.95-0.98, $p < 0.01$). In every country, except Sweden, the highest correlation was observed between low and medium educational level. In Sweden the highest correlation was observed between medium and high educational level ($r_s = 0.98$, $p < 0.01$). Except for the Netherlands, the lowest observed correlation was between low and high educational level. In the Netherlands, the lowest observed correlation was between medium and high educational groups ($r_s = 0.97$, $p < 0.01$).

We observed relatively less concordance of the responses between income levels across country. The correlation of the coefficients was better in Hungary (range r_s : 0.94-0.95, $p < 0.01$) than in the Netherlands (range r_s : 0.92-0.98, $p < 0.01$), Italy (range r_s : 0.89-0.95, $p < 0.01$) and Sweden (range r_s : 0.93-0.98, $p < 0.01$). The lowest correlation

was observed between medium and high income levels in the Netherlands ($r_s = 0.92$, p < 0.01) and between low and high income levels in Hungary ($r_s = 0.94$, p < 0.01), Italy ($r_s = 0.89$, p < 0.01) and Sweden ($r_s = 0.93$, p < 0.01). The highest correlation was observed between low and medium income levels in the Netherlands ($r_s = 0.98$, p < 0.01) and Sweden ($r_s = 0.98$, p < 0.01) and between medium and high levels in Hungary ($r_s = 0.94$, p < 0.01) and Italy ($r_s = 0.93$, p < 0.01).

We observed a higher correlation of the coefficients between disease experience status in Sweden ($r_s = 0.99$, p < 0.01) than in the Netherlands ($r_s = 0.97$, p < 0.01), Hungary ($r_s = 0.97$, p < 0.01) and Italy ($r_s = 0.96$, p < 0.01).

In all countries we observed a high correlation of the probit coefficients between sex (range r_s : 0.97-0.98, p < 0.01).

Overall, within country, we observed a lower correlation of the coefficients by income levels than by age groups, educational levels, sex and disease experience status.

Except for income level, Dutch participants showed higher correlation of the probit coefficients for every participants' characteristics.

7.3.4 Disability weights

"Distance vision, mild impairment" had the lowest DW in Hungary [H]: 0.007 [95% UI 0.004-0.013], Italy [I]: 0.004 [95% UI 0.002-0.008] and Sweden [S]: 0.005 [95% UI 0.003-0.009]). "Hearing loss, mild" had the lowest DW in Netherlands [N]: 0.004 [95% UI 0.002-0.009]. "Intensive care unit admission" had the highest DW for all the countries (H: 0.597 [95% UI 0.464-0.690]; I: 0.530 [95% UI 0.430-0.617]; N: 0.624 [95% UI 0.493-0.719] and S: 0.717 [95% UI 0.552-0.766])(Table 7.3).

The median DW of all health states based on the responses of the Hungarian respondents was 0.118 (range: 0.007-0.597), 0.101 (range: 0.004-0.530) in Italian respondents, 0.108 (range: 0.004-0.624) in Dutch respondents and 0.111 (range: 0.005-0.717) in Swedish respondents. The range of DWs was higher in Swedish participants (0.712) and lower in Italian participants (0.526) but the shape of the DW distributions were right-skewed in all countries (Figure 7.2) and highly correlated ($r_s \leq 0.99$, p < 0.01), including in the range below 0.2, where most of the European DWs reside ($r_s \leq 0.97$, p < 0.01).

The differences of DWs ranged from -0.135 ("Thrombocytopenic purpura") to 0.197 ("Lymphogranuloma Venereum-local infection") between Hungary and Italy, from -0.221 ("AIDS cases, not receiving ARV treatment") to 0.295 ("Motor plus cognitive impair-

ments, severe") between Hungary and the Netherlands and from -0.165 ("Musculoskeletal problems, generalized, severe") to 0.250 ("Stoma") between Hungary and Sweden. The differences of DWs also ranked from -0.203 ("End-stage renal disease, on dialysis") to 0.226 ("Motor plus cognitive impairments, severe") between Italy and the Netherlands, from -0.187 ("Intensive care unit admission") to 0.241 ("Stoma") between Italy and Sweden and from -0.232 ("Motor plus cognitive impairments, severe") to 0.154 ("Tuberculosis, not HIV infected") between the Netherlands and Sweden. The biggest observed differences of DW were for "motor plus cognitive impairments, severe" between Hungary and the Netherlands, between the Netherlands and Sweden and between Italy and the Netherlands (Hungary: 0.496, Italy: 0.426, The Netherlands: 0.200, Sweden: 0.432) and for "Stoma", between Italy and Sweden and between Hungary and Sweden (Hungary: 0.301, Italy: 0.292, Sweden: 0.051). There were no differences in DW between Hungary and Netherlands for "Near Vision Impairment", for "Distance vision, mild impairment" and "Infertility, primary" between Netherlands and Italy, for "Unilateral hearing loss" between Netherlands and Sweden, for "Hearing loss, mild", "Infectious disease, acute episode, mild" and "Chronic kidney disease (stage IV)" between Hungary and Sweden (Figure 7.3).

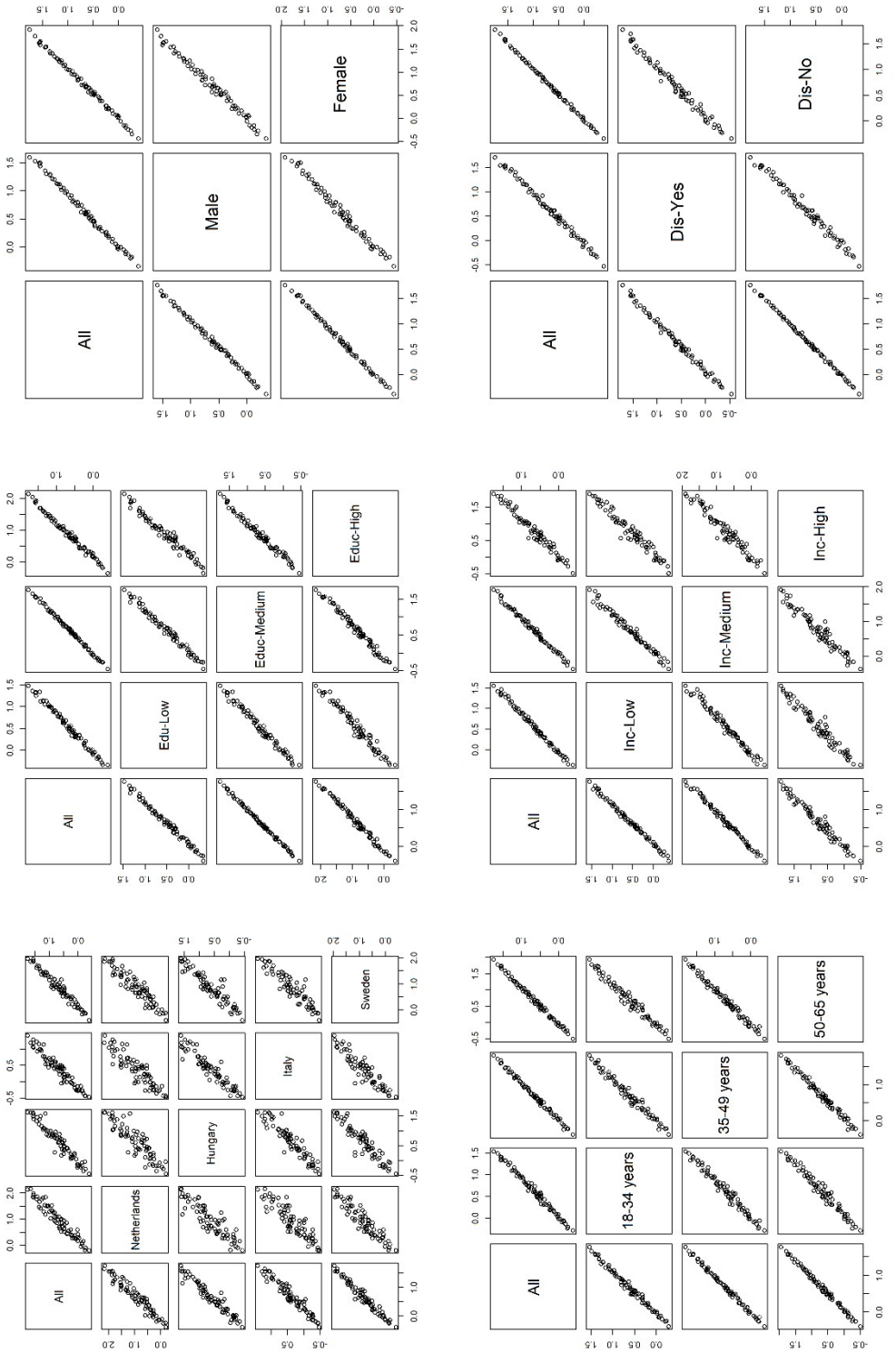


Figure 7.1: Correlation matrix of probit coefficients by country, educational level, sex, age, income level and disease experience status

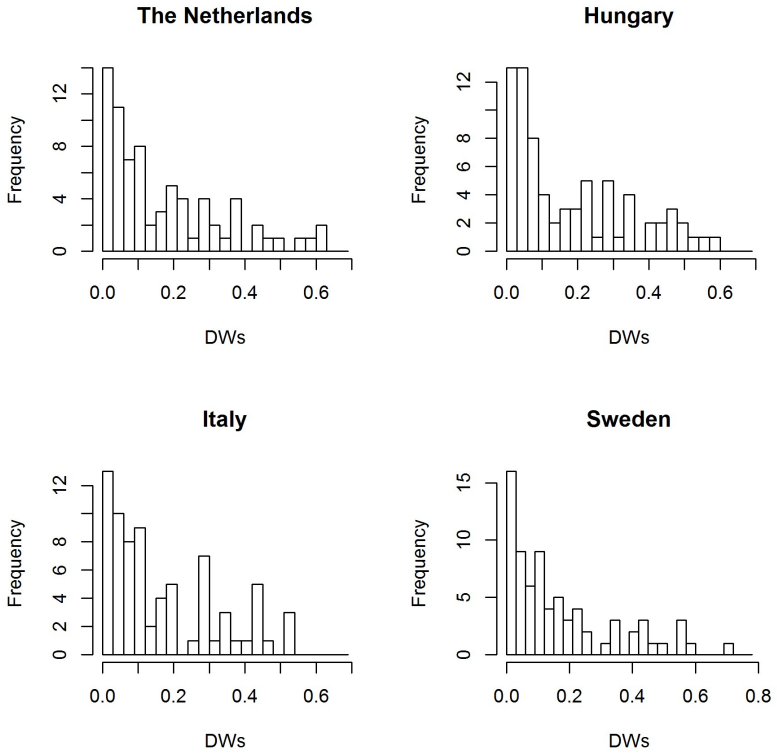


Figure 7.2: Distribution of disability weights by country

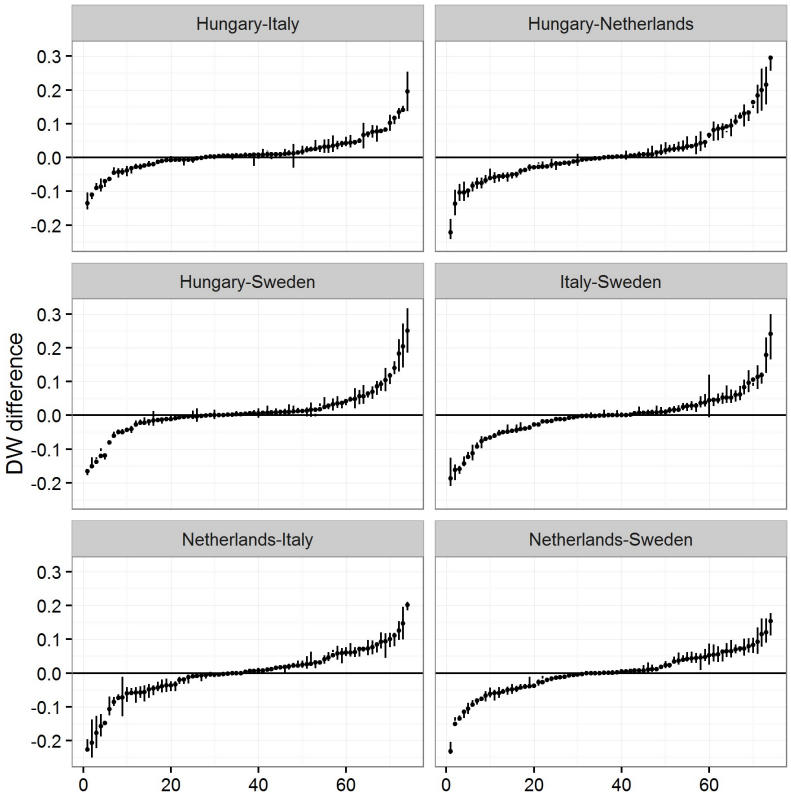


Figure 7.3: Distribution of the differences and 95% UI in elicited disability weights between countries

Table 7.3: Comparison of the rank order (descending) of the health states between countries

Health states	**Netherlands**	**Hungary**	**Italy**	**Sweden**
Intensive care unit admission	1	1	1	1
AIDS cases, not receiving ARV treatment	2	12	3	4
Terminal phase, without medication (for cancers, end-stage kidney/liver disease)	3	3	2	3
End-stage renal disease, on dialysis	4	5	14	7
Musculoskeletal problems, generalized, severe	5	11	8	2
Terminal phase, with medication (for cancers, end-stage kidney/liver disease)	6	7	5	6
Subacute sclerosing panencephalitis – phase 3	7	2	4	5
COPD and other chronic respiratory problems, severe	8	6	13	13
Tuberculosis, HIV infected	9	13	9	16
Musculoskeletal problems, generalized, moderate	10	22	15	12
Tuberculosis, not HIV infected	11	18	16	21
Encephalopathy-severe	12	8	10	11
Encephalopathy-moderate	13	10	12	10
Abdominopelvic problem, severe	14	15	24	15

HIV cases, symptomatic, pre-AIDS	15	19	11	17
Tuberculosis of vertebrae	16	20	20	18
COPD and other chronic respiratory problems, moderate	17	14	19	22
Motor impairment, severe	18	9	6	8
Infectious disease, post-acute consequences (fatigue, emotional lability, insomnia)	19	31	28	25
Crohn's disease or ulcerative colitis	20	29	30	24
Epididymo-orchitis	21	27	29	38
Diabetic neuropathy	22	32	37	26
Infectious disease, acute episode, severe	23	41	47	33
Diarrhea, severe	24	24	27	14
Motor plus cognitive impairments, severe	25	4	7	9
Subacute sclerosing panencephalitis-phase 2	26	16	18	19
Decompensated cirrhosis of the liver	27	34	32	31
Generic uncomplicated disease: anxiety about diagnosis	28	44	31	48
Thrombocytopenic purpura	29	39	23	34
HIV/AIDS cases, receiving ARV treatment	30	53	39	36

Chronic kidney disease (stage IV)	31	40	46	40
Diarrhea, moderate	32	36	41	23
Musculoskeletal problems, upper limbs, moderate	33	37	44	32
Distance vision blindness	34	26	26	29
Musculoskeletal problems, lower limbs, severe	35	28	35	30
Subacute sclerosing panencephalitis-phase 1	36	43	43	47
Motor plus cognitive impairments, moderate	37	30	22	20
Diarrhea, mild	38	55	54	41
Distance vision, severe impairment	39	25	25	28
Generic uncomplicated disease: worry and daily medication	40	50	38	53
Invasive device/drain	41	21	21	43
Abdominopelvic problem, moderate	42	33	33	27
Musculoskeletal problems, lower limbs, moderate	43	35	40	46
Stoma	44	17	17	51
Infectious disease, acute episode, moderate	45	56	56	55
Hearing loss, complete, with ringing	46	38	34	35
Hearing loss, moderate, with ringing	47	45	51	45

Hearing loss, profound, with ringing	48	42	36	39
End-stage renal disease, with kidney transplant	49	71	57	63
Lymphogranuloma Venereum-local infection	50	23	53	52
Irritable bowel syndrome	51	47	59	37
Hearing loss, mild, with ringing	52	54	58	50
COPD and other chronic respiratory problems, mild	53	61	68	60
Hearing loss, severe, with ringing	54	51	45	49
Motor impairment, moderate	55	46	52	42
Abdominopelvic problem, mild	56	69	65	64
Conjunctivitis without corneal scar	57	63	69	68
Hearing loss, profound	58	57	50	58
Musculoskeletal problems, upper limbs, mild	59	48	42	54
Distance vision, moderate impairment	60	49	55	62
Motor plus cognitive impairments, mild	61	52	48	44
Musculoskeletal problems, lower limbs, mild	62	60	60	56
Ear pain	63	65	64	65
Hearing loss, moderate	64	62	63	59
Motor impairment, mild	65	64	72	66

Hearing loss, severe	66	59	61	61
Infertility, secondary	67	68	73	73
Hearing loss, complete	68	58	49	57
Infectious disease, acute episode, mild	69	73	67	70
Near vision impairment	70	67	62	67
Infertility, primary	71	66	70	71
Unilateral hearing loss	72	70	66	69
Distance vision, mild impairment	73	74	74	74
Hearing loss, mild	74	72	71	72

7.4 Discussion

In this study we aimed to assess the impact of country, sex, age, disease or injury experience status, educational and income levels on the evaluation of infectious disease health states. We found that correlations of probit coefficients were high between all respondent characteristics, several differences have to be highlighted.

First, we found a lower correlation of the probit coefficients between countries than between the other respondent characteristics. It means that we observed more variation of the health states valuation between countries than between the other respondent characteristics. Especially the correlation of the probit coefficient was lower between Hungary and the Netherlands than between the other pairs. This translated in some major differences, as for "motor plus cognitive impairments, severe", that was ranked as the twenty-fifth worse health state in the Netherlands while instead fourth, seventh and ninth in Hungary, Italy and Sweden. We also observed that the model including country as covariate had the lowest AIC. This is line with the results of the correlation analysis. The observed variations of health state valuation across country could reflect a combination of different demographics and/or different attitudes but also expressed that the included characteristics did not fully explain the between country differences.

We found a high correlation of the probit coefficients between educational levels, both across and within countries. This means that educational levels had no influence on health valuation. In 2008, Haagsma et al. also demonstrated no significant effects of educational level on DWs for injury consequences in Dutch population [182].

In all countries, we observed a better correlation of the coefficients between 35-49 years and 50-65 years groups than between the other age groups. For example, in the Netherlands, Hungary and Sweden, the 18-34 years group gave less weight to "generic uncomplicated disease: anxiety about diagnosis" health state and more weight to "diabetic neuropathy" than the other age groups. In Hungary, Italy and Sweden, 18-34 years group gave less weight to "decompensated cirrhosis of the liver" than the other age groups. Dolan et al. also demonstrated that age group has an impact on health valuation [183, 184].

Within country we observed a lower correlation of the probit coefficients between income levels, especially between low and high income levels, except for the Netherlands where the lowest correlation was found between medium and high income levels.

Our results also showed that the DWs did not vary widely across disease experience status and sex.

Although this study highlighted the effect of participants' characteristic on health valuation using a sample of 30,660 answers, it also had some limitations. First, we performed a web-based survey and did not include respondents aged 65 years or older. Elderly people are more often affected by some health states as hearing loss or distance vision loss, and may suffer of comorbidities [185]. However, we did not demonstrate a relationship between DWs and disease experience status. Therefore this limitation might have a limited effect on the derived DWs.

Second, we showed that, except for Sweden, the mean income of the respondents was higher than in the general population. One of the explanations could be that Eurostat adjusted the income data on the size of the household which we had not done. Another explanation could also be that we used an approximate method to assess mean income by country because of the limited data. However because we had high number of respondents in each level of income this has a limited impact on the correlation results.

Third, as in the Salomon et al. study, our study elicited disability weights by presenting brief health state descriptions in lay language and some aspects of health states were inevitably omitted in the interest of brevity. For example, people suffering from chronic irritable bowel syndrome need to undergo a restrictive diet which can lead to a higher

long-term disability [186]. Also the disability of the "invasive device/drain" health state can probably be affected by the type and the location of the device. This could impact health state preferences of respondents and subsequently increase or decrease the value of the DW and impact the final ranking of the DWs.

Fourth, comparisons of DWs derived using a paired comparison approach across countries and participant characteristics are difficult and have to be interpreted with caution [156]. Due to the nature of the paired comparison questions, the results hold only relative information. It is therefore not possible to evaluate absolute differences in health state preferences across countries or between participants' characteristics. Instead, we explored different approaches for evaluating relative differences. First, we fitted different probit regression models to evaluate the interaction effects of country and participant characteristics. Comparison of models was only possible based on AIC values, which do not have an absolute interpretation and for which no null hypothesis distribution is available. AIC values thus do not allow to conclude on statistical significance of differences between models. Second, we used correlation coefficients to compare the rankings between different countries or participant characteristics. Because of the high number of observations, all correlation coefficients were significantly different from zero. Furthermore, the resulting correlation coefficients were all relatively high (> 0.84). However, a definition of what could be considered sufficiently high depends on context and cannot be provided by statistical models. Although we observed a high agreement of the health states valuation for every sub-groups, we still observed variation of the ranking of DWs between some sub-groups. This has to be considered because that could have an impact on the final derived DWs and indirectly on burden of infectious diseases estimates and policy priorities.

Despite these limitations, we believe that this study brings an empirical basis for understanding the health state preferences related to infectious diseases of a diverse set of European respondents. We observed that health state evaluations are highly correlated across participant's characteristics but that there exists some variation in health assessment across country and within country between income levels.

7.5 Conclusion

We observed that health state valuations are highly correlated across country, sex, age, disease experience status, income and educational levels, but there is some variation in health sates valuation across countries and within country between income levels. This means that country and income levels may have an impact on health state valuation.

These variations should be further explored in a systematic way, also in non-European countries. There is a need of future studies aiming to be more representative of study populations in future DW elicitation exercises. We also recommend future researches studying the effect of other characteristics of respondents on health assessment.

In the next chapter we will finish exploring how to improve burden estimates of bacterial FBD. We will explore strategies to derive DWs for infectious diseases in a more efficient way.

8

Mapping EQ-5D utilities to GBD 2010 and GBD 2013 disability weights

Adapted from

Maertens de Noordhout C, Devleesschauwer B, Gielens L, Plasmans MHD, Haagsma JA, Speybroeck N (2017) Mapping EQ-5D utilities to GBD 2010 and GBD 2013 disability weights: results of two pilot studies in Belgium. *Archives of Public Health*. 75:6.

8.1 Introduction

Disability weights (DWs) and utilities (also known as index values, preference weights or QALY weights) are common metrics allowing a quantitative evaluation of health states related to diseases, injuries or risk factors. They reflect the preference of individuals for a certain health state and quantify the severity of health loss associated with a certain health state. They are also crucial components in health economic evaluations and in disease burden assessments.

Disease burden assessments using the Disability-Adjusted Life Year (DALY) metric play an increasingly important role in public health research. The disability weight (DW) is a crucial component in the DALY formula, as it allows combining morbidity and mortality [38–41]. The DW expresses the relative reduction in Health-Related Quality of Life (HRQoL), on a scale from zero (perfect health) to one (worst possible health state). By weighing the years lived with disease, these years are "translated" into fully lost life years. Indeed, living 10 years with a 10% reduction in HRQoL (i.e., DW = 0.10) would be equal to losing one full year of good health (e.g., by dying one year before the life expectancy). As a result, both morbidity and mortality are expressed in the same currency, namely the number of healthy life years lost. Initially, DWs were elicited from participants who did not necessarily suffer from the studied health state, using time trade-off or person trade-off methods. However other valuation techniques for eliciting DWs exist [159]. Ideally DWs should be developed from international studies hence ensuring internal comparability. However, several health states are not included in such international initiatives. Therefore resorting to specific elicitation studies is the only option. For instance, to estimate the YLDs of stage 0 (in situ) melanoma in Belgium during the two first month of treatment, Tromme et al. multiplied the number of patients with stage 0 melanoma in Belgium for the 2009-2011 period, i.e. 1772 patients by the derived DW for the two first month of treatment, i.e. 0.3345 and by the duration, i.e. 2 months but the DWs obtained in these standalone studies are not comparable to an international set of disability weights [98].

As part of the Global Burden of Disease 2010 Study (GBD 2010), Salomon et al. proposed a wide set of DWs based on paired comparison questions for 220 health states in which respondents considered two health outcomes which were described briefly in lay language [38]. An update of these DWs was generated for the Global Burden of Disease 2013 Study (GBD 2013) by incorporating results of new surveys in four European countries (Hungary, Italy, the Netherlands, and Sweden). The two studies combined resulted in a set of DWs based on 60,890 participants [39, 40].

In health economic evaluations, health "utilities" are a crucial component of Quality-Adjusted Life Years (QALYs). A utility of 0 means that a health state is equivalent to death, whereas a utility of 1 means full health. These values can be derived using multi-attribute instruments such as the EuroQol 5 dimensions questionnaire (EQ-5D) [187]. The EQ-5D includes five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and five severity levels in each dimension (EQ-5D-5L). This self-completion questionnaire was developed by the EuroQol group and is applicable to a wide range of patient's health states.

To derive utilities, individuals are asked to score their health state using EQ5D questionnaire. Their scores may then be converted to a utility using a set of regression coefficients (or tariffs). These tariffs are obtained using direct valuations of a subset of health states from the general public using visual analog scale or trade-off methods and are available for certain countries. Some countries have integrated EQ-5D in their national health surveys, resulting in population average utilities that can be used as an indicator of general population health [188–191].

Many studies calculated utilities using EQ-5D for a wide range of diseases such as cancer [192], cardiovascular diseases [193] or diabetes [194]. EQ-5D has also been applied in the context of DALY-based disease burden studies. In these instances, the EQ-5D utilities had to be "translated" to DWs. So far, authors have assumed the DW to be equal to one minus the utility, or equal to the age and sex specific population average utility minus the elicited utility [182, 192]. However, these approaches do not guarantee comparability with the GBD 2010/2013 DWs. Mapping is a better strategy to predict DWs from utilities when DWs are not available for burden estimations [195].

The objective of this study was to propose an approach for mapping EQ-5D utilities to existing GBD 2010 and GBD 2013 DWs, and to predict "new" GBD 2010/2013 DWs based on EQ-5D utilities, i.e., for health states currently not included in the GBD studies.

8.2 Materials and Methods

8.2.1 Study design and participants

First Pilot study

Four health states representing the spread of the GBD 2010/2013 DW distribution were selected (Table 8.2). In other words, we selected four health states which values shared the GBD 2010/2013 DW distribution in three equal parts. Native speakers translated

existing health state descriptions developed by Salomon et al. [38] into French and back-translated them into English (Appendix 2 - *Available upon request to C. Maertens*). A written version of the EQ-5D-5L questionnaire excluding the visual analogue scale part was used and three different versions of the questionnaire were designed. As recommended by Euroquol group, we used the five level EQ-5D questionnaire (EQ-5D-5L) because the measurement properties of EQ-5D-5L are superior to the EQ-5D-3L in terms of feasibility, ceiling effects, discriminatory power and convergent validity [187].

Each version was composed of the same set of health states but with a different order of questioning, to explore possible order effects. The first version presented health states in increasing order of GBD 2010/2013 health state severity, the second version in decreasing order of GBD 2010/2013 health state severity, and the third one did not present health states in a certain order of severity.

The questionnaire consisted of two main parts. The first part was the same in each of the three versions of the questionnaire and included questions about age, sex and marital status. The second part included evaluation of four health states. Participants were asked to imagine being in a certain health state described by the lay descriptions developed by Salomon el al. [40], but without knowing the name of the health state. They would then select the most appropriate level of functioning for each of the five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Appendix 1 - *Available upon request to C. Maertens*). The respondents were students of the Public Health faculty at the Université catholique de Louvain (UCL), Brussels, Belgium, and were recruited during two courses in June 2014. There was no time limitation to answer the questionnaire and the study leader was present during the study allowing participants to ask any question.

Second pilot study

Twenty-seven health states representing the spread of the GBD 2010/2013 DW distribution were selected (Table 8.2). Native speakers with knowledge of the topic at hand, translated existing health state descriptions developed by Salomon et al. [38] into French and then back-translated them into English (Appendix 2 - *Available upon request to C. Maertens*). Dutch translation of the thirty-two health states came for the Haagsma et al. study [39]. A web-based version of the EQ-5D questionnaire excluding the visual analogue scale part, was developed using the Qualtrics software. As for the first study, the first part of the questionnaire included socio-demographics questions, with additional questions on disease/injury experience (yes/no answers), income and educational level. Income categories were derived from Haagsma et al. [39]. The second part included evaluation of four

health states. As in the first pilot study, participants were asked to imagine being in a certain health state described by the lay descriptions of Salomon et al. but without knowing the name of the health state [38]. Eight versions of the second part were developed. Each version included evaluation of four health states representing the spread of the GBD 2010/2013 DW distribution. The questionnaire was assigned to participants through a computer algorithm that attributed the questionnaire version with the lowest percentage of participants at the time of assignment. Participants had to answer all questions to validate their participation. The respondents were recruited by email among students of the Public Health faculty at the UCL and among principals of Brussels's primary and secondary schools and using a social network through general and private messages on Facebook. Snowball sampling [196] was used for the recruitment strategy, i.e., existing study participants were asked to recruit future subjects among their contacts. The data were collected in June 2015. A reminder was sent three weeks after sending the first email to the students of UCL and the principals of Brussels's schools. Through Facebook, a first request was published on the Facebook public wall of the two main leaders of the study on June 1 2015. Then, three recalls were sent through private messages to all friends of the two main leaders of the study on June 3, 16 and 22, 2015.

8.2.2 Data analysis

Two steps recommended by the EQ-5D-5L user guide were followed to transform the EQ-5D-5L scores reported by each participant into a utility [187]. A function previously developed by the EuroQoL group was used to translate the scores from a 5L to a 3L scale, because no Belgian tariffs exist for the 5L version. The EQ-5D-3L results were then converted to utilities using the tariff model developed by Cleemput et al. for the Belgian population [188].

8.2.3 Statistical analysis

For all EQ-5D utilities, overall means, medians, standard deviation and ranges were calculated. Utilities in this study were compared with GBD 2010 and GBD 2013 DWs using Spearman correlation coefficients. We used sample paired t-tests to test whether there was a difference of mean utilities between the pilot studies and the corresponding GBD 2010/2013 DWs.

A locally weighted scatterplot smoothing (loess) regression model was run between the utilities and the logit transformed corresponding GBD 2010/2013 DWs [38, 40]. We arbitrarily choose as anchor point that when DWs equated to 1, utility equated 0 and when DWs equated 0, utility equated 1. Logit transformed DWs were then predicted for

each of the utility scores from the loess fit. To retransform the scale and obtain DW values that range from 0 to 1, an inverse logistic transformation was applied to these predicted values.

Analyses were done with R version 3.0.2. R code and developed mapping function are available through: https://github.com/brechtdv/eq5d-mapping.

8.3 Results

8.3.1 First pilot study

In total 81 students completed the first survey, 57 were female (70.4%) and 57 had never been married (70.4%). They were on average 29.6 years old (SD 8.4) (Table 8.1).

Average utilities ranged from 0.667 (SD 0.131) for "Fractures, treated (long term)" to 0.289 (SD 0.203) for "Schizophrenia: acute state" (Table 8.2).

One participant attributed a negative utility (i.e., worse than death) to "schizophrenia, acute" (-0.158) and three participants attributed a utility of one (i.e., perfect health) to "severe wasting".

Table 8.1: Description of the study population N (%) - Mean (SD)

		Study 1 (n = 81)	**Study 2 (n = 393)**
		N (%)	**N (%)**
Age (years)- Mean (SD)	29.6 (8.4)	36.4 (12.5)	
Male		57 (70.4)	104 (26.5)
Marital status	Married	16 (20)	153 (38.9)
	Divorced	7 (8.8)	28 (7.1)
	Widower	0 (0.0)	5 (1.3)
	Separated	0 (0.0)	33 (8.4)
	Never been married	57 (71.3)	174 (44.3)
Income level (in euros)	$<$ 25 000		70 (17.8)
	25-44 000		84 (21.4)
	45-52 000		98 (33.4)
	$>$ 52 000		57 (14.5)
	Not available		84 (21.4)
Educational level	Primary		1 (0.3)
	Lower secondary		8 (2.0)
	Higher secondary		37 (9.4)
	Bachelor		156 (39.7)
	Master or higher		183 (46.6)
	Not available		2 (0.5)
Disease status	Yes		121 (30.8)

Table 8.2: Derived utilities by pilot study

ID	Health states	Mean-Utility study 1	SD-Utility study 1	Mean-Utility study 2	SD-Utility study 2	DW 2010	DW 2013
1	Fractures, treated (long term)	0.667	0.131	0.694	0.130	0.003	0.005
2	Distance vision, mild			0.826	0.154	0.004	0.003
5	Anemia, mild			0.813	0.138	0.005	0.004
8	Amputation of toe			0.650	0.127	0.008	0.006
11	Asthma, controlled			0.809	0.128	0.009	0.015
22	Claudication			0.644	0.177	0.016	0.014
29	Stroke, long term mild			0.550	0.168	0.021	0.019
37	Disfigurement, level 1 with itch or pain			0.639	0.177	0.029	0.027
47	Fracture of foot bones (long term, without treatment)			0.615	0.151	0.033	0.026
55	Headache tension type	0.530	0.169	0.350	0.204	0.040	0.037
60	Amputation of both legs (long-term with treatment)			0.304	0.244	0.051	0.088
77	Injured nerves (short term)			0.553	0.193	0.065	0.100
96	Fracture tibia, patella (short term)			0.389	0.170	0.087	0.050
107	Musculoskeletal problems (arms moderate)			0.474	0.173	0.114	0.117
111	Severe wasting	0.474	0.204	0.486	0.263	0.127	0.128
149	Crohn's disease			0.455	0.200	0.225	0.231
155	Parkinson's disease moderate			0.391	0.201	0.263	0.267
161	Gout, acute			0.193	0.212	0.293	0.295
174	Severe chest injury (short term, with or without treatment)			0.331	0.201	0.352	0.369
186	Fracture of pelvis short term			0.106	0.203	0.390	0.279
193	Headache (migraine)			0.548	0.194	0.433	0.441
200	Rectovaginal fistula			0.449	0.217	0.492	0.501
203	Terminal phase, without medication (for cancers, end-stage kidney/liver disease)			0.317	0.225	0.519	0.569
206	AIDS cases (not received ARV treatment)			0.360	0.228	0.547	0.582
214	Traumatic brain injury (long-term consequences)			0.200	0.257	0.625	0.637
219	Multiple sclerosis (severe)			0.144	0.198	0.707	0.719
220	Schizophrenia (acute)	0.289	0.203	0.341	0.192	0.756	0.778

There was a monotonic relationship between derived utilities and predicted GBD 2010/2013 DWs, i.e., the lower the utility, the higher the predicted GBD DW (Figure 8.1).

There was a negative correlation between utilities and GBD 2010 DWs (rho = -1, p = 0.083) and GBD 2013 DWs (rho = -1, p = 0.083).

There was a significant difference between the complement of the utilities (1-utility) and GBD 2010 DWs (p = 0.085) and between the complement of the utilities and GBD 2013 DWs (p = 0.099).

"Fractures treated, long term" was ranked first, i.e. with the lowest disability weight as in the GBD 2010 study (but ranked third in the GBD 2013 study) and "Schizophrenia, acute" was ranked last, i.e. with the highest disability weight as in the GBD 2010/2013 studies (Table 8.3).

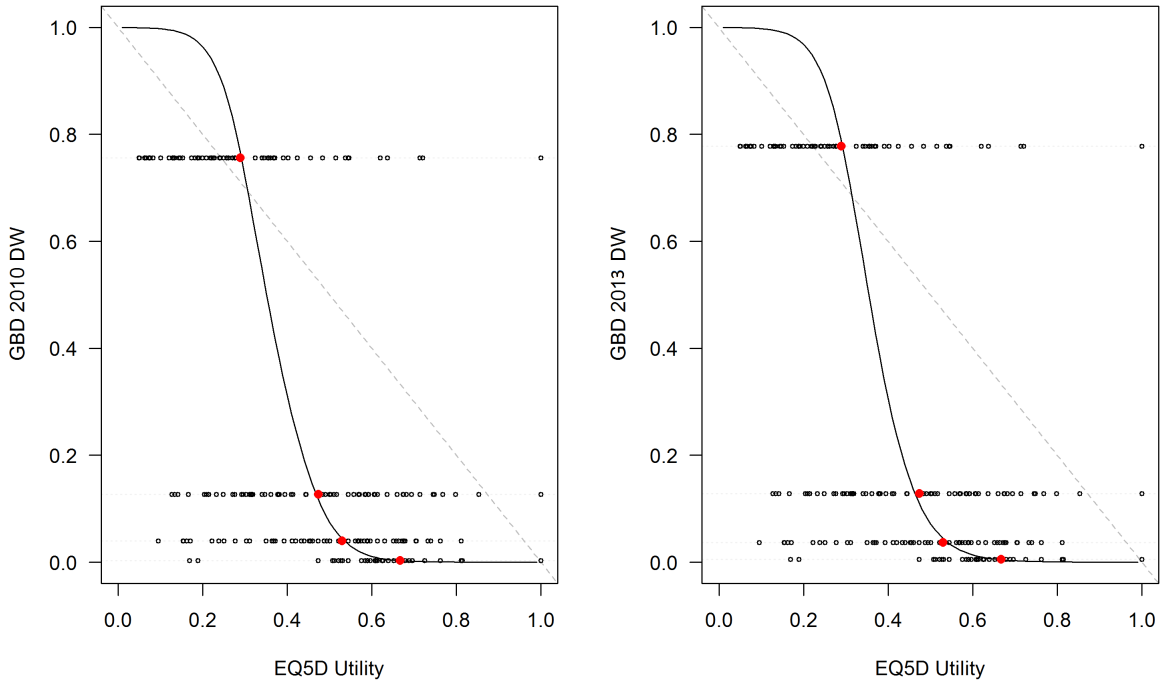


Figure 8.1: Mapping utilities developed in pilot study 1 vs GBD 2010 DWs and GBD 2013 DWs. Grey dots = individual utility value , red dots = mean utility, grey line = linear regression line, black line = loess regression line.

8.3.2 Second pilot study

393 respondents completed the second survey. The average age was 36.4 years (SD 12.5) and 26.3% of the respondents were male. 2.5% were younger than 20, 36% were between 20 and 29 years old, 26% were between 30 and 39 years old and only 4% were older than

60. The majority of the respondents were highly educated, i.e. 39.7% had a bachelor's and 46.6% had a master's degree. Most of the respondents had a medium income level, i.e. 54.8% had a household annual income ranging from 25,000 to 52,000 euros (∼27,000 USD–56,500 USD). Of all respondents, 30.8% already experienced a disease or injury experience in the past and 44.3% had never been married (Table 8.1).

The median of the utility distribution of the 27 health states was 0.455 (range: 0.106–0.826). The median of the selected 27 GBD 2010 DWs was 0.114 (range: 0.003–0.756). The median of the 27 GBD 2013 DW was 0.117 (range: 0.003–0.778). According to the utilities, the top three less severe health states in pilot study 2 were "Distance vision, mild", 0.826 (SD 0.154), "Anemia, mild", 0.813 (SD 0.138) and "Asthma, controlled", 0.809 (SD 0.128). "Fracture of pelvis short term", 0.106 (SD 0.203), "Multiple sclerosis", 0.144 (SD 0.198) and "Gout, acute", 0.193 (SD 0.212) were the top three more severe health states (Table 8.2 and 8.3 ; Figure 8.3). Most of the utilities were between 0.5 and 0.6, and corresponded to the health states with a moderate severity level.

Overall 64 of the participants (16%) in the second pilot study, attributed negative utilities to at least one health state. We obtained negative utilities for 11 health states (41%) among the 27 health states included in the second pilot study (Figure 8.2). In health states including negative values, the most common were "Fracture of pelvis short term" (22%), "Traumatic brain injury (long-term consequences)" (20%) and "Multiple sclerosis (severe)" (20%). Conversely, 64 participants (16%) attributed a utility of 1 to at least one health state. The top three most common health states with a utility of 1 were "Distance vision, mild" (25%), "Anemia, mild" (22%) and "Asthma, controlled" (16%).

The Spearman rank correlation coefficient between the utilities derived from pilot study 2 and the GBD 2010 DWs equaled -0.808 ($p < 0.001$). There was a significant difference between the complement of the utilities (1-utility) and GBD 2010 DWs ($p < 0.001$). The differences between the complement of the utilities and the GBD 2010 DWs ranged from -0.097 ("Schizophrenia, acute") to 0.645 ("Amputation of both legs (long-term with treatment)"). The average difference between 1-utilities and the GBD 2010 DWs was 0.30 (SD 0.18). The three highest observed differences between 1-utilities and the GBD 2010 DWs were "Amputation of both legs (long-term with treatment)" (0.645), "Headache tension type" (0.610) and "Fracture tibia, patella (short term)" (0.524). The three lowest observed differences were noticed for "Headache (migraine)" (0.019), "Rectovaginal fistula" (0.059) and "AIDS cases not received ARV treatment" (0.093) (Figure 8.3).

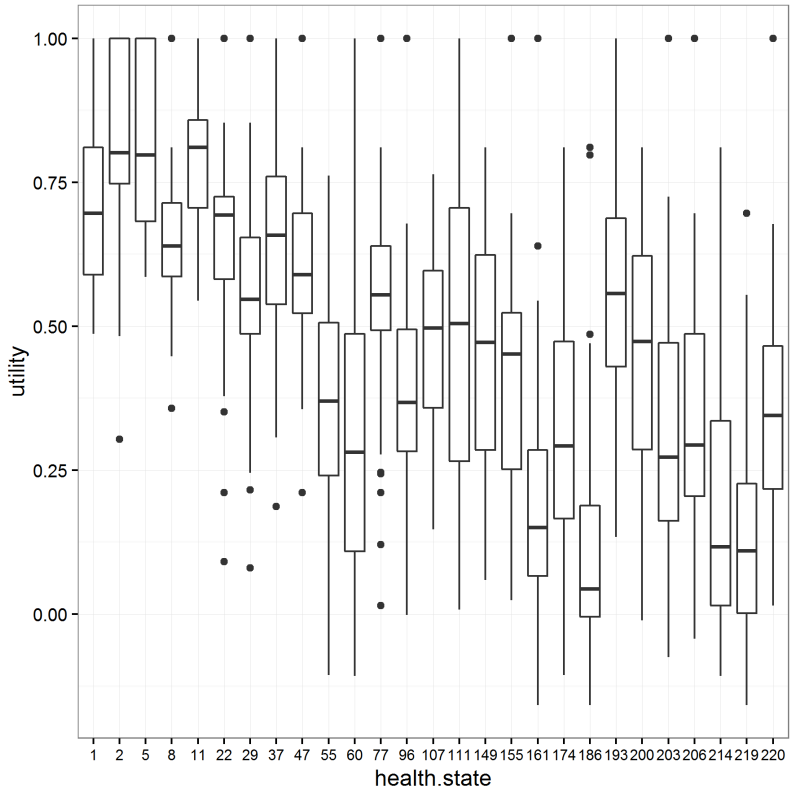


Figure 8.2: Distribution of utilities derived in pilot study 2. Medians and ranges of the 27 utilities. Black dots represent outliers. Health state IDs are available in Table 8.2.

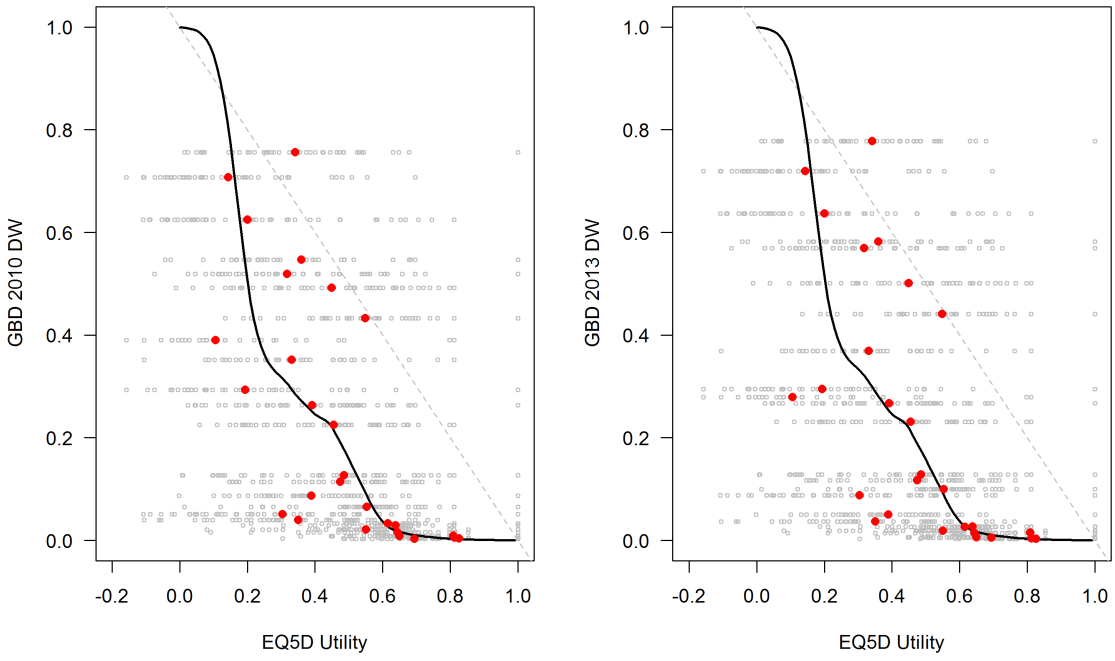


Figure 8.3: Mapping utilities developed in pilot study 2 versus GBD 2010 DWs and GBD 2013 DWs. Grey dots = individual utility value, red dots = mean utility, grey line = linear regression line, black line = loess regression line.

The Spearman rank correlation coefficient between the derived utilities from pilot study 2 and the GBD 2013 equaled -0.801 ($p < 0.001$). There was a significant difference between the complement of the utilities (1-utility) and the GBD 2013 DWs ($p < 0.001$). The differences ranged from -0.112 ("Schizophrenia, acute") and 0.613 ("Headache tension type"). The average difference between 1-utilities and the GBD 2013 DWs was 0.30 (SD 0.19). The three highest observed differences between 1-utilities and DWs GBD 2013 were for "Fracture of pelvis short term" (0.615), "Headache tension type" (0.613) and "Amputation of both legs (long-term with treatment)" (0.608). The three lowest differences "Headache (migraine)" (0.011), "Rectovaginal fistula" (0.05) and "AIDS cases (not received ARV treatment)" (0.06).

The relationship between the utilities and predicted DWs for both GBD 2010 and 2013 studies was not monotonic (Figure 8.3), meaning that both utilities and predicted DWs do not increase/decrease concurrently, and there were major differences in the ranking of health states between the second pilot study and the GBD 2010 and 2013 studies (Table 8.3). Most of the differences were located in the middle of the distribution, i.e. for health states that were located around the median of the distribution. "Amputation of both legs" was ranked 11th and 12th in the GBD 2010/2013 studies and fell to the 23rd place in this study. "Headache tension type" was ranked 10th in the GBD 2010/2013 studies and 19th in this study. On the other hand, participants of GBD 2010/2013 studies judged more severe "Headache migraine" and "Rectovaginal fistula" which held respectively the 21st and 22nd compared to pilot study 2 where they held the 11th and 15th rank.

Table 8.3: Ranking of the health states by study

Health states label	Study 1 (Descending)	Study 2 (Descending)	GBD2010 (Ascending)	GBD2013 (Ascending)
Distance vision, mild		1	2	1
Anemia, mild		2	3	2
Asthma, controlled		3	5	6
Fractures treated, long term	1	4	1	3
Claudication		5	6	5
Amputation of toe		6	4	4
Disfigurement, level 1 with itch or pain		7	8	9
Fracture of foot bones, long term without treatment		8	9	8
Stroke, long term		9	7	7
Injured nerves, short term		10	12	13
Headache migraine		11	21	21
Severe wasting	3	12	15	15
Musculoskeletal problems (arms moderate)		13	14	14
Crohn's disease		14	16	16
Rectovaginal fistula		15	22	22
Parkinson's disease moderate		16	17	17
Fracture tibia, patella, short term		17	13	11
AIDS cases, not received ARV treatment		18	24	24
Headache, tension type	2	19	10	10
Schizophrenia, acute	4	20	27	27
Severe chest injury, short term, with or without treatment		21	19	20
Terminal phase, without medication (for cancers, end-stage kidney/liver disease)		22	23	23
Amputation of both legs, long term with treatment		23	11	12
Traumatic brain injury, long term consequences		24	25	25
Gout, acute		25	18	19
Multiple sclerosis		26	26	26
Fracture of pelvis, short term		27	20	18
Median	**0.502**	**0.455**	**0.114**	**0.117**

8.3.3 Pilot study 1 versus pilot study 2

We also observed some differences of mean utility between study 1 and study 2. The differences ranged from -0.05 for "Schizophrenia, acute" to 0.180 for "Headache tension type" and we found higher agreement with health states located at the ends of the distribution, i.e. "Fractures, treated" and "Schizophrenia".

For "Severe wasting", most of the participants of the second pilot study assigned a score of three (i.e., moderate) to all five EQ5D dimensions. Participants of the second pilot study evaluated that "Severe wasting" caused more frequently none/moderate (Level 1 and 3) problems for mobility (Dimension 1), no problem of autonomy (D2) and weak (Level 2) pain/discomfort (D4). Participants of the first pilot study evaluated more frequently that "Severe wasting" caused weak (Level 2) problems of mobility (D1), weak (Level 2) problem of autonomy (D2) and none (Level 1) pain/discomfort (D4).

For "Headache tension" the participants of the second study attributed a higher level for three of the five EuroQol dimensions than participants of the first study. Participants of the second study evaluated more frequently that "Headache tension" caused severe pain/discomfort (Level 4–D4), severe problems to accomplish daily activities (Level 4–D3) and moderate anxiety/depression (Level 3–D5). Participants of the first study evaluated more frequently that "Headache tension" caused moderate pain/discomfort (Level 3–D4), moderate problems to accomplish daily activities (Level 3–D3) and weak anxiety/depression (Level 2–D5) (Figure 8.4).

Overall, in the first pilot study the scores for mobility (D1) and autonomy (D2) dimensions were in average higher than in the second pilot study. In the second pilot study, the scores for activities (D3), pain/discomfort (D4) and anxiety/depression (D5) dimensions were in average higher than in the first pilot study (Figure 8.4).

	D1: Mobility		D2: Autonomy		D3: Daily activities		D4: Pain/discomfort		D5: Anxiety/ depression	
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
ID = 1 Fractures, treated (long term)										
Level 1: None	25%	39%	63%	63%	37%	37%	5%	5%	69%	67%
Level 2: Weak	62%	44%	31%	31%	49%	49%	78%	78%	28%	28%
Level 3: Moderate	11%	17%	6%	6%	12%	12%	15%	15%	1%	6%
Level 4: Severe	2%	0%	0%	0%	1%	1%	1%	1%	1%	0%
Level 5: Extreme/Impossible	0%	0%	0%	0%	0%	0%	1%	1%	0%	0%
Mean	1.91	1.78	1.43	1.33	1.78	1.61	2.16	2.19	1.35	1.39
SD	0.67	0.72	0.61	0.48	0.71	0.73	0.58	0.52	0.57	0.6
ID = 55 Headache tension type										
Level 1: None	52%	30%	53%	48%	6%	2%	1%	0%	19%	16%
Level 2: Weak	37%	24%	30%	14%	32%	10%	12%	6%	47%	18%
Level 3: Moderate	10%	18%	14%	30%	51%	34%	56%	20%	28%	34%
Level 4: Severe	1%	22%	4%	4%	9%	44%	25%	60%	6%	24%
Level 5: Extreme/Impossible	0%	6%	0%	4%	2%	10%	6%	14%	0%	8%
Mean	1.6	2.5	1.68	2.02	2.69	3.5	3.22	3.82	2.22	2.9
SD	0.72	1.3	0.85	1.15	0.82	0.89	0.79	0.75	0.82	1.18
ID = 111 Severe Wasting										
Level 1: None	14%	28%	26%	42%	6%	25%	46%	23%	11%	19%
Level 2: Weak	32%	17%	35%	26%	17%	17%	30%	43%	20%	23%
Level 3: Moderate	27%	28%	27%	23%	43%	26%	20%	28%	37%	30%
Level 4: Severe	27%	19%	12%	6%	30%	25%	5%	6%	27%	23%
Level 5: Extreme/Impossible	0%	8%	0%	4%	4%	8%	0%	0%	5%	6%
Mean	2.68	2.6	2.26	2.04	3.07	2.74	1.84	2.17	2.95	2.74
SD	1.02	1.11	0.98	0.88	0.93	1.1	0.91	0.68	1.06	0.99
ID = 220 Schizophrenia										
Level 1: None	56%	73%	31%	73%	2%	13%	43%	38%	2%	4%
Level 2: Weak	16%	8%	22%	10%	7%	6%	22%	21%	1%	4%
Level 3: Moderate	19%	10%	35%	12%	17%	17%	15%	13%	10%	10%
Level 4: Severe	9%	8%	11%	6%	52%	42%	16%	19%	28%	25%
Level 5 : Extreme/Impossible	1%	2%	1%	0%	21%	21%	4%	8%	58%	58%
Mean	1.84	1.58	2.3	1.5	3.81	3.52	2.15	2.37	4.38	4.29
SD	1.09	1.07	1.07	0.92	0.94	1.28	1.25	1.37	0.9	1.05

Figure 8.4: Dimensions and levels frequency by study

8.4 Discussion

DALY-based burden of disease studies play an increasingly important role in public health research [101]. As the required DWs for the health states under study may not be available, flexible and practical ways of eliciting DWs that are comparable with existing GBD DWs are therefore needed. We proposed a mapping approach based on a loess regression model to easily predict any GBD 2010/2013 DW from EQ-5D5L utilities. To our knowledge, the current study is the first to map EQ-5D utilities to GBD 2010/2013 DWs.

Recently, Burstein et al. used loess regression to map SF-12 utilities to GBD 2010 DWs [197]. They showed a weaker rank order correlation (-0.7) between GBD 2010 DWs and SF-12 scores than we found between DWs and utilities (>-0.8). They also found that the relationship between GBD 2010 DWs and SF-12 scores was non-monotonic. The mapping function developed by Burstein et al. was less satisfactory than in the first pilot study but better than in the second pilot study. Burstein et al. selected 62 health states, collected data from a sample of 3791 respondents and corrected for outliers. Except that participants were enrolled in Seattle and during two GBD workshops, no information was available on age, educational or income level and disease experience status of their study population.

We observed major differences in the validity of the mapping function between both pilot studies, which could be influenced by the different study populations and questionnaire forms. Indeed, a higher prediction quality was observed when we derived utilities from a written version of the EQ-5D questionnaire compared to a web-based questionnaire. One explanation could be that during the first study, which included the written version of the EQ-5D questionnaire, one of the study leaders was present to answer the questions of the participants. This may have increased the understanding of the health state definitions. The wider standard deviations of the second pilot study underscore this hypothesis. Even though we used the updated version of the lay definitions developed by Salomon et al. [40], we still observed that descriptions were not straightforward to understand for lay population. In the second pilot study, we observed a weaker quality of the prediction for more severe disorders, for example “Schizophrenia, acute”, “Epilepsy severe” or “Rectovaginal fistula”.

In addition, we observed some overlap between the health state descriptions developed by Salomon et al. [40] and the five dimensions included in the EQ-5D questionnaire that could have influenced the health state valuations. For example, the definition of “Fracture of pelvis: short term” was, “You have severe pain, and cannot walk or do daily activities” which provided information on the level of mobility, self-care, usual activities and

pain/discomfort dimensions included in the EQ-5D5L questionnaire. We observed that utilities for health states with overlap in descriptions had lower variation. For example, in the second pilot study the lowest standard deviation was observed for "Amputation of toe" (SD 0.127) and "Asthma, controlled" (SD 0.128), both of them included information on pain and daily activities in their descriptions.

We also observed that there were some important differences of ranking between GBD 2010/2013 DWs and utilities derived in the second utilities study. Respondents of our study ranked amputation of both legs lower (more severe) and acute schizophrenia higher (less severe) than the respondents of the GBD 2010/2013 studies. In addition to the overlap between the health state descriptions described above, one explanation could be that for participants included in the pilot studies it was more difficult to imagine and evaluate functional limitations (D1-D3) for psychiatric disabilities than for impaired mobility.

Several limitations may also have influenced the final results.

In the second pilot study, a sample of 27 GBD 2010 health states was used, and each health state was evaluated at least 30 times. Chuang et al. determined that each health state has to be at least evaluated 100 times to be representative of the population of responses [198]. We indeed observed better results in the first study, where each health state was at least evaluated 81 times.

The study population was not representative of the Belgian population. The first study population (n=81) was composed of students in public health, mostly female and young adults. In the second study (n=393), and despite the snowball strategy, most of the participants were between 20 and 39 years (72%), were highly educated. The web-based questionnaire as well as the age of two main coordinators of the study could be an explanation of the study population characteristics. Hopefully, Haagsma et al. demonstrated no significant effects of educational level on DWs for injury consequences in the Dutch population [182]. However other studies, which also used EQ-5D questionnaire, demonstrated that participants aged 18-59 evaluated health states less severely than those aged 60 and over and that older participants attributed less weight to morbidities and pain experience than younger [183, 199].

In addition, some authors reported that the judgment of people who are in a certain health state and health professionals differ significantly from judgment of healthy people [193]. Thirty-one percent of the respondents included in the second study had a disease experience and mostly were expert in public health, which might have influenced

the results. Utilities could have been under or over estimated. However we do not recommend to restrict participants to healthy individuals because we believe that utilities have to represent the average "preference" of health of the studied population.

We chose to include negative values of individual utility in the Cleemput's model, indicating some health states to be worse than death for some participants. We obtained a negative value for one (25%) health state in the first pilot study and for 11 health states (41%) in the second pilot study. For a study including a larger population, it is recommended to constrain values between 0 and 1 to improve the prediction model [200] but in the practice, the issues raised by the negative values for EQ-5D health states are complex [201]. In addition, to perform the final mapping we arbitrarily chose that when DWs equated to 1, utility equated 0, indicating that it exists health state worse than death. This is one of the methodological and philosophical choice difference between the utilities derived from EQ-5D tool and DWs derived from pairwise comparison that could impact the predictions. This is also why assuming the DW to be equal to one minus the utility do not guarantee comparability with the GBD 2010/2013 DWs.

In addition, both "short" and "long" term health states were included in the study and the time framing was not explicitly defined. Some studies demonstrated that the duration of a health state has an impact on the health state valuations and that poor states of health became more intolerable the longer they last [182, 195, 199]. However Salomon et al. showed that the framing of paired comparison questions in terms of temporary or chronic outcomes in a pairwise comparison did not affect the valuation of the health states [40].

Finally, there are fundamental differences between the pairwise comparison (PC) and EQ-5D techniques. First, GBD PC was anchored to Population Health Equivalence answers, while EQ5D Flemish tariffs [188] was anchored to Visual Analogue Scale (VAS). Although there are systematic differences between those methods, both are indirect and should not affect the mapping. Second, EQ5D questionnaire was designed to assess Quality of Life (QoL) of patients, with a given scenario of health states but DWs were designed to quantify the severity of a single health state. In other words, utilities are patient specific, whereas DWs are health state specific. In this study, we deviate from this original definition by defining health state specific utilities. Both methods also do not evaluate health states on the same dimensions of health [202]. With EQ-5D instrument participants have to evaluate health states on five dimensions of health, each of them including five levels of severity and with pairwise comparison, two health states are presented to healthy people and they have to decide which they regarded as being healthier based on

their own judgment and experience. These fundamental differences of methodology can also explain the differences we observed between GBD 2010/2013 DWs and utilities.

8.5 Conclusion

This study suggests the possibility to translate any utility derived from EQ-5D scores into a DW, but also highlights important caveats. We observed a satisfactory result of this methodology when utilities were derived from a population of public health students, a written questionnaire and a small number of health states in the presence of a study leader. The results were however unsatisfactory when utilities were derived from a sample of the general population, using a web-based questionnaire. For the sake of validating the study, we recommend repeating the first study (i.e. using a printed version of the questionnaire coupled with an available support of the study leader and a small number of health states to evaluate) in a larger and more diverse sample to obtain a more representative distribution across educational levels and ages because DWs may vary between and within countries potentially impacting the mapping between utilities and GBD 2010/2013 DWs. Recommendations on future study designs in regards of an optimal sample size are not straightforward to provide, since knowledge on the variability of data in such studies is lacking. Moreover according to Brazier et al., the sample size (number of people giving responses) used in other mapping studies is very broad as it ranged from 68 to 23,647 [203]. We think that further studies using simulation process, could help to answer the sample size. However at least as important as the sample size, is the representativeness of the sample for the population at hand. To avoid selection basis a probability sample (e.g. random sample) of the participants is required.

9

General discussion

The main objectives of this thesis were: 1) to contribute to assessing the burden of bacterial foodborne disease (FBD) in the world and in Belgium and 2) to investigate methods to improve burden of bacterial FBD estimates.

To achieve the first objective, we conducted a systematic review and meta-analysis to estimate the number of cases, deaths and Disability-Adjusted Life Years (DALYs) caused by listeriosis in 2010 worldwide **(Chapter 3)**. We also calculated the burden of salmonellosis, campylobacteriosis and listeriosis in Belgium from 2012 to 2020 using a time series analysis **(Chapter 4)**. To reach the second objective, we evaluated comorbidities linked to listeriosis and the factors linked to death and central nervous system (CNS) infection in non-perinatal listeriosis cases **(Chapter 5)**. In **Chapter 5**, we also estimated the duration of the sequelae after a CNS infection caused by listeriosis. Then in **Chapter 6**, we elicited a new set of disability weights for infectious diseases based on European participants and in **Chapter 7** we evaluated differences in health valuation across the population characteristics. Finally we explored a mapping function to easily derive disability weights from utilities **(Chapter 8)**.

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

9.1 Objective 1: to assess the burden of bacterial foodborne disease in the world and in Belgium

9.1.1 Towards a better estimation of the global burden of listeriosis

In 2015, the World Health Organization (WHO) published the "the Global Burden of Foodborne Diseases" report in which the results of **Chapter 3** were included [4]. The aim of this initiative was to provide the first estimates of global incidence, mortality, and Disability-Adjusted Life Years (DALYs) due to foodborne diseases. For the global estimates, 31 foodborne hazards were evaluated, including *Listeria monocytogenes*.

In **Chapter 3**, we estimated that listeriosis resulted in 23,150 illnesses (95% CrI: 6,061-91,247), 5,463 deaths (95% CrI: 1,401-21,497) and 172,823 DALYs (95% CrI: 44,079-676,465) globally. We also found that including stillbirths in the DALY calculations for listeriosis increased the global burden by 14.7%.

Many data and knowledge gaps on listeriosis emerged. First, we were unable to identify incidence data for about half of the WHO regions. We found little data for some key parameters, such as the proportion of stillbirths caused by listeriosis or the proportion and duration of neurological sequelae caused by CNS infection. Next, no DWs were available for the CNS infections and neurological sequelae, and had to be elicited through experts in CNS infection. Finally, we observed that non-perinatal listeriosis cases were often linked with co-morbidities but these were never quantified as such and taken into account in burden of listeriosis estimations.

Since the publication of the burden of listeriosis estimates, there have been new international estimates of the annual number of listeriosis cases. According to the European Food Safety Authority (EFSA) and the European Center for European Centre for Disease Prevention and Control (ECDC) in the year 2014, listeriosis infections reported in humans increased by 16% compared with 2013: there were 2,161 confirmed cases in 2014 [204]. The US Centers for Disease Control and Prevention (CDC) reported an increase of 4% of invasive listeriosis cases compared with 2013 in the USA: there were 660 confirmed cases in 2014 [205]. Although this number is relatively low compared to other foodborne diseases, the reported listeriosis cases are of concern since they go hand in hand with higher case fatality rates than other foodborne diseases, particularly among patients with a weak immune system. Indeed, **in Chapter 3** we estimated that the case fatality rate of listeriosis was higher than 10% in AMR B, D and EMR B, D and SEAR B, D WHO regions. More recently, Feng et al. collected available data on listeriosis in China for the

past 40 years and estimated that the case fatality rate of listeriosis was around 26% [206]. In 2014, a listeriosis outbreak killed 15 people and affected 38 in Denmark [207] and in 2015 and 2016 CDC recorded five outbreaks in the USA, resulting in 70 cases and 11 deaths [58]. Because of the ageing of the population with an increasing number of multiple pathologies, listeriosis is a foodborne disease that has to be carefully reported and managed.

Regarding the DALYs estimations, there was a new estimate of the burden of listeriosis in the Netherlands. For the period 2007 to 2011, Van Lier et al. ranked listeriosis as the 20^{th} (in term of DALYs/year) most important disease among 30 other infectious diseases in the Netherlands. In the Netherlands, listeriosis had a higher impact on public health than hepatitis A infection, measles, syphilis or tetanus [123]. The WHO report [4] and **Chapter 3** demonstrated that among bacterial FBDs, listeriosis had the highest individual burden, resulting in nearly 8 DALYs per foodborne case. Although we observed that the burden of listeriosis at a population level is lower than other infections, the individual burden of listeriosis per case is particularly high. Moreover, in 2015 Thomas et al. estimated that 57 cases of a listeriosis outbreak costed nearly 2.8 million Canadian dollars in 2008 and that foodborne outbreaks due to severe pathogens, such as *L. monocytogenes* are the most costly from the individual and/or societal perspective [208]. As listeriosis has a high individual health burden and a high economic impact on society, it has to be considered as a priority in public health policies.

Although we observed that most of the efforts towards controlling listeriosis are seen from countries for which burden estimations included less uncertainty, the increasing resources and time dedicated to get a better picture of the impact of listeriosis worldwide are encouraging. We are encouraging AFR, EMR and SEAR WHO regions to implement epidemiological assessments of listeriosis. New evidence and knowledge on comorbidities and sequelae related to listeriosis may further contribute to improved estimations of the burden of listeriosis. This was addressed in **Chapter 5**.

9.1.2 Burden of foodborne diseases in Belgium

In Chapter 4, we estimated the burden of salmonellosis, campylobacteriosis and listeriosis in Belgium. In 2012, salmonellosis caused on average 102 DALYs (95% Uncertainty Interval [UI] 8-376), campylobacteriosis caused 1,019 DALYs (95% UI 137-3,181), acquired listeriosis caused 208 DALYs (95% UI 192-226) and perinatal listeriosis caused 269 DALYs (95% UI 208-347). Assuming a constant environment, the burden of salmonellosis and listeriosis will remain stable while the burden of campylobacteriosis may almost double

through 2020.

The combination of the results in **Chapter 3**, indicates that campylobacteriosis and listeriosis may require both specific attention from Belgian policy makers: campylobacteriosis because of the observed and predicted worrying trend and listeriosis especially because of the high individual health burden.

The Scientific Institute of Public Health (WIV-ISP) reported 83 confirmed cases of listeriosis in 2014, or 6.9 cases/month [209] which is not different than what we predicted in **Chapter 4** (6 (SD 3) cases/month). Time series analysis can be a powerful tool to evaluate the impact of policies. Indeed, we observed a dramatic drop in salmonellosis cases in Belgium from 2005, coinciding with a mandated monitoring and vaccination program set up in Europe in 2003 against *Salmonella* Enteritidis and *Salmonella* Typhimurium. Time-series analysis can also be a good tool to predict burden of FBDs and to anticipate priorities and future costs linked with FBDs if a constant environment is assumed.

The precision of our time series models could be improved further by including relevant covariates that were not available for the Belgium estimations. For instance, inclusion of data source, diagnostic method, sex, age, incidence of infection in animals, prevalence in food or consumption of proton-pump inhibitors, which can increase the risk of *Campylobacter* spp., *Salmonella* spp. or *Listeria* spp. infection [127, 128] could also be included in the model to decrease the uncertainty of the predictions and to produce more informed extrapolations. If new data becomes available, our models will have to be updated. This will probably increase the precision of our estimations but will require a re-evaluation of the selected model, especially for listeriosis for which little data was available at the time of this study.

An important issue faced in **Chapter 4** is the underestimation of salmonellosis and campylobacteriosis cases. Indeed, these diseases are not notifiable and reported cases are just the tip of the iceberg. Some patients do not seek healthcare, resulting in "*under-ascertainment*" and some cases are not adequately diagnosed or reported, resulting in so called "*under-reporting*". Underestimation is the sum of under-ascertainment and under-reporting. To estimate the true incidence/prevalence of these diseases, which would allow a true comparison of diseases and setting of more appropriate priorities, there is a need to develop multiplication factors [111]. There are several ways to develop multiplication factors: community-based studies, serological surveys, returning traveller studies, capture-recapture studies, modelling or expert consultation. In **Chapter 4**, we extrapolated reported cases of campylobacteriosis and salmonellosis cases in Belgium, using the underreporting factors (URF) developed for Belgium using a returning traveller method-

ology [111]. No URF are available for both salmonellosis and campylobacteriosis based on Belgian data. We recommend to develop Belgian URF using a community-based study because it will be directly based on Belgian data and so would better represent reality. Noteworthy is that in the Flemish part of Belgium, listeriosis has recently became non-notifiable. The influence of this on the underreporting is unknown, but should be monitored.

Although information on the burden of disease is crucial to inform policy [101], no additional estimates of the burden of foodborne disease in Belgium have been generated. At the end of 2016, the Belgian National Burden of Disease Study was launched [210] by the Belgian Scientific Institute of Public Health (WIV-ISP). This study will aim to estimate burden of disease in Belgium through DALY estimations. The final report is expected for 2020 and will include burden estimates for a selection of FBDs. In 2010, WHO estimated that diseases due to norovirus, *Campylobacter* spp., Non-typhoidal *Salmonella enterica* and acquired *Toxoplasma gondii* had the highest burden among FBDs in Euro WHO region. In addition to *L. monocytogenes*, we recommend to include estimation of burden of these FBDs in the Belgian National Burden of Disease study.

9.2 Objective 2: to investigate methods to improve burden of bacterial FBD estimates

9.2.1 Accounting for comorbidities in the burden of foodborne diseases

Comorbidity is the co-occurence of two or more diseases and is not uncommon, especially in the elderly and immunocompromised [211]. In **Chapter 5**, we studied comorbidities and risk factors linked with listeriosis and central nervous system infection after listeriosis infection through a clinical case series.

First, we observed that antibiotic monotherapy and the presence of renal disease were "protecting" factors for CNS infections. One explanation could be that people suffering from a chronic renal disease receive a prophylactic antibiotic therapy that may protect against CNS infection, and that patients with neurological listeriosis have more severe initial clinical symptoms and therefore receive more often broad-spectrum antibiotic therapy at admission. We also observed that severe cardiovascular disease was the main factor associated with death caused by listeriosis. Because of the retrospective design of this study and the non-representative sample of the Belgian population, conclusions have to

interpreted with caution and in the context of any other available information. Although listeriosis is a rare disease, a prospective study would bring useful information on risk factors linked with listeriosis and help clinicians and public health professionals to easily focus on a specific health condition. Such an initiative was launched in France, with the Monalisa study [212].

Then, we estimated that, at hospital discharge, 38% of the patients had neurological sequelae and that after a median follow-up of one year, 45% of these patients still suffered from their neurological sequelae. This information could be useful to improve the future burden of listeriosis estimation as data on duration of the neurological symptoms and proportion of people with neurological sequelae are rare. We recommend to use this information to update the meta-analysis performed in **Chapter 3** and decrease uncertainty in DALY estimates.

In the clinical series, we also observed that 84% of the patients suffered from an underlying disease. If we want to set priorities and compare the burden of listeriosis with that of other diseases, a crucial issue would be to take into account underlying diseases in future burden of listeriosis estimations. Indeed, some studies demonstrated that YLD estimations that do not account for multimorbidity can result in an overestimation of the burden of disease [133, 213]. Assume for instance a patient with a diabetic neuropathy and a moderate heart failure. Without comorbidity adjustment, the DW for this patient will be calculated as the sum of both DWs, i.e., $DW_{\text{diabetic neuropathy + heart failure moderate}} = DW_{\text{diabetic neuropathy}} + DW_{\text{heart failure moderate}} = 0.165 + 0.070 = 0.235$. Additivity could however lead to a multimorbid DW that is larger than 1, i.e., a situation "worse than death".

There are two issues when accounting for comorbidities in YLDs estimation: the DWs need to be adapted and data on prevalence or on incidence of the comorbidities have to be available.

There are three main possibilities to adapt DWs beyond the additive approach. The first option is to use the *maximum limit approach*. In this situation the DW for our patient equals $\max(DW_{\text{diabetic neuropathy}}, DW_{\text{heart failure moderate}}) = \max(0.165, 0.070) = 0.165$ [39]. The second option would be to use the *multiplicative approach* [133, 214]. For example, $DW_{\text{diabetic neuropathy + heart failure moderate}} = 1 - (1 - DW_{\text{diabetic neuropathy}}) * (1 - DW_{\text{heart failure moderate}}) = 1 - (1 - 0.165) * (1 - 0.070) = 0.223$.

In addition to adapting the DWs, prevalence or incidence data of all diseases and disabilities individuals are suffering from have been collected. These data should have to

be collected from population-based health surveys but because of the large number of possible causes of ill health, it is impossible to measure all possible diseases in a population sample [215]. In GBD 2010 and GBD 2013, prevalence of comorbidity was mainly calculated assuming independence between the prevalence of individual diseases. In our example, this means that prevalence of both diabetic neuropathy and moderate heart failure equals the product of the prevalence of diabetic neuropathy and the prevalence of moderate heart failure. According to Murray et al., the error associated with the independence assumption is low if the prevalence is calculated within each age-sex group. In addition, no study corrected burden estimates for incidence approach. Indeed, the GBD 2010 and 2013 and 2015 calculated prevalence-based DALYs which is more easy to correct for comorbidity, because they did not correct for the durations of comorbidities from this moment to the future. There is a need to develop methods to deal with comorbidities in incidence-based DALYs approach.

Finally, some could argue that a similar adaptating approach may be applied to YLL estimates, i.e. accounting for the terms used in death certificates. However research on this is in its early stage [213]. Others could argue that there is no comorbidity issue with mortality because people can only die once, due to only one underlying cause. In other words, humans can have other causes and risk factors that have contributed to their death, but then it is a matter of attributing the single death to any of these causes. Or, as it is done for risk factors, we could attribute death to multiple causes using partitioning procedures [216–218].

9.2.2 Developing new DWs based on an European population

In **Chapter 6** we assessed disability weights (DWs) for 255 health states based on the responses of more than 30,000 European participants from the Netherlands, Hungary, Sweden and Italy. In this work, as similar methodology was used as in Salomon et al. for the GBD 2010 study [38] to evaluate health states, i.e. Population Health Equivalence (PHE) and paired comparison method (PWC). We proposed DWs for 43 new health states, 171 original GBD 2010 health states, 34 modified GBD 2010 health states and 7 experimental health states.

In the latter study, two major issues emerged. First, we observed a poor quality of the PHE data, i.e. the person trade-off questions that were included in the questionnaire allowing to anchor the responses on a scale form 0 to 1. The PHE could not be used to anchor the paired comparison responses in order to estimate the DWs and we used the GBD 2010 DWs instead. One explanation of the poor quality of the PHE may have been

the web design, but in the GBD study, the PHE was included in the web-based survey as well [38]. However, the educational level of the respondents of the GBD study was higher as compared to our study, and respondents to the GBD survey were a self-selected group who were evidently interested in the content of the survey to participate voluntarily. This may have resulted in greater attention to the question and care in weighing the responses, both of which are likely to have improved the signal-to-noise ratio in the responses. In this study the discrete choice formulation of the PHE may not be suitable for use in a general population survey administered by the internet. We recommend new research to study if other aspects can contribute to the poor performance of the PHE. For future health state valuation studies that use a similar design and a similar panel composition, we recommend considering different techniques to anchor estimates from paired comparisons onto the DW scale, such as the time trade-off. Second, although we found a high degree of consistency between DWs of the four countries we caution against over-generalization of the findings. Apart from cultural differences, other differences between high- and low-income settings may also influence how people weigh different health outcomes. Further research is needed to gain greater insight into the effects of cultural differences on DWs, particularly in low-income settings. This was addressed in **Chapter 7**.

In 2015, Salomon et al. combined data from this study with data previously collected in the GBD 2010 disability weights measurement study allowing the assessment of DWs for 183 health states based on more the 60,000 answers [40]. For the GBD 2013 study, Salomon et al. also revised the health state descriptions of some health states such as severe epilepsy. For some health state descriptions that were revised in the Salomon's study, resulting disability weights were substantially different between GBD 2010 and GBD 2013 studies. This allowed Salomon et al. to conclude that disability weights are sensitive to particular details in descriptions of health states.

9.2.3 Towards a better understanding of the effect of population characteristics on health valuation

In **Chapter 7**, we evaluated if participant characteristics had an impact on health valuation. We observed that health state valuations are highly correlated across country, sex, age, disease experience status, income and educational levels, but there is some variation in health sates valuation across countries and within country between income levels. This means that country and income levels may have an impact on health state valuation and therefore on derived disability weights (DWs).

Comparisons of DWs derived using a paired comparison approach across countries and

participant characteristics were difficult due to the nature of the paired comparison questions, and the results therefore only hold relative information. It was therefore not possible to evaluate absolute differences in health state preferences across countries or between participant characteristics.

In 2016, Neethling et al. assessed DWs of 51 health states through a household study in replicating the GBD 2010 Salomon's study, using as respondents a sample of the resource-deprived community (low socio-economic population) of Cape Town. Then, they compared the 51 derived DWs with the 220 GBD 2010 DWs using correlation and ranking analysis. In line with our findings, the study reported a poor correlation ($r = 0.44$, $p = 0.0015$) between the DWs of the local study and those of the GBD 2010 study [219]. In 2008, Haagsma et al. did not observe significant effects of educational level on DWs for injury consequences in the Dutch population [182]. The latter study used the visual analogue scale (VAS) and the time trade-off as evaluation methodology and in a smaller population sample with wider age range (from 19 to 82 years) making the comparison of results difficult. Our results are also not in agreement with results of other studies such as Dolan demonstrating that age-group had an impact on health valuation and that participants aged 60 and over attributed less weight to health states than those aged 18-59 [184]. However this study was only conducted in UK, using one-to-one interviews, EQ5D questionnaire and TTO valuation techniques which is known to be age/time dependent. Moreover, Dolan showed that when the scores of older respondents were adjusted for negative values, the differences in health valuation between the two age groups greatly diminished. Dolan also concluded that additional studies are needed to evaluate the sources of differences of health valuation observed.

There is a need for additional studies to further explore differences of health valuation across participants characteristics, also in Non-European countries. Other respondents characteristics also have to be explored such as religion. Indeed, if these characteristics have an impact on health valuation, and so on derived DWs, they have to be taken into account in the selection of study populations of future studies aiming to assess DWs.

9.2.4 Mapping function to easily derive disability weights from utilities

To develop disability weights, it is necessary to make design choices, in particular with respect to valuation techniques. In **Chapter 6** and **Chapter 7** we used the pairwise comparison method, a discrete choice valuation technique developed by Salomon et al. to elicit DWs [38]. At first glance, the pairwise comparison approach seems simple to

implement but still needs an anchoring step allowing to define DWs on a scale from 0 to 1 and can be difficult to understand for untrained people. Because of that, time trade-off (TTO) and scales (VAS) have been applied most extensively [220]. However, independent of the valuation technique used, DW elicitation remains a demanding exercise implying, among others things, the design of a valuation tool, the creation of the health state definition, the recruitment of representative participants of the general population and the data analysis. Therefore in **Chapter 8** an alternative technique to easily derive DWs was proposed. We presented an approach for mapping EQ-5D utilities to existing GBD 2010 and GBD 2013 DWs, and for predicting new GBD 2010/2013 DWs based on EQ-5D utilities. We obtained satisfactory results with this methodology when utilities were derived from a population of public health students, using a written version of the EQ-5D questionnaire, presenting a small number of health states and with the study leader being present to answer questions. The results were however unsatisfactory when utilities were derived from a sample of the general population, using a web-based questionnaire.

In 2016, Ock et al. proposed an alternative to easily derive DWs. They used a paired comparison as the main valuation method and included directly "being dead (1)" and "full health (0)" as anchor points to rescale the predicted probability of each cause of disease on a scale of 0 to 1 in the self-administrated questionnaire [221]. By including "full health" and "being dead" as anchor points without resorting to a person trade-off. However, this method is debated because some health state valuation researchers judge that this is methodologically incorrect [222]. Finally, inclusion of death as a health state could also be discussed as some people may claim that death cannot be considered as a health state as such.

As the results presented in the **Chapter 8** helped to conclude that translating any utility derived from EQ-5D scores into a DW was possible but that the results were unsatisfactory when using a web-survey, we recommend to repeat this study in a larger and more diverse sample of the general population using a face-to-face interview. We also believe that further research on easy to manage valuation of health methods has to be conducted to increase the DW panel.

9.2.5 Bridging research and policy

Although the results of this thesis have been picked up by certain media and bloggers[1], we do not know the impact of this work on decision makers. There is a need to study how to transfer research results to relevant authorities, as the Federal Agency for the Safety of the Food Chain or the Scientific Institute of Public Health in Belgium, and to policy makers.

The role of research in public health is to promote, protect and improve population health through evidence for policy making and clinical guidelines. However there is a gap between research results and the use of evidence in clinical practice and policy making. The Knowledge Transfer and Exchange (KTE) strategy is an interactive process which can be used to fill this gap [223]. KTE involves the interchange of knowledge between research users and researcher producers through a set of activities. Different KTE models depending on the field of activities. For maximizing the impact of research output, some controllable factors have to considered. First would be the *accessibility*. Indeed, a lot of studies highlighted the importance of presenting results in an accessible and understandable way [224–226]. Murphy et al. also noted that peer reviewed journals were not necessarily the best way to reach authorities [227]. We published some results of this thesis in non-peer-reviewed literature and gave two interviews to media. We also presented some of our findings directlty to the Federal Agency for the Safety of the Food Chain. We recommend to increase this type of activities for future researches. Second, some authors also noted the importance of *the relationship between the stakeholders in the KTE strategy*. Indeed, it seems essential to involve the research users at the very beginning of the research to increase the engagement in the research and the chance that results would be used by authorities [224, 225]. In our case, this involvement could have been made through a collaboration with the Belgian Scientific Institute of Public Health for elaborating the burden of foodborne diseases. In this respect, two days of courses were conducted during which we introduced the DALY metric and present some burden estimates. Finally, incorporating scientific evidence in the policy cycle is especially difficult in Belgium with its complex decision making process. We must acknowledge that incorporating scientific evidence in the policy cycle in a complicated task. Even if we presented our results directly to the concerned agencies, our findings would not necessarily

[1] http://www.foodsafetymagazine.com/magazine-archive1/junejuly-2013/the-burden-of-listeriosis,
http://www.foodqualitynews.com/R-D/Urgent-efforts-needed-to-fill-Listeria-data-gap-in-developing-countries-WHO-study,
http://www.foodsafetynews.com/2014/10/study-measures-global-burden-of-listeria/,
https://foodpoisoningbulletin.com/2014/who-study-evaluates-global-listeria-burden/,
http://blog.neogen.com/first-ever-global-listeria-report-release/,
http://www.foodonline.com/doc/who-releases-first-of-its-kind-global-listeria-report-0001,
http://barfblog.com/2014/09/listeria-still-isnt-nice-to-pregnant-women-and-others/

have been translated into policy.

Capacity building (CB), i.e. enhancing the abilities of individuals, organizations and systems to undertake and disseminate high quality research efficiently and effectively, is also an important driver of policy transfer. At an individual level, evidence on FBD burden can be improved by involving the development of researchers and teams via training, to design and undertake research, write up and publish research. At organizational and institutional levels, data can be improved by developing the capacity of research departments in universities and by addressing the political and the regulatory context and the resource base in which research is undertaken and used by policy makers [228].

Finally, the complexity of the Summary Measures of Population Health and particularly of the DALYs, can make them less intuitive for policy makers. Indeed, different methodologies exist for generating DALYs and for presenting DALY estimates. In addition to the complexity of the metric, DALYs give only a part of the information useful for health prioritization. Economic impact as well as availability of effective control measures are also important inputs for policy makers. In reality, decisions have to be made in absence of such evidence, or may be influenced by personal interests of decision makers and stakeholders. Despite this possible lack of a link between political decisions and findings based on DALYs, burden of disease estimates are crucial to promote population health and must continue to be further developed.

9.3 Conclusions and recommendations

9.3.1 Concluding remarks

The first objective of this thesis was to contribute to assessing the burden of foodborne diseases in the world and in Belgium. We estimated that listeriosis resulted in hundreds of thousands DALYs globally. These estimations were included in the first WHO estimations of the global burden of foodborne diseases which ranked listeriosis as the seventh most important disease in terms of DALYs per case, coming after fascioliasis. We also highlighted the lack of data on the incidence of listeriosis for half of the world and lack of evidence on proportions of health outcomes and duration of health outcomes caused by listeriosis. We also estimated that listeriosis and salmonellosis cases will remain stable but that campylobacteriosis cases will increase in the following years in Belgium. The second objective of this thesis was to investigate methods to improve burden of bacterial FBD estimates. We showed that most of the listeriosis cases had comorbidities and risk factors that have to be taken into account in future burden of listeriosis estimates. We

also observed that most of the patients with listeriosis still suffered of their neurological sequela, one year after hospital discharge. Next, we assessed disability weights for more than 250 health states based on a European population and these were used for the elaboration of new DWs in the GBD 2013 study. We also concluded that country and income levels may have an impact on health valuation and therefore have to be taken into account in the selection of study populations of future studies aiming to assess DWs. We finally concluded that the mapping approach is an easy valuation technique to derive DWs but that additional research is needed to better implement the technique. This work may in this sense be a starting point for future studies on the burden of FBDs.

9.3.2 Recommendations

This work identified the following avenues for future research:

Objective 1: to contribute to assessing the burden of bacterial foodborne disease in the world and in Belgium.

- **Estimation of the incidence of listeriosis in AFR, EMR and SEAR WHO regions.** In line with **Chapter 3**, we are encouraging AFR, EMR and SEAR WHO regions and countries within these regions to implement epidemiological assessment of listeriosis. Although epidemiological data collected using a representative sample of the population is the gold standard, data collected through clinical series could already attest to the presence of listeriosis in the country and be a starting point for more extended efforts.

- **Underestimation of foodborne diseases in Belgium.** In line with **Chapter 4**, we recommend to develop multiplication factors to estimate the true incidence of FBDs in Belgium. A community-based study may be appropriate in this context, because such a study will be based directly on Belgian data and so would better represent reality.

- **Burden of foodborne diseases in Belgium.** In line with **Chapter 4**, we believe that future studies to calculate the burden of norovirus and *Toxoplasma gondii* in Belgium may be useful to assist policy makers. Calculating the burden of listeriosis, salmonellosis and campylobacteriosis in Belgium in the next few years may be appropriate as well. The Belgian Scientific Institute of Public Health may want to strengthen the national surveillance of *Campylobacter* spp. cases and put back listeriosis as a notifiable disease.

Objective 2: To investigate methods to improve burden of bacterial FBD estimates.

- **Prospective national study on invasive listeriosis.** As it is the case in France, we recommend to implement a prospective observational Belgian study for listeriosis. This implies a strong collaboration between the Belgian hospitals and the Belgian Scientific Institute of Public Health but would generate useful information on risk and prognostic factors linked with listeriosis, evaluate the long-term outcome of listeriosis, and study the impact of sepsis and central nervous system infection linked with perinatal listeriosis in the development of children.
- **Understanding the effect of population characteristics on health valuation.** There is a need for additional studies to further explore differences of health valuation across participants characteristics, also in Non-European countries. Other characteristics also have to be explored such as national health care system or religion.
- **Mapping EQ-5D utilities to GBD 2010 and GBD 2013 disability weights**. We recommend to replicate the study we performed in **Chapter 8** but using a representative sample of the Belgian population and a face-to-face questionnaire.

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Summary

Chapter 1 provided the background for this thesis.

Foodborne diseases are diseases transmitted through the consumption of contaminated food, including a broad group of illnesses caused by viral, parasitic, chemical and bacterial agents. Gastroenteritis is the most common consequence of FBDs and can lead to mild symptoms which don't require medical treatment. In at risk people, FBDs can however produce more severe complications leading to life-long sequelae and even death. *Salmonella* spp. and *Campylobacter* spp. are among the most common bacteria to cause FBDs and *Listeria monocytogenes*, through infrequent, is often severe and has a high case-fatality ratio.

To promote and protect population health, public health policy needs to informed through evidence on the health status of the population. The impact of a disease on population health is often referred as the "burden of disease". The disease burden can be described by a variety of indicators, public health being a multifactorial phenomenon with many facets and different ways to measure it. Given the importance of combining morbidity and mortality, the last decades have seen important methodological advances in so-called "Summary Measures of Population Health" (SMPH). SMPH were further developed in the 1980s and included health measures such as Disability-Adjusted-Life Years (DALY). In this thesis we used the DALY metric because it has been developed as the indicator of choice for the Global Burden of Disease (GBD) project in the early 1990s. The DALY measures the burden of a disease, i.e. it aggregates the total health loss at the population level into a single metric by summarizing: 1) years lived with disability (YLD), and 2) years of life lost (YLL). YLD represents the healthy time lost with a disease and YLL represents the time lost through premature mortality. Disability Weights (DWs) are an important component of the YLDs because is meant to capture the severity of functional limitations in different domains of health.

FBDs are a growing public health concern because of developments such as rapid urbanization and the emergence of antibiotic resistance. Changing consumer habits and global warming further affect food safety risks. Since the Bovine Spongiform Encephalopathy crisis at the end of 1980s and the dioxin crisis in 1999, food safety became a priority in Europe. The European Food Safety Authority (EFSA) was set up as a source of scientific advice and communication on risks associated with the food chain and in Belgium the Belgian Sentinel Network Laboratories (SNL) and the Agency of the Safety of Food Chain (FASFC) were created to monitor trends in infectious diseases and to ensure maximum safety for the consumer. Despite these efforts, the number of cases of bacterial FBDs

remains high in Europe.

Chapter 2 introduced the rational and objectives of the thesis. The main objective of this thesis is two-fold: 1) To contribute to the assessment of the burden of bacterial foodborne diseases and, 2) To investigate methods to improve burden of bacterial foodborne disease estimates.

In Chapter 3, a part of the first objective was achieved by calculating the global burden of listeriosis through a systematic review and meta-analysis. We estimated that listeriosis resulted in hundreds of thousands of DALYs globally. These estimations were included in the first WHO estimations of the global burden of FBDs which ranked listeriosis as the seventh most important disease in terms of DALYs per case. We also highlighted the lack of data on the incidence of listeriosis for half of the world and the lack of evidence on proportions of health outcomes and duration of health outcomes caused by listeriosis.

In **Chapter 4**, we answered the first objective of the thesis by estimating and forecasting the burden of FBDs in Belgium through time series analysis techniques. We estimated that campylobacteriosis had a higher impact on Belgian population health than salmonellosis and listeriosis. We also indicated that listeriosis and campylobacteriosis cases would remain stable but that campylobacteriosis cases may increase in the following years in Belgium.

We then started completing the second objective of the thesis in **Chapter 5**. A clinical cases series to investigate comorbidities and risk factors linked with listeriosis and central nervous system (CNS) infection after listeriosis infection, indicated that antibiotic monotherapy and the presence of renal disease were "protecting" factors for CNS infections, and that severe cardiovascular disease was the main factor associated with death caused by listeriosis. We further observed that 22% of the patients died during hospitalisation, 45% had CNS infection and 38% of the patients had neurological sequelae at hospital discharge. Moreover 84% of the patients suffered from an underlying disease which may have to be taken into account in future burden of listeriosis estimates.

In **Chapter 6**, we assessed disability weights for 255 health states based on the responses of more than 30,000 European participants form the Netherlands, Hungary, Sweden and Italy. In this study, a methodology to evaluate health states was used similar to the one used in the GBD 2010 study, i.e. paired comparison method. We proposed DWs for 43 new health states, 171 original GBD 2010 health states, 34 modified GBD 2010 health states and 17 experimental health states. In 2015, Salomon et al. combined data from this study with data previously collected in the GBD 2010 study allowing the

assessment of DWs for 183 health states based on more than 60,000 answers.

In **Chapter 7**, we evaluated if participant characteristics had an impact on health valuation. We observed that health state valuations are highly correlated across country, sex, age, disease experience status, income and educational levels, but some variation in health states valuation across countries and within country between income levels was noticed. This means that country and income levels may have an impact on health state valuation and therefore on derived disability weights (DWs).

In **Chapter 8**, we proposed an alternative and simplier technique to derive DWs. We presented approaches for mapping EQ-5D utilities to existing GBD 2010 and GBD 2013 DWs, and for predicting new GDB 2010/2013 DWs based on EQ-5D utilities. We obtained satisfactory results when utilities were derived from a population of public health students, using a written version of the EQ-5D questionnaire, presenting a small number of health states and with the study leader being present to answer questions. The results were however unsatisfactory when utilities were derived from a sample of the general population and using a web-based questionnaire.

In **Chapter 9**, we placed our findings in a broader perspective, discussed their main limitations and presented avenues for future research.

Our work contributed to assessing the burden of bacterial foodborne disease in the world and in Belgium. However our results were limited by the data and knowledge gaps on listeriosis for about half of the world. We recognised that the time series models we developed for listeriosis, campylobacteriosis and salmonellosis in Belgium could be further improved by including relevant covariates. We also expressed concerns related to the possible underestimation of salmonellosis and campylobacteriosis cases in Belgium. Future research may have to develop multiplication factors allowing to better estimate the true incidence of FBDs in Belgium.

Methods to improve burden of bacterial FBD estimates were explore as well. The conclusions on comorbidities and factors associated with non-perinatal cases were limited by the non-representative and retrospective design of this study. We recommend to implement a prospective observational study for listeriosis as it is the case in France. The study to better understand the effects of populations characteristics was mainly limited by the nature of the paired comparison approach. Our conclusions have to interpreted with caution and we encourage future, additional studies to further explore differences of health valuation across participants characteristics. Finally the mapping function we proposed to translate any utility derived from EQ-5D scores into DWs was feasible but unsatisfactory when using a web-survey. We encourage future similar studies using a larger and

more diverse sample of the general population and using face-to-face interviews.

The ultimate aim of disease burden estimations is to inform decision makers on setting the right research and control priorities. Although results of this thesis have been picked up by the media, we do not know the impact of this work on decision makers. We strongly recommend to include Knowledge Transfer and Exchange and Capacity Building strategies in similar, future projects. We do believe that it is crucial to continue producing disease burden estimates because "*Nobody knows if anyone pays any attention*" (C.J.L. Murray).

Résumé

Le **Chapitre 1** est l'introduction cette thèse.

Les maladies d'origine alimentaire (MOA) sont des maladies transmises par le biais de la consommation d'aliments contaminés, comprenant un vaste groupe de maladies causées par des agents viraux, parasitaires, chimiques et bactériens. La gastroentérite est la conséquence la plus courante d'une intoxication alimentaire et peut mener à des symptômes bénins qui ne nécessitent pas de traitement médical. Chez les personnes à risque, les MOA peuvent engendrer des complications plus graves conduisant à des séquelles à vie, voire à la mort. Les bactéries *Salmonella* spp. et *Campylobacter* spp. sont les bactéries les plus courantes qui provoquent des MOA et la *Listeria monocytogenes* est peu fréquente mais est souvent sévère et a un taux de létalité élevé.

Pour promouvoir et protéger la santé de la population, les politiques ont besoin de preuves et de données sur l'état de santé de celle-ci. L'impact d'une maladie sur la santé de la population est souvent désigné comme le "*fardeau de la maladie*". Le fardeau de la maladie peut être décrit par une variété d'indicateurs, parce que la santé publique est un phénomène multifactorielle aux multiples facettes. Compte tenu de l'importance de combiner la morbidité et la mortalité liées aux maladies, les dernières décennies ont vu des avancées méthodologiques importantes dans le développement de ce qu'on appelle les "Summary measures of Population Health" (SMPH) ou "mesures synthétiques de la santé de la population". Les SMPH ont été développées dans les années 1980 et incluent des mesures de santé telles que les années de vie perdues en bonne santé (DALY). Dans cette thèse, nous avons utilisé le DALY parce qu'il a été conçu comme la mesure de choix pour le projet "Global Burden of Disease (GBD)" ou "Fardeau mondial de la maladie" de l'Organisation Mondiale de la Santé (OMS) dans le début des années 1990. Le DALY mesure le fardeau d'une maladie, c'est-à-dire qu'il regroupe la perte totale de santé à l'échelle de la population dans une mesure unique en résumant ; 1) les années vécues avec une incapacité (YLD) ou un handicap et 2) les années de vie perdues à cause d'un décès prématuré (YLL). Les YLDs représentent le temps perdu en bonne santé à cause d'une incapacité ou un handicap et les YLLs, le temps perdu en bonne santé à cause d'une mortalité prématurée. Les coefficients d'incapacité (DWs) sont une composante importante des YLDs car ils visent à capturer la sévérité des limitations fonctionnelles dans les différents domaines de la santé.

L'attention accordée aux MOA est croissante dans le domaine de la santé publique notamment à cause de l'urbanisation rapide ou de l'émergence des résistances aux antibiotiques. L'évolution des habitudes de consommation et le réchauffement climatique aug-

mentent également les risques pour la sécurité alimentaire. Depuis la crise de l'encéphalopathie spongiforme bovine à la fin des années 1980 et la crise de la dioxine en 1999, la sécurité alimentaire est devenue une priorité en Europe. L'autorité européenne de sécurité alimentaire (EFSA) a été mise en place comme une source de conseils scientifiques et de communication sur les risques liés à la chaîne alimentaire. En Belgique, un réseau sentinelle de laboratoires et l'agence de la sécurité de la chaîne alimentaire (AFSCA) ont été créés pour surveiller les tendances des maladies infectieuses et assurer une sécurité maximale pour le consommateur. Malgré cet effort, il y a encore de nombreux cas de MOA liées aux bactéries en Europe.

Le **Chapitre 2** introduit le rationnel et les objectifs de la thèse. Les deux objectifs principaux de cette thèse sont: 1) contribuer à évaluer le fardeau des maladies bactériennes d'origine alimentaires et, 2) investiguer les méthodes pour améliorer les estimations du fardeau des maladie bactériennes d'origine alimentaire.

Dans le **Chapitre 3**, nous avons commencer à répondre au premier objectif de cette thèse en calculant le fardeau mondiale de listériose à l'aide d'une revue systématique et d'une méta-analyse. Nous avons estimé que la listériose a causé des centaines de milliers de DALYs dans le monde en 2010. Ces estimations ont été inclues dans le rapport de l'OMS sur fardeau mondial des MOA et la listériose a été classée comme la septième maladie la plus importante en termes de DALY par cas. Nous avons également mis en évidence l'absence de données sur l'incidence de la listériose pour la moitié de la planète et l'absence de connaissances sur les proportions et les durées des séquelles liées à la listériose.

Dans **Chapitre 4**, nous avons terminé de répondre au premier objectif de cette thèse en estimant le fardeau des MOA en Belgique à l'aide d'analyses de séries temporelles. Nous avons estimé que la campylobactériose avait un impact plus important sur la santé de la population belge que la salmonellose et la listériose en 2012. Nous avons également estimé que les cas de listériose et campylobactériose resteront stables, mais que les cas de campylobactériose augmenteront dans les prochaines années en Belgique.

Nous avons ensuite commencé à répondre au deuxième objectif de cette thèse dans le **Chapitre 5**. Nous avons étudié une série de cas cliniques pour évaluer les comorbidités et les facteurs de risque liés au décès et aux infections du système nerveux central (CNS) en lien avec la listériose non-périnatale. Nous avons observé que le traitement antibiothique administré en monothérapie et la présence d'une maladie rénale étaient des facteurs "protecteurs" contre les infections du système nerveux central, et que les maladies cardiovasculaires graves étaient le principal facteur associé à la mort. Nous avons

également constaté que 22% des patients sont décédés au cours de l'hospitalisation, 45% avaient une infection du système nerveux central et 38% des patients avaient des séquelles neurologiques à la sortie de l'hôpital. Nous avons également constaté que 84% des patients souffraient d'une maladie sous-jacente qui devrait être prise en considération lors des futurs estimations du fardeau de la listériose.

Dans le **Chapitre 6**, nous avons évalué des poids d'incapacité (DWs) pour 255 états de santé à partir des réponses de plus de 30,000 participants venant des Pays-Bas, de Hongrie, de Suède et d'Italie. Dans cette étude, nous avons utilisé une méthodologie similaire à celle de l'étude GBD 2010 pour évaluer les états de santé, c'est-à-dire la méthode de comparaison appariée. Nous avons proposé des DWs pour 43 nouveaux états de santé, pour 171 états de santé dont la description était identique à celle l'étude GBD 2010, pour 34 états de santé avec une description modifiée et finalement pour 17 états de santé expérimentaux. En 2015, Salomon et col. ont combiné les données de cette étude avec les données précédemment recueillies dans l'étude de GBD 2010 permettant l'évaluation de 183 DWs basés sur plus 60,000 réponses.

Dans le **Chapitre 7**, nous avons évalué si les caractéristiques des participants avaient un impact sur l'évaluation des états de santé. Nous avons observé que l'évaluation des états de santé était fortement corrélée entre les pays, les sexes, les groupes d'âge, le statut d'expérience de la maladie, les niveaux de revenu et d'enseignement. Nous avons cependant observé certaines variations dans l'évaluation des états de santé entre les pays et dans les pays entre niveaux de revenu. Cela signifie que le niveau de revenu et l'origine pourraient avoir un impact sur l'évaluation des état de santé et par conséquent sur les coefficients d'incapacité (DWs). D'autres études visant à évaluer l'impact des caractéristiques des participants sur les DWs devraient être mises en place, également pour étudier l'impact d'autres caractéristiques et d'autres nationalités.

Dans le **Chapitre 8**, nous avons proposé une technique alternative et plus facile pour dériver des DWs. Nous avons présenté une approche pour cartographier des utilités EQ-5D existants en poids d'incapacité GBD 2010 et GBD 2013. Nous avons obtenu des résultats satisfaisants avec cette méthodologie quand les coefficients d'utilités provennaient d'une population d'étudiants en santé publique, à l'aide d'une version écrite du questionnaire EQ-5D, présentant un petit nombre d'états de santé à évaluer et avec le responsable de l'étude étant présent pour répondre aux questions. Les résultats n'étaient toutefois pas satisfaisants quand les coefficients d'utilité étaient tirés d'un échantillon de la population générale, à l'aide d'un questionnaire en ligne.

Dans le **Chapitre 9**, enfin, nous avons placé nos conclusions en perspective, et avons

discuté de leurs principales limites ainsi que des pistes de recherche pour le futur.

Notre travail a contribué à l'évaluation du fardeau des maladies bactériennes d'origine alimentaire dans le monde et en Belgique. Cependant, nos résultats étaient limités par le manque de données d'incidence de la listériose pour environ la moitié de la planète. Nous avons également reconnu que nos modèles de séries temporelles développés pour la listériose, la campylobactériose et la salmonellose en Belgique pourraient être améliorés en incluant certaines covariables. Nous avons également fait face à une importante question de sous-estimation des cas de salmonellose et de campylobactériose en Belgique et les recherches futures devraient élaborer de nouveaux facteurs de multiplication pour estimer l'incidence réelle des MOA en Belgique.

Notre travail a aussi étudié des méthodes pour améliorer l'évaluation du fardeau des maladies bactériennes d'origine alimentaire. Nos conclusions sur les comorbidités et les facteurs associés à la listériose non-perinatal étaient limitées par le design non représentatif et rétrospective de notre étude. Nous recommandons de mettre en oeuvre une étude observationnelle prospective pour la listériose, comme c'est le cas en France avec l'étude Monalisa. Notre étude visant à mieux comprendre l'effet des caractéristiques de la populations sur les poids d'incapacité a été principalement limitée par la nature de l'approche de la valorisation des états de santé par comparaison appariée. Nos conclusions sont donc à interpréter avec prudence et nous encourageons des études supplémentaires afin de mieux étudier les différences d'évaluation de la santé en fonction des caractéristiques des participants. Enfin, la fonction de cartographie que nous avons proposé afin de traduire n'importe quel coefficient d'utilité EQ-5D en un DW était possible mais insatisfaisante lorsque nous utilisions une enquête en ligne. Nous encourageons les futures recherches à reproduire cette étude à l'aide d'une échantillon plus grand et plus diversifié de la population général et à l'aide d'un questionnaire en face-à-face.

Le but ultime de l'estimation du fardeau des maladies est d'informer les décideurs politiques qui définissent les priorités de recherche et de contrôle. Bien que les résultats de cette thèse ont été repris par certains médias et blogueurs, nous ne connaissons pas l'impact réel de ce travail sur les décideurs politiques. Nous recommandons fortement d'inclure des stratégies de transfert des connaissances et d'échange et de renforcement des capacités dans des futurs projets. Nous pensons qu'il est crucial de continuer d'estimer le fardeau des maladies car "*Nobody knows if anyone pays any attention*" (C.J.L. Murray).

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