

University of Bielefeld  
Faculty of Health Sciences – School of Public Health  
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**The Burden of Disease framework –  
success story but necessities for adaptations**

*Potentials and challenges when measuring the disease burden of infectious diseases  
and the disease burden at a sub-national level*

**Dissertation Thesis**

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## **Publications forming the basis of the thesis**

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McDonald SA, van Lier A, Plass D, Kretzschmar ME (2012) The impact of demographic change on the estimated future burden of infectious diseases: examples from hepatitis B and seasonal influenza in the Netherlands. BMC Public Health. Vol. 12 (1) 1046. (*Impact Factor 2012: 2.08*)

Plass D, Chau PYK, Thach TQ, Jahn HJ, Lai PC, Wong CM, Kraemer A (2013) Quantifying the burden of disease due to premature mortality in Hong Kong using Standard Expected Years of Life Lost. BMC Public Health. Vol. 13(1): 863. (*Impact Factor 2012: 2.08*)

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## **List of abbreviations**

BCoDE – Burden of Communicable Diseases in Europe

BoD – Burden of Disease

DALY – Disability-Adjusted Life Years

ECDC – European Centre for Disease Prevention and Control

EEA – European Economic Area

EFTA – European Free Trade Association

EU – European Union

GBD – Global Burden of Disease

HE – Health Expectancy

HG – Health Gap

HIV – Human Immunodeficiency Virus

HRQoL – Health-Related Quality of Life

ICD – International Classification of Diseases

MF – Multiplication Factor

NCD – Non-Communicable Diseases

NRW – North Rhine-Westphalia

PYLL – Potential Years of Life Lost

RLE – Remaining Life Expectancy

SAR – Special Administrative Region

SARS – Severe Acute Respiratory Syndrome

SEYLL – Standard Expected Years of Life Lost

SMPH – Summary Measures of Population Health

UI – Uncertainty Interval

WHO – World Health Organization

YLD – Years Lived with Disability

YLL – Years of Life Lost

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## **Summary**

### **Background and research objectives**

Demographic and epidemiologic transitions have resulted in important shifts in population health patterns all over the world. The most advanced stages of these transitions can be found in high-income countries. Disease patterns have shifted from frequently fatal infectious short-course diseases to chronic conditions associated with sometimes lifelong disabilities. These changes in population health patterns have led to the need for new indicators that are able to comprehensively quantify the impact of disease conditions on health. Summary measures of population health capture the overall impact of diseases by combining the effects of mortality and morbidity into a single indicator. Many summary measures exist, but there is one outstanding measure that is increasingly used throughout the world. Introduced in the first Global Burden of Disease study, the disability-adjusted life year (DALY) measure was used to quantify the burden of disease at global, regional, and national levels. Burden of disease analyses are increasingly performed to present the health of populations and to identify the major drivers of ill health, as well as the determinants that cause these decrements of health. Population health measures can also foster debate about priority-setting in the health-care sector and for health research. Despite the success of the burden of disease approach, there are still some substantial requirements, on the one hand, for adjustments of the DALY to better reflect the characteristics of infectious conditions and, on the other hand, for sub-national estimates of disease burden. This thesis takes up these two major objectives and introduces an appropriate methodology to measure the disease burden of infectious conditions, and also presents sub-national burden of disease estimates.

### **Methodological concepts**

To meet the first objective of the thesis, the basic DALY methodology was tailored to reflect the characteristics of infectious diseases. Therefore, the perspective was changed from the disease endpoint to the pathogen perspective. Acute disease courses and future short- and long-term sequelae were accommodated by use of an outcome tree representing the natural history of an infectious disease. Incidence data, obtained from national surveillance systems and corrected for underestimation were used as the main input to the natural history models. In addition to the calculation of the current disease burden for hepatitis B virus, influenza virus, measles virus and *salmonella spp.* in Germany, projections of future burden were performed for the Netherlands, mainly focusing on the effects of population ageing and growth, as well as on the impact of intervention measures.

To meet the second objective of the thesis, SEYLL as a standardized measure of disease burden due to premature mortality was used to estimate the years of healthy life lost at sub-national level for Hong Kong, SAR (China) and North Rhine-Westphalia (Germany). The focus was on testing the feasibility of using the SEYLL measure and identifying its potentials at a sub-national level. A further aim was to highlight the impact of social value choices on the SEYLL estimates.

## Results

Introducing the incidence- and pathogen-based DALY approach, the highest disease burden in Germany (2005–2007) was estimated for infections with influenza virus (33,116 (95% UI: 29,504–36,849) DALYs/year), followed by *salmonella spp.* (19,115 (95% UI: 14,803–24,328) DALYs/year), hepatitis B virus (8,708 (95% UI: 7,335–10,163) DALYs/year) and measles virus (740 (95% UI: 413–1,066) DALYs/year). Infections with hepatitis B virus and *salmonella spp.* showed the highest burden related to sequelae with 98% and 56.6% of the overall burden, respectively. Predicting the disease burden from 2000 to 2030 in the Netherlands showed increases of disease burden from 1,196 (95% UI: 1,003–1328) DALYs to 1,343 (95% UI: 1,194–1,493) DALYs for infections with hepatitis B and from 22,712 (95% UI 21,132–24,290) DALYs to 51,609 (48,212–55,198) DALYs for infections with influenza virus. The greatest reductions in the future disease burden due to hepatitis B infections were calculated for the scenario simulating the uptake of vaccination in all age groups (resulting in a per year decrease of incidence of 2%) with reductions in DALYs of 32% (compared to baseline). For influenza, the greatest reductions were simulated in the scenario with more effective age-targeted vaccination (resulting in a decrease of incidence of 5%) with reductions in DALYs of 45% (compared to baseline).

Using the SEYLL as a measure of premature mortality at sub-national level resulted in 1.75 million SEYLLs in North Rhine-Westphalia in 2005 and 524,707 SEYLLs in Hong Kong in 2010. Non-communicable diseases accounted for the highest shares of SEYLLs, with 89.1% in North Rhine-Westphalia and 78.8% in Hong Kong. In comparison to prioritization by standard death counts, both studies highlighted self-inflicted injuries for males rising in priority from 13<sup>th</sup> to 8<sup>th</sup> rank in North Rhine-Westphalia and from 9<sup>th</sup> to 6<sup>th</sup> rank in Hong Kong, when using SEYLL as a measure of premature death. Scenario analysis identified that using different assumptions about social value choices decreased the SEYLLs by up to 51.6% (scenario I) and had a selective impact on the different disease groupings. Changing the standard life expectancy values to the ones observed in Hong Kong, the disease burden increased by 10.8%.

## Conclusions

The results of the thesis showed that going beyond the one-size-fits-all solution as used in the global burden of disease study and drilling down estimates to a sub-national level can provide sound additional information on population health patterns. The use of the incidence- and pathogen-based DALY approach highlighted sequelae of infections with hepatitis B and *salmonella spp.* in particular as an important component of the overall disease burden. Furthermore, the approach also revealed the importance of including asymptomatic hepatitis B infections, because not considering these would have resulted in an underestimation of the disease burden by 80.1%. This is of major importance when prevention measures aim at avoiding the initial infection. In addition, the results of the thesis highlighted that this approach can also be used to predict future disease burden by including the impact of population and disease dynamics. The results presented in the thesis further fill existing data gaps for sub-national burden of disease estimates and introduce the SEYLL as a suitable measure for such assessments. The studies also demonstrated the advantage of using the SEYLL measure over standard measures of mortality, because considering age at death and estimating the loss of healthy years has considerable impact on disease priorities. Comparing the shares of group one and group two conditions highlights that the epidemiologic and demographic transitions in North Rhine-Westphalia were already far more advanced in 2005 than they were in Hong Kong in 2010.

Overall the thesis showed that the DALY and its components can serve as powerful indicators of population health, but there is a need to adjust the measures for specific settings. Furthermore, the thesis also emphasized the critical need for transparency when using the burden of disease approach and population health measures. Finally, it also accentuates the importance of increasing the quality of epidemiological estimates, because in the end summary measures are only as good as the epidemiological input data.

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## **1. Introduction**

During the last two decades, health-care demands and costs have increased dramatically but public spending on health care has remained restricted, making budget constraints and health-care cuts inevitable. As a result, due to the observed global financial downturn, economic and political areas, as well as research, face an increasing demand for reasonable prioritization approaches to allocate the scarce resources. Prioritization processes, especially in health policy-making, are very complex and require not only financial but also ethical, legal and many other aspects to be taken into account [1-4]. Setting priorities in the health sector always involves trading off different diseases, risks and their impacts on health against each other, allowing us to decide where the spending of resources might result in the highest pay-offs in terms of health benefits. These can be considered as pay-offs for individuals, increasing their health status, or for a whole population, resulting in health benefits for a group of people, a geographical area or country. Taking the population perspective, it is of great value to identify the health status and related health/disease patterns of populations along with the major drivers of ill health [2]. Traditionally, the health status of populations was measured by classical (aggregated) epidemiological surrogate parameters such as overall or cause-specific mortality, mortality of children aged less than five years (under-5-child-mortality) or derivative measures such as life expectancy that are based on mortality trends observed in the past [2, 5]. The effects of diseases on health, however, go far beyond death and include a wide range of impacts. In the era of emerging trends observed as demographic and epidemiologic transitions, it became evident that indicators of mortality are of limited use in many settings because they miss important information which is necessary in order to make a comprehensive and informed choice [5].

During the phase of epidemiologic transition, the disease patterns (e.g. in a country or region) are shifting from infectious, frequently fatal conditions (e.g. diarrheal diseases or respiratory tract infections) to chronic, primarily non-fatal conditions (e.g. diabetes, cardiovascular diseases or neuropsychiatric disorders) that may often last for decades and incur substantial health expenditure [6-8]. In addition, it became evident, that many people do not suffer from only a single disease but have many co-morbidities, making assessments of population health and predictions about disease progression difficult [6, 9]. The demographic change is characterized by a change from high to low fertility- and mortality rates and increased life expectancy. These changes result in transformations of the population structure, with an increasing proportion of elderly and decreasing proportions of young segments [10, 11]. Both transition concepts have resulted in remarkable changes in health/disease patterns, especially

in developed, high-income countries, and have required the introduction of adequate health indicators that are able to capture the mortality, as well as the morbidity effects of diseases and injuries [12]. Despite the remarkable shifts in health patterns of high-income countries towards chronic conditions, infectious diseases still play an important role as new infections are emerging, old infections are reemerging and links between infectious agents and chronic conditions are becoming evident [13-16]. All these different processes pose a demand for population health measures that are sensitive to the different characteristics of diseases and allow a comprehensive and comparable view of health patterns.

The increasing importance of diseases that do not primarily lead to death but impact on quality of life has highlighted the need for measures that are able to cover the different dimensions of population health [2]. To accommodate diseases with different characteristics, summary measures of population health (SMPH) were developed to comprehensively measure the impact of different health-reducing conditions. Summary measures have a long history [17], and many types have been developed and used over the last decades [2, 18, 19], but one of the most prominent and frequently used measures is the Disability-Adjusted Life Years (DALY), a measure of lost healthy years that was introduced during the late 1980s [20-22]. The DALYs are used in burden of disease (BoD) studies and quantify the health status of populations. Estimating the disease burden in a population is of major importance in identifying the key drivers that contribute most to the loss of health. BoD analyses allow a comprehensive, comparable and internally consistent assessment of population health. By giving researches the opportunity to compare heterogeneous conditions, analyses of the disease burden can provide effective and evidence-based supplementary information for priority-setting purposes in the health sector. In contrast to classical health monitoring indicators, such as incidence, prevalence and mortality, BoD analyses rely on the combination of epidemiological information into one single metric. The quantification of health losses into a single, standardized measurement unit has the advantages that: a) the different characteristics of heterogeneous conditions can be comprehensively taken into account and b) ad hoc comparisons between conditions and countries and over time are possible.

The development of the BoD methodology and the dissemination of the results were mainly driven by the Global Burden of Disease (GBD) studies firstly initiated by the World Health Organization (WHO) in cooperation with the World Bank and the Harvard School of Public Health [20, 23]. Despite the tremendous benefits of the GBD estimates, the methods employed in the studies have received considerable criticism from the scientific community [24-27]. Much of the criticism was related to methodological choices and inputs (e.g. time-

discounting, age-weighting or disability weights) for the calculation of the DALY. However, the quality of the epidemiological input data that form the backbone of the DALY was not much of an issue. Furthermore, in line with the aim of the GBD study, to provide global estimates, the results are limited to the country level. However, having an average (mean) loss of healthy life years for a whole country might be misleading due to existing regional, social or cultural health inequalities. In addition, it is also questionable whether the one-size-fits-all methodological solution is fully appropriate for widely diverse conditions (e.g. communicable diseases, non-communicable conditions and injuries) and whether approaches more tailored towards the specific characteristics of diseases might result in more accurate estimates.

This dissertation takes up two relevant challenges and focuses on: a) the adjustment of the BoD methodology to meet the characteristics of infectious diseases and b) the application of BoD analyses at a sub-national level.

The thesis first provides an overview of the theoretical frameworks of population health and BoD and focuses on key methodological concepts of the BoD methodology, highlighting SMPH and the DALY as the core metric. This part of the dissertation will elucidate potentials and methodological limitations, as well as shortcomings regarding the limited regional differentiation of the currently available BoD estimates and the need for adjustments when estimating the disease burden of infectious pathogens. The subsequent sections will provide the methodological specifications of the approaches used in the analyses, introducing the methods developed for the Burden of Communicable Diseases in Europe (BCoDE) Project and the Standard Expected Years of Life Lost (SEYLL) as a standardized measure of premature mortality. The application of these concepts will be illustrated by BoD studies in Germany (BCoDE), and SEYLL studies in Hong Kong and North Rhine-Westphalia (NRW). The results of the studies and the related implications for the further development of the BoD framework will be elaborated and discussed in the final chapters of the thesis.

The six publications relevant to the dissertation are the following:

- “The Pathogen- and Incidence-Based DALY Approach: An Appropriate Methodology for Estimating the Burden of Infectious Diseases” – an article describing the methodological specifications of the BCoDE Project (published in PLOS ONE) [28].
- “Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods.” – an article investigating the methods that are currently used to quantify underestimation in infectious disease surveillance data (published in BMC Public Health) [29].
- “The disease burden of hepatitis B, influenza, measles and salmonellosis in Germany: first results of the Burden of Communicable Diseases in Europe Study” – an article presenting an application of the developed methodology in Germany (published in Epidemiology and Infection) [30].

- “The impact of demographic change on the estimated future burden of infectious diseases: examples from hepatitis B and seasonal influenza in the Netherlands” – an article focusing on a further extension of the BCoDE methodology (published in BMC Public Health) [31].
- “Measuring the burden of disease due to premature mortality using Standard Expected Years of Life Lost (SEYLL) in North Rhine-Westphalia, a Federal State of Germany, in 2005” – an article focusing on a sub-national BoD analysis in Germany (published in Journal of Public Health) [32].
- “Quantifying the burden of disease due to premature mortality in Hong Kong using standard expected years of life lost” – an article investigating the feasibility of applying standardized BoD measures at a sub-national level and the effects of social value choices on estimates of disease burden (published in BMC Public Health) [33].

## **2. Theoretical constructs of population health and burden of disease**

The description of diseases and their impact on health has a long history and in general there are two distinctly different perspectives to be taken when health and disease are the focus of investigations. Traditionally when considering the impact of diseases and injuries on human health, the first perspective is the individual one, where the aim is to detect, diagnose and treat a disease and if possible heal a single individual of his individual disease-specific symptoms. Since the early efforts of John Snow, the first epidemiologist, who investigated a cholera outbreak in London, another important perspective has also been highlighted [34]. Focusing on the health situation of a group of individuals and how a single disease or set of diseases are distributed among different population groups taking the population perspective is a necessary step [35]. Describing the health of a population not only allows researchers to present the health status of this population but also to identify the key drivers contributing to ill health [36]. Population based health information is necessary to identify the determinants that incur a substantial disease burden and influence health patterns [12, 37, 38]. This information can be used in a descriptive manner to monitor trends and developments of diseases in a population but also in an analytical manner, by which health determinants and their contribution to population health can be analyzed [39]. Population health is a relatively new terminology and a final definition is not yet fully agreed upon [40]. However, Kindig stated that population health describes “the health outcomes of a group of individuals, including the distribution of such outcomes within the group” ([37] p. 381). Figure 1 presents the framework of population health and identifies three major branches and their interactions that are of interest for population health – 1) health outcomes and their distribution in a population, 2) patterns of health determinants over the life-course and 3) policies and interventions at the individual and social levels that influence health determinants and the processes by which these factors impact on health [37]. Kindig and Stoddart refer to Dunn and Hayes who describe population

health as the health status of a defined population, “[...] as measured by health status indicators and as influenced by social, economic and physical environments, personal health practices, individual capacity and coping skills, human biology, early childhood development, and health services” ([41] p. S7). Population health can be described as an umbrella concept encompassing a wide range of health aspects including health determinants, and thus can provide a broader view and more integrated concepts [40]. Public health, in its narrow definition, has evolved into a very specific field of research with many specialized areas, which can be broken down into many different sub-disciplines, covered by different organizational institutions with different responsibilities in a society [40]. All these sub-disciplines introduce specific measures to improve the health status of populations in different sectors of social life. To shed additional light on the joint effects of these measures, population health as a discipline aims to combine the evidence from different fields of health research to provide a full overview of overall health patterns and the effects of intervention and prevention options on a certain population [37].

Using the population health perspective allows researchers to identify critical aspects of the health situation of a population and thus enables decision-makers to include this important information when allocating scarce resources in the health sector. Decisions about resources are inevitable and the rationale for these decisions is not always based on scientific evidence; in the worst case, it can be guided by political issues or the gut feelings of experts. To avoid biased decisions, it is important to reach decisions from transparent information. Many efforts have been made in the field of evidence based public health to increase the use of scientific evidence to inform political decisions [42, 43]. Solid information about the health status of a population presented in a comprehensive and communicable way is one of the factors often lacking when priority-setting processes are taking place. These processes can be guided by various epidemiological indicators of population health. When describing the effects of disease and injuries, these indicators allow a simplified distinction between two effects – morbidity and mortality.

Measuring the effects of mortality in general is more straightforward because mortality is a dichotomous measure of being alive or dead [44]. To capture mortality effects on population health, it is important to know how many people are dying overall (overall mortality) in a population in order to have the consistent death envelope and also to be able to identify the causes people are dying from (cause specific mortality).

Morbidity effects are far more complex and pose the need for a wide array of different indicators to capture the impact of non-fatal disease and injury conditions. They range from

data obtained from (ideally representative) community-based surveys to nationwide surveillance systems (e.g. mandatory infectious disease surveillance). From the population health perspective indicators of disease occurrence, such as incidence: the number of new cases in a population over a fixed time period, and prevalence: the number of current cases at a certain point in time (point-prevalence) or over a set time-frame (e.g. three-month prevalence), are frequently used measures of morbidity in a population. Information about disease frequency is important but limited because these indicators do not capture the severity of a condition and do not inform us about the level of health-related quality of life (HRQoL). This information is necessary, however, to allow comparisons of different disease outcomes. HRQoL can describe both subjective and objective judgments about the impact of health reducing-conditions on different dimensions of human health. Thus, in order to capture and quantify the effects of morbidity it is insufficient to only enumerate the number of incident or prevalent cases and including the impact of a condition on health is inevitable.

When prioritizing diseases with heterogeneous characteristics, regarding their impact on population health, focusing on only one of these two epidemiological indicators might result in misleading priorities because a condition might score high on the level of morbidity but low on the level of mortality. If this condition is then compared with another condition that scores low on both levels, and only the mortality indicator is considered, both conditions might get the same priority, even though the first condition scores higher on the morbidity level [2]. For instance, one can take the example of two conditions, namely depression and infertility. Depression scores high in morbidity and low in mortality. Infertility might score much lower than depression on the level of morbidity but, like depression, would not result in any deaths. Drawing comparisons from the mortality perspective would result in the same impact on health, but if morbidity were also considered, this would result in significant differences and probably a higher priority would be given to depression.

Comparing broad sets of conditions, such as communicable diseases, non-communicable conditions and injuries, thus poses the need for a framework that enables researchers to combine the available epidemiological information into a single measurement unit. Therefore, the BoD framework was developed for the first GBD study [20]. The GBD study accommodated a set of distinctly different disease and injury conditions and using single epidemiological indicators was therefore insufficient. The BoD framework introduced for the first time a standardized, conceptual and methodological concept for capturing the overall levels of population health and the causes of loss of health [45]. In addition to facilitating the comparison of various health-reducing conditions, this standardized framework also enabled

comparisons across countries and regions, and over time. Furthermore, as health data are not distributed equally across or within populations the BoD framework also provided a set of techniques to supplement missing data and to fill the existing data gaps [45]. If data are not available for a certain population group or health condition, it is often wrongly concluded that where there is no data there is accordingly also no burden. This is frequently wrong, because data for the most vulnerable populations is often lacking, making improvements in population health data a major imperative [12]. The BoD approach relies on measures of population health that, according to Parrish, can be subdivided into measures of a) mortality, life expectancy and premature death b) health function and subjective well-being c) the distribution of health in a population and d) summary measures of population health [46].

### **2.1. Summary measures of population health**

The demand for high-quality data in health care is increasing because health data can serve as a powerful instrument for different stakeholders in health care but also in other adjacent sectors [2, 12, 47, 48]. The increasing quantity and quality of health data has resulted in a massive overload of often complex indicators making informed decision-making a difficult task [2, 48].

The attempt to condense indicators of population health into one single measurement unit has a long history [17, 49-51] and many SMPHs have been developed and used to pursue various objectives and in many settings [18]. All summary measures have the common aim of presenting the health status of a population as one quantity, making heterogeneous conditions comparable. As disease patterns have changed over the last few decades, the development of SMPHs was a necessary step to accommodate conditions that cause non-fatal decrements in health but not mortality [2]. From the public health perspective, SMPHs present a powerful tool of descriptive epidemiology because they capture the health situation of a population and are able to identify key drivers of health decrements and conditions, thus increasing the potential for reductions in the disease burden. Where this information is available, measures of intervention and prevention that have an impact at the population level can be guided more thoroughly as compared to the use of uni-dimensional indicators. Furthermore, these quantifications of health status can lead to reasonable comparisons between different populations (e.g. countries) and help to evaluate health-system performance overall [52]. This enables the furthering of debate about the important questions of why health patterns differ between populations, to what extent health systems can be held responsible for these differences, and which prevention and intervention measures have led, and in future may lead, to the best pay-offs [2]. SMPH can also be a general indicator of the current stage of

development of a country and can also reflect innate societal and cultural differences. As a standardized measure of health SMPH further allows the monitoring of population health over time and, thus, the tracking of overall health trends or changes in health patterns after intervention measures. This retrospective view is of major importance as it identifies achievements, challenges and unfinished agendas in health research. A further benefit of using SMPH arises from the unequal distribution of health, not only between populations but especially within populations or population groups. SMPH can be used at different population levels (global, regional, national and sub-national) to help in identifying inequalities in population health and the possible reasons (e.g. risk factors, socio-economic determinants) for this unequal distribution [32, 53-56]. This might stimulate national and international debates, introducing normative aspects into SMPH. With the characteristics described, SMPH is a useful tool help in setting priorities, on the one hand, for resource allocation in terms of prevention, intervention and care, and on the other hand, in research and development.

Various types of SMPH exist and the number of newly developed indicators has been continuously increasing over the last few decades. From a general and technical point of view, SMPH can be broadly subdivided into two kinds of “families” – “health expectancies” (HEs) and “health gaps” (HGs). As indicated by their names, HEs measure positive quantities of health and HGs quantify decrements. Figure 2 describes the concepts of these families in a simplified framework of a hypothetical cohort and its survival [18]. The green line indicates the general survival of the hypothetical cohort along a time span of 100 years and enumerates the percentage of people in this cohort surviving at each age. Some of the people may die while they are completely healthy, e.g. due to a car accident, some may suffer a short-course infectious disease before death, and another segment of the population may suffer long-lasting chronic diseases before death. To tease these differences apart, in the first step the black curve indicates the proportion of people surviving at each age without any restrictions on their health (full or ideal health). The area/integral (A) under the optimal-health-survivor curve can be described as the life expectancy without any decrements of health. Area B presents the time lived in health states that are less than ideal. The sum of areas A and B represents the overall life expectancy. Area B can also be differentiated into areas describing a gradient of health status with a part of the area B (f (B)) still counting as healthy and another part counting as non-healthy years. Combining areas A and the “healthy” part of area B results in the number of healthy years expected to be lived by the hypothetical cohort (healthy life expectancy) [18]. In contrast, an HG measures the loss of health (healthy years) according to a selected norm. The normative health goal, as represented by the vertical line at age 100 in

Figure 2, can be an arbitrary limit to the length of life (100 years in the selected example) or any other chosen norm that can be selected according to the research objectives. This limit is then used to capture the difference between this normative health goal and the observed survival of the population. Therefore, area C represents the loss of health (healthy years) due to the effects of mortality.

As SMPH is intended to measure the full spectrum of disease impact on health, adding the part of area B that represents ill health ( $g(B)$ ) to area C allows us to include both the health losses due to time lived in a state of less than full health and time lost due to dying before having reached the normative health goal [18]. Even though the theoretical framework of SMPH describes HGs and HEs as complementary, there are two important aspects that need to be considered. SMPH in general can take an absolute, and thus age-dependent, or an age-independent form. HEs in general are independent of the age structure and do not allow an additive decomposition. HGs are often expressed as absolute values and are thus dependent on the age structure of the underlying population. In contrast to HEs, HGs enable additive decomposition. For instance, the lost years in different age groups within a population would add up to the envelope of overall lost years. For HE measures, adding up the life-expectancy values of the different age groups would not yield meaningful results [57]. Several variants of both health expectancy [58-62] and health gap [63] measures have been developed but there is one outstanding measure used in many BoD analyses – the disability-adjusted life year.

## **2.2. Disability-adjusted life years**

One of the most prominent members of the health-gap family is the DALY measure. The DALY was developed as the core indicator for the first GBD study [20, 22] and was subsequently used in ongoing updates of the GBD estimates [64-70], in national (e.g. [71-74]), and some sub-national BoD studies (e.g. [53, 56, 75]) and also in condition- and risk-specific assessments (e.g. [76-79]). The DALY as it was introduced in the first GBD study is an SMPH that captures the effects of both mortality and non-fatal health outcomes. In order for these effects to be combined, the unit to measure the disease burden was chosen to be time (years) and, as a health gap-measure, the loss of time. Because they use time as the common outcome currency, the DALY estimates have the advantage of being a comprehensible and illustrative way to describe population health.

“The DALY concept has the potential to revolutionize the way in which we measure the impact of disease, how we choose interventions, and how we track the success or failure of our intervention. [...]” ([80] p. 1705).

This quote describes the potential objectives of the DALY. It measures the impact of disease on population health, and the resulting priority rankings can guide resource-allocation processes towards reasonable intervention measures, which finally can also be evaluated by tracking the DALY through time. Despite its potential and benefits, the DALY has been subjected to a lot of criticism by scientific community. It was not argued that the DALY, as a construct, was inadequate to measure population health, but rather, the detailed assumptions and decisions that were agreed upon for the first GBD study were criticized [24-27]. There were four major points of criticism raised.

The first point was the standard life expectancy that set female life expectancy at 82.5 and male life expectancy at 80 years. The female life expectancy was based upon the highest observed value, which was at that time found in Japanese women [22]. The two and a half year difference between the life expectancies of women and men was not consistent with the truly observed gender gap, which is related both to biological differences and, to a large extent, to life-style-related factors, causing a lower life expectancy in men. It was argued that the gap chosen for the GBD study should only consider the biological differences between males and females and should not include life-style-related factors [22]. This artificial increase in male life expectancy might overestimate the disease burden of men and thus might result in misleading priorities [81]. Furthermore, it was also argued that using a global standard might be adequate for global assessments but, for national-based priority setting using a national or even sub-national life expectancy might be more appropriate.

The second and third points relate to the concepts of age-weighting and discounting, two approaches which allow different weighting of years: a) lived at different ages and b) in the future. Both concepts highlight the economic perspective and are optional social value choices that were included in the first GBD study but have been partly disregarded in many subsequent studies [22]. Age-weighting is a concept that gives different weights to years lived at different ages and thus refers to the concept of human capital and the theory of social roles [22]. Years lived in age groups of people with the most valuable roles for a society, such as persons of productive age, received higher weights than the remaining younger and older age groups. The concept of discounting relates to years lost in the future, which in general economic terms are discounted because the value of goods – as shown in population-based trials – is considered to be higher at present than in the future, indicating a discounting of future goods.

The fourth point is related to the quantification of the impact of non-fatal conditions on health. In the DALY measure, the severity of a condition is measured by disability weights

that describe the impact of diseases and injuries on health using a numerical value anchored on a scale from zero, representing full health, to one, a health state comparable to death. These disability weights form a bridge between mortality and non-fatal health outcomes. All conditions considered for the first GBD study were valued by a group of health professionals using the person trade-off technique [20]. The derived disability weights received a lot of criticism which, on the one hand, was guided by the argument that, when allocating public goods, the preferences of the public should be taken into account and, on the other hand, by the fact that a multi-dimensional construct such as health has been condensed to a uni-dimensional scale ranging from zero to one. Another aspect of criticism was that it was assumed that the weights assessed by a group of experts would count equally throughout the world without any country- or cultural-specific variation in the perception of disease severity or the impact of diseases and injuries on human health [82]. Despite these criticisms, the first set of disability weights as assessed for the first GBD study was subsequently used in several BoD studies due to reasons of comparability but also due to the fact that no other consistent, comprehensive and comparable set of weights was available until the update of the GBD study [82]. When calculating the DALY it is very important to provide a transparent overview of all the assumptions that were made because altering the social value choices might have a considerable impact on the priorities arising from the DALY estimates.

The DALY as introduced by the first GBD study is a composite health measure consisting of two sub-measures – the years of life lost due to premature mortality (YLL) and the years lived with disability (YLD). The technical basis for the calculation of the DALY is shown in Box 1. The DALY was used in many different variants and settings, but the GBD study, its updates and the complete revision of the GBD are the landmark studies promoting the use of SMPH, and especially the DALY, as the core measure of the GBD [20, 69, 70, 83].

### **3. Current state of burden of disease research**

Before the first GBD study [20, 23] no internally consistent set of data was available to describe the health status of the world's population. Estimates of overall deaths and cause-specific death rates were not consistent and summing all cause-specific death rates resulted in more deaths than were actually observed and counted. Thus, health data were highly fragmented and an ambiguous description based on cause-specific estimates resulted in skewed priorities. Therefore, the initiators of the GBD study placed major emphasis on constructing a framework that combined all the available epidemiological information and produced internally consistent estimates [20]. This is only possible if all the inconsistencies

between data sources are identified and resolved [84]. In their first GBD study, Murray and Lopez came up with an initial comparable view of the world's health status and for the first time information on diseases with heterogeneous characteristics was gathered together and conditions were presented in a priority ranking, identifying the major drivers of ill health. It was evident that the inclusion of the impact of non-fatal health outcomes meant that many conditions, such as major depressive disorders that primarily contribute to YLDs, would be left under-prioritized if e.g. the focus was set towards cause of death statistics, or mortality indicators in general. The first set of DALY estimates was presented for eight world regions [20] and subsequent updates introduced country-specific estimates. The GBD study also introduced a specific classification system which in general is related to the ICD system but is more instrumental for presenting the results of population health patterns<sup>1</sup>.

For the current update of the GBD study, conducted by the Institute for Health Metrics and Evaluation (IHME), the complete methodology and especially the data inputs were reconsidered and the new methodology was applied to estimate the global disease burden in 2010. In addition the new concepts were also applied for the full time period between 1990 and 2010 to generate a fully comparable time series of DALY estimates [70]. Furthermore, all estimates provided by the GBD 2010 study consider uncertainty, both in the available epidemiological data and stemming from the modeling procedures used. This increases the transparency and may help to identify conditions where uncertainty is high, indicating a rather low quality or quantity of available health data.

Even though the estimates of the GBD studies are of major importance in providing an overview of global health patterns, all the estimates presented are average values for a super-region, region or country. Since data quantity and quality, especially in high-income countries, are increasingly available in a higher spatial resolution it is a necessary step to drill down the assessments to small-scale analyses of the disease burden.

### **3.1. Sub-national burden of disease studies**

Research on health inequality has shown that health, and burden of disease as the equivalent, are not equally distributed either between or within countries [85]. This is strongly related to the determinants of health, which operate at different dimensions of human health (e.g.

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<sup>1</sup> All causes from the ICD classification system can be redistributed to the entities of the GBD classification. The GBD classification system is structured into several levels of detail. At the first and broadest level, conditions are split into group one, two and three conditions. Group one includes communicable diseases, and maternal, neonatal, and nutritional disorders. Group two encompasses non-communicable conditions and group three represents injuries. At the next level all conditions are split into by 21 main cause groups (e.g. malignant neoplasms or mental and behavioral disorders). The following levels show further details of single-disease conditions such as HIV/AIDS, liver cancer, or road traffic injuries. This classification system allows a very intuitive way of presenting health patterns.

physical or mental wellbeing) and also at different population levels (e.g. country, district or population groups that have common characteristics) [38]. Therefore, the estimates given by the GBD study can only provide a limited view of population health and its distribution among heterogeneous population sub-groups. A necessary step is to differentiate the overall disease burden estimates into smaller spatial levels or specific subpopulations (e.g. indigenous population [54]). With the assessment of disease burden at a sub-national level, priority-setting processes become more meaningful and intervention and prevention strategies can be tailored more carefully towards the identified needs. Few assessments have focused on the application of the disease burden at a sub-national level and more studies are generally needed [53, 56, 75, 86-89]. Overall, most studies have aimed to apply the burden of disease methods to small-scale analysis, e.g. at the level of a Swiss canton [75], boroughs in London [53] or for specific population groups, such as the employees of General Motors [88]. All these studies have in common that they use the mortality component, YLL, as the basis to estimate the DALY. Having mortality data at hand and being short of local estimates for morbidity surrogate parameters, the YLDs were estimated by using a YLL/YLD ratio from available national or regional estimates. For these studies, the YLL/YLD ratios from regions/countries were assumed to be akin to the ones observed locally. This might hold true for many conditions but can also lead to significant differences mainly related to potential regional differences in e.g. access to health care or socio-economic status. Depending on availability and quality, average YLL/YLD-ratios might under- or overestimate the disease burden due to YLD and thus have considerable impact on the estimated DALYs. Due to the lack of morbidity data, a few assessments have also focused on estimating single components of the DALY, namely the YLL, or more specifically SEYLL, which are a standardized measure of premature mortality [90-93]. Compared to data on morbidity, mortality data is collected more comprehensively and is available for smaller spatial units. SEYLL offer a distinct perspective on mortality patterns and are of value in identifying the drivers of premature death causing losses of healthy life years. Overall, sub-national estimates of the disease burden are widely lacking throughout the world. Even in high-income and data-rich countries, information on sub-national population health patterns is scarce. This thesis takes up the need for sub-national assessments of the disease burden in Germany and China and aims at reduce this research gap.

### **3.2. Burden of infectious diseases**

Estimates from the GBD studies clearly highlight that infectious diseases cause major decrements of population health in low-income countries [69, 70]. Conditions such as

HIV/AIDS, malaria, lower respiratory infections, and diarrheal diseases cause deaths and reductions to health and despite the ongoing efforts to fight those diseases, it still seems to be an unfinished agenda. Results from the GBD 2010 study showed that, even though successful intervention and prevention strategies led to a decrease in the disease burden from 1990 to 2010 of 45% for lower respiratory infections and 52% for diarrheal diseases, these two conditions are still the leading causes of DALYs in the developing world [94]. For HIV, the trends indicated an overall increase of 389% from 1990 to 2010 in developing countries; however, this masks the fact that rates have declined since about 2005 from 1,768 DALYs/100,000 to 1,474 DALYs/100,000 in 2010 [95]. The same holds true for malaria, where overall trends from 1990 to 2010 showed increases in the malaria burden of 18%, but a decreasing trend in rates since 2005 from 1,934 DALYs/100,000 to 1,476 DALYs/100,000 [95].

In developed countries, infectious diseases are considered to be under good control and from a population health perspective prevention and control measures for non-communicable chronic diseases (NCDs) currently receive higher priority. According to the GBD estimates for 2010, most of the DALYs in the developed world are due to NCDs, which have reached about 83% of the overall burden [95]. The low burden of infectious diseases can, however, be explained by previous investments in the improvement of hygiene standards and the development and introduction of highly effective treatment and preventive measures, such as vaccination. Many of those measures are operating at the population level and rigorous vaccination regimes have successfully reduced the disease burden due to many infectious conditions such as measles, whooping cough, and tetanus [94]. Despite the successful battle against many infectious diseases, observed especially in most Western European countries [96], newly emerging and re-emerging infectious diseases pose threats to the health of populations [97-100]. Pandemics such as that introduced by the severe acute respiratory syndrome (SARS) in 2002 [101] or the H1N1 pandemic influenza in 2009 [102] have hit even the developed world and caused a considerable disease burden, with 8,096 cases and 774 deaths for SARS and 94,512 cases and 429 deaths for H1N1 observed globally during the outbreaks [103, 104]. Such outbreaks are not predictable as they are associated with new or genetically mutated strains for which effective treatment options need to be sought to prevent further spread. In contrast to newly emerging infectious conditions, re-emerging diseases seemed to be under control or have even been largely eradicated from the European continent. Different societal changes however, have led, and probably will again lead, to the re-emergence of such conditions. Tuberculosis is an important example and presents as a major health problem in Eastern European and

former Soviet countries. During and after the breakdown of the Soviet Union, health-care services were not able to sustain successful treatment of tuberculosis patients. The incidence, and accordingly the burden, of tuberculosis and co-infections of tuberculosis with HIV are on the rise and not only pose a threat to the population of origin but might also have an impact on neighboring countries due to the effects of migration [105]. In particular, increasing rates of drug-resistant strains, due to inadequate treatment of tuberculosis patients, are a major threat to population health in the former Soviet countries [106]. Another important example of a re-emerging infectious disease is measles, where effective vaccination is available and the disease is fully preventable. Nevertheless, many European countries face outbreaks of measles mainly related to under-vaccinated pockets within the country. The reasons for the low vaccination coverage vary widely but in many cases can be related to anthroposophic or religious beliefs leading to measles outbreaks, as recently observed in the “bible-belt” of the Netherlands [107].

Despite well-established surveillance systems in most of the high-income countries situated in the European area, comprehensive and comparable estimates of the disease burden are lacking. Even though prioritization processes for infectious conditions are increasingly being introduced [108], there is a missing link to the priority-setting mechanisms used for non-infectious conditions. Burden of disease estimates as measured by the DALY are only provided by the GBD study and national estimates for the infectious disease burden are lacking or only give estimates for certain conditions, condition groups, years or a given outbreak of an infectious disease (e.g. chikungunya [76] pandemic influenza [77] or foodborne pathogens [109, 110]). For infectious diseases, it is generally of increased interest to have disease-burden estimates for specific pathogens. Such estimates, which are of particular importance from the public health perspective, are generally lacking, or only provide a fragmented view of the overall disease burden of infectious diseases. It has been identified that, especially for Germany, BoD estimates are generally lacking and that there is a need for pathogen-specific estimates. The pathogen-specific approach offers new perspectives for BoD research, especially for public-health interventions aimed at preventing new infections.

### **3.3. Research needs for methodological refinements and regional differentiation**

From the currently available estimates of disease burden, three major challenges were identified and these three aspects form the backbone of the research conducted for this dissertation.

The first point relates to the one-size-fits-all solution of the BoD approach as currently used for the GBD study and other assessments. As the aim of the GBD study was to accommodate a large set of heterogeneous disease and injury conditions and the objective was to generate a global overview, a common framework was developed. This forced compromises, which had a selective impact on the sensitivity of the framework to adequately capture specific aspects of diseases. Unique characteristics of particular diseases might not be considered adequately, resulting in skewed estimates and, consequently, in misguided priorities. When transferring the approach to specific settings, probable adjustments seem to be worthwhile and necessary, to increase the suitability of the methods used. Here, infectious diseases in particular, their dynamics and complicated natural histories, with acute illnesses and short- as well as long-term consequences resulting from the initial infection, deserve special attention. In particular, if the aim of the study is to set priorities within a group of conditions, such as infectious diseases, a framework can be tailored specifically towards the demands of this set of conditions, thus achieving more robust estimates. Current estimates of the infectious disease burden either do not include the full spectrum of infectious disease consequences and thus miss important sequelae when only focusing on the acute disease state, or use attributable (etiological) fractions of subsequent health states, making regular assessments time and resource consuming [111, 112]. Furthermore, as in the current GBD study, future sequelae, e.g. liver cancer due to hepatitis B, are included in the estimates but at the end are counted as part of the non-communicable disease burden. This is surely a matter of perspective, because from the perspective of current health-care needs it is important to know how many liver cirrhosis cases are currently prevalent, without paying particular attention to the initial cause of the disease. Taking the intervention perspective, and estimating the pay-offs of interventions such as vaccination against hepatitis B, it is important to consider all the consequences and fully acknowledge them as being part of the infectious disease burden, because successful prevention of an infection or preventing the further spread of a pathogen reduces the disease burden not only from the acute infection but also from the ultimate consequences related to it.

The second point is related to the fact that most estimates of disease burden are based on country-level epidemiological data and provide an average value for the whole country. This is important when comparing different countries from a broad perspective but, due to considerable health inequalities within countries, it is also necessary to provide estimates of disease burden at a sub-national level. These estimates can contribute to debates about local resource allocation and strengthen priority-setting processes by tailoring them to specific local

needs. Here it is of major importance to test the feasibility of the BoD approach, and especially SMPH and their components, for sub-national analyses with special focus on data availability and quality, and also to identify the strengths and weaknesses, as well as data demands, in order to investigate how well these measures of population health perform for sub-national purposes [2].

The third point elaborates on how public health can benefit from the two aspects described above. Taking the public health perspective and generating understanding of the value of population-based health indicators and how these can be used for the subsequent improvement of population health are the important aspects considered. Here especially the analytical application of the BoD approach will provide an additional benefit to the generally descriptive and cross-sectional analyses of the current burden. For public health projecting trends of population health development and the impacts of interventions is a helpful exercise to improve the preparedness of health systems for future threats, because at the moment updated projections are generally lacking or outdated [113, 114]. Population health measurements can provide sound additional information about the current and future impact of diseases on population health and can serve as the basis for further assessments such as economic analyses [109].

#### **4. Research program and objectives**

The research program for the dissertation is guided by two major streams, as indicated by the desiderata identified from the current state of research and the need to provide supplementary estimates of disease burden a) for infectious diseases and b) at a sub-national level. The research presented here covers both the aspects of methodological adaptation and application with the aim of providing sound supplementary aspects broadening the scope of current research in the field of BoD. The overarching aim is to shed light on how population health and measures of disease burden can stimulate debate about priority setting in public health to provide a sound evidence base to inform health policy decision-making processes.

The three major fields of research elucidated in Chapter Three will be covered by six articles published in peer-reviewed journals. Two of them will focus on the application of the burden of disease technique in sub-national BoD analyses, with major emphasis on using SEYLL. Four articles will focus primarily on the adjustment of the BoD methodology, and especially the DALY framework, towards infectious diseases and the application of the developed methodology from the perspective of descriptive epidemiology, as well as from the perspective of analytical epidemiology focusing on projections of the disease burden,

including the effects of demographic change and assumptions about the potential effects of intervention measures.

The goals of this thesis were to apply the concepts of the BoD framework and provide specific and necessary estimates of disease burden by addressing important questions dealing with the two settings described. It was intended to add BoD estimates to areas where information is currently lacking, even though the necessary data to calculate the disease burden is available. It was also of importance to shed light on how the assumptions used to calculate the disease burden can influence the resulting priorities.

The objectives of the thesis can be operationalized in the following guiding research questions:

- [1] How can the burden of disease approach be tailored to better meet the needs of infectious diseases?
- [2] Is the standardized framework applicable to a heterogeneous set of infectious pathogens?
- [3] How can burden of disease estimates be used to predict the future disease burden considering dynamic changes of the population and impact of intervention measures?
- [4] Is it feasible to use the burden of disease approach on sub-national levels and what are the major limiting factors?
- [6] What are the benefits of sub-national burden of disease assessments?
- [5] How do social value choices impact on estimates of disease burden?

These objectives and the related research questions indicate that the research conducted and the articles published cover both the application of the burden of disease methodology and its further development. Thus, the presentation of the papers will highlight these two main aims. All the articles are also guided by the overarching aims of highlighting the importance of burden of disease assessments for public health and of providing further insights into data availability and quality, because burden of disease analyses are strongly dependent on data availability, quality and the reliability of the data sources used. Thus, methods for correcting and adjusting epidemiological input data will also be considered.

## **5. Methodological concepts**

As the objectives of this dissertation encompass both methodological refinement and the application of the burden of disease approach this chapter will lay out the constructs of the BCoDE methodology to quantify the disease burden due to infectious diseases and it will also describe the SEYLL approach to measure the effects of premature mortality.

### **5.1. The BCoDE framework (Papers 1-2)**

This chapter describes the development of an appropriate methodology to estimate the disease burden of infectious conditions. It covers Paper one, describing the method developed and Paper two, presenting important implications for data adjustment when using the pathogen- and incidence-based DALY approach. The methodology presented here is closely tied to the European-based project “Burden of Communicable Diseases in Europe” (BCoDE) initiated by the European Center for Disease Prevention and Control (ECDC). Within the BCoDE project it was aimed to generate a methodology explicitly tailored for assessments of infectious disease burden and priority-setting purposes. With limited availability of comprehensive and comparable estimates of the disease burden in Europe, the focus of the project was to quantify the disease burden for 32 selected pathogens in all EU, EFTA and EEA member states by using a standardized framework [115].

#### *The pathogen- and incidence-based DALY approach (Paper 1)*

The DALY measure as introduced by Murray and Lopez in the first GBD study, follows the disease-specific approach and thus estimates the burden for disease endpoints, giving lower priority to the actual etiology of a disease [22]. Many disease endpoints, however, might have distinctly different causes, which need to be tackled by diverse prevention and intervention strategies in the field of public health. Especially for infectious conditions, which depending on the causative agent/pathogen have highly heterogeneous characteristics, natural disease histories, and prevention and treatment options, it is important not only to consider the acute infection with a pathogen as one disease endpoint but also to include all the multiple endpoints that are associated with the initial infection but occur either as short-term or, in the case of long chronic or latent conditions, as long-term consequences several years after the infection. In order to capture the comprehensive disease burden of infectious conditions the methodology used has to accommodate both aspects and should be able to summarize both effects. Therefore, the pathogen-based DALY approach is an appropriate measure because it estimates the years of healthy life lost according to the natural history of a disease [28, 115-117]. The prerequisite for calculating the DALYs in the pathogen-based approach is a set of natural history models that from now on will be referred to as outcome trees. These outcome trees form the backbone of the methodology and are a qualitative representation of the natural history of a disease. Outcome trees include the outcomes of acute illness and all relevant short- and long-term consequences, referred to from now on as sequelae. In an outcome tree, which starts with exposure to a pathogen, all health outcomes are ordered by time and linked by conditional probabilities describing the consecutive flow from one health outcome to the

next (see Figure 3). In addition, where necessary a health outcome can be further differentiated into several health states describing different severity levels (e.g. mild, moderate, or severe) or health states that present a complicated case. For the outcome trees only sequelae with sufficient evidence to be caused by the initial infection were considered [118]. To propagate the identified uncertainty around the conditional probabilities the parameters were assumed as a distribution of values. Depending on the available data, distributions (e.g. uniform, PERT, beta) were selected for the parameters and the Monte Carlo technique was used to model uncertainty and estimate the 95% uncertainty intervals (UI).

The natural start of an infection is the exposure to a pathogen. However, this event is not easily measurable and thus not covered by available health statistics from surveillance systems. The point at which health statistics become available is when an infected person develops symptoms and seeks health-care services. Surveillance systems for many pathogens with mandatory reporting mechanisms capture those cases, which in most of the infectious conditions can be considered as acute incident cases. This might not hold for pathogens with chronic disease courses where differentiation between acute and chronic infections is difficult. Having the surveillance data for many infectious diseases at hand, and using the pathogen-based DALY approach, it was decided to use the incidence-based DALYs. The entry point for incidence data in the natural history models is the orange box in the outcome tree labeled “acute infections” (see Figure 3). Technically the DALYs are then calculated for all health outcomes included in the outcome tree. To estimate the DALYs the YLDs for non-fatal health outcomes and YLLs for the health outcomes leading to death were calculated separately.

The original formula for YLDs was adjusted, resulting in the following representation:

$$[5] \ YLD = \sum_l n_l^{a,s} * t_l^{\tilde{a},s} * w_l^{\tilde{a},s} \quad ^2$$

The adjusted formula for YLLs reads as follows:

$$[6] \ YLL = \sum_l d_l^{a,s} * e_l^{\tilde{a},s} \quad ^3$$

All input parameters in both YLD and YLL formulae were chosen to be age ( $a$ ) and sex ( $s$ ) dependent when such information was available, where  $a$  stands for age at infection and  $\tilde{a}$  for age at onset of a condition or death. The outcome tree models and necessary DALY formulae

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<sup>2</sup> YLDs are estimated for each health outcome ( $l$ ) by multiplying the number of incident cases ( $n$ ) by the disability weight ( $w$ ) for a specific health outcome ( $l$ ) and the duration of the disabling condition ( $t$ ) (formula 5).

<sup>3</sup> YLLs for those health outcomes ( $l$ ) that can lead to death, are estimated by multiplying the number of fatal cases ( $d$ ) for a specific health outcome ( $l$ ) for an infection acquired at age ( $a$ ) by the remaining life expectancy ( $e$ ) at age  $\tilde{a}$  (formula 6).

were implemented in Microsoft Excel and the add-on software @Risk was used for probability modeling.

*Measuring the underreporting and under-ascertainment for infectious disease data (Paper2)*

As incidence data were the central but also very sensitive input to the models a careful examination of data availability and quality was necessary to ensure rigorous estimates of the number of incident cases. Even though data availability and quality in many European countries and for the diseases with mandatory reporting is extremely high and national health institutes provide detailed data sets stratified by age and sex, it is also known that surveillance systems, as they are currently in place, are selectively affected by different degrees of underestimation and the data reported might only represent the tip of the iceberg as many infections might go undetected. There are several reasons for underestimation, which can be broadly differentiated into underreporting and under-ascertainment. Under-ascertainment (community level) refers to cases that do not seek health-care services because of mild symptoms and knowledge about the self-limiting characteristic of a disease or asymptomatic disease course. The latter is especially important for diseases with sequelae from asymptomatic infections. Furthermore, asymptomatic infections might also serve as a reservoir for further infections and thus cause substantial disease burden. Underreporting (health-care level) refers to cases that do seek health care, but due to a) failure in diagnosis (no diagnosis at all or misdiagnosis) or b) failure in notification (no reporting at all or misreporting) are not fully, or correctly, reported to the national health surveillance systems. Underestimation can thus selectively impact on the number of incident cases reported by national and international bodies. Estimating the “true” incidence is essential, especially when it forms the backbone of disease burden. Thus, it becomes necessary to correct the reported data. As a part of the BCoDE study it was decided to use country, sex and age-specific “multiplication factors” (MF) to correct the raw incidence data. These MFs are based upon information from different kinds of studies that allow the derivation of a correction factor. One example is community-based studies which aim to capture pathogen carriage or infection in a, preferably representative, sample of the population. Comparing the estimates from these studies with cases notified, an MF can be derived, correcting these numbers. Another type of study is serological surveys that test biological samples and detect the sero-incidence and sero-prevalence of an infection. The advantage of serological testing is that, depending on the pathogen, detailed information on e.g. symptomatic, asymptomatic, past, acute or chronic infections can be gathered. These kinds of studies, when combined with a questionnaire instrument, are especially important for pathogens with asymptomatic and chronic infections

that can lead to sequelae (e.g. hepatitis B, Chlamydia) to estimate the symptomatic/asymptomatic fraction. A third type of study is the returning traveler study. Here, the risk of infection for travelers from one country (A) visiting another country (B) is estimated by taking the number of infected travelers returning to their home from country B from surveillance records as a numerator, and the total number of travelers from country A visiting country B from travel pattern databases as the denominator. This measure of risk can then be used to generate an adjusted estimate of incidence in country B. Comparing this estimate with the number reported in the national surveillance records of country B, an MF can be obtained to correct the reported data. A final type of study mainly covering the effects of underreporting, is the capture-recapture study. These studies combine different data sources that capture incidence, such as hospitals, general practitioners, or laboratory data and use unique personal identifiers to crosslink the cases, identify any overlap between data sets and quantify the number of cases not captured by each data collection system. Based on these estimates, a “true” incidence can be estimated. To obtain MFs from published studies, disease-specific search strings were developed and literature databases were systematically screened for appropriate studies. Data on the different types of studies as identified from pathogen-specific literature reviews, served as the initial input to derive, in the best case, country-, age- and sex-specific multipliers to correct for underestimation in the national surveillance systems. Having an MF at hand, the raw incidence data were corrected and used as the initial model input to calculate the pathogen- and incidence-based DALYs.

## **5.2. Standard expected years of life lost as a measure of premature mortality**

As described in the previous chapters, most disease-burden estimates are restricted to the national level and sub-national assessments are rarely available; however, they are necessary because understanding regional differentiation of the disease burden is an important step towards gaining detailed information about health patterns. There are several epidemiological indicators that, at least in high-income countries, are available at a sub-national level and mortality statistics from vital registration systems allow for small-scale analyses. However, the simple death counts or death rates that are mostly used to present the patterns of mortality associated with disease burden are insufficient measures as they do not account for age at death and do not consider the actual loss of healthy years.

The SEYLL metric which reflects the mortality component of the DALY, quantifies the years of life lost due to premature death in a population. Using a normative health goal, the SEYLL measures the gap between the ideal health goal and observed mortality patterns. In the case of the SEYLL, the difference (in years) between the remaining life expectancy at age of death,

and the age of death itself is the outcome of interest. Technically, the normative health goal for the SEYLL is set to life expectancy values derived from a standard life table (West Level 26). The formula for undiscounted and not age-weighted SEYLL is the following:

$$[6] SEYLL = N \times RLE_x^4$$

Introducing age-weighting and discounting, the resulting formula is:

$$[7] SEYLL = N C e^{(ra)} / (\beta + r)^2 \left[ e^{-(\beta+r)(RLE+a)} [-(\beta + r)(RLE + a) - 1] - e^{-(\beta+r)a} [-(\beta + r)a - 1] \right]^5$$

Cause of death data serve as the initial input. The raw data are redistributed from the original classification (e.g. ICD 10) to the GBD classification systems and are corrected for miscoding of death causes.

## 6. Empirical findings

The empirical findings of the thesis identify the potentials and challenges of both approaches for increasing the availability of population health estimates. The results presented fill existing gaps because assessments of burden of disease using composite health measures are not available either for infectious diseases in Germany, or at the sub-national level for NRW or Hong Kong.

### 6.1. Applying the BCoDE methodology (Papers 3-4)

To test the feasibility of applying the pathogen- and incidence-based approach, two strategies were chosen following two objectives. The first objective was to use the framework to produce a set of descriptive estimates for Germany and four selected pathogens (Paper 3). The second objective was to use the approach in an analytical framework to predict the future disease burden of two selected pathogens in the Netherlands with an additional focus on the potential impact of intervention strategies (Paper 4).

To test the applicability of the pathogen- and incidence-based DALY approach in Germany, hepatitis B virus, influenza virus, measles virus and *salmonella spp.* were chosen for the experiments (details on the model specifications can be obtained from the supplementary material in the articles). These pathogens were selected as they differ not only in their characteristics (e.g. natural history, transmission) but also in terms of the availability of vaccines and their different occurrence (e.g. epidemic, endemic, or outbreak related). Raw

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<sup>4</sup> SEYLL are calculated by multiplying the number of deaths ( $N$ ) at a certain age of death with the remaining life expectancy ( $RLE$ ) at age of death ( $x$ ) [58].

<sup>5</sup>  $N$  is the number of deaths,  $r$  is the discount rate (0.03),  $C$  is the age-weighting correction constant (0.1658),  $e$  is a constant ( $\approx 2.718$ ),  $\beta$  is the parameter from the age-weighting function (0.04),  $a$  is the age at death and  $RLE$  the remaining life expectancy at age of death [39].

notification data (average) for the years 2005 to 2007 were corrected for underestimation and served as the initial input to the models. The average reported number of acute incident cases per year was 1,137 for hepatitis B virus, 11,772 for influenza virus, 1,217 for measles virus, and 52,322 for *salmonella spp.*. After correction for underestimation 16,170 (95% UI: 14,438–17,909) cases of acute hepatitis B, 1,236,269 (95% UI: 1,120,752–1,354,268) cases of acute influenza, 2,840 (95% UI: 2,738–2,925) cases of acute measles, and 565,981 (95% UI: 477,435–657,638) cases of acute salmonella infections were modeled. The highest burden was estimated for influenza virus, with 33,116 (95% UI: 29,504–36,849) DALYs/year. 51.6% of the burden was due to the effects of premature mortality. DALY-rates were higher for males, with 41.3 (95% UI: 34.7–47.6) DALYs/100,000 as compared to 39.3 (95% UI: 33.5–45.1) DALYs/100,000 for females (for more details see Figure 4). The highest DALYs were estimated for the acute infection with 29,439 (95% UI: 26,283–32,708) DALYs/year accounting for 88.9% of the overall disease burden. 11.1% was due to long-term consequences caused by acute respiratory distress syndrome (1,878 (95% UI: 1,647–2,117 DALYs/year)) and sepsis (1,794 (95% UI: 1,573–2,021) DALYs/year). The second highest disease burden was estimated for *salmonella spp.*, with 19,115 (95% UI: 14,803–24,328) DALYs/year. In contrast to influenza, the major part of the disease burden was due to the effects of morbidity, with 61.2% of the overall DALYs related to the YLDs. Higher DALY-rates were estimated for the female population, with 24.1 (95% UI: 16.9–34.0) DALYs/100,000 in contrast to 22.2 (95% UI: 15.5–31.1) DALYs/100,000 for males. Acute illness (gastroenteritis) had a 44.4% share of total DALYs indicating the considerable impact of the sequelae, mostly due to irritable bowel syndrome (IBS) 10,459 (95% UI: 8,593–12,528). Reactive arthritis (ReA) also contributed to the sequelae burden, with 173 (95% UI: 102–257) DALYs/year. The third largest burden was estimated for hepatitis B virus. According to our model for hepatitis B virus we estimated 8,780 (95% UI: 7,335–10,163) DALYs/year related to infections with hepatitis B, with 55.1% (4,798 DALYs) due to YLL. Hepatitis B showed a higher burden for males, with 12.4 (95% UI: 9.9–15.2) DALYs/100,000 as compared to females with 8.8 (95% UI: 6.7–11.1) DALYs/100,000. The sequelae that were the largest contributors to disease burden were hepatocellular carcinoma (2,795 (95% UI: 1,833–3,810), chronic hepatitis (2,763 (95% UI: 2,248–3,097) DALYs/year), and decompensated cirrhosis (2,182 (95% UI: 1,791–2,594). Overall, only 2% of the overall burden was related to the acute illness, indicating the importance of the sequelae in causing high DALYs for hepatitis B. Within the four selected pathogens, the lowest disease burden was estimated for measles virus, with 740 (95% UI: 413–1,066) DALYs/year, with most of

the DALY due to YLL (90.8%) and the acute illness (93.0%). The disease burden of the long-term consequences due to encephalitis and post-infectious encephalomyelitis were estimated at 16 (95% UI: 16–17) and 33 (95% UI: 20–45) DALYs/year, respectively.

The results showed that it was feasible to apply the pathogen- and incidence-based DALY approach to the four selected pathogens (see Table 1 for an overview). Furthermore, these are the first estimates of the infectious disease burden for Germany measured by DALYs. Due to a lack of overall estimates for the disease burden in Germany, comparison of the results is limited to these four pathogens. However, the estimates clearly highlight the importance of including the effects of morbidity and especially emphasize the contribution of short- and long-term sequelae. Here, when looking at the upper extreme case of hepatitis, not considering long-term sequelae would result in an underestimation of the disease burden by 98%.

The estimates presented in Paper three have already nicely shown the value of burden of disease estimates for infectious disease as modeled with the pathogen- and incidence-based DALY approach. The estimates provided include the acute stage, as well as short- and long-term sequelae and are thus able to present the total impact of infectious diseases on population health. From a preventive point of view, where the aim could be to introduce effective prevention measures such as vaccination to avoid new infections, the introduced approach can also be used in an analytical exercise to predict future burden and can include the expected impact of intervention and prevention measures. Estimating these kinds of impact in the pathogen- and incidence- based DALY approach would not only consider the cases of acute illness that have been prevented but would also include the potential benefits of intervention strategies in avoiding the heavy burden of sequelae and thus might result in more appropriate estimates of the effect of prevention measures.

Therefore, Paper four aimed to predict the disease burden of two pathogens, hepatitis B and influenza virus in the Netherlands from 2000 to 2030. To increase the value of these predictions two major aspects of demographic development were taken into account when estimating the future burden. Population growth and aging were considered, whereas a steady state for disease incidence was assumed based on the average of reported incidence rates in the Netherlands between 2000 and 2010. The disease burden was modeled using the pathogen- and incidence-based DALY approach. To address the effect of intervention measures for hepatitis B, one scenario introduced a 2% per year decrease in incidence for all age groups (simulating the effects of an increase in vaccination coverage for all age groups) and in contrast a second scenario assumed a decrease of 5% per year only in the population

younger than 15 years (simulating the effects of age-targeted vaccination). To estimate the effect of age-targeted vaccination for influenza virus in the age group 60+, three scenarios were calculated with decreases in incidence in this age group of 5% and 2% per year (simulating uptake of vaccination coverage) and increases in incidence by 2% per year (simulating declines in vaccination coverage). In our baseline scenario for hepatitis B virus, a slight increase in disease burden from 1,196 (95% UI: 1,003–1,328) DALYs/year in 2000 to 1,343 (95% UI: 1,194–1,493) DALYs/year in 2030 was estimated. Compared to a static approach, where population size, age distribution and life expectancy were kept constant, an overall higher burden in the dynamic approach was estimated, with DALYs being from 1.34-fold higher in the year 2000 up to 1.50-fold higher in 2030. The scenario simulating a 2% decrease of incidence in all age groups resulted in the strongest decline of disease burden, by 32%. In contrast, the 5% decrease of incidence in the population aged less than 15 years only resulted in a marginal decrease of 3%. The baseline scenario for influenza yielded a remarkable increase from 22,712 (95% UI: 21,132–24,290) DALYs/year in 2000 to 51,609 (95% UI: 48,212–55,198) DALYs/year in 2030. Compared with the static approach, an identical disease burden was estimated for the dynamic model for the year 2000 but a 2.27-fold higher disease burden for 2030. In the scenario analyses a decrease of 23% and 45% in the disease burden was estimated when assuming a 2% and 5% decreasing trend in incidence rates per year (for the age group 60+), respectively. In contrast, an increase of 2% per year in incidence rates would result in the disease burden being 34% higher than estimated in the baseline scenario.

The results presented clearly show that a) dynamic demographic processes and b) intervention measures such as vaccination can have a huge impact on infectious diseases. The results especially highlight the impact of universal vaccination for hepatitis B and age-targeted vaccination for influenza. The results indicated that, for predicting the future disease burden from a population-health perspective, SMPH are a very useful alternative to classical epidemiological indicators because they include the full impact of diseases on health.

## **6.2. Sub-national burden of disease assessments in high-income areas (Papers 5-6)**

Papers five and six are related to the aim of testing the feasibility of applying the burden of disease approach, and especially a standard measure of premature mortality, at a sub-national level. Both articles focus on the assessment of disease burden and present patterns of causes of premature death for high-income areas located in different regions of the world. The articles highlight the advantages and challenges of the approach and compare the estimates to standard measures of mortality. Both studies close existing data gaps by providing sound

additional information on population health. Paper five presents results generated for NRW, a federal state of Germany, and paper six lays out estimates for the special administrative region of Hong Kong in China. Paper six in particular extends the value of the SEYLL estimates by including scenario analyses highlighting the choice of assumptions in the estimation process. Paper five focuses on the implementation of the SEYLL concept at a sub-national level and highlights the importance of taking into account the age of death and thus the years lost due to premature death [32]. Estimates of the burden due to premature death in Germany are generally incomplete at both national and sub-national levels. In addition, indicators such as the Potential Years of Life Lost (PYLL) are used, which are not adequate to capture the full impact of premature mortality, because they use a potential limit to live (e.g. 75 years) and thus are not able to capture the benefits of interventions aiming at preventing deaths above this age limit. [119]. Therefore, the research objective of this study was to estimate the burden of disease due to premature mortality by applying the methodology at a sub-national level and calculating the SEYLLs for NRW. The study used mortality and cause of death data from regional and national statistical health authorities. Despite full coverage of cause of death data, a considerable number of cases was attributed to ICD codes that were either generally unspecific (e.g. ill-defined categories coded R00–R99 in the ICD 10) or could not be considered the primary cause of death (e.g. cardiac arrest). Therefore, these data were reallocated to specific codes according to an algorithm provided by the methodological constructs of the GBD study [83, 120]. Furthermore, the data was also redistributed to meet the GBD classification system, as presented in Chapter Three. The SEYLL for 2005 were calculated using a three percent time discount and uniform age weights to achieve comparable estimates to other existing BoD studies. In total, a loss of 1.75 million SEYLLs was estimated for NRW, with higher shares observed for females (52.6%). The overall burden was mainly due to the effects of group two conditions, which accounted for 89.1%. Group one and three conditions had a share of 5.6% and 5.3%, respectively. These results highlight “ischemic heart disease” as the leading cause of premature death, with 321,617 SEYLLs, followed by “trachea, bronchus and lung cancers” (131,529 SEYLLs) and “cerebrovascular disease” (105,639 SEYLLs). Major differences were identified compared to standard death counts in the higher priority attached to “trachea, bronchus and lung cancers”, which represented the second leading cause of SEYLLs (ranked 3<sup>rd</sup> in death counts) and “liver cirrhosis” ranked 7<sup>th</sup> (ranked 11<sup>th</sup> in death counts) in NRW. In particular, the SEYLL estimates identified “self-inflicted injuries” as important drivers of premature death for the male population ranking them 8<sup>th</sup>, whereas if using classical death counts this cause will not be one of the top ten

leading causes (ranked 13<sup>th</sup>) [32]. The results for NRW indicated typical patterns of premature mortality, comparable to other assessments in high-income areas. The results particularly highlighted diseases occurring at earlier stages of life and this indicates great potentials to intervene and reduce the years of healthy life lost due to premature death.

The analyses for NRW were guided by the standard assumptions used in the GBD study. However, changing these assumptions can have considerable impact on the resulting priorities and thus, it is important to show the impact of the different value choices on the estimates of SEYLL. While its primary focus is on estimating the sub-national disease burden due to premature death in Hong Kong Paper six also presents the quantification of effects introduced by age-weighting, time-discounting and by using an alternative standard life expectancy [32]. After consulting misclassifications of reported death cases and redistributions of deaths to the GBD classification system, SEYLLs were calculated with no time-discounting and uniform age weights in the baseline scenario. The assumptions about value choices were considered in various scenario analyses. Overall, the baseline scenario yielded 524,707 SEYLLs for Hong Kong, SAR in the year 2010, with a greater share observed for males, at 55.6%. 78.8% of the SEYLLs were estimated to be caused by group two conditions and represent the majority of years of healthy life lost due to premature death. Group one and three conditions contributed 8.5% and 12.7% to the SEYLLs, respectively. At the second level of disaggregation, malignant neoplasms (39.1%), cardiovascular diseases (21.7%) and respiratory infections (8.9%) were the leading cause groups, accounting for about 70% of all SEYLLs. At the third level of disaggregation “trachea, bronchus and lung cancers” (52,242.1 SEYLLs; 10.0%), “ischemic heart disease” (51,542.2 SEYLLs; 9.8%) and “lower respiratory infections” (46,503.2; 8.0%) were the three major leading causes of SEYLLs. Despite the fact that Hong Kong is a high-income country, the epidemiological transition seems to be not fully advanced when compared to the results of other studies in high-income areas. “Lower respiratory infections” still cause major decrements in population health. Overall, the share of SEYLLs due to group one conditions is still considerably higher than in other high-income areas such as Spain (6.4%) and Germany (5.6%) [32, 91]. Contrasting further, “trachea, bronchus and lungs cancers” were identified as the leading cause of SEYLLs in Hong Kong, which again is different from other studies which identified “ischemic heart disease” as the leading cause [32, 93]. This might be explained by the effects of past and current smoking habits in Hong Kong with high overall smoking rates in the past and currently high rates still observed in men aged 30+. If death counts were consulted “trachea, bronchus and lung cancers” would only rank 3<sup>rd</sup> and would be surpassed by “lower respiratory infection” (1<sup>st</sup>) and “ischemic

heart disease” (2<sup>nd</sup>). Furthermore, “self-inflicted injuries” (suicides) were identified as an important driver of SEYLLs in Hong Kong, being ranked 6<sup>th</sup> and 7<sup>th</sup> for males and females, respectively. Using death counts, “self-inflicted” injuries would only rank 9<sup>th</sup> for men and 17<sup>th</sup> for women and thus would grossly underestimate the priority of this condition. For women, SEYLLs drew greater attention to two important cancers sites, with rank changes for breast cancer from 8<sup>th</sup> to 6<sup>th</sup> and liver cancer from 7<sup>th</sup> to 4<sup>th</sup> position.

In order to consider the effect of age-weighting and discounting three scenarios were calculated. In addition to the baseline estimates (0,0) scenarios with (I) a three percent time-discount and non-uniform age weights (3,1), (II) a three percent time-discount and uniform age weights (3,0), and (III) no time-discount and non-uniform age weights (0,1) were calculated. Scenario I resulted in the greatest reductions in SEYLLs of 51.6% indicating a large impact on the overall burden (see Figure 5). The analysis also highlights that time-discounting and age-weighting had a selective impact on the different disease groups. Group one conditions, which mostly affect the very young and very old segments of the population, received greater decrements, with reductions in SEYLLs of 55.1% as compared to 51.7% and 45.9% for group two and three conditions, respectively. The lowest reductions in the overall burden were estimated for scenario II, with an overall decrease of 25.5% compared to the baseline SEYLL. Even though the overall decrease is the lowest compared to the other scenarios, there was an obviously imbalanced selective impact on the three main cause groups. Group one and two conditions showed comparable reductions of 22.8% and 24.4%, respectively. Group three conditions, however, were reduced by 39.8%, because most of the injuries considered in this group occur in younger age groups. In contrast, the scenario only using non-uniform age weights (III) that give higher weights to people in the most economically productive ages, gave an increase in priority to “self-inflicted injuries” from 5<sup>th</sup> to 3<sup>rd</sup> rank, even surpassing “lower respiratory infections”. Changing the global standard for life expectancies resulted in a considerable increase of disease burden, of 10.8% which was mostly related to higher values for life expectancy, especially for the female population. Here the life expectancy was between 1.5 and 3.5 years (depending on age group) higher than in the global standard. Thus, the increases in the SEYLLs were also higher in the female population with a rise of 15.1% as compared to 7.4% for males.

Both studies have shown that applying the SEYLL measure at a sub-national level is generally feasible. The results are of particular interest for local planning of interventions, and including the information about age at death offers new perspectives, presenting the SEYLLs as a sound alternative for going beyond standard measures of mortality.

## **7. Discussion**

This discussion is guided by the general question of why population health measures such as the DALY and its components are important for research and prioritization processes in public health. It also considers how setting specific adjustments increase the value of these estimates and can help to identify the important drivers of ill health. This section will also highlight how SMPH can give added value to overall health statistics and how important availability and quality of data is to generate reliable and evidence-based estimates. The discussion will also accentuate the significance of going beyond national estimates and argues that, even though the one-size-fits-all methodology in general might be desirable at a global scale, to accommodate heterogeneous sets of conditions, there is a growing interest in more specific and thus more adequate measures, when target-specific interventions at the population level are intended.

Indisputably, the health of each individual is a key value and maintaining a good health status of each individual is the main goal of health services. Nevertheless, the individual health perspective only provides a fragmented view and does not allow the creation of a comprehensive and comparable overview of the health situation of a population. These estimates are needed in order to generate a general understanding of health trends, the distribution of ill health in a population and the effects of health determinants at a broader level. Furthermore, many public-health intervention measures operate at the population level and not only result in health benefits for a single individual but can also help to improve the health of an entire population. It becomes evident that population health measures, such as the DALY and its components, that allow to capture the comprehensive health status of a population can serve as markers for the overall health status. They can also, in the long run, be very sensitive indicators of the health trends introduced by demographic, epidemiologic and risk factor changes, as well as provide valuable information about the success or failure of public-health measures or the overall performance of health systems.

In the past, a large number of donor agencies have spent huge amounts of resources to improve the health status across the world, but since the financial downturns in almost all areas of global society, especially since the recent financial crisis in 2008, all sectors face budget cuts and so the health-care sector is no exception [121, 122]. Especially in the health sector, demands and costs have increased substantially, whereas spending on health has remained quite stable, indicating that mechanisms of priority setting are in place and decisions are made based on more or less solid grounds [123]. There are several approaches to allocating scarce resources, ranging from data-driven approaches, where indicators allow

setting up priority listings, to decisions based on the consensus of experts, which might lead to choices guided by specific personal interests (e.g. for a certain disease or treatment) [124-126]. To reduce the number of biased decisions, standardized health indicators of disease burden, such as the DALY and its components, that make use of a wide array of available data on diseases and injuries, are an increasingly favored source of information for health policy decision making, and also for setting priorities in the field of health research. Despite, the overarching objectives of the GBD study to capture the global health status, the methods used in the study also have great potential to expand their initial scope. Going beyond the one-size-fits-all solution and national boundaries provides sound and valuable additional information that will help the public health community not only to identify the major drivers of disease burden but also to highlight areas where investment in prevention and intervention measures has great potential to improve health status.

This thesis has shown that adjustments in the methodology for measuring the disease burden of infectious conditions and expansion its scope to sub-national level provide valuable insights into population health patterns for public health. The burden of disease framework, and especially the DALY measure, are very flexible and can be adjusted to meet specific needs. This is of major importance, especially for infectious diseases because they present with very specific and, depending on the pathogen, distinctly different characteristics. The currently available assessments of disease burden, use the disease-specific DALY approach to a great extent, capturing the disease burden related to disease endpoints (e.g. liver cirrhosis, hearing or vision loss) rather than to the etiological cause (e.g. a pathogen) [20, 70]. For infectious conditions this means that the burden of acute infections are mostly covered, but other disease endpoints that might have an infectious etiology are either not considered as part of the infection [20], or even if related to a certain etiology, simply not counted as being part of the infectious disease burden [70]. The idea behind is, that in general, to capture the current state of disease burden, which is relevant to allocate current spending on health care, for many disease endpoints the initial cause is probably not of an issue because the conditions may require similar treatment. This perspective loses strength, however, when the view is changed from the curative to the preventive perspective. Here it becomes evident that the etiology of a disease outcome is crucial, especially when estimating the full impact of intervention measures. It is therefore necessary that the approach taken to measure infectious disease burden accommodates the acute infection as well as the health outcomes considered as part of the natural history. The pathogen- and incidence-based DALY approach used for the analyses in this thesis has the benefit that, on the one hand, it covers the acute illness and, on the other

hand, it estimates the potential future burden arising after the initial infection [28]. By including this information, measurements of the impact of interventions aiming at avoiding the initial infection would consider the entire disease burden of that infection. When this methodology is applied at a national level for Germany, the results clearly show that sequelae contribute significantly to the disease burden, especially for diseases with long chronic phases such as hepatitis B, where potential sequelae occur after a long period of more than 40 years, but also for salmonellosis where sequelae develop shortly after the acute infection [30]. In both cases the disease burden caused by the sequelae is generally higher than the burden caused by the acute illness, accounting for 98% and 55.6% of the DALYs for infections with hepatitis B virus and *salmonella spp.*, respectively [30]. This is not only important for measuring the disease burden of these pathogens but it is also a crucial issue when economic aspects are taken into account. Estimating the impact of prevention measures and only focusing on avoiding the acute illness will result in skewed cost-effectiveness and may result in the denial of any prevention measures.

Using the pathogen-based approach and the related outcome trees can further increase the preparedness of health-care systems. Using information about duration for the health outcomes, this approach also allows to track the evolving potential future disease burden [31]. This is of major importance for diseases with long chronic or latent stages, such as infections with the hepatitis B virus or HIV. The pathogen-based approach allows modeling of the potential future burden along time and, in the case of a hepatitis B infection, indicates that after a long period of chronic infection with an intermediate disease burden, a peak of disease burden arises at about 40 years after infection, mainly induced by the long-term sequelae such as liver cirrhosis and hepatocellular carcinoma (see Figure 6). Health-care services can profit from these insights, gaining the opportunity to foster preparedness for the impact of a future burden due to sequelae arising in the future.

Different epidemiological data can serve as the input to calculate the DALY, but when using the pathogen-based approach, a necessary prerequisite is to take the incidence perspective and use incidence and not prevalence data as the central input for the DALY calculation [28]. With data on the prevalence of an infection, the time point of initial infection with a pathogen, and thus the concrete entering point/time in the natural history model is generally not known and thus the starting point in the outcome tree cannot be determined, hampering consistent calculations of the disease burden. In contrast, using incident cases can limit the comprehensiveness of the chosen modeling strategy, especially for chronic infections where prevalent infections give rise to the current disease burden. With the incidence-based

approach, prevalent infections are not included. For hepatitis B, this is of major importance for low-endemic countries with considerable numbers of infected migrants entering the country from high-endemic areas. Again, the initial perspective and the modeling objectives play the most important role. When the aim is to capture the current disease burden and the resulting priorities of interest are to examine current health-care demands (and costs), the prevalence and disease endpoint approach is the adequate choice [70]. Whenever the perspective is shifted to deal with aspects of prevention and intervention strategies, especially in the case of infectious diseases, the incidence approach is the more appropriate choice. The incidence approach allows not only to capture the current disease burden but, combined with the pathogen perspective, it also enables us to include the potential future burden of sequelae. This potential burden is a major issue when avoiding the initial infection is a primary focus of decision-making processes. Another argument for using the incidence-based approach for infectious diseases is that incidence is a more sensitive indicator of the current epidemiology of a disease. In contrast to prevalence, which is generally defined as stock measures, incidence is a flow measure and can capture dynamic conditions such as infectious diseases more precisely [127]. For instance, infectious diseases, often presenting with short durations, are not easily captured by point or period prevalence, especially when the acute phase of an infection is of major interest.

Testing the methodology for four pathogens in Germany indicated that the basic methodology developed is generally applicable to conditions with varying characteristics. With a comprehensive assessment of both acute illness and the sequelae following the infection, by means of outcome trees, the whole spectrum of infectious pathogens can be covered. The results for Germany already indicate that comparisons between the four pathogens are feasible, and reveal the urgent need for burden of disease estimates for all remaining pathogens in order to arrive at a comprehensive assessment of the infectious disease burden in Germany. Using the DALY as the outcome metric, the effects of mortality and morbidity can be measured in one single unit of measurement. Adjustments towards the pathogen-based perspective then allow us to identify differences in the disease burden due to the relevance of acute illness and sequelae (see Figure 7). Without information about non-fatal health outcomes (YLD), the disease burden would be underestimated for infections with hepatitis B virus by 44.9%, with influenza virus by 48.4%, with measles virus by 9.2% and by a huge 61.2% for infections with *salmonella spp.*, indicating an important added value compared with classical epidemiological indicators. Furthermore, using the adjusted approach enables to include asymptomatic infections, which in the case of hepatitis B give a large rise to disease

burden; and not considering these asymptomatic cases would result in an underestimation of disease burden by 80.1% [30]. The estimates provided for Germany and future estimates for the remaining 28 pathogens might offer new perspectives and can foster debate about current priorities and the methods used to determine these priorities.

The purpose of the methodology developed in this research was to accommodate the characteristics of infectious diseases and to provide estimates of the burden of disease that better reflect the current situation of infectious conditions. The resulting estimates already provide additional insights for the descriptive epidemiology and fill existing data gaps. Taking the public health perspective, descriptive estimates are the first and necessary step towards unfolding the health status of a population. Information about the current state of health is important for planning current health services, but health systems also need to be prepared for future trends and upcoming needs and thus require information about the development of the future disease burden. This requires analytical steps to be taken and the pathogen- and incidence-based DALY approach allows going beyond descriptive analyses. It can be utilized to estimate the impact of different trends from a population perspective, which was also shown by this thesis. There are different trends impacting on the future development of a disease. Some trends are inherent in a population, such as those trends described as demographic, epidemiologic and risk transitions. Other trends are related to the dynamic nature of infectious diseases and make predictions of future burden a complex undertaking where several determinants and their uncertain developments need to be considered. Two very important aspects of infectious disease development are certainly demographic changes and the implementation of interventions strategies. Demographic changes in high-income countries have led to large shifts in the population structure towards older ages and the predictions presented for the Netherlands show that by 2030 the share of the age group older than 75 years will double from 6% (2000) to 12% [31]. With increasing age, the ability of the immune system to cope with infectious pathogens wanes, increasing the probability of elderly people attracting infections, which may also have more severe disease courses than infections attracted at younger ages, presenting with e.g. increased case-fatalities. Furthermore, the increased life expectancy of the population may also allow long-term chronic infections to reach their sequelae endpoints more often than in the past. Predictions of the future development of the infectious disease burden that take such effects into account are necessary and can help strategic health service planning to prepare for changing demands or to show/predict the impact of planned interventions. Combining the incidence- and pathogen-based DALY approach with a demographic model indicated that this standardized approach

can be applied to diseases with different natural histories. The study compared infections with hepatitis B virus to infections with influenza virus and showed how demographic change impacts on the future disease burden. For hepatitis B, two major effects were identified. The first effect of the demographic change impacts on the most vulnerable groups for hepatitis B infections. Here we see a general decline in the vulnerable population size and thus a modeled decrease in the incidence. This would lead to a decrease in the disease burden over time, with respect to YLDs. However, increasing life-expectancy over time leads to a higher cumulative probability of the population to develop future sequelae. This in turn leads to an increase in the disease burden, mostly due to YLLs. Both effects level out and result in a moderate increase in the overall disease burden (DALYs) for hepatitis B virus [31]. For influenza, the effect of demographic change is mostly seen in YLLs, where the increase is closely related to the growth of the population aged 75+. Incorporating the effects of demographic changes has already provided important insights into the future development of the disease burden. However, from the public health perspective, the opportunity to avoid this future burden is crucial. Especially for diseases caused by hepatitis B and influenza virus, where effective vaccines are available, the impact of varying vaccination regimes on the future disease burden can stimulate debate by providing sound estimates of the potential changes in population health induced by these regimes. Though an exploration of the impact of vaccination regimes on population health, different scenarios can be investigated; for instance, contrasting the effects of age-targeted or universal vaccination. For infections with hepatitis B virus, it was estimated that reductions in the disease burden due to age-targeted vaccination regimes aiming at vaccination of the population under 15 years of age would be much lower than those achieved through the uptake of universal vaccination coverage [31]. For influenza, however, vaccination regimes aiming at the older segments of the population (60+) would result in remarkable reductions in the disease burden [31]. Using the pathogen- and incidence-based DALY as an indicator for the impact of interventions extends the currently available estimates. The predictions presented here are, however, limited to the inclusion of a) demographic changes in the population and b) the impact of interventions. For pragmatic reasons (at least in the baseline scenario), we assumed a constant trend for the incidence and thus estimated the disease burden for an epidemiologic steady-state. With constant changes in the epidemiology of infectious pathogens, driven by genetic conversions of viruses or bacteria, changes in contact patterns within the society, changes in sexual behavior patterns and many other influences, describing future trends by retaining the steady-state assumption might result in under- or overestimation of the disease burden. All these factors are highly

uncertain and to a large certain extent not truly and precisely predictable. To predict the future disease burden of infectious diseases more accurately, infectious disease dynamics such as contact and mixing patterns in a population should be incorporated [128, 129]. Including such patterns would result in more rigorous estimates of future incidence and would in particular account for the potential spread of infections with asymptomatic disease courses.

Another factor introducing considerable uncertainty is the quality of the data that is used for the calculations of disease burden. High-quality data is necessary to provide sound estimates of disease burden. This aspect is important for both mortality and morbidity data. Despite the full coverage of vital registration systems in high-income countries, the effects of misclassification/miscoding have a considerable impact on the mortality estimates for specific causes. Misclassification of causes of death is related to the fact that deaths are simply not coded correctly to the primary cause of death or are coded in residual categories resulting in many deaths not being correctly assigned to a cause or being assigned to a cause that per se cannot be a primary cause of death. In the GBD 2010 study, considerable numbers of death counts were considered to be in the so-called “garbage” coding groups, resulting in wrong coding of deaths ranging from 5.5% in Finland to 69.9% in Sri Lanka [130]. Within the GBD framework, concepts were developed that redistribute wrongly coded deaths to the appropriate locations [45, 120, 131]. This framework allows country-specific corrections of miscoding and thus is of importance in improving the data quality of mortality estimates. It can be assumed that the provided nationally specific correction algorithms might even be specific to sub-national coding practices. However, as correction algorithms are not available at this level, the corrections of the mortality data used for calculations of SEYLLs in NRW and Hong Kong were based on country-specific algorithms for Germany and China, respectively [32, 33]. Even though these redistributions are necessary to provide a correct overview of mortality patterns, Polinder et al. showed in their review of BoD studies that use DALYs as the main outcome measure, that several studies did not consider the re-allocation of ill-defined/garbage codes or simply did not report any redistribution [132].

Nevertheless, the quality of mortality data in countries with well-established vital registration systems is high. In contrast, the availability and quality of data with respect to morbidity is far from perfect and nationally representative estimates for many morbidity indicators are lacking. For instance, when considering infectious diseases, most high-income countries have installed sophisticated surveillance systems that capture trends for infectious diseases. The reporting protocols for capturing those diseases can be of a mandatory or voluntary nature. This already has a significant impact, as voluntary reporting is associated with a lower

likelihood of a case being ascertained and reported to the health authorities [29]. The findings of this thesis showed that, for infectious pathogens/diseases, underestimation is a crucial factor and the data provided by the surveillance systems only represent a small fraction of the “true” number of infections in a population [29]. When data from surveillance systems serve as the input for BoD models, it is therefore necessary to adjust for the underestimation prevalent in the surveillance data. Correcting for underestimation is strongly dependent on the pathogen studied, and the study performed in Germany showed that correction factors vary widely between 1.5 for acute measles infections and 26.8 for acute infections with nontyphoidal *salmonella* spp. [30]. This also highlights the fact that, without correction, the disease burden of infectious diseases will clearly be underestimated. These corrections need to be considered very carefully, because in comparison to other input parameters they are the major drivers of disease burden. Furthermore, it was aimed to have sex and age-specific MF to account for the inherent differences. The process of literature review however, showed that such detailed information is widely lacking and sometimes only available for selected pathogens, countries or time frames. These aspects have and will further stimulate debate about what national surveillance systems capture and what they do not, as well as strategies to tackle these shortcomings.

This thesis has also shown that the assumptions a modeler makes have a substantial impact on the resulting calculations of disease burden. This raises the issue of transparency when dealing with BoD analyses. The review by Polinder et al. showed that, even though BoD studies in general rely on the methods and constructs provided by the GBD study, they vary regarding their social value choices or do not report their choices adequately [132]. This in consequence limits the comparability of results and it is not clear whether the differences between estimates relate to truly observed variance in population health or are simply driven by the arbitrary choices of the modeler. This thesis highlighted the fact that the use of age-weighting and discounting strongly influences the disease burden estimates and, more importantly, selectively impacts on different disease groups and single-disease entities. It was estimated that for the SEYLLs in Hong Kong the implementation of both concepts would result in an overall decrease in SEYLLs of 51.6% and would have a higher impact on group one conditions. Time-discounting alone diminished the overall burden by 25.5% with greater impact on injuries (group three), reduced by 39.8%. Age-weighting alleviated the overall SEYLLs by 33.7% with the largest reductions, of 38.0%, estimated for group one conditions [33]. Another important choice when estimating a health-gap measure is the selection of the normative health goal. In general, if comparisons across countries are intended, the use of a

standard life table as proposed by the GBD approach is appropriate and the review by Polinder et al. indicated that most of the included studies used life expectancy values obtained from the Standard West Level 25 or 26 life tables [132]. Using a global standard ensures comparability across countries, but setting specific choices (e.g. nationally observed life expectancies) can result in more sensitive estimates of burden of disease and can provide a more accurate overview of population health. This thesis used scenario analyses to estimate the impact of altering the standard life expectancy values to those observed in a) Hong Kong [33] and b) Germany [30]. The effects of changing the life expectancy are generally smaller than those observed for time-discounting and age-weighting but again had a selective impact on different disease entities. The SEYLLs as calculated for Hong Kong increased by 10.8% with the biggest increases estimated for group one conditions, of 13.5%. In addition to condition-specific differences sex-specific differences were also identified. For instance, SEYLLs due to group one conditions rose by 18.6% for women and only 9.4% for men, as compared to the baseline scenario in Hong Kong. Furthermore, an impact on the disease ranking could also be identified and the leading cause of death was no longer “trachea, bronchus and lung cancers” but “ischemic heart disease” [33]. These estimates for the four selected pathogens in Germany confirm the condition-specific impact. The estimates showed a varying impact from a decrease in DALYs of -1.1% for infections with hepatitis B virus to an increase of 8% for infections with influenza virus. DALYs due to *salmonella spp.* increased moderately by 5.7% whereas DALYs due to infections with measles virus remained relatively stable with a marginal increase of 0.4%. [30]. Thus, it can be concluded that social value choices are an important and very sensitive input to SMPH and it should be strongly recommended that the publication of BoD estimates should always be accompanied by a detailed description of the model specification, data inputs, and the selected value choices.

The thesis also highlighted the urgent need for sub-national estimates because comprehensive and comparable estimates of disease burden are not only important at a national level but can also help to identify differences in health patterns within countries. Sub-national estimates are generally lacking and are of value especially for countries such as China or Germany, which were selected for testing the SEYLL methodology at a sub-national level in countries with a well-functioning vital registration system and increased availability of health data. China shows significant regional differences in disease patterns ranging from patterns as seen in developed countries (in rural areas) to patterns showing the health status of a developed country with a high share of e.g. chronic diseases (urban areas) [133]. Therefore, estimating a national average as was done in the GBD assessments is of only limited sensitivity and, thus,

also of limited use for setting priorities and introducing setting-specific prevention and intervention measures. This is also the case for the Special Administrative Unit of Hong Kong. Hong Kong shows a premature disease burden pattern that is comparable to other high-income areas. However, lower respiratory infections generally cause a higher burden than in other high-income areas [32, 33, 91, 92]. The data also show a high burden for “trachea, bronchus and lung cancers”, denoting smoking as one public health problem for Hong Kong and indicating a need for increased spending on e.g. anti-smoking campaigns. In Germany, a high-income country, the burden of premature death patterns is dominated by chronic conditions; infectious diseases, at least for the premature death patterns, do not play an important role. In the case of Germany, it is necessary to go beyond differences in premature death patterns arising from epidemiological patterns, and to consider differences in the disease burden related to social determinants. Even though Germany in general is a high-income country, it faces variously faceted socioeconomic inequalities (e.g. income) which in turn may result in health inequalities [134]. The estimates for NRW highlighted “ischemic heart disease” as the leading cause of SEYLL which is in agreement with other assessments of SEYLL in high-income countries [91-93]. Unfortunately, the estimates for NRW cannot be compared to the SEYLLs for other federal states because this is the first assessment of premature mortality for Germany, indicating the urgent need for further assessments. This also holds for the estimates in Hong Kong. Nevertheless, both studies indicated that using the SEYLL as a measure of premature mortality is generally feasible. Both studies highlighted the advantage of the SEYLLs over standard mortality statistics that only count the numbers of death and do not consider the age at death. To measure the effect of premature mortality, time-based measures counting the years of life lost are more appropriate.

Overall, this thesis has shown that despite the success of the BoD approach, setting specific adjustments and sub-national assessments of the disease burden will provide sound additional information to currently available health statistics.

## **8. Conclusions and implications for public health**

The ongoing efforts of public health to inform decisions about the spending of resources with sound evidence are crucial. However, the use of SMPH as shown in this thesis raised several challenges that need to be considered when applying SMPH. Combining epidemiological surrogate measures of health into a single metric is generally preferable to the use of single measures. Nonetheless, one must be aware that even though SMPH such the DALY, or at least the general meaning of a lost year of healthy life, is easy to understand and to

communicate, the interpretation of these kinds of estimates can be very misleading without transparent information about all the input data that informed the calculations. SMPH often have a blackbox reputation because not all assessments of BoD provide information about all the epidemiological data or assumptions about social value choices [84, 132]. This can result in biased information about the health status of a population and in extreme cases lead to biased priorities. Keeping the history of the DALY in mind the GBD study presented the global health status for the first time and included an impressive number of widely heterogeneous health conditions. However, most of the estimates do not currently provide information about sub-national health patterns. It is therefore important to stress the need for such estimates, because ill health, at least in most countries in the world, is not distributed equally across populations. It differs by location, social status, culture and many other determinants that impact on health. Public health can profit from such assessments, which identify the specific needs of those populations and can tailor strategies to improve their health status. According to the objectives of the GBD study, the framework had the aim of accommodating a large set of conditions within a single framework using the DALY as the main outcome measure. This standardized approach might have a selective impact on conditions, as it might not take into consideration the specific aspects of individual diseases. Due to their flexibility, the burden of disease framework and the DALY measure itself have the potential to be adjusted to specific settings. This has already been shown for many specific disease groups [117, 135-137]. Especially for infectious diseases, the pathogen- and incidence-based DALY approach seems to be promising, because it takes into account the specific characteristics of infectious diseases and is able to capture their comprehensive impact. It also allows effects of interventions to be taken into account and can serve as a tool for predictions of future disease burden. Estimating the disease burden in terms of DALYs can additionally serve as the first step for including monetary aspects and conduct cost of illness and cost-effectiveness analyses [109, 138].

This thesis highlighted the value of population health measures, especially for the continuous monitoring of population health. With a standardized framework, it is possible to track changes in population and identify the major drivers of ill health. SMPH are a valuable tool for public health to present the health status of populations, but they also help to identify gaps in the data and can raise debate about the quality of the available data. When using SMPH one must always keep in mind that at the end of the day the BoD estimates are only as strong and reliable as the data input. With the use of SMPH, public health can foster debate about the availability and quality of health data to ensure continuous improvements.

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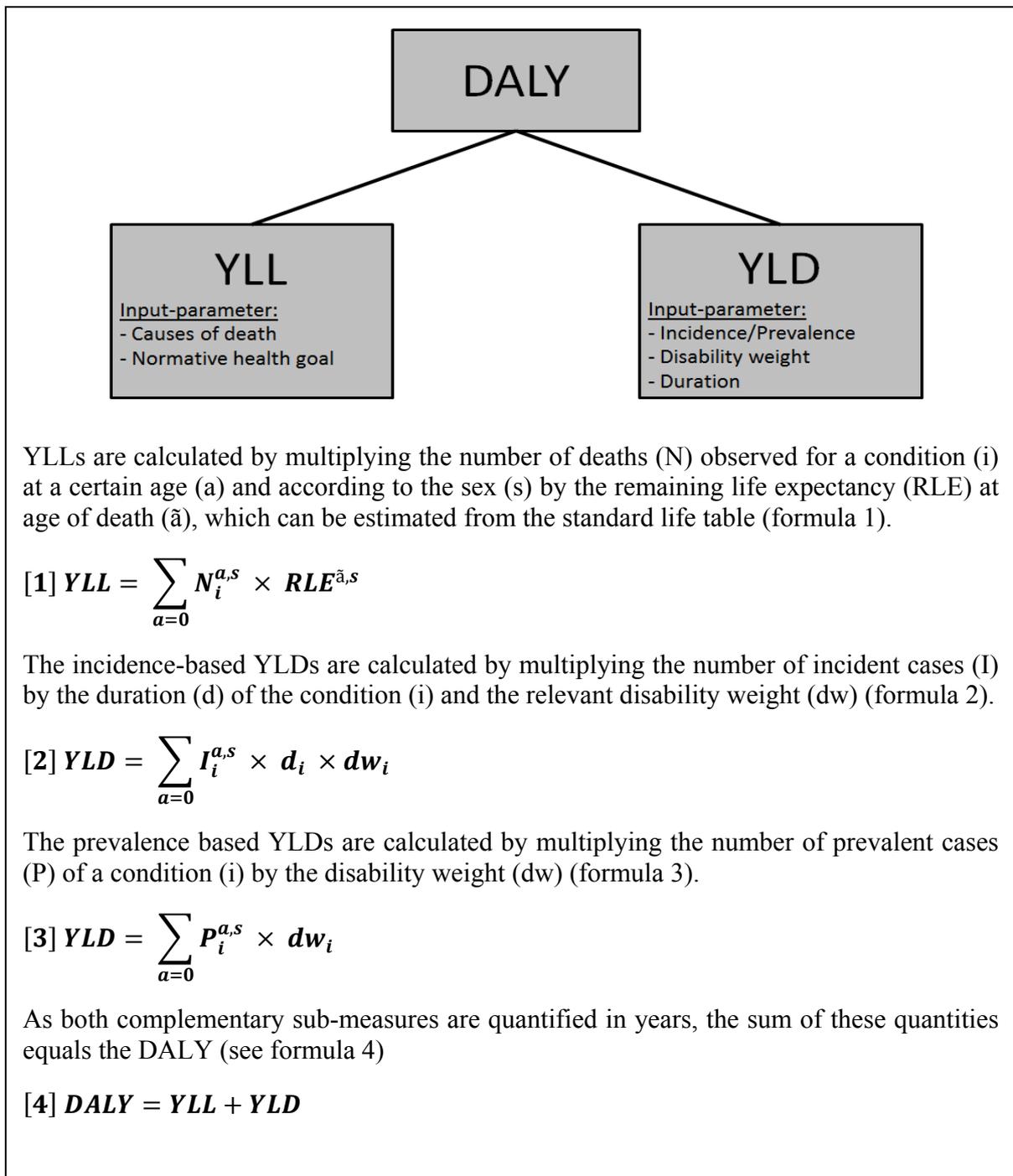
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## 10. Figures and Tables



Box 1: Technical details of the DALY metric

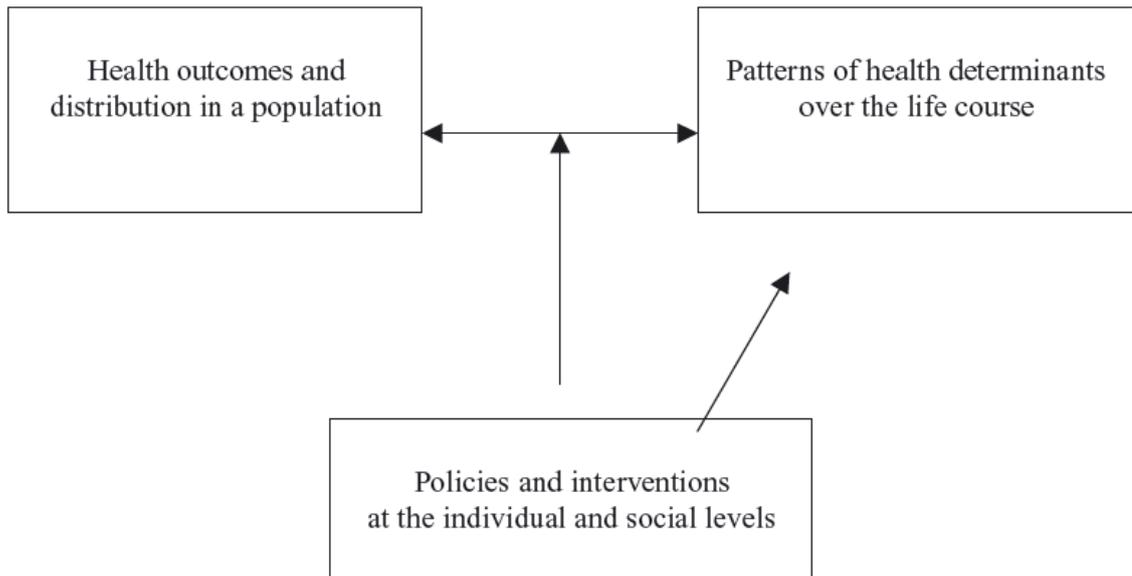


Figure 1: A simplified theoretical framework of population health [37]

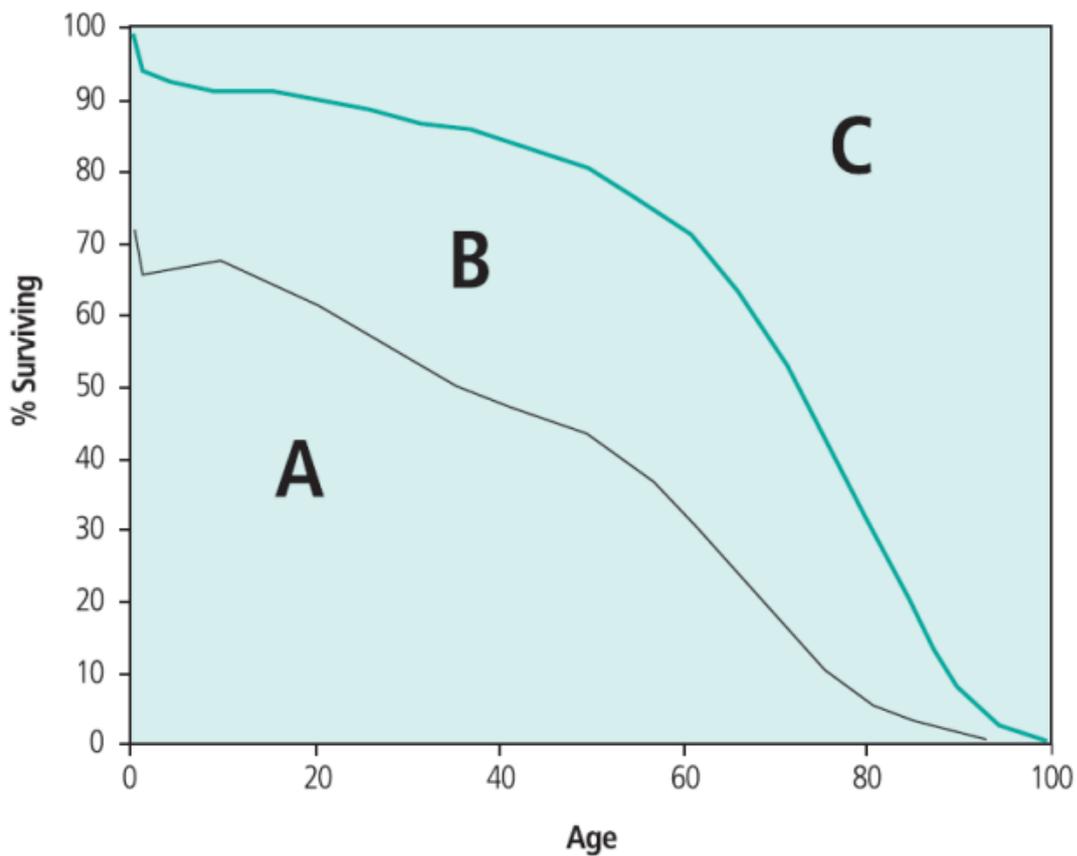


Figure 2: Conceptual framework describing the two basic SMPH families [18]

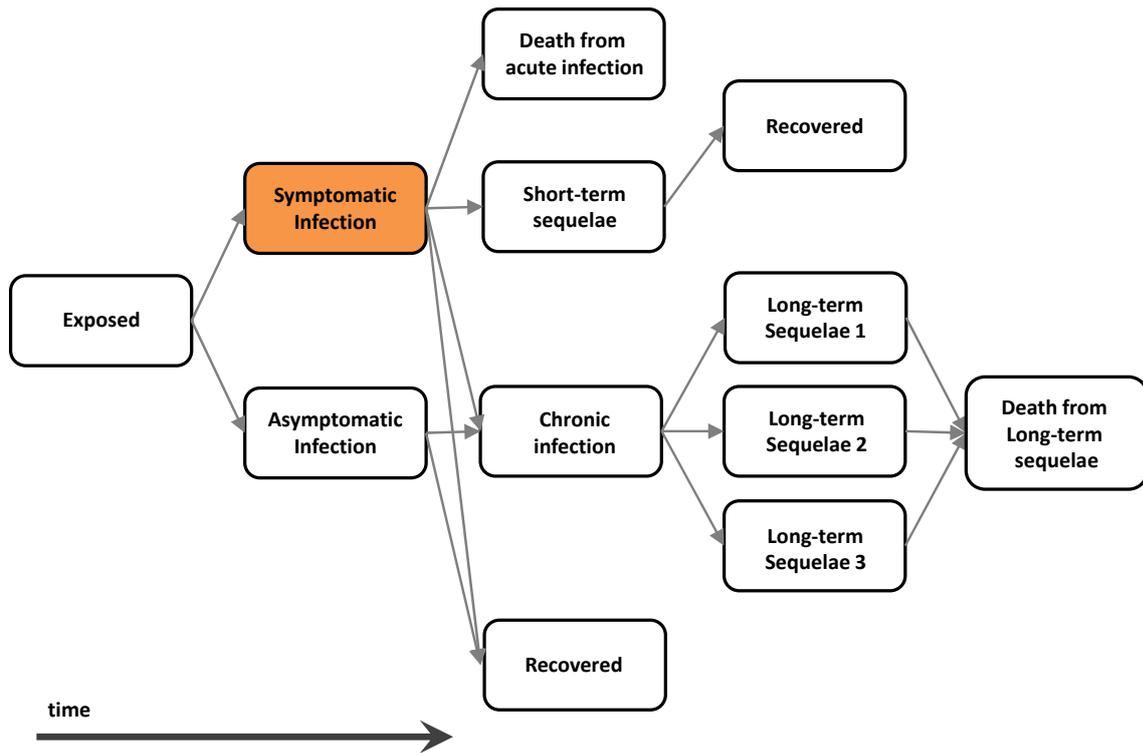


Figure 3: Generic representation of an outcome tree

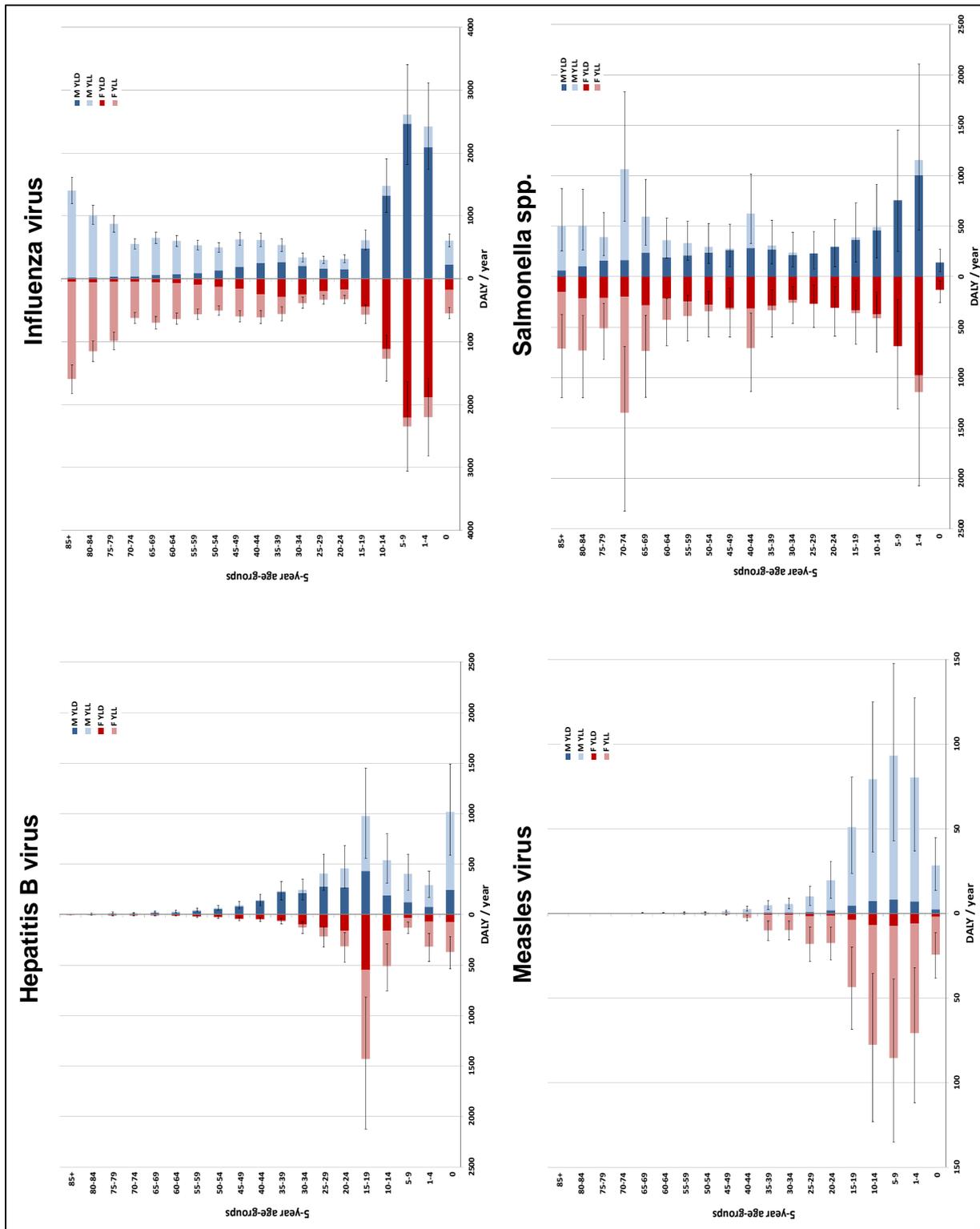
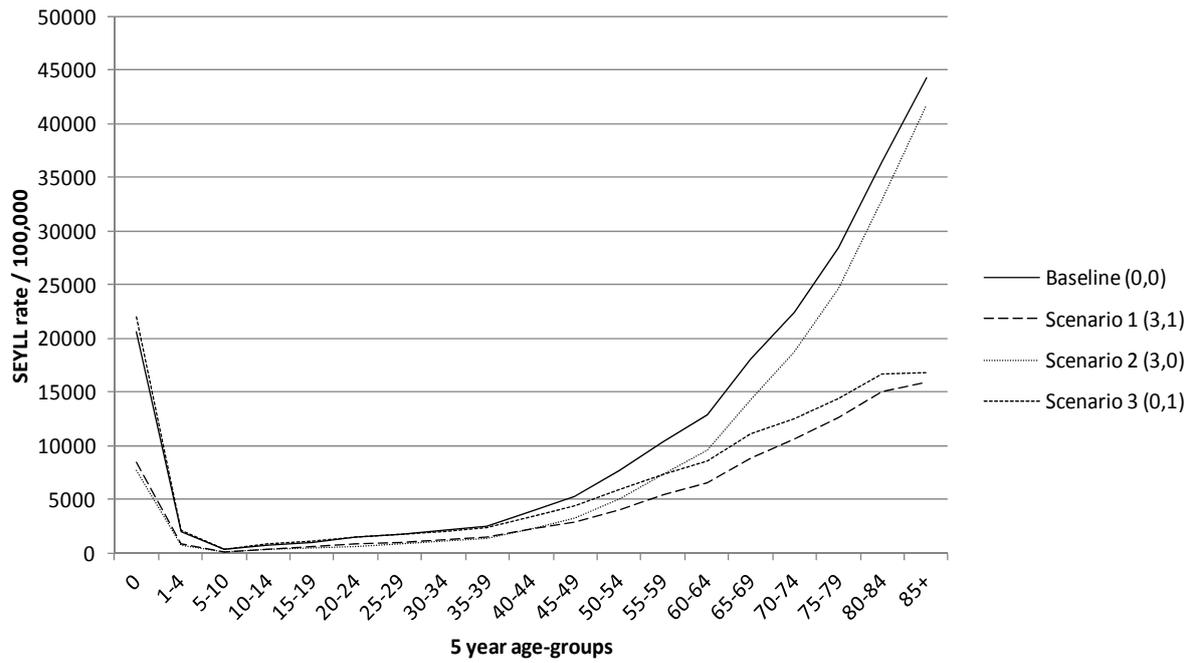


Figure 4: Average DALYs, YLDs per year by sex and age group (Error-bars indicate 95% UIs) (adapted from [30])



Baseline scenario (0,0): standard SEYLL without time-discounting and uniform age-weighting  
 Scenario 1 (3,1): 3% time-discounting and non-uniform age weights  
 Scenario 2 (3,0): 3% time-discounting and uniform age-weights  
 Scenario 3 (0,1): no time-discounting and non-uniform age weights

Figure 5: Scenario analysis with different assumptions about age-weighting and time-discounting [33]

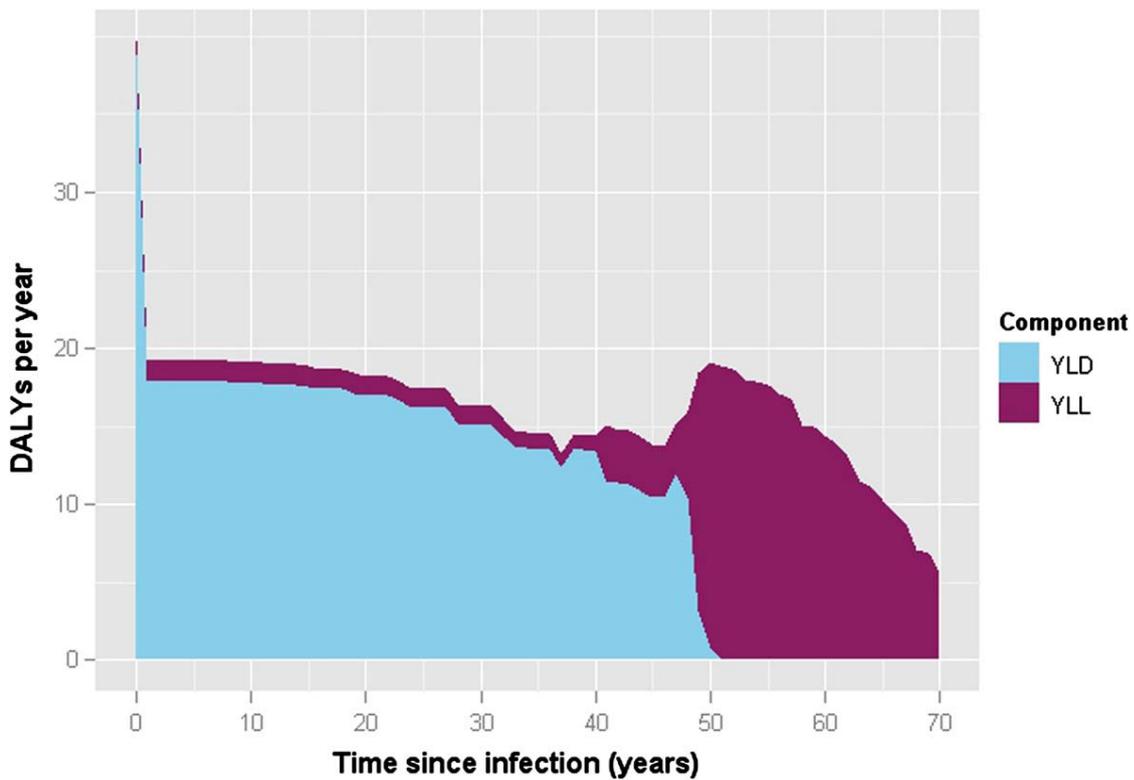


Figure 6: Temporal distribution of disease burden after infection with hepatitis B virus [31]

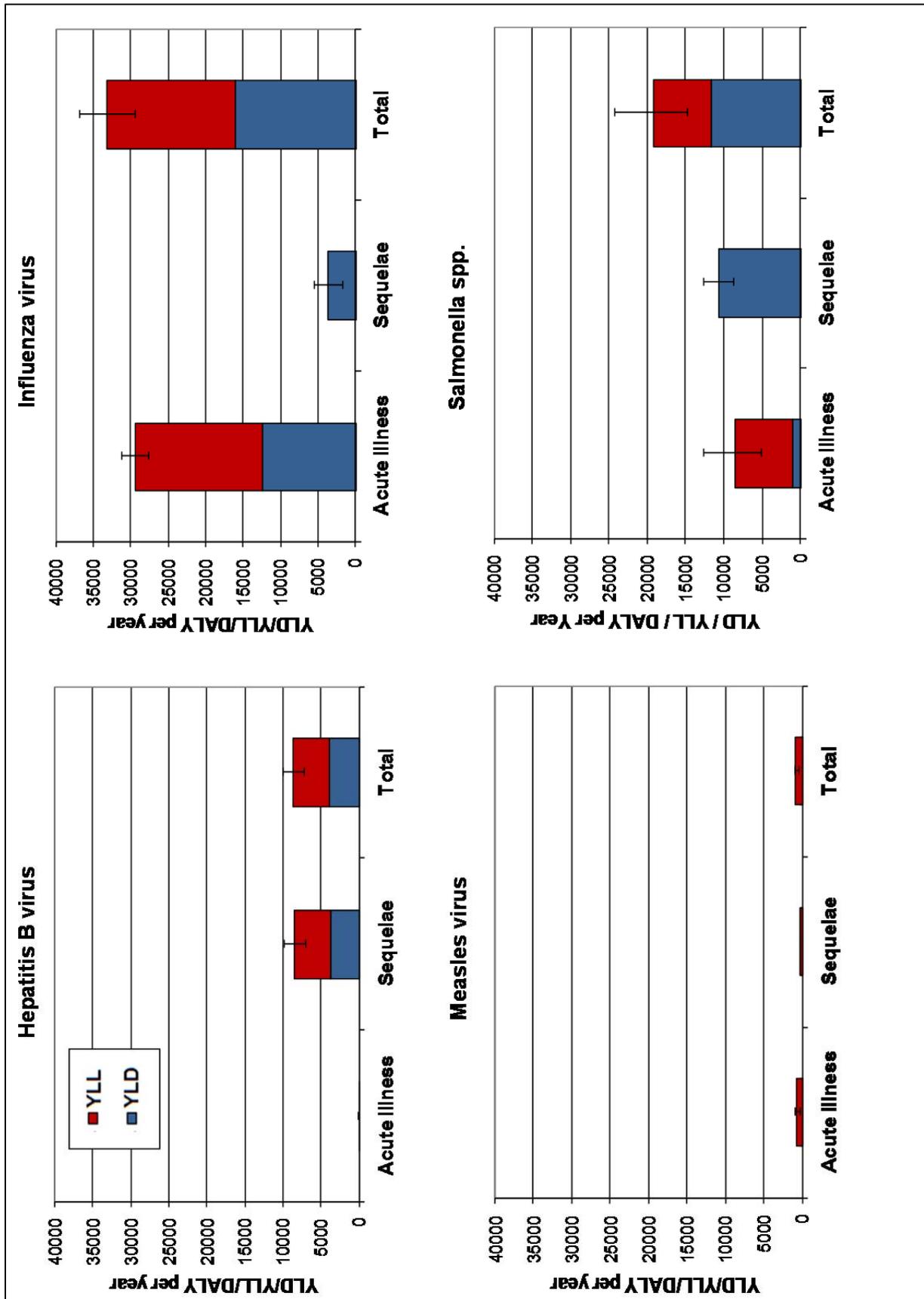


Figure 7: Comparison of the disease burden for the four selected pathogens (error bars indicate 95% UI) (adapted from [30])

Table 1: Results overview of disease burden for the selected pathogens expressed in average YLD, YLL, DALY with 95% UI [30]

	Hepatitis B virus	Influenza virus	Measles virus	<i>Salmonella</i> spp.
<b>Total per year</b>				
YLD	3910 (3431-4389)	16040 (14260- 17882)	66 (53-79)	11697 (9655-13928)
YLL	4797 (3774-5888)	17077 (15244-18965)	674 (348-998)	7418 (4227-11635)
DALY	8708 (7335-10163)	33116 (29504-36849)	740 (413-1066)	19115 (14803-24328)
<b>Acute illness per year</b>				
YLD	170 (151-189)	12363 (11029-13739)	17 (17-18)	1065 (898-1237)
YLL	0	17077 (15244-18965)	671 (345-996)	7418 (4227-11635)
DALY	170 (151-189)	29439 (26283-32708)	688 (363-1013)	8482 (5239-12752)
<b>Sequelae per year</b>				
YLD	3740 (3272-4270)	3677 (3224-4144)	49 (36-62)	10632 (8731-12715)
YLL	4797 (3774-5888)	0	3 (3-3)	0
DALY	8537 (7171-9986)	3679 (3224-4144)	52 (39-65)	10632 (8731-12715)
<b>DALY per 100,000</b>				
Total	10.57 (8.9-12.33)	40.2 (35.8-44.7)	0.90 (0.5-1.29)	23.19 (17.96-29.52)
Acute illness	0.21 (0.18-0.23)	35.7 (31.9-39.7)	0.83 (0.44-1.23)	10.29 (6.36-15.47)
Sequelae	10.34 (8.7-12.12)	4.5 (3.9-5)	0.06 (0.05-0.08)	12.9 (10.59-15.43)
<b>DALY per case</b>				
Total	1.84 (1.54-2.51)	0.03 (0.03-0.03)	0.26 (0.14-0.38)	0.03 (0.03-0.04)
Acute illness per case	0.04 (0.04-0.04)	0.02 (0.02-0.02)	0.24 (0.13-0.36)	0.01 (0.01-0.02)
Sequelae	1.97 (1.51-2.11)	0.01 (0.01-0.01)	0.02 (0.01-0.02)	0.02 (0.02-0.02)

Note: The DALY results presented have been rounded to significant numbers and thus the summary rows do not always add up to exactly 100%

## **Declaration of Originality**

I herewith certify that the work presented is the result of my own independent investigation. Wherever the work is indebted to the work of others it has been acknowledged and cited. This thesis has not been accepted in substance for any other degree, nor is it concurrently being submitted in candidature or achievement of any other degree at any other university.

I further declare that I did not have previously made attempts to do a doctorate at any national or international university

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Dietrich Plaß