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Health Adjusted Life Years (HALY) – A Promising Measure to Estimate the Burden of Zoonotic Diseases on Human Health?

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1. Introduction

Reliable, comprehensive and comparable information on the impact of (zoonotic) diseases on population health are important for policy decision making in Public Health to support allocation processes of scarce resources with best available evidence. Although the availability and quality of health data has increased in the recent past (Boerma et al. 2007, Murray, 2007), there are still relevant limitations when traditional health indicators are used to prioritize diseases and to allocate resources for intervention measures. Difficulties especially come up when comparisons over time, between sub-groups or even between diseases are intended.

In the past, major efforts have been made to describe adverse health effects on population level by using traditional epidemiological indicators such as mortality and the derivative life expectancies (e.g. Greenberg et al. 1989; Shi 1993). Infant mortality rates, life expectancies at birth and other indicators from this group are estimated using information on mortality and thus only reflect the fatal contribution to disease burdens. The morbidity of human populations is usually assessed by using incidence or prevalence measures, giving no information on the severity of the disease for human health. Comparability of disease impacts on the health of populations and health related quality of life is limited due to the characteristics and the large variety of indicators. Composite measures such as Health Adjusted Life Years (HALYs) aspire a comprehensive and comparable description of the burden of disease by integrating the impact of both, mortality and morbidity on population health. Especially for zoonoses which can significantly contribute to mortality as well as morbidity, the concept of HALYs can be a helpful technique to comprehensively assess the burden of disease. In addition HALYs can also be an useful metric for the intangible costs of morbidity and mortality to be used in economic analyses evaluating potential control programs for zoonotic diseases considering also their impact on human health.

Zoonoses were historically defined as diseases only affecting the animal species. In a postulate from 1959 the World Health Organization (WHO) defines zoonotic diseases as an "(...) infection that is naturally transmissible from vertebrates to humans (...)." Further, "(...)

zoonoses may be bacterial, viral or parasitic, or may involve unconventional agents (...)" (WHO, 1959). This definition, still in use, highlights that there is the need to concentrate on two major hosts (animals and humans) that can be affected by various types of agents. Currently, more than 200 zoonotic disease entities, with highly heterogeneous clinical and epidemiological characteristics are known and cause adverse health effects in both humans and animals (Krauss et al. 2004; Palmer et al. 1998). Zoonoses, as well as other infectious diseases play a major role in countries that are characterized by low- and middle income levels. But also so-called high-income countries are not free of threats by zoonotic diseases as has been shown in the recent epidemics of Q-fever in the Netherlands, with more than 999 reported cases in humans in 2008, the largest known Q-fever epidemic so far in the world (VWA, 2011). Inadequate hygienic conditions, close contacts with animals and raw animal products are potential transmission routes for zoonotic diseases.

Several epidemiologic indicators were used to describe the impact of zoonoses on population health (e.g tick-borne encephalitis in Russia; Tokarevich et al. 2011). However, a comprehensive and comparable assessment of zoonoses is a still ongoing effort. In the first Global Burden of Disease and Injury (GBD) Study the impact of 108 disease conditions was estimated for 192 WHO member states (Murray & Lopez, 1996) – a groundbreaking study estimating the health status of the world's population. The GBD study estimated the disease burden of highly heterogeneous disease entities including 27 disease entities defined as infectious diseases. Using the strict definition of natural transmission from animals to humans, 20 of these 27 disease entities can also be classified as zoonoses (Coleman, 2002). In the GBD study the Disability Adjusted Life Years (DALY) was used as the unit of measure to quantify the impact of diseases on population health. The DALY measure belongs to the family of HALYs and was thus considered qualified to comprehensively assess the global burden of disease.

Since the first GBD study, HALY measures and especially the DALY have increasingly been used in Public Health to inform about the overall health status of a population, and to support policy-decision-making processes and/or research priorities. The term HALY covers a broad range of measures that have the feature in common to quantify, both the impact of morbidity and premature mortality, due to diseases (e.g. zoonotic diseases) or other hazards on human population health (Lopez et al. 2006; Mathers et al. 2007). HALY measures have widely been used in human burden of disease (BoD) studies but have also been applied in cost-effectiveness analyses to assess human health-related outcomes resulting when evaluating intervention programs (Zinstag et al. 2007; Roth et al. 2003).

This chapter therefore aims at giving an introduction to the concept of HALYs and discussing their applicability for zoonotic diseases. The first part of the chapter (section 2) will introduce the main ideas and applications of burden of disease analyses and further provide an overview of HALYs. In section 3 major focus is put on the DALY measure. As the DALY was initially developed for the GBD study, a part of this section is dedicated to the main concepts and ideas of the GBD study and will introduce current estimates of zoonoses as presented by the WHO, using the latest estimates available for the year 2004. Section 4 will then give a short overview of studies that used DALY as an outcome-measure to present the disease burden of zoonotic agents and discuss the suitability and usefulness of the HALYs when used for estimating the burden of disease due to zoonotic pathogens. In section 5 we will present and discuss the use of DALYs in cost-effectiveness analyses.

2. Burden of Disease (BoD)

In this section we will introduce the main ideas and applications of burden of disease analyses. Also we will provide an overview of HALYs putting major focus on the DALY measure.

2.1 Burden of Disease – A rationale

In the field of Public Health there is no unambiguous definition and understanding of the term and idea of burden of disease. Burden of disease or the sometimes synonymously used phrase "burden of ill-health" are mainly used to describe heterogeneous concepts that have the idea in common to assess and quantify the impact of adverse health effects on human health (Connecticut Department of Public Health, 1999). Since the early 1990s the term "Burden of Disease" has become closely related and associated with the framework of the Global Burden of Disease and Injury project (GBD) that was jointly initiated and conducted by the WHO, the Harvard School of Public Health and the World Bank. This first and groundbreaking GBD study provided a first comprehensive and comparable overview of disease burden patterns for 192 WHO member states, included both disease and injury conditions, and allowed for stratification by age, sex and WHO regions. The main aims of the GBD study were to provide consistent, comprehensive and globally comparable estimates of the impact of mortality and non-fatal health outcomes on population health. In addition to the first estimates for the year 1990, the GBD project has introduced the public health community to a new conceptual and methodological framework to integrate, validate and analyze incomplete or fragmentary information on disease and injury consequences. The BoD concept as it was used in the GBD study was comprehensively defined by Colin Mathers as:

"a standardized framework for integrating all available information on mortality, cause of death, individual health status, and condition-specific epidemiology to provide an overview of the levels of population health and the causes of loss of health" (Mathers, 2006).

According to this definition BoD can be understood as a conceptual and methodological framework that aims at providing a consistent and comprehensive assessment of disease and injury consequences in humans by combining several sources (mortality and morbidity) of information on the health status of a population. The BoD framework further makes use of composite measures also known as Summary Measures of Population Health (SMPH) for comprehensive assessments of the disease burden (Field & Gold, 1998).

The results and concepts introduced by the first GBD study – though having been critically discussed - have increasingly been used in several countries to provide information for disease prioritizing and health policy decision making processes (e.g. Arnesen & Nord, 1999; Anhand & Hanson, 1997; Arnesen & Kapiriri, 2004). Since the first GBD study the results and methodology were disseminated throughout the public health community and updated results of the GBD study for the years 2000, 2001 and 2004 were generated and are publicly available (Mathers et al. 2003; Lopez et al. 2006; WHO, 2008a). Additionally to the GBD results, the concept was used in several national burden of disease assessments (USA, The Netherland, South Africa) and assessments related to specific disease entities (chikungunya, dengue, foodborne pathogens) (e.g. Melse et al. 2000; Bradshaw et al. 2003; Kemmeren et al. 2006; Michaud et al. 2006; Lier & Havelaar 2007; Krishnamoorthy et al.

2009; Luz et. al 2009). The majority of all these studies used the DALY measure to quantify the impact of various conditions on population health. The DALY is one of the most frequently used and increasingly accepted measure of the HALY family.

2.2 Health adjusted life years – Concepts and definitions

In the literature, three terms are used synonymously to describe population health measures that include both mortality and morbidity information: Health Adjusted Life Years, Summary Measures of Population Health and Composite Health Measures. HALYs are defined by Gold and colleagues as measures "(…) that allow the combined impact of death and morbidity to be considered simultaneously." (Gold et al. 2002). With this characterization HALY share their definition with the so called summary measures of population health (SMPH) which are systematically defined by Field and Gold as:

"Measures that combine information on mortality and non fatal health-outcomes to represent the health of a particular population as a single numerical index"
(Field & Gold, 1998)

According to the definitions both HALY and the more systematized SMPH, have the feature in common to include information on mortality and morbidity and to represent the health situation of a particular population by a complementary measure. These features enable HALYs for comparisons of populations, diseases and interventions and thus present HALYs as being qualified for disease burden assessments.

HALYs can be broadly divided into two major branches – health expectancies and health gaps. Health expectancy measures estimate the time span expected to live in full health taking the impact of disabling conditions on health related quality of life into account (Mathers, 2002). Health expectancies can be understood as an extended idea of the life expectancy indicator that additionally includes morbidity information. A wide of range of health expectancy measures are available and used to quantify healthy life expectancy patterns of various populations. Healthy Life Years (HLY), Disability Free Life expectancy (DFLE) and Disability Adjusted Life Expectancy (DALE) are exemplary entities that have frequently been used in the past. Technically, these measures are built upon the so called Sullivan method, which requires a period life table based on age- and sex- specific death counts in a population and the implementation of information on age- and sex-specific prevalence of people living in a state that is considered to be less than full health (Sullivan, 1966). The HLYs are e.g. used by the European Union as a structural indicator to describe the health situation of the European population (Jagger et al. 2008). Using the same underlying method, DFLE and DALE mainly differ in their definition and quantification of disability. The DFLE uses a dichotomous definition presenting as disability or no disability. In contrast, the DALE measure uses a graduated valuation of severity and includes so called disability weights. The DALE was introduced as a component of the GBD study to elucidate the life expectancies of populations when considering the underlying prevalence of disability (Murray & Lopez 1997; Mathers et al. 2001).

Another well-established member from the group of health expectancies is the Quality Adjusted Life Year (QALY) that is frequently used in the field of health economics. The QALY was developed by economists, operations researchers, and psychologists and is mainly used in cost-effectiveness analyses to quantify the intangible costs of bad health and

premature mortality. Using the QALY in cost-effectiveness analyses allows for assessing the effect of a certain intervention measure (e.g. preventive or curative) by calculating the QALYs gained resulting from positive intervention effects. One QALY can be seen as one year lived in perfect health. Quality of life in the QALY concept is defined as "utility", a measure of preference that people assign to health outcomes. The quality scale of the QALY ranges from death (0) and a state of perfect health (1) (Gold et al. 2002). The QALY has been used as outcome measure in numerous cost-effectiveness and cost-utility analyses all over the world and is mainly associated with the field of health economics. But in particular in high-income countries QALYs, which are data-intensive, has become a standard tool in health technology assessment studies (Belli et al., 1998). QALYs are widely used for diseases like cancer, whereas for infectious diseases there no, or only poor QALYs available, and in particular for infants and children (WHO, 2008b).

In contrast to health expectancies, health gaps measure the time of healthy life lost due to certain disease or injury conditions. The health gaps as a normative measure use a predefined (arbitrarily set or observed) health goal that is expected to be reached by a certain population. Having this normative feature, health gaps then can be used to quantify the difference between the ideal health and the current patterns observed in a population. Figure 1 shows the conceptual framework of health gap measures. In this figures a survivorship curve of a hypothetical initial birth cohort is presented. The x-axis shows age in years and the y-axis the percentage of the hypothetical population surviving over a lifespan of 100 years. The upper curve in the figure indicates for each age along the x-axis the proportion of the hypothetical cohort that will remain alive at that age and includes people living in an ideal health state as well as people living in a state worse than perfect health.

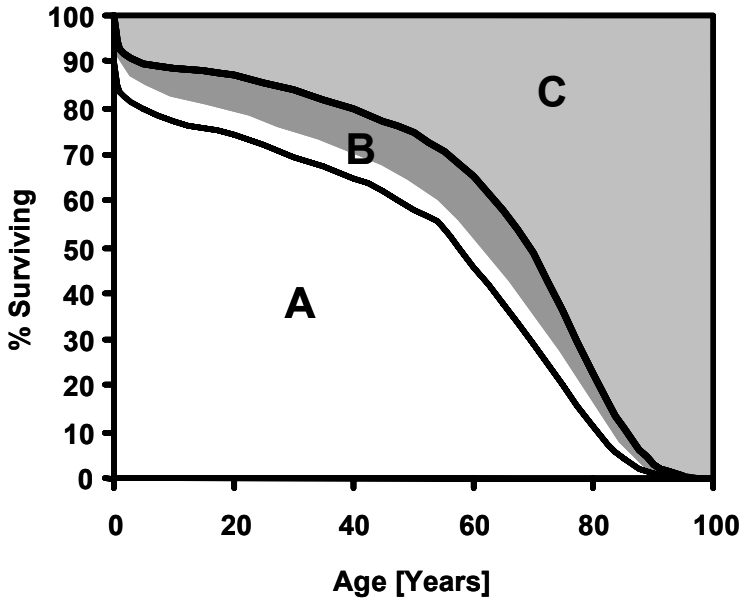

Fig. 1. Basic understanding of the complementary measures - health gaps and health expectancies (modified according to WHO, 2001)

Having identified the percentage of people living in optimal health and people living in health states less than full, an additional second curve (in this example indicated by the lower curve) can be drawn in order to allow for estimates of the burden due to non-fatal health outcomes. Also, setting the health goal and identifying the population in health states less than full will result in the delineation of three areas. While areas A and B under the survivorship curve can be used to derive e.g. life expectancy at birth, health expectancies can be derived from these areas by taking into account some lower weights for area B, i.e. the years lived in health states worse than perfect. As health gaps measure health losses, additional information on the normative health goal is needed to assess the difference between the current health of the population and the potential goal for population health. In figure 1, the health goal is represented by the upper horizontal line enclosing area C. Thus, it is in this particular case assumed that every person in this hypothetical cohort lives in ideal health until the age of 100 years. By adding this health goal, health losses due to both mortality and morbidity can be derived. In figure 1, the losses due to mortality are represented by the area C. Health losses due to living in health states worse than perfect are assessed by adding the upper part of area B to the losses in area C due premature mortality. The size of the part of area B is estimated by using weighting factors, the so called disability weights that estimate the severity of the impact of a certain disease or injury condition. The weights are anchored on a scale from scale between 0 and 1, with zero indicating a state of full health and 1 associated with a state that is comparable to death.

Summing up both health expectancies and health gaps are qualified to present the health status of populations. Health expectancies are using a positive quantification of expected years in full health and health gaps are using a normative description to inform about health losses due to mortality effects and additional impacts of non-fatal health outcomes. For the health expectancies the QALY measure is the one most frequently used in the field of economics to assess the cost-effectiveness of e.g. preventive or curative interventions measures.

One of the most commonly used and globally accepted members of the health gap family are the Disability Adjusted Life Years developed and used as the core measure in the first and all sub-sequent GBD studies to assess the disease burden of a wide range of disease and injury conditions.

3. The Disability Adjusted Life Year (DALY)

The DALY as a member of the health gap family quantifies losses of healthy life years according to a normative health goal. This measure provides estimates of the burden of disease by using a single number reflecting the comprehensive negative impact of heterogeneous conditions on human health. Understanding and interpreting DALY estimates requires having a look beyond the DALY's methodological curtain. The DALY offers several optional inputs, when calculating the disease burden and thus requires to be well informed about how the particular DALY is constructed. Therefore, the following section aims at a) providing detailed information on the DALY concept and b) presenting the complexity of the measure that is needed to comprehensively understand and correctly interpret the DALY estimates. In addition, this chapter will also provide a critical discussion on the use of the DALY for estimating the disease burden of infectious diseases and zoonotic diseases in particular.

The DALY measure as it was used for several regional, national and local burden of disease assessments was initially developed to meet the GBD study objectives (Begg et al. 2007, Michaud et al. 2006 , Murray, 1994). Tailored according to this needs the DALY was introduced as a measure that allows for incorporating effects of mortality and morbidity on health and thus for comprehensively and comparably quantifying health losses globally in one single measurement unit (Murray & Lopez, 1996). One general assumption that was met in the GBD study to allow for e.g. cross-national comparisons was to treat like events occurring in different settings (e.g. countries, socio-economic environments, living conditions) equally. Considering this e.g. an amputation of a leg in Zimbabwe should result in the same disease burden as an amputation of a leg in Turkey (Murray, 1994). Different circumstances e.g. living conditions may have effects on how people can cope with a certain disability. An amputation of a leg that requires the use of a wheelchair may have a smaller disabling effect on an individual who is living in developed nation where facilities are handicapped accessible. Irrespective of e.g. the living conditions both events should contribute equally to the overall disease burden and thus need to be treated equally (Murray, 1994). Thus, to assure comparability of different groups or of a certain group over time it was decided to construct the DALY detached from socioeconomic or environmental conditions (Murray, 1994). Technically, the DALY quantifies the disease burden in terms of years of healthy life lost either due to premature death or due to the impact of non-fatal disease outcomes on population health. Time was chosen as the unit of measure in burden of disease assessments because time, as a general unit of measure is qualified for use in a composite health measure as it presents a simple and intuitive method to subsume effects of mortality and morbidity.

The DALY as a summary measure is calculated by combining complementary information from Years of healthy Life Lost due to premature mortality (YLL) representing the fatal component and from Years of healthy Life lost due to Disability (YLD) reflecting the impact of non-fatal health outcomes.

3.1 Years of Life Lost due to premature death (YLL)

The YLLs basically inform about health losses due to impact of fatal disease and injury conditions. Measuring time lost due to premature mortality, the YLLs can be estimated by the use of different approaches that result in different estimates for the numbers of years lost. Before calculating the YLLs, it is therefore needed to define which approach fits best with the underlying research objectives. To calculate the YLLs, it is further essential to define the health goal that then can be used as a reference value to calculate the difference between the ideally expected and the truly observed values and patterns. There are at least two concepts of life-expectancies that can be used for setting up health goals. On the one hand, there is the idea of a potential life expectancy which sets a potential limit to life at e.g. 65 years of age. People who die before having reached this potential limit would then contribute to the YLLs. E.g. a death of a person at 40 years would contribute to 25 years of healthy life lost. These so called Potential Years of Life Lost (PYLL) are e.g. used by the Organization for Economic Co-operation and Development (OECD) as an indicator for the mortality related disease burden. The OECD uses a potential limit of 70 years and estimates lost years according to this reference value (OECD, 2009). In literature, it was argued that

the concept of PYLLs neglects deaths beyond the chosen age limit and thus does not take into account mortality patterns of the elderly population. Further, interventions focusing on health of the elderly population would result in no benefit when using PYLLs as primary outcome measure (Murray, 1996).

On the other hand, there is also the idea of using concepts that focus on remaining life expectancies. Calculating remaining life-expectancies requires for setting up life tables. Life tables include information on previously observed mortality patterns and trends in populations and thus are qualified to estimate the life expectancy at a certain age. Having arranged the life expectancies allows for estimating the lost remaining life expectancy for a death at a certain age. Technically, there are different techniques to derive life tables that can be used to estimate Period Expected Years of Life Lost (PEYLL), Cohort Expected Years of Life Lost (CEYLL) or Standard Expected Years of life Lost (SEYLL). PEYLLs are based on a period life table, CEYLL on a cohort life table and SEYLL are based on a standard life table, respectively. The DALYs as used in the GBD study follow the concept of Standard Expected Years of Lost and calculate health losses based on the West Level 26 standard life table (WHO, 2001). This life table was derived for a hypothetical cohort using the highest life expectancy at birth observed for Japanese women at the time of the first GBD study. Thus, life expectancy at birth for women and men was set to 82.5 and 80 years, respectively. The two and a half years difference between men and women does not represent the empirically observed, but was chosen in order to only account for the life expectancy differences that can be explained by biologic factors. It was decided not to include lifestyle related, gender-specific differences such as occupational risks, or increased high risk behavior (alcohol, smoking, injuries) (Murray, 1994). Even though this assumption was discussed in literature, the authors of the GBD project postulated, that using the biological sex difference allows for more balanced estimates of YLLs especially when observing the narrowing of the gender gap in low-mortality, high-income countries (Murray, 1994). Technically, the YLLs in the GBD study are calculated as shown below in the formula by multiplying the number of death cases (N) at a certain age of death with the remaining life (L) expectancy at age of death (x) as taken from the standard life table.

$$YLL = N \times L_x$$

Thus e.g. three female neonatal death would contribute to 3 x 82.5y = 247.5 YLLs. As the SEYLL concept uses remaining life expectancy values even deaths at high ages still contribute to the disease burden and interventions aiming at the elderly population would still possibly result in measureable benefits. The values of the West Level 26 standards life table were used to calculate the disease burden for all 192 WHO member states. It can be argued that using this standard set of values sometimes may over- or underestimate the true and observed life expectancy in a certain country, but having the idea of burden of disease in mind this feature enables the estimates to be compared over time, and between age, sex and country (Murray, 1994).

3.2 Years of Life Lost due to Disability (YLD)

As the main idea of the DALY measure was to comprehensively assess and comparably quantify the disease burden, a second and complementary measure, the Years of Life Lost due to Disability (YLD) was used to describe the impact of disabling conditions primarily

non-fatal conditions on population health. There are different concepts of how to describe and quantify the effects of non-fatal health outcomes. The understanding of non-fatal outcomes implemented in the GBD studies is based on the concept of disability as it was defined by the International Classification of Impairments, Disabilities and Handicaps (ICIDH). In the ICIDH of the WHO, disability is described as the lack of ability to perform certain activities in a manner that is normal for human being (WHO, 1980). Using this general definition of disability as a proxy for the impact of conditions on health related quality of life allows for excluding social and environmental aspects. This feature ensures that disabling conditions in different circumstances are measured equally. This narrow definition of disability was used to meet the need for globally comparable information on the impact of disabling conditions.

Further, to assess the impact of diseases and injuries on human health the GBD study provided a set of so called "disability weights" reflecting and quantifying the severity of a disabling condition. Basically, disability weights describe the impact of a disease or an injury on health related quality of life arranged on a scale from zero to one. Zero is representing a status of full health and no disability. In contrast the value one represents life-threatening disability comparable to death. There are different approaches to derive disability weights. Common techniques used are visual analogue scales, methods of standard gambling, person trade-off or time trade-off to derive disability weights in panel settings. These panel settings again may differ in their composition (experts, lay-men and/or patients). Therefore, in literature it was argued that using different panels may result in varying disability weights (Anand & Hanson, 1995). For the GBD study the disability weights were derived for 22 indicator conditions using the person trade-off (PTO) exercise in a group of health professionals who were asked to trade of the life extension of individuals living in different hypothetical health states (Murray & Lopez, 1996). A comprehensive list of disease and injury specific disability weights was presented by Lopez and colleagues (Lopez et al. 2006). Since the first GBD study several additional studies aimed at improving disability weights and resulted in complementary sets of weighting factors (Stouthard et al. 1997; Haagsma et al. 2008; Haagsma et al. 2009). Though, methodological differences do not allow for ad hoc comparisons between the different disability weight sets the studies provide additional (missing) disability weights and introduce methods that allow for more adequate assessment of disability weights. The currently ongoing 2005 update of the GBD study, which is coordinated by the Institute for Health Metrics and Evaluation (IHME) will provide new disability weights based on global panel using an online questionnaire. For more details see (www.globalburden.org).

To calculate the years of life lost due to disability for a particular disease, it is needed to have information on the number of incident cases and the duration of the disease/injury as well as information on the severity of the disease/injury is needed. Technically, the YLDs are calculated using the following simplified formula:

$$YLD = I \times DW \times D$$

In this formula, I describes the number of incident cases, DW the disability weight (on a scale from 0 to 1) and D the duration of the disabling state. According to the formula, e.g. five female cases of mental retardation after a bacterial meningitis with disease onset at 10 years of age would contribute to 5 x 0.483 (DW for mental retardation) x 72,99 y (remaining life expectancy at 10 years from the West Level 26 standard life-table) = 176,3 YLD.

3.3 Calculating DALYs

Having estimated the YLLs and YLDs for a particular disease/injury and a given population, DALYs are then estimated as the sum of both measures.

$$DALY = YLL + YLD$$

3.4 Social value choices

Apart from the disability weights that are used to provide condition-specific preference values, there are two other features of the DALY that can optionally be used to introduce social value choices into the DALY estimates - age-weighting and time-discounting. Both concepts can be incorporated to weigh DALYs reflecting certain preferences about societal concepts.

The time-discounting concept has its source in the field of economics. Basically, time-discounting reflects that most of the people if asked about, prefer benefits today rather than in the future and thus discount the value of future goods (Murray, 1996). It was argued that these preferences can also be applied for health when it is considered as a good. From an individuals' perspective, it was concluded that being healthy today is more worthy then being healthy somewhere in the future. To implement this concept, a 3% time-discount rate was applied in the GBD study to discount future health losses, a rate that is also recommended in the field of economics (Tan-Torres Edejer et al. 2003).

The age-weighting concept is based on the theory of human capital (Drummond, 1997). Human capital describes the value of people for the society they are living in. The main idea of an age-weighting is to provide higher weights to people that are in productive ages (high value for the society because of their roles for economic and social welfare) and lower weights to very young and old people as they are somehow dependent on care and financial support (e.g. pension) of people in productive ages.

In general, the inclusion of social value choices into the DALY has critically been discussed in literature. The main criticism to both of these concepts arises from the ethical perspective. Both age-weighting and time-discounting attach different weightings to years of life lost. Thus for age-weighting e.g. the value of life of an 80 years old person is seen as not of same worth as compared to a person who is 25 (Anand & Hanson 1997). Murray counters this thinking with his view that "unequal age weights (…)" is "(…) an attempt to capture different social roles at different ages " and further, "higher weights for a year of time at a particular age does not mean that the time lived at that age is per se more important to the individual, but that because of social roles the social value of that time may be greater" (Murray, 1994). Thus it is not the worth of a year of an individual, but more the value for society (Murray, 1994). Murray describes the very young and old as being dependent on the rest of society for physical, emotional and financial support. When using both time-discounting and age-weighting one should be aware of possible double counting for certain age groups.

The DALY calculation for the first GBD study used a 3% time discount and non-uniform age-weighting (Murray & Lopez 1996). Since a lot of criticism was expressed the estimates of 2001 and also the most recent update for 2004 were provided using different scenarios with age-weighting and discounting, with age-weighting and no discounting, with discounting but no age-weighting, or even without the inclusion of these social value choices. However

data on the scenarios is only publicly available for WHO regions. Country, age and sex specific data for 2004 is only available with non-uniform age-weights and a 3% time discount rate. DALY measure and especially the social value choices were discussed critically. The main results as presented in the WHO's 2004 update document still use a 3% time-discount rate and non-uniform age-weighting (Arnesen & Kapiriri, 2004; Anand & Hanson, 1997; Anand & Hansen, 1998).

3.5 Incidence versus prevalence

DALYs can be based on both incidence and prevalence data. Since the first GBD study, there is an ongoing debate whether to use the incidence or the prevalence approach. For fatal conditions and the calculation of YLLs it is obvious that using incidence data is obligatory. But for YLD both prevalence and incidence data can be used to estimate the impact of non-fatal health events. Using the prevalence approach and thus assuming a steady state for diseases may result in inaccurate DALY estimates. It was further argued, that the dynamic nature of populations and diseases is more adequately reflected by the use of the incidence approach. For the GBD study it was decided to use the incidence approach to provide estimates being more sensitive to changes in disease trends (Murray, 1994).

3.6 DALY estimates of zoonoses in the GBD estimates of 2004

The GBD studies provide comprehensive and comparable estimates on the current burden of disease for the 192 WHO member states and for 108 disease and injury conditions. The most recent estimates published in 2008 present the burden of disease results for the year 2004 (WHO, 2008a). To get a comprehensive overview of the disease burden, a particular disease classification system was compiled for the GBD study. The GBD disease classification system disentangles in a tree-structure with up to four levels of disaggregation. At first level the disease burden is split up by group I, II, and III conditions. Group I conditions represent communicable, maternal, perinatal, and nutritional conditions and thus, include the entities from the zoonotic disease group. Group II conditions include all non-communicable disease entities (e.g. malignant neoplasms, neuropsychiatric conditions). Group III conditions further incorporate all intentional and unintentional injuries. Single disease conditions such as measles or tetanus are arranged at the fourth and last level of disaggregation. The GBD classification system is complementary to the WHO International Classification of Diseases revision 9 and 10, allowing for converting ICD coded data to the GBD disease classification system.

For the year 2004, a total of 1.52 billion DALYs were lost worldwide. Of these 1.52 billion DALYs about 730 (48% of the total burden) million DALYs were lost due to group II conditions, 187 (12.3% of the total burden) million DALYs due to group III conditions and 603 (39.7%) million DALYs due to group I conditions, respectively. Highlighting group I conditions, which include infectious and thus also zoonotic diseases about 301 million DALYs (19.8% of total burden) were attributable to infectious and parasitic diseases (WHO, 2008a). According to Coleman, who used WHO GBD data for 1999, 20 of the 27 infectious diseases listed in the 1999 GBD classification system by definition belong to the group of zoonotic infections (Coleman, 2002). 26 of the 27 diseases can also be found in the GBD classification of 2004. Hepatitis, caused by hepatitis E virus was not included in the 2004 GBD update. From the remaining 26 diseases there were then 19 conditions related to

zoonotic origin. Thus, about 193 million DALYs (64.2% of the infectious burden) can be attributed to these 19 conditions. Figure 2 shows the percental distribution of the disease burden of those 19 disease entities sharing the definition of zoonotic diseases.

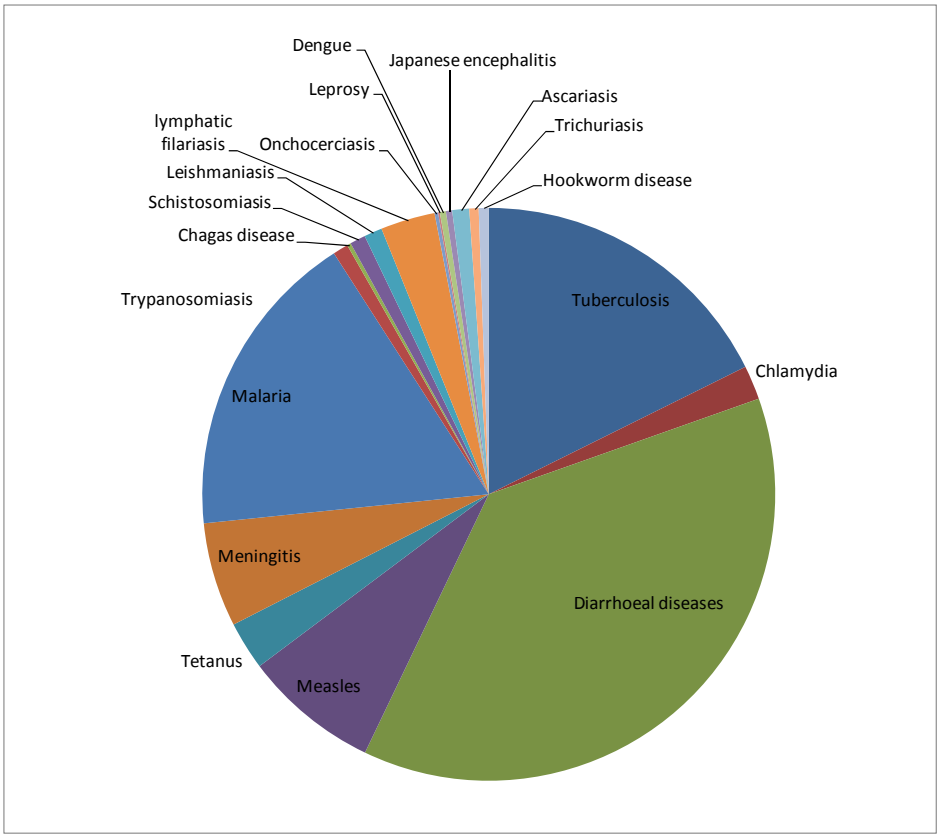

Fig. 2. Percental distribution of disease burden (120 Mio. DALY) due to zoonotic diseases

The figure indicates diarrheal diseases, tuberculosis, and malaria with 37.5, 17.7 and 17.5% as the major drivers of the zoonotic disease burden. Looking at the transmission cycle of the zoonotic disease described in figure one the entities can further be subdivided in two subgroups. 13 of the 19 zoonotic diseases can be attributed to the group with antrhoponotic (human-to-animal; human-to-human) transmission and for the remaining 6 diseases (trypanosomosis, schistosomiasis, leishmaniasis, chagas disease, Japanese B encephalitis, hookworm disease) increased evidence was provided for the high impact of animal-to-human transmissions indicating potential starting points for (veterinary) intervention measures to reduce the transmission and disease burden (Coleman, 2002).

The results of the Global Burden of Disease study indicate a high relevance of zoonoses for human health, including so-called food- and waterborne pathogens whereby some animals are often a reservoir for infections. The burden estimates for e.g. diarrheal disease also include cases that probably are not induced by a zoonotic agent. Therefore, it can be

assumed that when focusing on the definition of Coleman and only using the GBD estimates one may overestimate the disease burden of Zoonoses. However, according to the different transmission cycles of the 19 disease entities, potential intervention measure should not only aim at reduction of human-to-human transmission but also take into account intervention measures, starting from the farm and moving to the table, to reduce the global zoonotic disease burden.

4. Using the DALY measure for assessing the disease burden of infectious diseases/zoonoses

In this section we will give a short overview of studies using DALY as an outcome-measure to present the disese burden of zoonotic agents and discuss the suitability and usefulness of the HALYs when used for estimating the burden of disease due to zoonotic pathgoens.

The heterogeneous characteristics and the dynamic nature of infectious diseases raise special requirements towards HALYs. In the GBD study the DALY is used for a set of very heterogeneous conditions such as non-communicable chronic diseases, injuries, or infectious diseases. Having the unique nature of infectious diseases in mind, it was argued that the DALY measure does not adequately capture the whole spectrum of infectious conditions and further seems to underestimate the true burden due to infectious diseases (Zou, 2001; Arnesen & Karpiriri, 2004; ECDC, 2010). As DALYs are based on epidemiological indicators (e.g. incidence, death cases) the quality of DALY estimates is highly dependent on data availability going further than notified data and mortality registration only.

For infectious diseases many countries have set up sophisticated surveillance measures whereby observed cases will have to be notified, but still high rates of under-estimation (under-reporting and under-ascertainment) are observed even in countries with high surveillance standards (Sethi et al. 1999; Wheeler et al. 1999; Food Standard Agency, 2000; Poggensee et al. 2009). Also there are high rates of asymptomatic cases (e.g. hepatitis B and C) not detected and therefore not reported to the health authorities and thus substantially mask the current true infectious disease burden. Having the example of hepatitis B, individuals with an infection who experience an asymptomatic disease course may later progress to severe disease states such as liver cirrhosis and hepatocellular carcinoma. These burdensome entities have a severe and sometime fatal course and thus would contribute to a high disease burden. However, GBD estimates usually take into account only acute symptomatic infectious cases and for most of the diseases neglected the disease burden caused by the sequelae associated with the initial infection. Further, the acute illness data e.g. from mandatory notification systems may be masked by under-estimation and thus only represent a small percentage of the real disease burden. Additionally to incomplete statistics, and inadequate attention towards long-term disease sequelae, coding practices of death cases also hamper the completeness of infectious disease burden as measured in the original GBD study. For example, an incidental death case has to be classified according to the ICD 10 classification system. The etiology of liver cirrhosis allows for multiple causes, such as alcohol use disorder, autoimmune disorders, viral hepatitis and many others. A certain number of deaths cases that result as a consequence from e.g. liver cirrhosis or hepatocellular carcinoma, though induced by a long lasting hepatitis B infection are incorrectly counted as e.g. neoplasms not related to an initial infection (Zou, 2001; Pinheiro et al. 2010). These misdiagnoses may lead to essential underestimation of infectious disease burden.

4.1 Incidence and pathogen-based approach

To better account for infectious disease characteristics several burden of infectious disease studies prefer the use of the so called pathogen-based approach rather than using the disease-specific one from the GBD study (e.g. Havelaar et al. 2004; Mangen et al 2005; Kemmeren et al., 2006; Cressey and Lake, 2007; ECDC, 2010). In the incidence and pathogen-based approach, the initial infection with a pathogen is used as the starting point for disease burden estimations. The pathogen-based approach is mainly based on so called outcome-trees that describe the natural course of a disease (figure 2). Starting with an initial infection the outcome-tree provides transition probabilities that inform about the percentage of people moving from one state to another after being infected by a certain pathogen. Using the outcome-trees allows for including all possible resulting short- and long-term sequelae and thus presenting the detailed pathways of an infection (see figure 2).

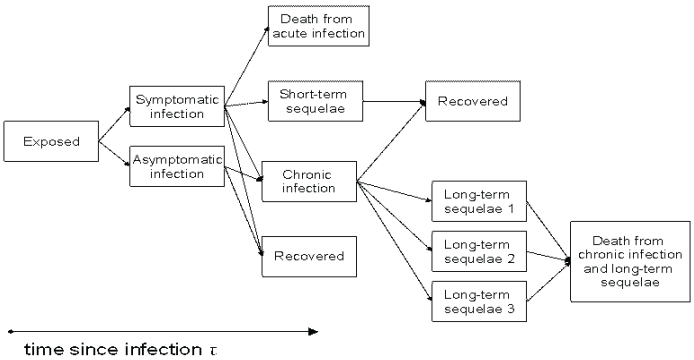

Fig. 3. The standard outcome-tree with possible sequelae (ECDC, 2010)

Using the information about the initial infection the pathogen-based and the included outcome-tree feature allow to comprehensively assess the disease burden due to infectious pathogens. The incidence and pathogen-based DALY approach is currently in use for a European study on infectious diseases (ECDC, 2010). In this study the disease burden of 32 infectious pathogens, including several zoonotic diseases is calculated for the European Union and EEA / EFTA countries (ECDC, 2010).

But next to this European study, there are also some national studies using the incidence and pathogen-approach, in particular for prioritization of foodborne pathogens (e.g. for the Netherlands (Kemmeren et al., 2006; Haagsma et al., 2009; and recently updated by Havelaar et al., 2012); for New Zealand (Cressey and Lake 2007)). In the recent update of Havelaar and colleagues, disease burden for a total of 14 foodborne pathogens was estimated. These were thermophilic Campylobacter spp.; Shiga-toxin producing Escherichia coli O157 (STEC O157); non-typhoidal Salmonella spp.; norovirus; rotavirus; Cryptosporidium spp.; Giardia spp.; C. aureus; Bacillus cereus; Clostridium perfringens; Staphylococcus aureus; hepatitis A virus; hepatitis E virus; Listeria monocytogenes and Toxoplasma gondii. The incidence of community-acquired non-consulting cases, patients consulting their general practitioner, those admitted to hospital, as well as the incidence of sequelae and fatal cases was estimated using surveillance data, cohort studies and published

data. Data were combined with results from an expert survey to assess the fraction of cases attributable to food, and the main food groups contributing to transmission. The authors estimated that these fourteen pathogens would have in 2009 accounted for a total of 1.8 million cases of disease (approx. 10,600 per 100,000) and 233 deaths (1.4 per 100,000), resulting in 13,500 DALY (82 DALY per 100,000), or 11,300 DALY if discounted with 1.5% (according to Dutch guidelines) and 9,700 DALY if discounted with 3.5% (according to UK guidelines). Foodborne transmission was responsible for approximately 680,000 cases (approximately 4,100 per 100,000), 78 deaths (0.5 per 100,000) and 5,800 DALY (35 per 100,000) (Havelaar et al., 2012). In particular for pathogens like thermophilic Campylobacter spp.; Shiga-toxin producing Escherichia coli O157 (STEC O157); non-typhoidal Salmonella spp.; Listeria monocytogenes and Toxoplasma gondii did the associated sequelae result in far higher disease burden then if considering acute illness only (Havelaar et al, 2012). All studies that used the incidence and pathogen-based approach highlight the impact of short and long-term sequelae of infectious pathogens on the estimated disease burden. Therefore this approach allows for more comprehensive assessment of infectious disease burden.

4.2 Advantages, weaknesses and challenges of the DALY measure

The advantages of the DALY measure are in short:

- The biggest advantage is that morbidity (YLD) and mortality (YLL) effects are combined in one measure.
- DALY allow the comparison between different health hazards, why prioritization is possible.
- Also the DALY measure offers the ability to assess the impact of prevention strategies (as will be discussed in more detail in the following section)

The weakness of the DALY measure in short are:

- The used disability weights for YLD are based on subjective measures, whereby the applied technique and the used panel (e.g. experts, patients or lay-people) have a strong influence on the obtained disability weights.
- There is an on-going debate over their validity
- The DALY measure is not widely recognized outside the health sector.

The biggest challenges of the DALY measure consist in:

- Getting estimates of the total number of infections in the population due to a particular pathogen.
- When using the incidence and pathogen-based approach, defining the outcome tree with all relevant health outcomes for a particular pathogen.
- Getting appropriated transmission probabilities for the different health outcomes represented in the outcome tree.

5. Use of DALYs in economic analyses

This section will discuss the use of DALY in cost-effectiveness analysis. For a better understanding we will shortly highlight why to conduct an economic analysis; what economics is; list the potential perspectives that can be used in economic evaluations and shortly describe the different types of economic evaluations. Before then discussing the use

of DALYs in cost-effectiveness analyses, illustrated by published studies of cost-effectiveness for controlling zoonotic diseases / foodborne pathogens. Foodborne pathogens will be included because they show some similarities with zoonotic diseases. Both have economic effects on all type of stakeholders from the stable to the table, and both affect also human health, though, foodborne pathogens do mostly not affect animal health. Consequently, monetary effects are obvious in several sectors of the society (e.g. farmers, food chain, consumers, health care sector).

5.1 Why conducting an economic analysis?

Once prioritization has taken place, interventions might be planned to tackle the problem. But given that most decision makers have to deal with limited budgets (e.g. the Minister of Health; Animal Health Authorities), the question is: "Which of the potential interventions will yield the best value for the money invested?". In order to answer this question, an economic analysis (e.g. cost-effectiveness analysis) is required (Drummond et al. 1997; Belli et al. 2001), in which either different potential interventions could be compared with each other (e.g. Is it more cost-effective to control Campylobacter at farm level, at slaughterhouse level or at consumer level? (Havelaar et al. 2007)), or a single intervention would be compared with no intervention (e.g. Is it cost-effective to introduce rotavirus vaccination in the National Immunization program? (Mangen et al. 2010a; Esposito et al. 2011)). In such an economic analysis, HALYs could be used to measure the intangible costs of bad health and premature mortality. HALYs and costs are estimated for each intervention separately and then compared. The incremental cost-effectiveness is then calculated in order to determine which intervention will offer the best value for money invested.

5.2 What is economics?

Economics, as a discipline, studies how people and societies make choices about scarce resources that could be used elsewhere or in another way (Belli et al, 2001). The main purpose of an economic analysis is hereby to provide a framework for analyzing the full implications of potential choices. Whereby an economic analysis is most useful if applied before the implementation of a new project, as supporting the decision-making process and identifying poor projects (Belli al. 2001). If conducted after the implementation of a project, economic analysis can only help in the decision of whether or not to continue with a project (Belli et al. 1998).

Opportunity-cost or the potential use of any scarce resource in alternative programs is an important factor in economic analyses. Opportunity-cost is what people give up, now and in the future, to accomplish a particular undertaking (Sassone and Schaffer 1978). The 'return' or 'opportunity' that could have been gained in other projects using the same resources is therefore the real cost of accomplishing an undertaking, not simply the money spend. Therefore opting to use resources for one particular purpose always means giving up the opportunity to use them in other desirable ways. The key question in economics is therefore: Are the benefits from what is 'chosen' greater than what is 'forgone? (Sassone and Schaffer 1978).

5.3 Economic evaluations

A full economic evaluation is characterized by two facts, namely:

- that there is a comparison with at least one alternative, even if this alternative is "do nothing" (or care-as-usual);
- and that both, costs and outcomes of the alternatives are analyzed.

If one of these two conditions is not fulfilled, because either the evaluation considers only costs, or only consequences, or there is no comparator, then it is only a partial evaluation that lacks the context to judge the relative performance of a program.

There are four techniques used to conduct full economic evaluations. These are: cost-minimization analysis (CMA); cost-effectiveness analysis (CEA); cost–utility analysis (CUA) and cost–benefit analysis (CBA). CMA requires equal effectiveness of all programs and is therefore only applied if two or more options have the same outcome (Drummond et al. 1997). Only monetary costs incurring in the alternative programs are considered and compared. Measuring consequences (outcomes) is not necessary. Interventions to control infectious diseases /zoonoses, however, usually have different effects, why CMA is seldom an adequate methodology to apply. Cost-effectiveness analysis is applied to interventions that have a single non-monetary effect, common to all of them but different in magnitude, and which is measured in physical units (Drummond et al. 1997; Belli et al. 1998; Belli et al. 2001). However, all other effects such as costs (inputs) and outcomes of the program under study are measured and evaluated in monetary terms. The ratio of interest in a CEA is then the net cost (monetary costs corrected for monetary benefits) per unit of effect (e.g. the net cost per averted Brucellosis infection; the net cost per averted Q-fever infection of goats, etc.). A big disadvantage of the CEA technique is that a comparison is only possible for program with the same outcome. However this non-monetary single effect is often more meaningful to specialist(s) than e.g. DALYs. Cost–utility analysis or weighted cost-effectiveness analysis is a variation on cost-effectiveness analysis (Belli et al. 2001). Although some authors prefer not to make a distinction between CEA and CUA (Drummond et al. 1997). CUA requires a valuation scheme that combines various effects into a single combined measurement, for which some weighting scheme is required (Belli et al. 2001). E.g. DALYs (disability-adjusted life years) and QALYs (quality-adjusted life years) are such metric units whereby effects on human morbidity and mortality are weighted and transferred into a single metric unit. The CUA methodology is then also widely used in public health economic evaluations (Gold et al. 1996; Drummond et al. 1997; Tan-Torres Edejer et al. 2003; WHO 2008b). All other consequences (costs and benefits), however, are measured and valued in monetary terms, as in a CEA. Also as in the CEA, the results of a cost–utility analysis are expressed in terms of net cost per unit of weighted combined effect (e.g. net costs per DALY averted). The most cost-effective program is the one with the lowest net cost per unit of weighted combined effect. By weighting and combining effects into a weighted unit, CUA allows the comparison of sometimes very different programs, such as vaccination programs and environmental programs. However, the terms (such as health outcome) have to be the same for all programs compared and, as with the CEA methodology, comparison with projects having different non-monetary effects is not possible. Theoretically cost-benefit analysis is the 'gold standard' in economic evaluation (Belli et al. 2001), whereby all effects, both monetary and intangible, direct and indirect, are measured and expressed in monetary terms. CBA results can be presented as net present value, internal rate of return (the remuneration against investment stated as a proportion or percentage) or as cost–benefit ratios. The main advantage of CBA is that all effects are valued in monetary terms, allowing the comparison of a given program with any other

program, both in the same sector as well as in different sectors, and is therefore recommended by Belli et al. (2001) when health sector investments are compared with investments in other sectors. Unlike other economic evaluations, CBA allows you to consider allocated efficiency in its widest sense, by comparing the net economic impact of very different activities (Belli et al. 2001). For example, the societal gain from a newly introduced Brucellosis vaccination program of the cattle livestock might be compared with the gain to society from building a bridge. CBA is the most complete quantitative approach from an economic standpoint. However, assigning a monetary value to non-monetary benefits such as human health outcomes is much more complicated. Therefore one of the major problems, and also often the weakness in this type of evaluation, is the valuation of non-monetary factors.

There is no 'ideal' type of economic evaluation. All of them have their limitations. The analyst must therefore first identify the problem, define the boundaries, chose potential alternatives, define the target population (e.g. cattle livestock; children; inhabitants from country *x*; farmers; etc.); define the type of evalutions to evaluate; and choose the most appropriate perspective for answering the question, before then selecting the technique that best answers the question (Belli, Anderson et al. 2001). If the project objective is narrow, such as increasing the number of vaccinated livestock or increasing the number of vaccinated people, then the focus will be only at alternative ways of increasing the number of vaccinated livestock /persons and the success will be judged in terms of the number of vaccinated livestock /persons reached (Belli et al. 2001). Whereas if the program under study tries to achieve a broader objective, such as improvement of health status by e.g. vaccination of goats against Q-fever in order to reduce infections in humans, then in the evaluation we will not only look at alternative ways of reaching a maximum of goats, but also at alternative interventions that might reduce infections in humans, and as such reduce morbidity and mortality of the target human population. The judgment of success of the project is then the impact on human health status.

Therefore starting with a clear definition of the program reduces the number of alternatives to consider, and helps selecting the most appropriated type of evaluation and the performance indicators to look at (Belli, Anderson et al. 2001). The differences between the situation with and without the program are the basis for assessing the incremental costs and benefits of the project (Belli, Anderson et al. 2001), why it is important to clarify what happens if the program is carried out or not. Another important question is about the alternatives. Their choice has a fundamental impact on the type of evaluation, the data collected and the interpretation of the findings (WHO 2008). In the case of zoonoses, interventions might be targeted at the livestock and/or at human health. And might target either the whole human population and/or livestock in a country and geographic area, respectively, or at a specific group of persons/livestock within a country. In all cases does the target group strongly influence the choice of effects considered (monetary and non-monetary), as well as the results of an economic evaluation.

Economic evaluations can be applied at a number of levels. Potential perspectives that are used in public health economic evaluations are: individual perspective (e.g. patient); health care providers (e.g. hospital, doctor, etc.); third payer (i.e. often health insurance perspective); health authorities; manufacturers and society (a country, for example the Netherlands, or the international community, for example the EU; WHO; etc.). However, for zoonoses and foodborne pathogens the impact of these diseases does not only affect human

health and as such the health care sector, but has also an impact on other sectors and stakeholders in the society. Therefore, other perspectives might be necessary. For example one of the following perspectives: another authority than health authorities (e.g. in the case of zoonosis it could be the animal health authority or ministry of agriculture, etc.); individual stakeholder affected (e.g. farmer; slaughterhouse; etc); another sector than health care (e.g. farmers' associations, slaughterhouses, or any other stakeholder in the chain or related industry); consumer. The chosen perspective determines which potential costs and consequences to be included in an economic evaluation.

Further should the time frame (the period over which the intervention is applied) and the analytic horizon (the period over which the costs and outcomes that occur as results of the intervention are considered) be long enough to capture all relevant positive and negative effects (WHO 2008b). Their respective durations are influenced by the type of intervention evaluated, the program itself, the target population and the model used (WHO 2008b).

The type of intervention to be analyzed determines what type of epidemiological model is required to capture key elements of the disease. Jit and Brisson (2011) conducted a literature review on infectious diseases and modeling, whereby looking at interventions such as vaccination, screening, social distancing, post-exposure treatment and culling (for animal and plant diseases only). Based on their findings they developed a flow diagram with seven key questions. Based on the answers to these seven key questions the analyst can evaluate which type of model would be the most appropriated choice.

5.4 Cost-effectiveness

After having assessed costs and effects of an intervention, and the comparator, the next step in an economic evaluation is to link these results in the form of a ratio, mostly in the form of an (incremental) cost-effectiveness ratio (ICER).

An ICER compares the differences between the costs and health outcomes of two alternative interventions that compete for the same resources. It is generally described as the additional cost per additional health outcome. The ICER numerator includes the differences in program costs and can include in addition the averted costs, depending on the choice of the perspective. Similarly, the ICER denominator is the difference in the measured effect e.g. DALY:

$$ICER = \begin{pmatrix} C_{Intervention\ A} - C_{Intervention\ B} \\ E_{Intervention\ A} - E_{Intervention\ B} \end{pmatrix}$$

whereby *C* stays for costs and *E* for effects.

5.5 Cost-effectiveness studies using DALY in zoonoses and foodborne diseases

Most published cost-effectiveness studies in zoonoses and foodborne diseases are mostly only restricted to animal health and related industry. The impact on human health is seldom considered.

Nevertheless there are a few examples whereby also human health was considered, using DALY to measure the impact of the intervention on human health (e.g. Roth et al 2003; Budke et al 2005; Mangen et al 2007). A nice example of economic evaluations studying the impact of intervention on zoonoses and using DALY to express the intangible costs of bad health and

premature mortality is the one by Roth et al. (2003). Using a dynamic model of livestock-to-human brucellosis transmission these authors simulate for Tibet the impact of vaccinating the livestock against brucellosis on the national animal health and national human health, and consequently expressed their results as costs per DALY averted. Another example of such an economic evaluation is the CARMA project (Havelaar et al. 2007; Mangen et al. 2007). These authors studied several interventions controlling campylobacter infections in the Dutch population. They looked at interventions at farm-level; in the slaughterhouse and at consumer level. For all these interventions the effect on human health was measured in averted infections, as well as in averted DALY. But also interventions costs were considered, as well as averted costs due to averted infections were considered in this study.

Both studies are nice demonstrations for the usefulness of the DALY approach in economic evaluations when aiming at measuring the impact of an intervention on human health.

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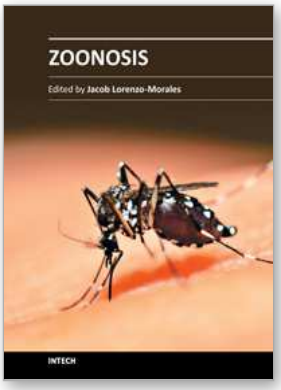

Zoonosis

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Zoonotic diseases are mainly caused by bacterial, viral or parasitic agents although "unconventional agents" such as prions could also be involved in causing zoonotic diseases. Many of the zoonotic diseases are a public health concern but also affect the production of food of animal origin thus they could cause problems in international trade of animal-origin goods. A major factor contributing to the emergence of new zoonotic pathogens in human populations is increased contact between humans and animals. This book provides an insight on zoonosis and both authors and the editor hope that the work compiled in it would help to raise awareness and interest in this field. It should also help researchers, clinicians and other readers in their research and clinical usage.

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