EU Proposal/Contract no.: 506122

Project acronym: Med-Vet-Net

Project full title: Network for the Prevention and Control of Zoonoses

NETWORK OF EXCELLENCE PRIORITY 5: Food Safety and Quality

Report no. 07-002

Methodological choices for calculating the disease burden and cost-of-illness of foodborne zoonoses in European countries

Date of Report: August 2007

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Report funded as part of Med-Vet-Net Workpackage 23

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A general trend in public health research is the use of integrated metrics as one aspect for indicating areas of priorities for actions. Infectious diseases typically have several possible health outcomes, ranging from acute self-limiting diseases to chronic disabilities or even death. These different outcomes can be combined in single composite measures such as the Disability Adjusted Life Years (DALYs) or the (monetary) cost-of-illness. Disease burden and cost-of-illness calculations involve the need to make several choices on the exact methodology that have an impact on the final results. These choices must be appropriate for the decision context of the study, and should reflect the values that exist in the societies under study. The choices for this particular project are discussed below.

Disability Adjusted Life Years (DALYs)

The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death to include equivalent years of 'healthy' life lost in states of less than full health, broadly termed disability. One DALY is thus one lost year of healthy life (WHO definition). The DALY methodology has been described by Murray and co-workers in the Global Burden of Disease (GBD) project[16 18] using the following equation:

$$DALY = YLL + YLD.$$

YLL is the number of years of life lost due to mortality and *YLD* is the number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability. The *YLL* due to a specific disease in a specified population is calculated by summation of all fatal cases (*d*) due to the health outcomes (*l*) of a specific disease, each case multiplied by the expected individual life span (*e*) at the age of death. Thus:

$$YLL = \sum_{l} d_l \times e_l$$

YLD is calculated by the product of the duration of the illness (*t*) and the disability weight (*w*) of a specific disease, accumulated over all cases (*n*) and all health outcomes (*l*):

$$YLD = \sum_{l} n_l \times t_l \times w_l$$

Cost of illness

Cost-of-illness is calculated by accumulation of direct health care costs (DHC), direct non-health care costs (DNHC), and indirect non-health care costs (INHC). In accordance with (Dutch) guidelines of Oostenbrink *et al*.[19], the study will not consider indirect health care costs. Indirect health care costs would comprise the future savings in health care costs in the life years lost due to premature death.

Direct health care costs (DHC)

The direct health care cost category included valuation for medical services such as general practice (GP) consultations, specialists' consultations, hospitalisation, drugs, rehabilitation and other medical services. The direct health care costs were estimated for each pathogen separately, the total direct health care costs were estimated by accumulating the costs for the different medical services for all illness and for all disease severity states related to this pathogen.

For each health outcome (*l*) of a specific disease and for each specific medical service, the direct health care costs related to a specific pathogen are estimated by multiplying the number of cases requiring health care service (*m*) by the required health care service units per case (*p*) and by the costs per health care service unit (*mc*). The formula for direct health care costs for a specific pathogen for health outcomes *l* and for health care service *i* is in basic notation:

$$DHC = \sum_{l} \left(\sum_{i} m_i \times p_i \times mc_i \right)_l$$

Direct non-health care costs (DNHC)

Travel costs of patients, costs for additional diapers, and co-payments by patients for medicines, informal care etc., are some examples of direct non-health care costs. For each health outcome (*l*) of a specific disease and for each specific non-health care service *j*, the direct non-health care costs related to a specific pathogen were estimated by multiplying the number of cases requiring non-health care service (*r*) by the required non-health care service units per case (*q*) and by the costs per non-health care service unit (*rc*). The formula for direct non-health care costs for a specific pathogen for health outcomes *l* and for non-health care service *j* is in basic notation:

$$DNHC = \sum_{l} \left(\sum_{j} r_j \times q_j \times rc_j \right)_l$$

DNHC are relatively small compared to DHC and INHC, and reliable information is usually lacking. Therefore, DNHC will not be included in the analysis.

Indirect non-health care costs (INHC)

Indirect non-health care costs, which are defined as the value of production lost to society due to disease can be the consequences of:

a) temporary absence from work;

b) permanent or long-term disability; and

c) premature mortality.

We estimate the productivity losses that occur due to sickness leave of sick individuals, and, where available, information on third persons taking care of patients. The indirect non-health care costs for a specific pathogen are estimated for each health outcomes (l) of a specific disease and for each types of sickness leave (k) separately by multiplying the number of cases with sickness leave (s) by the duration of sickness leave (u) by the wage costs (v) per day. The formula for indirect non-health care costs for a specific pathogen for health outcomes l and for each episode of sickness leave k are in basic notation:

$$INHC = \sum_{l}\left(\sum_{k} s_k \times u_k \times v_k\right)_l$$

Pathogens

The following pathogens will be evaluated, subject to further results regarding data availability and available resources:

GE pathogens:	Campylobacter
	STEC 0157
	Norovirus
	Salmonella
	Cryptosporidium
	Yersinia
	Shigella
	EPEC/ETEC

For the GE pathogens, clinical symptoms will include gastro-enteritis but also Inflammatory Bowel Syndrome (IBS: all pathogens), reactive arthritis (ReA: Campylobacter, Salmonella, Yersinia and Shigella), Haemolytic Uraemic syndrome (HUS: STEC O157 and Shigella) and Guillan-Barré syndrome (GBS: Campylobacter).

non-GE pathogens:

first priority:	Hepatitis A virus
	Listeria monocytogenes (both acquired and congenital)
second priority:	Clostridium botulinum

	Creutzfeldt-Jakob disease (CJDv).
third priority:	Trichinella
	Brucella
	Echinococcus
	Toxoplasmosis

Incidence or prevalence approach

In the incidence-based approach to disease burden and cost-of-illness calculations, all health outcomes (including those in future years) are assigned to the initial event, i.e. the acute (symptomatic) infection. The incidence approach reflects both the future burden of disease and the future costs of illnesses, based on current events. This approach contrasts with the prevalence approach, in which the health status of a population and the related cost-of-illness at a specific point of time is assessed, possibly followed by attribution of the prevalent diseases to etiological agents or conditions. The prevalence approach reflects the current burden of disease and the current cost-of-illness, based on previous events. However, assuming a steady state situation there should be no difference between both approaches. Also, there are no differences for outcomes that have a duration less than one year. In practice, it is found to be difficult to rigidly apply one or the other approach and some compromises must be made.

In this study, we choose the incidence approach for several reasons. Firstly, most communicable diseases have such a rapid course that prevalence is not very informative. Secondly, because the incidence approach is based on current events it is more sensitive to current epidemiological trends than the prevalence approach. Thirdly, the incidence approach is more informative on health gains and related savings of avoided cost-of-illness expenses that can be obtained now and in the future by current control programs that aim to prevent new cases (= incidence). Lastly, with the incidence approach calculation of time lived with disability is more consistent with the calculation of time lost due to mortality: the burden is ascribed to the age of onset (instead of to the age at which the disability is lived) or the age at which death occurs[16]. This applies also to the cost-of-illness estimation. Using the incidence approach costs-of-illnesses made due to chronic and long-lasting diseases in the remaining life time are ascribed to the age of onset, similar to the estimations of productivity losses due to premature mortality that are ascribed to the age at which death occurs.

Outcome or agent-based approach

The outcome-based approach assigns the disease burden and the associated costs-of-illness to clinically defined categories of diseases (ICD-codes), irrespective of their cause. This approach is mainly used to assess the overall public health situation and the associated costs in a country or region. Major international studies (e.g. the Global Burden of Disease studies and the Dutch Public Health Status and Forecast reports) use the outcome-based approach.

In contrast, the agent-based approach focuses on all relevant health outcomes and the associated costs that can be attributed to one particular agent. These outcomes can cover

different disease categories (ICD-codes). The latter approach gives a more complete insight into the public health impact and related costs of a particular cause or set of causes, allowing more detailed comparisons. Also, the expected impact of preventive measures on both public health costs and associated costs will be more fully quantified. Therefore, the agent-based approach is chosen in this project. It must be noted that this choice implies that direct comparisons with other studies cannot directly be made[1]. There is a risk of not (sufficiently) accounting for co-morbidity that must be taken into account. For some sequelae (HUS, GBS) an outcome-based approach is chosen based on data availability.

Outcome trees

To provide a basis for disease burden and cost-of-illness calculations, the construction of an outcome tree is a useful first step. An outcome tree represents a qualitative representation of the disease progression over time by ordering relevant health states following infection and illustrating their conditional dependency. For infectious diseases, the first blocks in the outcome tree typically represent the incidence of infection and acute illness in a particular period. Subsequent blocks represent the incidence of possible outcomes, including recovery, and/or request of specific resources. For late outcomes, this incidence is accumulated over the lifetime of affected individuals so that the link between the blocks reflects the lifetime probability of developing an outcome/requesting a specific resource, given the previous outcome/resource request. Once the outcome tree is designed, valuations of each block can be made. In this project, valuations related to health related quality of life and to resource requests.

Sensitive subgroups will be taken into account when constructing outcome trees. This may lead to either qualitative changes in the tree (i.e. other outcomes for sensitive groups than for the general population) or to quantitative changes (i.e. different parameter values in an otherwise similar tree).

Constructing outcome trees implies making choices on which outcomes and/or resource requests to include and which to exclude. This is ideally based on systematic literature reviews. However, most infectious diseases are associated with a large number of clinical outcomes, some of which may be rare and/or of limited severity. Deciding which outcomes to include in the tree requires preliminary estimations of a) the relative impact of all possible outcomes on the total disease burden and b) the relative impact of all possible resource requests on the total cost-of-illness. Outcomes and/or resource requests may not be included if they contribute little to the final result (because they are extremely rare and/or because their severity is low and/or because the associated costs are only minor). Construction of outcome trees is usually also guided in part by data availability. It is an iterative process that involves reviewing the tree while the study progresses.

[1] It is expected that this approach is complementary to WHO's Global Burden of Disease approach, and more specifically the anticipated work of the Foodborne Epidemiology Reference Group (FERG). An attempt will be made to compare and possibly combine these approaches.

For some outcomes, the causal link with the agent of concern may not be fully established. For example, a statistical association has been reported but this has not (yet) been repeated in other independent studies and/or the causal mechanism has not (yet) been elucidated. In that case, a professional but subjective choice must be made whether or not to include this outcome in the baseline model. The impact of this choice can be evaluated by scenario analysis both on the disease burden and the cost-of-illness estimate.

For this project, inclusion of outcomes will be based on criteria defined in the Gulf War and Health – Infectious Diseases[13] study and will comprise outcomes for which there is

a) Sufficient Evidence of a Causal Relationship [2]; or

b) Sufficient Evidence of an Association [3].

Other categories defined in this report will not be included.

Perspective of the evaluation

A critical step in economic evaluations is to define the perspective taken. This perspective determines which potential 'costs' and eventual 'benefits' are included in the evaluation. Possible perspectives are the patient perspective, the societal perspective and the third player perspective (health insurances and/or ministry of health). Most published cost-of-illness studies use either the third payer perspective or the societal perspective. In this project we used the societal perspective to estimates disease burden and cost-of-illness, which is the most complete evaluation possible.

Discounting

In most programs financial costs and revenues occur on different points over time. In order to be able to value and compare different projects, the net present values (NPV) of each single program is estimated taking into account all investments and revenues made over time. This is achieved by calculating the *net* cash flow in each period, and then discounting this stream back to the present. According to Drummond *et al.* [5] the applied rate is often the real rate of return on long-term government bonds. This concept is not only applied to financial costs and revenues, but, although not undisputed, is also commonly applied in economic analysis of medical or other public health interventions for the non-monetary health effects. When the principle of discounting is applied in disease burden estimates, it means that future life years are assigned less value than those lived today. This is based on the economic concept that

[2] Sufficient Evidence of a Causal Relationship:
The evidence is sufficient to conclude that there is a causal relationship between exposure to a specific agent and a specific health outcome in humans. The evidence is supported by experimental data and fulfills the guidelines for sufficient evidence of an association (defined below). The evidence must be biologically plausible and must satisfy several of the guidelines used to assess causality, such as strength of association, a dose–response relationship, consistency of association, and a temporal relationship.

[3] Sufficient Evidence of an Association:
The evidence from available studies is sufficient to conclude that there is an association. A consistent association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent associations and are sufficiently free of bias, including adequate control for confounding.

immediate profits are generally preferred over benefits later in time [17]. In general, health today is valued higher than health in the future because there is uncertainty about future possibilities to 'better' treat diseases and about possible future co-morbidity.

Discounting of health benefits is disputed because its application results in a lower efficiency of prevention programs, whereas not discounting, or the use of a low discount rate - lower than the discount rate used for the costs - favor preventive measures due to benefit in the far future. We will show both discounted and undiscounted estimates.[4] This allows a comparison of our results with other work using discounted or undiscounted health effects, but also to analyze the impact of discounting on the results.

Data needs

For all relevant outcomes as represented in the outcome tree, data must be available on mortality, incidence, duration and severity in order to estimate the disease burden. For the cost-of-illness estimate data must be available for all relevant outcomes on resources used, the quantity required of each used resource and the cost price per used resource unit, where the chosen perspective of economic evaluation decides which resources to include in the analysis and which not. However, as the resources used are not only depending on outcomes but often also on the age, additional information on the age of the patients affected is required.

Furthermore, the impact of infectious diseases on a society and their related costs can be measured at different levels, often represented by the "iceberg" metaphor or surveillance pyramid (see Figure I). The impact of illness and/or the related costs at different levels of the pyramid may differ greatly, as well as the availability of data. Therefore it is useful to separate these different levels in burden of disease studies and in cost-of-illness studies. The degree of underreporting varies greatly between diseases as well as between countries or even within one country in different periods.

To calculate disease burden and costs, data on mortality, incidence, duration, severity and resources used, including the quantity required and their associated costs is used. All these data need to be broken down into different age and sex categories where possible. In the current project we use the following age categories:
0; 1-4; 5-9; 10-14; 15-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80-89; 90+

[4] The discount rate is to be decided in the economist meeting.

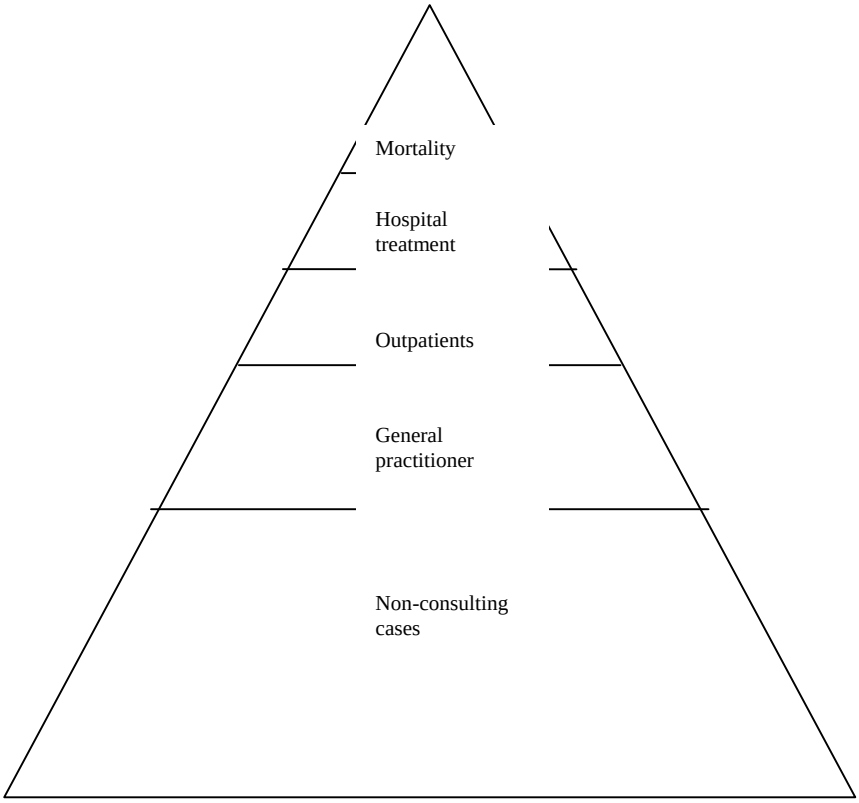

Figure I. The surveillance pyramid of communicable diseases [1]

Incidence of non-fatal health outcomes

Depending on the complexity of the outcome tree, the incidence must be assessed for a varying number of non-fatal outcomes. Ideally, this task would involve the establishment of the incidence of one outcome at the root of the tree (e.g. acute gastro-enteritis) and the (conditional) probability of progressing to the next stage or to recovery. In practice, such data are rarely available for a complete outcome tree and supplementary data are necessary. Such probabilities may be available from cohort or outbreak studies. It is also possible to directly use surveillance data or special studies for the incidence of the specific outcomes. As many outcomes can be triggered by more than one agent, information on the attributable fraction must also be available. Note that these two approaches are only equivalent in a stable situation, if this cannot be assumed some kind of back-calculation should be applied.

Ideally, data are available for all relevant levels of the surveillance pyramid: non-consulting cases, cases consulting a GP and hospitalized cases. In this order, data availability may be expected to increase, but will seldom be complete. Readily available from the Basic Surveillance Network or Dedicated Surveillance Networks will be used, but needs to be corrected for underreporting. Some countries have performed incidental studies (for example IID[23] in the UK and SENSOR [4]and NIVEL[3] in the Netherlands), other countries have performed desk studies to account for underreporting in surveillance data (for example

France [9]). Data include all community-acquired infections, including travel-related cases but excluding illness contracted in closed settings such as hospitals and nursing homes.

Duration of non-fatal health outcomes

In this project duration of non-fatal health outcomes will be derived from various publications (both Dutch and non-Dutch studies), the Global Burden of Disease study and review articles. Preference is given to relevant, large cohort studies.

Number of fatal cases

Mortality from infectious diseases is typically underreported in most routine surveillance systems. However, YLLs often are an important component of the total disease burden and lost productivity due to premature death and can be an important component of the total cost-of-illness, especially if the human capital approach is applied. Therefore, this problem of underreporting requires further attention. We will obtain additional data from case-fatality ratios in outbreak studies, from relevant, large cohort studies etc. We then apply this data to incidence estimates for different blocks of the outcome tree. Extrapolation to different levels of the surveillance pyramid might be problematic. Consideration will also be given to WHO's "Envelope of mortality" approach.

Life expectancy of fatal cases

In the absence of co-morbidity, the life expectancy of fatal cases can directly be derived from standard life tables if the age distribution of fatalities is known. This information may typically not be available in routine surveillance data and as a result additional datasets must be sought. These may include broad categories (e.g. the age distribution of deaths from gastro-enteritis as a proxy for any specific pathogen-associated GE) or special studies (e.g. intensified surveillance). In the presence of co-morbidity, the use of standard life tables may overestimate the YLL and cohort-specific data must be obtained.

For this project we will use the global life table as developed for the GBD project, which is based on Japanese survival tables for 2003 (the Japanese have the highest realized life expectancy in the world). This promotes comparison with other international studies. In Europe, the life expectancy (in particular of men) is several years shorter than in Japan, so use of a European life table would result in slightly lower disease burden estimates.

Information on the age at death and the life expectancy of fatal cases is also important when estimating the productivity losses and the indirect health care costs that would have been made in the remaining life-years if the illness would not have been fatal.

Co-morbidity

Accounting for co-morbidity is an important but difficult issue in economic evaluations of the impact of (infectious) diseases. Is a fatal case of salmonellosis fully attributable to the Salmonella infection, or was the deceased person already suffering from underlying illnesses? In that case, assigning an age-specific statistical life expectancy might overestimate the true burden of disease and costs as part of the life years lost should be assigned to the underlying cause of death. Note that this "distribution" of life years is potentially a stronghold of using

integrated metrics: a fatal case can be assigned to two causes but this will not result in double counting if the life years are appropriately distributed. Suitable data are difficult to obtain, however, and co-morbidity will only be considered if it is a major factor in the epidemiology of a foodborne illness (e.g. listeriosis). Likewise, the possible effect of co-infections with several pathogens will not be considered due to a lack of information.

Time period

The incidence of infectious diseases can vary markedly between years. To provide a more stable estimate, we will use a five-year average (2001-2005) whenever possible.

Disability weights for non-fatal outcomes

Disability weights reflect the health impact of a condition and they are based on the preferences of a panel of judges. Ideally, the disability weights used in DALY calculations reflect the preferences of the society under study. In the elicitations of disability weights, there are several aspects to be considered, including:

Magnitude of the scale. In this project the disability weights range between 0, reflecting the best possible health state, and 1, reflecting the worst possible health state. This is in contrast to some studies, which allow disability weights greater than 1, reflecting conditions that are considered worse than dying (which is then assigned a weight of 1).

Whose values? Ideally, disability weights based on preferences of the general public are used in burden of disease studies aimed to inform policy making at the national or international level. Disability weights based on elicitation panels consisting of lay persons are increasingly becoming available. Previous work has depended on panels of medical professionals. Preferences of patients who actually suffer from the disease are biased because of coping behavior. The international transferability of disability weights is also of concern. A study in Western Europe[20] concluded that there was "a reasonably high level of agreement on disability weights in Western European countries with the visual analogue scale (VAS) and time trade-off (TTO) methods, but a lower level of agreement with the person trade-off (PTO) method". Üstün *et al*.[22] concluded that ranking of weights is relatively stable across countries, but differences are large enough to cast doubt on the universality of experts' judgments of disability weights. A recent study [10] concluded that "Meaningful differences exist in directly elicited TTO valuations of EQ-5D health states between the US and UK general populations". Hence, disability weights are ideally based on specific elicitations for the population under study, but this may be very difficult to realize for the EU[5]. We will use one set of disability weights for all countries involved, which also promotes comparability of results.

Preference measurement methods. Several preference measurement methods are available for panel elicitation, including the standard gamble (SG), TTO, PTO and VAS. All methods give different results (VAS > TTO > PTO > SG), but they are highly correlated. The SG and VAS are not considered informative because they are only sensitive to severe disease (SG) or very

[5] The possibility to elicit disability weights in the participating countries will be explored.

sensitive to mild diseases (VAS) leading to compression at either end of the scale. Additionally, the VAS is not choice-based because it does not allow a trade-off. The TTO and PTO methods are generally used. When available, disability weights will be obtained from international project (GBD), supplemented with disability weights from national studies.

Annual or period profiles. For chronic diseases, most descriptions are based on the impact of a disease in the course of a year. However, many infectious diseases have a rapid course, and consequently the disability weight can be assessed by focusing on the phase of acute disease only (period profile) or by focusing on a year in which an episode of acute illness is experienced (annual profile[6]). Both methods have been used in disease burden studies. In practice, large differences may be found between these two methods for diseases that have a high incidence but low severity (e.g. norovirus-associated gastro-enteritis). For such diseases, using annual profiles may lead to very high estimates of disease burden. One proposed solution is to introduce a threshold, based on the median weight of the respondents in an elicitation study. Earlier work on foodborne infections in the Netherlands has used period profiles but weights are now also available for annual profiles. Because of international comparability, period profiles will be used in the baseline model. The impact of annual profiles will be evaluated by scenario analysis.

Age-weighting

In the original GBD project, age-weighting was applied to reflect the fact that individuals have different roles and changing levels of dependency and productivity with age. Therefore it may be appropriate to consider valuing the time lived at a particular age unequally [7 14 15]. Age-weighting is highly debated. Although the principle of age-weighting makes sense, the exact quantitative implementation is controversial [2]. In this project, age-weighting will not be applied. The disease burden estimate of the current study reflects solely the impact of illness and premature death on public health, independent of any other factors. However, the fact that individuals have different roles and changing levels of dependency and productivity with age is nevertheless not neglected in this study, but is taken into account in the cost-of-illness estimate, which we consider more relevant. Furthermore, the cost-of-illness estimates allows, in comparison to disease burden, not only a distinction of changing levels of dependency and productivity with age, but allows also to distinguish, if required, age-dependent resource requests of any kind.

A specific aspect of age-weighting is whether or not to include fetal losses in the calculations. The GBD study has not included fetal losses up to now, but is reconsidering it's position. Another option is to include all fetal losses after 22 weeks of gestation [8]. Both scenario's will be explored, the baseline scenario will be chosen in accordance with the WHO approach.

[6] When using an annual profile, the duration of the illness is 1 year by definition.

Cost categories

There are several ways to split up the costs related to illness, and depending on the economic evaluations' perspective taken, all categories, or only some of the categories will be considered. Taking the payers perspective, there are four possible categories: 1) direct health care costs paid by health insurances and public health authorities; 2) indirect health care costs paid by health insurances and public health authorities; 3) costs paid by patients themselves; and 4) (indirect) costs paid by other stakeholders in the society than the health insurances/ public health authorities or the patients.

The first category includes the valuation for medical services such as general practice (GP) consultations, specialists' consultations, hospitalization, drugs, rehabilitation and other medical services used by the patients themselves as a consequence of the illness acquired. In most European countries, the largest part of these costs would be covered by health insurances, if the patient is insured. However, in some countries, co-payments of patients for some medical services may be required.

Indirectly related health care costs would comprise the future savings in health care costs in patients who die prematurely.

Travel costs of patients, informal care, adjusting houses for disabled patients, additional diapers in case of gastro-enteritis of infants, and other co-payments paid by patients are some examples for costs that are directly related to the illness, but that occur outside the health care sector, and are mostly paid by the patients themselves and/or by social security plans.

In the fourth category all types of costs occurring in other sectors than the health care sector would be considered. Most of these costs are indirectly related to the illness. Productivity losses due to work absence of patients and/or third persons taking care of sick people are the major costs in this category. Production losses could be the consequences of: a) temporary absence from work; b) permanent or long-term disability; and c) premature mortality. Apart from productivity losses, both from paid and unpaid work, there are other costs such as the costs for special education or re-education after having been disabled due to illness. Costs for monitoring and follow-up of (food borne) outbreaks are also included in this category.

In this project we consider the categories 1), 3) and 4) but not 2) (indirect health care costs). This last category is hardly ever considered in cost studies. Reasons for exclusion are primarily ethical considerations, and also lack of data.

Differences in cost of illness valuations

Apart for the evaluation of productivity losses, there exist only few differences in the valuation of health care costs, patient costs or any other costs occurring. The main differences for these types of cost categorizations are caused by differences in the different health care systems (e.g. consulting a specialist directly, or only after being referred by GP; needing a medical referral after one, three or ten days, etc.).

In the case of productivity loss, there are currently two methods in use, the human capital approach and the friction cost approach. The human capital approach, which is based on

neoclassical labour theory, estimates the value of *potential* lost production (or the potential lost income) as a consequence of disease. In the case of permanent disability or premature death at a specific age the total productivity value (or income) from that age until the age of retirement is counted as productivity losses. But according to Koopmanschap *et al.* [11], the real production losses for society are smaller. The aim of the friction cost approach is to adjust the human capital estimates of productivity costs for the compensations that are likely to occur as a result of a labour market [21]. The friction cost method considers only production losses for the period needed to replace a sick, invalid or dead worker, the 'friction period'[6]. The friction cost method takes explicitly into account the economic processes by which a sick, invalid or dead person can and will be replaced after a period of adaptation [12]. The length of the friction period depends on the situation of the labour market. A high unemployment rate generally allows fast replacement of a sick, invalid or dead person, whereas in the case of a low unemployment rate, on average more time is needed. The friction cost method places a zero value on persons outside the labour market, such as children aged 15 or younger and retires of 65 and older.

In the current project we will present results from both the friction cost method and the human capital approach[19].

Productivity loss

Apart from the age at death, additional information on work relation and salary of the individuals are required. However, this information is often not available. Therefore, in the current project we use estimated productivity losses for an average (working) person in the working life of a specific age (e.g. as given in Oostenbrink *et al.* [19] for the year 2005 in the Netherlands), increasing these costs by using the national consumer price index when extrapolating to other years.

Resources used, the quantity demanded and the cost per resource unit used

Ideally, data with respect to resources used, their quantity demanded and the costs per resource unit should be available for all relevant levels of the surveillance pyramid. In this project information on resources used and the quantity demanded will be collected from incidental studies such as the UK IID study, the Dutch SENSOR and NIVEL studies and case-control studies, as well as from surveillance data. If there are no data available, experts will be consulted and scenario analysis conducted. In this project, we use solely national prices for the cost price per resource unit, following wherever possible the recommended prices given in the national guidelines[19].

Uncertainty

Different types of uncertainty existed in the available data. These consisted of:

- Statistical uncertainty (small sample size)
- Systematic uncertainty (representativeness)
- Lack of data

Monte Carlo simulation methods to account for uncertainty are preferred. If not possible, statistically uncertain parameters will be represented by low, most likely and high estimates. Scenario analysis will be employed to explore the impact of systematic uncertainty and lack of data. In addition, there is typically a large degree of variability in the model parameters. Variability may reflect different courses of the disease in different individuals, seasonal or multi-annual differences in incidence, differences in the values attached by individuals to disease outcomes etc. This variability will not be formally included in the project, and arithmetic mean values will be used as point estimates.

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