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Disease burden of infectious diseases in Europe: a pilot study

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Abstract

Disease burden of infectious diseases in Europe: a pilot study

Consequences of different infectious diseases cannot be adequately compared with each other on the basis of the number of patients or mortality data only. It is better to combine all health effects and express the total impact as disease burden, which also takes duration and severity of diseases into account. Information on disease burden also helps to set priorities in European policy for infectious disease control.

In a pilot study, the disease burden of seven infectious diseases in Europe has been estimated. In spite of various limitations with regard to availability and quality of data, it was found that HIV infection, tuberculosis and influenza cause, among the selected infectious diseases, the highest disease burden in Europe. Foodborne diseases caused by the bacteria *Campylobacter* spp., enterohaemorrhagic *Escherichia coli* and *Salmonella* spp. and, in particular, measles, are associated with a lower burden.

The current disease burden of infectious diseases reflects the balance between the disease threats and the effectiveness of preventive strategies. A low burden stresses the need for the continued support of these strategies, while a high burden indicates the need for additional interventions. Based on this pilot, the RIVM recommends that a full burden of disease study - combining several methods of investigation - be conducted in cooperation with different European institutes.

Key words: disease burden; priority setting; infectious diseases; Disability Adjusted Life Year; DALY; Europe

Rapport in het kort

Ziektelast van infectieziekten in Europa: een pilot studie

De gevolgen van verschillende infectieziekten zijn onderling niet goed te vergelijken op basis van het aantal patiënten of sterftecijfers alleen. Het is beter om alle gezondheidseffecten te combineren en de totale impact uit te drukken in ziektelast, dat ook rekening houdt met duur en ernst van ziekten. Informatie over ziektelast helpt prioriteiten te stellen in het Europese beleid op het gebied van infectieziektebestrijding.

In een pilotstudie is de ziektelast geschat van zeven infectieziekten in Europa. Ondanks verschillende beperkingen in beschikbaarheid en kwaliteit van gegevens wordt geschat dat HIV-infectie, tuberculose en influenza van de geselecteerde infectieziekten de grootste ziektelast in Europa veroorzaken. Voedseloverdraagbare ziekten die worden veroorzaakt door de bacteriën *Campylobacter* spp., enterohemorragische *Escherichia coli* en *Salmonella* spp., en mazelen in het bijzonder, zijn geassocieerd met een lagere ziektelast.

De huidige ziektelast van de infectieziekten weerspiegelt de balans tussen bedreigingen van de ziekten en effectiviteit van preventiemaatregelen. Een lage ziektelast benadrukt de noodzaak van voortdurende ondersteuning van deze maatregelen, een hoge ziektelast duidt erop dat aanvullende acties nodig zijn. Op basis van deze pilotstudie adviseert het RIVM om samen met verschillende Europese instituten een uitgebreidere studie uit te voeren, die verschillende onderzoeksmethoden combineert.

Trefwoorden: ziektelast; prioritering; infectieziekten; Disability Adjusted Life Year; DALY; Europa

Contents

Summary

Background
The European Centre for Disease Prevention and Control (ECDC) has a responsibility to identify, assess and communicate current and emerging threats to human health from infectious diseases. As one of the elements to fulfil the above responsibility, the ECDC is producing the Annual Epidemiological Report on Communicable Diseases for 2005. The aim of this report is to give a comprehensive overview of the threat of infectious diseases in the European Union in 2005. The report analyses incidence trends and patterns of the 46 diseases under mandatory surveillance, together with SARS, avian influenza and West Nile virus. The trends identified give one indication of which diseases require priority action, and including mortality, prevalence (very little data) and sequelae would give additional indications. However, such assessments, if used individually, make it difficult to get an overall assessment of disease burden, as the diseases and their consequences are heterogeneous in terms of mortality and morbidity.

Composite health measures attempt to overcome those issues by combining mortality, incidence (and/or prevalence) and the sequelae due to an infectious agent. ECDC wishes to evaluate whether a composite measure could be useful to inform its decision making process. If successful, then the composite measure could be used as **one** element to gain insight in (expected) trends to guide public health policy and actions within the group of 49 infectious diseases. Several composite measures of disease burden have been developed and are increasingly used, including Disability Adjusted Life Years (DALYs). It is important to remember that absolute values of such measures (be they DALYs or any other) are of little significance. It is only their relative values that are important in indicating and guiding public health policy and action. Furthermore, disease burden is only one of the criteria that can be used for priority setting. Other priority setting criteria are incidence, severity, potential to spread among the general population, socioeconomic burden, preventability, potential to drive public health policy, risk perception, changing patterns in time[1] and outbreak potential.

As a first step, a pilot study was carried out to illustrate the **potential** of the disease burden concept, to explore data availability and quality, to recommend future studies and to stimulate debate. This study was conducted in a short period of time to fit into the time schedule of the production of ECDC's Annual Epidemiological Report on Communicable Diseases for 2005. Due to time and resource limitations, it was decided to only include generally available data such as those of Eurostat, WHO and dedicated surveillance networks. Seven diseases were included in this pilot: influenza, measles, infection with Human Immunodeficiency Virus (HIV-infection), campylobacteriosis, infection with enterohaemorrhagic *Escherichia coli* (EHEC-infection), salmonellosis and tuberculosis. These diseases were mainly selected based on the availability of incidence and mortality data and previous experience at RIVM so that comparisons could be made.

It is recognised that the results of this initial study, based on generally available information, do not reflect the full disease burden of the selected infectious diseases in Europe, due to potential underreporting in the available data on morbidity and mortality. Also, as the extent of the potential underreporting varies between different diseases (and countries), even the current relative comparisons of disease burden could be biased. Furthermore, not all relevant outcomes could be included in this preliminary assessment. To explore the uncertainty resulting from those limitations, scenario analyses were carried out and the disease burden estimates were compared with those of previously published more detailed studies.

Methods

The DALY methodology has been described by Murray and co-workers in the Global Burden of Disease (GBD) project,[2, 3] 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:

$$YLL = \sum_l d_l \times e_l$$

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

$$YLD = \sum_l n_l \times t_l \times w_l$$

Applying the DALY methodology involves making several choices on details of the analysis which should reflect value choices that are relevant to the decision maker. For this pilot project, the choices were made (in many cases due to pragmatic reasons coming from the three months duration of this pilot) in consultation with staff members of ECDC:

- incidence approach (in contrast to prevalence approach)
- agent-based approach (in contrast to outcome-based approach)
- selection of outcomes to be included in the outcome tree for each of the diseases
- European life expectancy (in contrast to life expectancy from a standard life table)
- no application of discounting and age-weighting
- severity weights based on period profile if available (in contrast to annual profile)

Data sources and limitations

Depending on data availability, as many as possible member states of the European Union and EEA/EFTA* countries were included. Generally available data have been derived from:

YLL	*d*	= Number of fatal cases	: Mean number of deaths 2003-2004 reported to Eurostat/WHO
	e	= Life expectancy at age of death	: European life expectancy 2004
YLD	*n*	= Number of cases of illness	: Mean incidence 2003-2005 reported to - EuroHIV (HIV-infection) - EuroTB (tuberculosis) - EISS (influenza, mean 2002/2003-2004/2005) - Eurostat (other diseases)
	t	= Duration of illness	: Literature (mainly Global Burden of Disease study)
	w	= Severity weights	: Literature (mainly Global Burden of Disease study)

Major limitations in data availability were:

- inconsistent morbidity and/or mortality by some countries and/or for some years;
- very limited information on the age-distribution of morbidity for most diseases;
- no reporting of the incidence of complications and chronic sequelae;
- no consistent set of severity weights available.

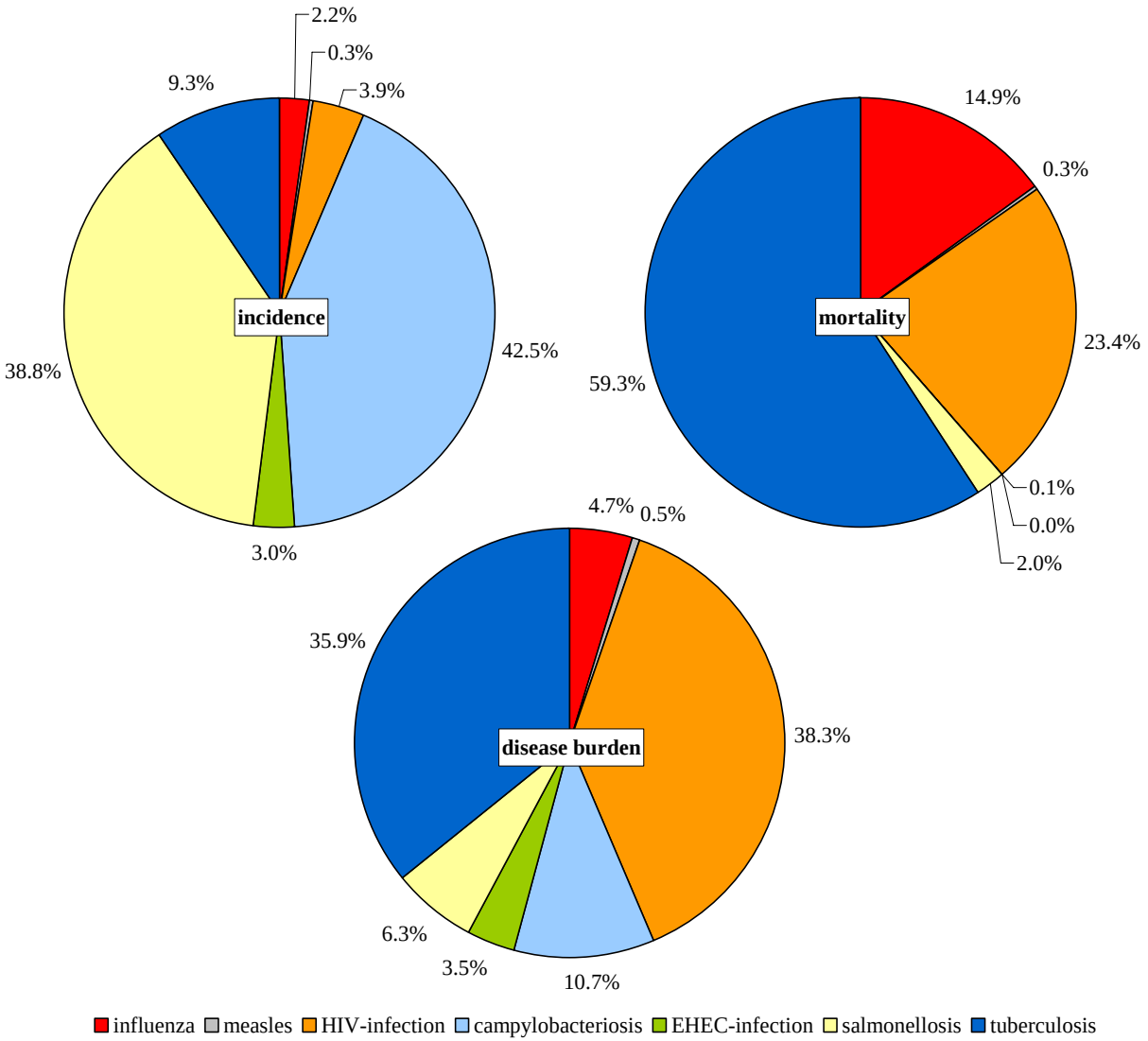
Major limitations with regard to data quality were:

- no information on underreporting of morbidity and mortality;
- no information on possible variation between countries of the duration, severity and rate of complications and chronic sequelae;
- differences between reports from different sources (national, Eurostat and WHO).

* European Economic Area (EEA) / European Free Trade Association (EFTA)

Results

This study makes clear that the relative burden of diseases as measured by disease burden is quite different compared to the relative burden as measured by just incidence or mortality data (Figure 1). Based on incidence data individually, the foodborne diseases cause relatively the greatest burden, while mortality data indicate the relatively high burden of tuberculosis. Disease burden (DALYs) shows a quite different picture with a relative high burden for HIV-infection and tuberculosis.



Based on data for twelve countries (data available for all seven diseases):

Austria	Ireland	the Netherlands	Sweden
Czech Republic	Latvia	Poland	United Kingdom
Germany	Lithuania	Slovenia	Norway

Figure 1 *Relative burden of the seven selected diseases based on different indicators:*
- incidence (mean number of reported new cases per year in the period 2003-2005)
- mortality (mean number of reported deaths per year in the period 2003-2004)
- disease burden (DALYs per year based on above mentioned incidence and mortality)

In Figure 2 an estimate of the total disease burden per 100,000 population for the seven selected diseases is shown, for those countries for which YLD **and** YLL **and** DALY could be calculated. An analysis based on twelve countries for which the disease burden could be calculated for **all** diseases, shows a quite similar picture (see Appendix V). HIV-infection and tuberculosis have the highest disease burden in Europe, measles the lowest.

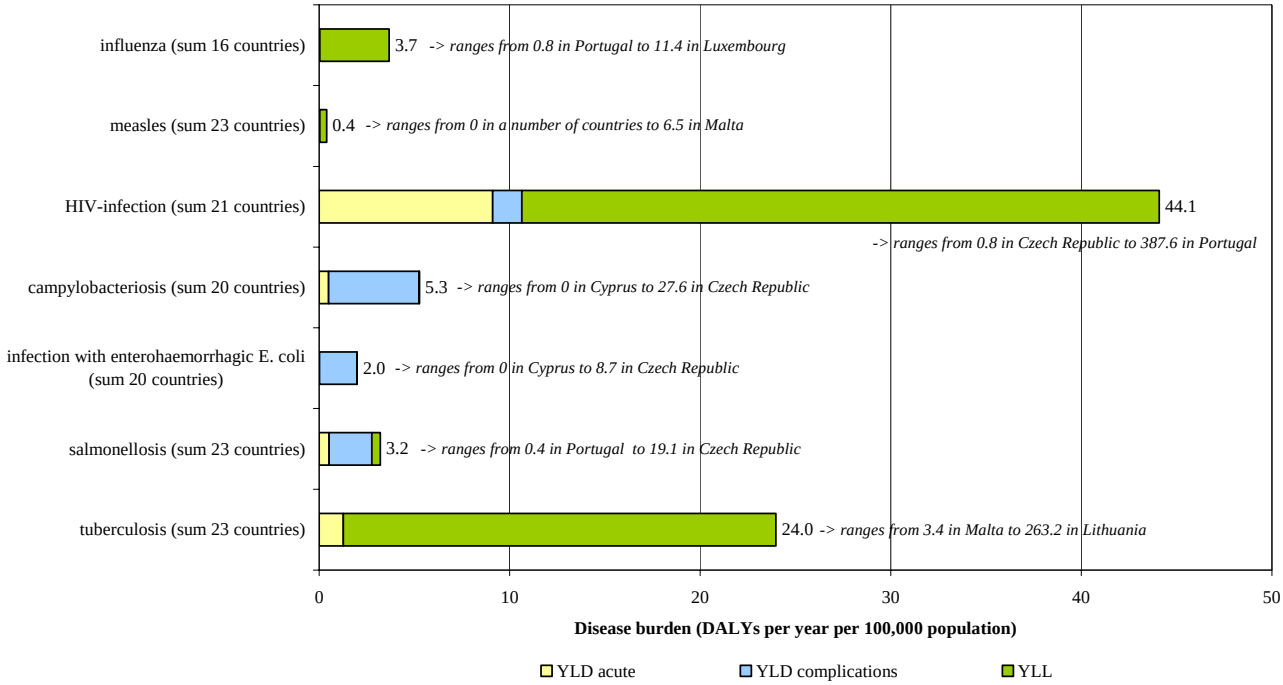
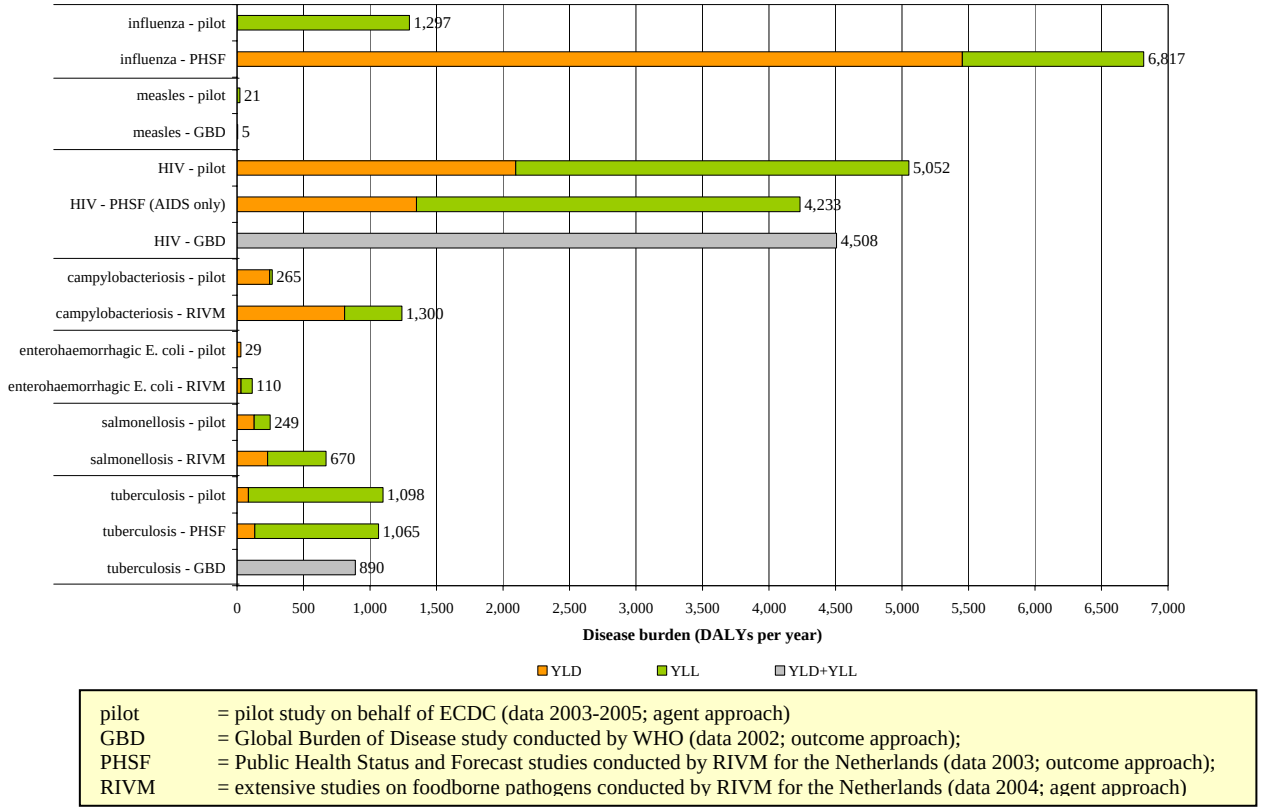


Figure 2 *Sum of disease burden per 100,000 population of all countries for which data are available for at least one disease (for each disease number of countries is different) (Table 3.1 shows per disease which countries could not be included)*

For the Netherlands comparisons with more extensive studies (Figure 3) and results from scenario analysis have suggested that the disease burden of influenza is seriously underestimated (especially morbidity). Especially for HIV-infection the information on long-term outcomes of current infections and the effect of Highly Active Anti-Retroviral Therapy (HAART) is incomplete. Furthermore, morbidity and in particular mortality of foodborne diseases (campylobacteriosis, EHEC-infection and salmonellosis) were likely to be underestimated due to underreporting. Estimates of the burden of measles and tuberculosis appear to be less uncertain.



pilot	= pilot study on behalf of ECDC (data 2003-2005; agent approach)
GBD	= Global Burden of Disease study conducted by WHO (data 2002; outcome approach);
PHSF	= Public Health Status and Forecast studies conducted by RIVM for the Netherlands (data 2003; outcome approach);
RIVM	= extensive studies on foodborne pathogens conducted by RIVM for the Netherlands (data 2004; agent approach)

Figure 3 Comparison of results from the pilot study for the Netherlands with previously published more extensive (Dutch) studies

Conclusions

The relative burden of diseases as measured by disease burden is quite different compared to the relative burden as measured by just incidence or mortality data. Taking into account the limitations in data availability and quality, it was found that (based on data for 2003-2005 when available) the disease burden in Europe is estimated to be highest for HIV-infection and tuberculosis, followed by campylobacteriosis, influenza and salmonellosis, and was lowest for measles and EHEC-infection. Scenario analysis limited to the Netherlands suggested that this ranking is not likely to be affected by better data. However, the relative burden of influenza is likely to increase. It must be noted that differences between countries sometimes are considerable and may be due to differences in reporting.

The current disease burden reflects the balance between threats and the effectiveness of preventive strategies. A low burden stresses the need for the continued support of these strategies. A high burden indicates the need for additional interventions. Disease burden estimates provide an integrated representation of the burden of infectious diseases. However, for priority setting other factors, such as threats and trends, costs and perception should be taken into account as well.

Recommendations

Disease burden (DALYs) calculations should be extended to other infectious diseases as well, because this composite measure gives more insight in burden than incidence or mortality data on its own. A full burden of disease study is recommended and would benefit from an approach that combines and triangulates several methods of investigation, including epidemiological modelling. In this short term pilot pragmatic choices had to be made, a full study should include a systematic and critical review on other disease burden estimates and on aspects like most suitable data sources, extent of underreporting, severity weights, outcome trees etcetera for each of the diseases under study. Furthermore there needs to be general agreement on methodological issues discussed in Chapter 2 like using a standard life table instead of the European life expectancy (that changes over time) or showing both discounted and undiscounted results in the future. Where possible a full burden of disease study should join other international efforts in this field (i.e. the WHO update of the Global Burden of Disease for the year 2004). With regard to priority setting, besides disease burden other aspects such as economical costs or outbreak potential should also be taken into account.

In order to obtain better insight in the epidemiology of infectious diseases in general and in the disease burden in particular, the following recommendations are made:

- improve the completeness and consistency of reporting of the incidence of morbidity and mortality in Europe, including information on the age-distribution;
- conduct cohort studies on the incidence of complications and chronic sequelae, including possible variability between countries and factors associated with that variability;
- conduct studies addressing sources of underreporting of morbidity and mortality in order to calibrate the data and to decrease inconsistencies in reporting between countries;
- improve quantification of the mortality risks due to infectious diseases by cohort-studies;
- integrate mathematical modelling to better understand the current and future burden, in particular for the HIV/AIDS epidemic including the impact of HAART;
- promote standardized data collection on disease severity and duration across Europe;
- conduct studies on severity weights and obtain consensus on the protocols for such studies, including national differences;
- develop a standardized approach to value choices inherent in disease burden calculations.

1. Introduction

The European Centre for Disease Prevention and Control (ECDC) has a responsibility to identify, assess and communicate current and emerging threats to human health from infectious diseases. As one of the elements to fulfil the above responsibility, the ECDC is producing the Annual Epidemiological Report on Communicable Diseases for 2005. The aim of this report is to give a comprehensive overview of the threat of infectious diseases in the European Union in 2005. The report analyses incidence trends and patterns of the 46 diseases under mandatory surveillance, together with SARS, avian influenza and West Nile virus for the different countries (Appendix I and II). The trends identified give one indication of which diseases require priority action, and including mortality, prevalence (very little data) and sequelae would give additional indications. However, such assessments if used individually make it difficult to get an overall assessment of disease burden, as the diseases and their consequences are heterogeneous in terms of mortality and morbidity. For example, diseases that do not (or seldom) result in death would not figure as high priority using mortality, whereas just incidence (or prevalence if such data were universally available) would underplay the effect of diseases with high case fatality ratios.

Composite health measures (such as Disability Adjusted Life Years) attempt to overcome those issues by combining mortality, incidence (and/or prevalence) and the sequelae due to an infectious agent. ECDC wishes to evaluate whether a composite measure could be useful to inform its decision making process. If successful, then the composite measure could be used as **one** element to gain insight in (expected) trends to guide public health policy and actions within the group of 49 infectious diseases. Several composite measures of disease burden have been developed and are increasingly used, including Disability Adjusted Life Years (DALYs). It is important to remember that absolute values of composite measures (be they DALYs or any other) are of little significance. It is only their relative values that are important in indicating and guiding public health policy and action. Furthermore, disease burden is only one of the criteria that can be used for priority setting. Other priority setting criteria are incidence, severity, potential to spread among the general population, socioeconomic burden, preventability, potential to drive public health policy, risk perception, changing patterns in time[1] and outbreak potential.

The Dutch National Institute for Public Health and the Environment (RIVM) has considerable experience in applying the DALY concept at the level of the Dutch population, dating back to the Public Health Status and Forecast study document published in 1997.[4] The emphasis in this document was on the impact of major diseases such as cardiovascular disease and cancer. However, the disease burden of a number of infectious diseases has also been assessed.[5] Further work at RIVM on infectious diseases has focussed on foodborne pathogens including thermophilic *Campylobacter* spp.[6] and Shiga-toxin producing *Escherichia coli* O157.[7]

Disease burden estimates have been used for estimating the cost-effectiveness of interventions to reduce the contamination of broiler meat with thermophilic *Campylobacter* spp.[8] and as an aspect of priority setting of foodborne pathogens.[9] This latter study also included disease burden estimates of non-typhoidal *Salmonella* spp., noroviruses, rotaviruses, listeriosis and toxoplasmosis. Therefore, the RIVM has been invited by ECDC to perform a pilot study on disease burden of infectious diseases at European level.

The ultimate goal is to produce an estimate of disease burden of infectious diseases at European level and gain insight in (expected) trends to guide public health policy and actions. This pilot study was carried out to illustrate the **potential** of the disease burden concept, to explore data availability and quality, to recommend future studies and to stimulate debate. This study was conducted in a short period of time to fit into the time schedule of the production of ECDC's Annual Epidemiological Report on Communicable Diseases for 2005. Due to time and resource limitations, it was decided to only include generally available data such as those of Eurostat, WHO and dedicated surveillance networks. Given time and data limits, as a first step only a limited number of diseases have been assessed in a pilot, based on generally available information and using methodology appropriate to give results from existing data and within time limits of the initial stages of this work. The diseases which met one or more of the selection criteria (Table 1.1) were included in a pilot study. The most important criteria were the availability of incidence and mortality data and previous experience at RIVM so that comparisons could be made.

Table 1.1 Selection criteria for inclusion of infectious diseases in the pilot study

		Selected infectious diseases						
	Criteria	**Influenza**	**Measles**	**HIV-infection**	**Campylo-bacteriosis**	**EHEC-infection**	**Salmo-nellosis**	**Tuber-culosis**
a)	European data on incidence and mortality available	(X)	X	X	X	X	X	X
b)	Expected high burden of disease	X		X				X
c)	Priority for additional control (prevention possibilities)	X		X				X
d)	Former disease burden experience at RIVM	X		X	X	X	X	X
e)	Upward trend			X	X			

HIV: Human Immunodeficiency Virus; EHEC: enterohaemorrhagic *Escherichia coli*

It is recognised that the results of this initial study do not reflect the full disease burden of the selected infectious diseases in Europe, due to potential underreporting in the available data on morbidity and mortality. Also, as the extent of the potential underreporting varies between different diseases (and countries), even the current relative comparisons of disease burden could be biased. Furthermore, not all relevant outcomes could be included in this preliminary assessment. To explore the uncertainty resulting from those limitations, scenario analyses were carried out and the results were compared with those of previously published more detailed studies.

This report presents the results of the pilot project. Chapter 2 describes the methods used. In Chapter 3 limitations in both data availability and data quality are discussed. Chapters 4-10 provide information on a first estimate of the burden of disease for each of the seven selected infectious diseases: influenza, measles, HIV-infection, campylobacteriosis, EHEC-infection, salmonellosis and tuberculosis. In Chapter 11 a comparison between diseases is shown. Finally, Chapter 12 gives a general conclusion on the results obtained so far and recommendations for further work.

2. Methods

A general trend in public health research is the use of disease burden, or the amount of health loss caused by diseases, 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 one single composite measure; the Disability Adjusted Life Years (DALYs) is one such measure.

2.1 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,[2, 3] 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 severity weight (*w*) of a specific disease, accumulated over all cases (*n*) and all health outcomes (*l*):

$$YLD = \sum_l n_l \times t_l \times w_l$$

Applying the DALY methodology involves making several choices on details of the analysis which should reflect value choices that are relevant to the decision maker. For this pilot project, the choices were made (in many cases due to pragmatic reasons coming from the three months duration of this pilot) in consultation with staff members of ECDC and are described below.

2.2 Incidence approach

In the incidence-based approach to disease burden calculations, all new cases are counted and all health outcomes (including those in future years) are assigned to the initial event, i.e. the acute (symptomatic) infection. This approach contrasts with the prevalence approach, in which the health status of a population at a specific point of time is assessed, possibly followed by attribution of the prevalent diseases to etiological agents or conditions. However, assuming a steady state situation there should be no difference between both approaches. In the field of infectious diseases prevalence data are rare, so following earlier work on foodborne pathogens in the Netherlands the incidence approach was used in this pilot project as far as possible.

2.3 Agent-based approach

The outcome-based approach assigns the disease burden to clinically defined categories of diseases (ICD-codes), irrespective of their cause. This approach is mainly used to assess the overall public health situation in a country or region. In contrast, the agent-based approach focuses on all relevant health outcomes that can be attributed to one particular agent. These outcomes can cover different disease categories (ICD-codes). Following earlier work on foodborne pathogens in the Netherlands, the agent-based approach was chosen. There is a risk of overestimation because co-morbidity could not be taken into account.

2.4 Outcome trees

Infectious diseases typically have several possible health outcomes, ranging from acute self-limiting diseases to chronic disabilities or even death. In order to assess the burden of disease for the different selected infectious diseases, the disease outcomes following each specific infectious agent had to be defined. For each infection an outcome tree has been designed in consultation with experts from both ECDC and RIVM; because of the short duration of the pilot pragmatic choices had to be made. An outcome tree represents a qualitative representation of the progression of disease in time by ordering relevant health states following infection and illustrating their conditional dependency. For infectious diseases, the first blocks in the tree typically represent the incidence of infection and acute illness in a particular period. Subsequent blocks represent the incidence of possible outcomes, including recovery. 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, given the previous outcome.

Constructing outcome trees implied making choices on which outcomes to include and which to exclude from the analysis. This was based on preliminary estimations of the relative impact of all possible outcomes on the total disease burden. Outcomes that contribute little to the final result (because they are extremely rare and/or because their severity is low) have not been included. 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. 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 was made whether or not to include this outcome in the baseline model.

2.5 Other choices

When working with the DALY concept, it is important to make clear what value choices and assumptions are made, especially with regard to the choice of:

- life expectancy
- discounting
- age-weighting and
- disability weighting[10]

Former research pointed out for example that the combined effect of age-weighting and discounting is that the burden attributed to younger age groups is considerably less than it would have been without these value choices.[10]

Life expectancy

In the absence of co-morbidity, the life expectancy of fatal cases can be derived from life tables if the age distribution of fatalities is known. By choosing the national life expectancy for each country, it would mean that the death of a 40-year old person in a country with a low life expectancy contributes less to the European burden of disease than the death of a 40-year old person in a country with a high life expectancy, which is not preferable. In the Global Burden of Disease study, the years of life lost due to a death at a given age has been calculated using the life expectancy at that age in standard life tables (West Level 26) with life expectancy at birth fixed at 82.5 years for females and 80.0 years for males. This standard has been chosen to match the highest national life expectancy observed (Japanese females).[11] In Europe however the difference in life expectancy between men and women is greater and therefore the mean life expectancy of the 25 EU-countries in 2004 has been used (calculation based on total mortality and average population 2004, data Eurostat; see Appendix III).

Discounting

When the principle of discounting is applied, it means that future life years are assigned less value than those lived today. This is based on the economic concept that one prefers benefits now rather than in the future.[11] Discounting is disputed because its application results in a lower efficiency of prevention programmes.[12] Therefore, some studies show both discounted and undiscounted results. In this pilot project discounting has not been applied.

Age-weighting

Age-weighting is applied to reflect 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.[11] Age-weighting is highly debated and the exact quantitative implementation is controversial.[13, 14] In this pilot project, age-weighting has not been applied.

Disability weighting

Disability weighting means that each outcome of a disease is assigned a different value on a scale from 0 (perfect health) to 1 (death). Although it seems controversial to weigh health outcomes, a Dutch study on toxoplasmosis indicates that disease burden results are more affected by using different data sources than different severity weights.[15] This is also true for heart failure and rheumatoid arthritis but depends on the disease under study.[16]
Ideally, the severity weights used in the calculations reflect the values in the societies under study. The Global Burden of Disease study divides the spectrum from health to death into seven disability classes[17] (Table 2.1).

Table 2.1 Disability classes and severity weights according to the Global Burden of Disease study[17]

Disability class	Severity weights	Examples
1	0.00-0.02	Vitiligo on face, low weight
2	0.02-0.12	Watery diarrhoea, severe sore throat, severe anaemia
3	0.12-0.24	Infertility, rheumatoid arthritis, angina
4	0.24-0.36	Amputation, deafness
5	0.36-0.50	Down syndrome
6	0.50-0.70	Depression, blindness
7	0.70-1.00	Psychosis, dementia, quadriplegia

Severity weights can be derived through different methods. Ideally, values of the general public are reflected in severity weights that are used to inform policy making at the national or international level. Weights based on elicitation panels consisting of lay persons are increasingly becoming available. Previous work has depended on other panels e.g. of medical professionals. Values from patients who actually suffer from a disease are not considered informative because of coping behaviour.

Different protocols are available for panel elicitation, including the standard gamble (SG), time trade-off (TTO), person trade-off (PTO) and visual analogue scale (VAS). All methods give different results (VAS > TTO > PTO > SG), but they are correlated. The SG and VAS are not considered informative because they are only sensitive to severe disease (SG) or very sensitive to mild diseases (VAS). This leads to compression at either end of the scale. The TTO and PTO methods are generally used.

For chronic diseases, most descriptions are based on the impact of a disease in the course of a year. Many infectious diseases have a rapid course, and the disease burden 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). Both methods have been used and using the annual profile may overvalue disability weights.[18] Hence for self-limiting diseases of short duration, large differences may be found between these two methods (e.g. norovirus-associated gastro-enteritis). For such diseases, using annual profiles may lead to very high estimates of disease burden. In this pilot study period profiles were used except for influenza (acute illness) for which only an annual profile was available.

The international transferability of severity weights is also a matter of concern. A study in Western Europe concluded that there was “a reasonably high level of agreement on disability weights in Western European countries with the VAS and TTO methods, but a lower level of agreement with the PTO method”.[19] However, a recent study[20] concluded that “Meaningful differences exist in directly elicited TTO valuations of EQ-5D health states between the United States and United Kingdom general populations”. Hence, severity weights are ideally based on specific elicitations for the population under study, but this may be very difficult to realise for the EU or even a specific country. In this study, internationally available severity weights were used (mainly from the Global Burden of Disease study, see Appendix IV).

2.6 Data and data analysis

The impact of infectious diseases on a society can be measured at different levels, often represented by the “iceberg” metaphor (see Figure 2.1). The impact of illness at different levels of the iceberg may differ greatly, as well as the availability of data. Therefore it is useful to separate these different levels in burden of disease studies. The degree of underreporting varies greatly between diseases as well as between countries or even within one country in different periods. In this pilot only **generally available** data could be used and the study did not attempt to adjust for under-reporting.

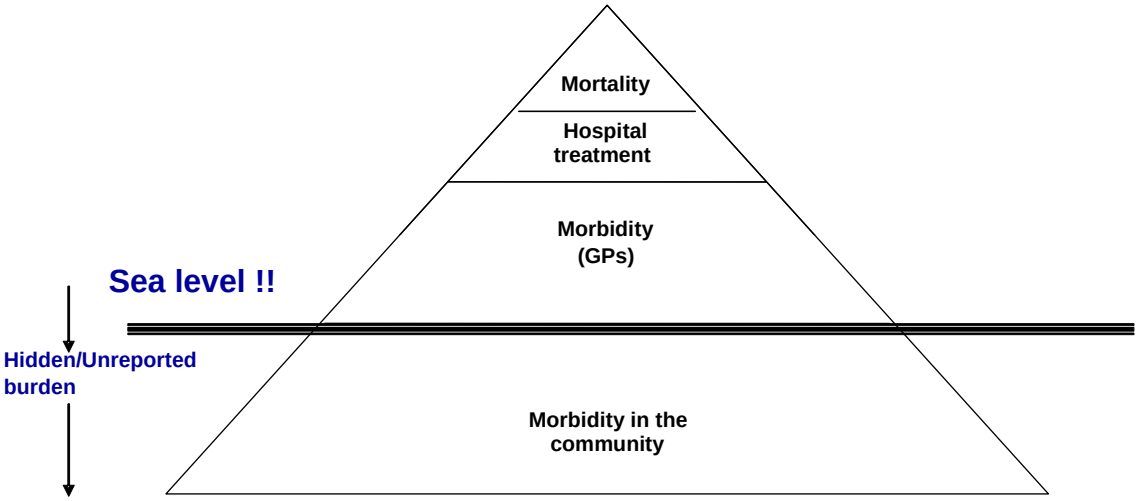


Figure 2.1 The "iceberg" of the burden of infectious diseases in society[21]

Depending on data availability, as many as possible member states of the European Union and EEA/EFTA countries (Appendix II) have been included as they are the focus of the activities of ECDC. To reduce the impact of short-term fluctuations, preferably a three-year period (2003-2005) was considered, depending on data availability. A period of three years instead of a period of five years has been chosen because HIV surveillance is recently implemented or modified in a considerable number of countries. Reported HIV-infections before 2003 may therefore include a considerable number of prevalent infections diagnosed in the past.[22] Because of comparability for all diseases the period of 2003-2005 was used. To be able to calculate DALYs, data on mortality, incidence, duration and severity were broken down into different age and sex categories where possible.

Number of fatal cases

In this pilot reported mortality data of Eurostat/WHO over the period 2003-2004 have been used; 2005 was not yet available for many countries (mortality data were last updated in the first week of January 2007). The ICD-codes used for each of the diseases are described in Appendix IV. Mortality from infectious diseases is typically underreported in most routine surveillance systems. As YLL usually are an important component of the total disease burden, for some diseases the impact of underreporting was explored by scenario analysis. There was no information available about underlying causes of death.

Incidence of non-fatal health outcomes

Depending on the complexity of the outcome tree, the incidence had to 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. However, such data were not available for the complete trees and supplementary data were necessary. These included the direct use of surveillance data or special studies for the incidence of the specific outcomes. The incidence data should ideally also be differentiated according to different

levels of the iceberg: non-consulting cases, cases who consult a general practitioner and hospitalised cases. In this order, data availability may be expected to increase, but will seldom be complete. An estimate of the degree of underreporting and of possible biases (from special studies) in the data is necessary. Such probabilities may be available from cohort or outbreak studies. Alternatively, the incidence may be calculated from independent surveillance data or special projects in the incidence of the (late) outcome of concern, and the attributable fraction for the agent of concern. 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 iceberg. In this pilot project, only surveillance data generally available from Eurostat (last update from the website in the first week of January 2007), EuroHIV (provided in October 2006), EuroTB (provided in March 2007) and EISS (based on annual reports) have been used. No information was available on the sensitivity of these surveillance systems for different levels of the iceberg, nor on the differences between countries. Data included all incident cases in a country in the chosen time period 2003-2005, including travel-related cases.

Duration and severity of non-fatal health outcomes
Duration of non-fatal health outcomes and severity weights have been derived from different publications, such as the Global Burden of Disease study,[17, 23] the Public Health Status and Forecast studies for the Netherlands,[24] former experience at RIVM[9] and review articles (see Appendix IV).

Data analysis
For each country and each disease the disease burden or Disability Adjusted Life Years (DALYs per year) have been calculated using spreadsheets. Data are presented from a societal perspective (DALYs per year per country and per 100,000 population per country) and from an individual perspective (DALYs per year per individual case).

If possible, the disease burden estimates in this pilot have been compared with estimates derived from more extensive studies:

- The Global Burden of Disease study conducted by WHO (data 2002; outcome approach): extensive study on disease burden in general (both non-infectious and infectious diseases) that includes estimates of duration and severity of different outcomes.[25]
- The Public Health Status and Forecast studies conducted by the RIVM for the Netherlands (data 2003; outcome approach): in this study the emphasis is on the impact of major diseases such as cardiovascular disease and cancer, however the disease burden of a number of infectious diseases has also been assessed.[26]
- More extensive studies on disease burden of foodborne pathogens conducted by the RIVM for the Netherlands (data 2004; agent approach): in this study campylobacteriosis, EHEC-infection, salmonellosis, noroviruses, rotaviruses, listeriosis and toxoplasmosis were included.[9]

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

- statistical uncertainty (small sample size)
- systematic uncertainty (representativeness)
- lack of data

No formal uncertainty analysis was performed in this pilot project. Scenario analysis was employed to explore the impact of uncertain factors or assumptions in the calculations. Within the scope of this pilot, it was only possible to conduct a scenario analysis for the Netherlands. 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 etcetera. This variability was not formally included in the project, and arithmetic mean values were used as point estimates.

3. Limitations

For the baseline disease burden estimates a number of limitations regarding data availability and data quality were identified which should be kept in mind when interpreting the results of this pilot study. Some limitations were addressed by scenario analysis.

3.1 Data availability

Incidence

- Data on incidence of the acute illness were not available for all countries for all years
  -> YLD (and DALY) have not been calculated for those countries with no information at all (see Table 3.1)
  -> YLD was based on the mean incidence for countries with data available for 1, 2 or 3 years
- Data on incidence of most of the complications were not available (except for AIDS and multidrug-resistant tuberculosis)
  -> The probability of most complications has been based on (Dutch) literature and previous experience at RIVM

Duration and severity weights

- For most diseases the incidence data were not age-specific (except for HIV-infection and tuberculosis)
  -> For duration of chronic conditions (= remaining life expectancy) a proxy has been taken (e.g. for the measles outcome “deafness due to otitis media” full life expectancy was taken as a proxy because in general incidence of measles is highest in the youngest age groups)
  -> In case of age-specific severity weights a proxy has been taken (e.g. for the measles outcome “deafness due to otitis media” the mean severity weight for the youngest age groups 00-04 year and 05-14 year has been taken)
- Not for all different outcomes of all diseases information on duration and severity weights was available
  -> In case of lack of information a similar outcome has been chosen as a proxy

Mortality

- Data on mortality were not available for all countries
  -> YLL (and DALY) have not been calculated for those countries (see Table 3.1)

Life expectancy

- There was no recent European life expectancy generally available
  -> A calculation based on Eurostat data for 2004 has been used (total mortality + average population 2004 of the EU-25 countries)

Table 3.1 Countries for which the disease burden could not be calculated

DATA	influenza	measles	HIV-infection	campylo-bacteriosis	EHEC-infection	salmonellosis	tuberculosis
NO YLD	Cyprus Estonia Finland Greece Hungary Iceland Liechtenstein Malta	Liechtenstein	Cyprus Liechtenstein Spain	Greece Liechtenstein Luxembourg Portugal	Belgium France Italy Liechtenstein Luxembourg Portugal	Liechtenstein	Liechtenstein
NO YLL	Belgium Denmark Italy Liechtenstein Slovakia						

HIV: Human Immunodeficiency Virus; EHEC: enterohaemorrhagic *Escherichia coli*

3.2 Data quality

Incidence

- There was no information on the sensitivity of the different surveillance systems (tip of the iceberg)
- There was no information on the case definition of incidence data from Eurostat
- Incidence data were not always available for whole countries (only for some regions within a country) and extrapolation was not possible
- There was no information on variation in complication rates between countries, a constant complication rate was assumed
- Incidence provided by Eurostat is not always identical to national incidence

Duration and severity weights

- The duration and severity weights have been derived from different literature sources, so there is no consistency in the used methodology
- There was no differentiation in duration and severity possibly related to need of medical care
- There was no information on variation between countries (for some outcomes GBD duration data differ between Established Market Economies, Formerly Socialist Economies and Middle Eastern Crescent)
- Duration and severity could not be based on recent literature which means that for example for HIV-infection HAART could not be taken into account

Mortality

- There was no specific information on the degree of underreporting for each of the diseases
- Some countries report mortality in general but specific causes are missing
  -> assumption of 0 deaths has been used
- For some countries there are differences in the number of reported deaths between Eurostat and WHO
  -> preference for Eurostat data in case of differences

4. Influenza

Influenza is defined as an acute respiratory disease caused by influenza viruses (type A, B or C are recognized) which spreads via the respiratory route. Influenza is not only associated with increased general practice consultation rates, hospital admissions and excess deaths but also with increased days lost to absence (work or school).[27]

4.1 Outcome tree

The outcome tree for influenza is presented in Figure 4.1. In approximately 50% of the cases the infection is subclinical.[28] Influenza symptoms are abrupt onset of fever and chills, accompanied by headache and sore throat, myalgia, malaise, anorexia and a dry cough.[29] In uncomplicated influenza the fever usually lasts 2-5 days and healthy people recover within 1-2 weeks without sequelae.[30] According to Meier et al. 9.5% of the influenza cases in the United Kingdom between 1991-1996 had clinical complications (respiratory tract, heart, central nervous system, kidneys or other) within 30 days after diagnosis and 0.2% of the cases died within 30 days after diagnosis.[31] Most common complications of influenza are secondary bacterial infections, especially otitis media and pneumonia.[28] These complications were therefore included in the outcome tree.

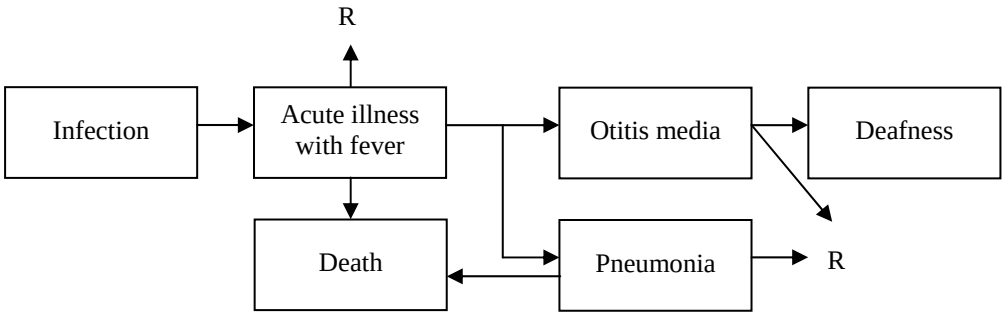


Figure 4.1 Outcome tree influenza (R=recovery)

The influenza vaccine is effective in reducing illness, hospitalization and mortality, albeit effectiveness varies by target group and season.[32, 33, 34] Annual vaccination of groups with high risk is the major strategy for controlling influenza infections.[35, 36] The vaccination coverage among elderly in the European Union is known from only a limited number of countries and varies between 25% in Finland to 81% in the Netherlands, for other risk groups few data were available.[37] Based on the number of doses of vaccine distributed in a country per 1,000 population, in 2000 vaccine use was lowest in Eastern Europe followed by the Scandinavian countries.[38]

4.2 Baseline estimate of disease burden

Specific data sources and assumptions regarding mortality, incidence, duration and severity of the different outcomes in the outcome tree of influenza are described in Appendix IV (Table IV.1 and IV.8). Based on this information the YLD, YLL and DALY for influenza have been calculated (Table 4.1). The disease burden for influenza is mainly dominated by mortality, and the burden due to complications (otitis media including deafness and pneumonia were taken into account) is considerably smaller than the burden due to the acute illness.

Table 4.1 Morbidity, mortality and disease burden (DALYs per year) for influenza

	Morbidity				Mortality		DALY per year		
countries	incidence	YLD acute	YLD compl.	YLD total	deaths	YLL	DALY total	DALY per case	DALY per 100.000
Austria[1]	566	5.7	0.0	5.7	12	170.8	176.5	0.3	2.2
Belgium	874	8.7	0.0	8.8	-	-	-	-	-
Cyprus[4]	-	-	-	-	0	0.0	-	-	-
Czech Republic	236	2.4	0.0	2.4	35	317.5	319.9	1.4	3.1
Denmark	117	1.2	0.0	1.2	-	-	-	-	-
Estonia	-	-	-	-	1	2.0	-	-	-
Finland	-	-	-	-	55	600.9	-	-	-
France[3]	2,650	26.5	0.1	26.6	475	4,631.7	4,658.3	1.8	7.5
Germany	1,372	13.7	0.1	13.8	212	2,147.7	2,161.5	1.6	2.6
Greece	-	-	-	-	0	0.0	-	-	-
Hungary	-	-	-	-	23	418.1	-	-	-
Ireland	179	1.8	0.0	1.8	7	114.8	116.6	0.7	2.9
Italy	621	6.2	0.0	6.2	-	-	-	-	-
Latvia	525	5.2	0.0	5.3	3	52.3	57.5	0.1	2.5
Lithuania	5	0.1	0.0	0.1	6	156.5	156.6	29.4	4.6
Luxembourg[2]	54	0.5	0.0	0.5	3	51.2	51.7	1.0	11.4
Malta	-	-	-	-	1	8.5	-	-	-
Netherlands	400	4.0	0.0	4.0	150	1,292.8	1,296.8	3.2	8.0
Poland	39	0.4	0.0	0.4	84	922.8	923.2	23.5	2.4
Portugal	400	4.0	0.0	4.0	11	80.0	84.0	0.2	0.8
Slovakia	200	2.0	0.0	2.0	-	-	-	-	-
Slovenia	146	1.5	0.0	1.5	3	16.5	18.0	0.1	0.9
Spain	570	5.7	0.0	5.7	135	925.7	931.4	1.6	2.2
Sweden[1,3]	1,667	16.7	0.1	16.7	79	630.9	647.7	0.4	7.2
United Kingdom	1,956	19.6	0.1	19.6	61	1,180.2	1,199.9	0.6	2.0
Iceland	-	-	-	-	2	10.5	-	-	-
Liechtenstein	-	-	-	-	-	-	-	-	-
Norway	566	5.7	0.0	5.7	36	290.8	296.4	0.5	6.5

Note
incidence = mean # of respiratory specimens tested positive for influenza 2002/2003-2004/2005 (data EISS)
mortality = mean # of deaths 2003-2004 (data Eurostat/WHO)
- = no data available
[1] = incidence data 2004/2005 only
[2] = incidence data 2003/2004 - 2004/2005 only
[3] = mortality data 2003 only
[4] = mortality data 2004 only

The disease burden is relatively high in the Scandinavian countries, the Netherlands, France and Luxembourg. In these countries the number of reported deaths due to influenza is relatively high. In the baseline estimate for disease burden the number of respiratory specimens tested positive for influenza reported to the European Influenza Surveillance Scheme (EISS) has been used as an estimate of the influenza incidence. However, usually the disease is self-limiting and diagnoses are generally not laboratory-confirmed. Therefore the true incidence of influenza is considerably higher than the reported incidence based on respiratory specimens tested positive for influenza. Table 4.1 also makes clear that based on laboratory data the incidence of influenza is substantially underestimated: in some countries (like for example Poland) the number of registered deaths due to influenza even exceeds the number of positive respiratory specimens.
In the baseline scenario reported influenza mortality has been used to estimate YLL. However, research has shown that clinicians often attribute influenza-related deaths to a pre-existing underlying condition (for example pneumonia) rather than to influenza.[39] Therefore, it is difficult to identify true mortality due to influenza. Some other estimates for both incidence and mortality have been addressed in scenario analysis (section 4.3).

4.3 Scenario analysis

The incidence of influenza based on laboratory-confirmed data only (baseline scenario) is underestimated. Another indication that influenza morbidity was underestimated, is that the Public Health Status and Forecast studies estimated the Dutch morbidity for influenza in 2003 on 5,454 YLD[26] compared to 4 YLD in this pilot (Figure 4.2). In the Dutch study, the incidence of non-fatal cases was estimated from the number of general practitioner visits because of influenza-like-illness (corrected for the part of patients that will not seek medical attention but not corrected for the fact that not all influenza-like-illness can be ascribed to influenza). Figure 4.2 also shows the results of a scenario analysis for the Netherlands. Scenario 2 and 3 provide other morbidity estimates while scenario 4 provides another mortality estimate.

In scenario 2 the mean number of general practitioner visits because of influenza-like-illness in the seasons 2003/2004 to 2005/2006[40] has been used as incidence estimate (n=260,655). This incidence has been corrected for the assumption that only 30% of the influenza patients in the Netherlands will visit their general practitioner[24] and only 32,2% of the influenza-like-illnesses in the Netherlands can be ascribed to influenza[41] (based on laboratory confirmation for the influenza season 2005/2006). For the Netherlands the influenza incidence in this scenario was 279,770 cases per year (compared to 400 in the baseline scenario). This has a considerable impact on the morbidity estimate that changes from 4 YLD in the baseline scenario to 2,808 YLD in scenario 2.

In England and Wales approximately 800,000 GP consultations for respiratory illnesses each year are attributed to influenza,[42] this incidence would result in 8,030 YLD compared to 20 YLD for the United Kingdom in the baseline scenario.

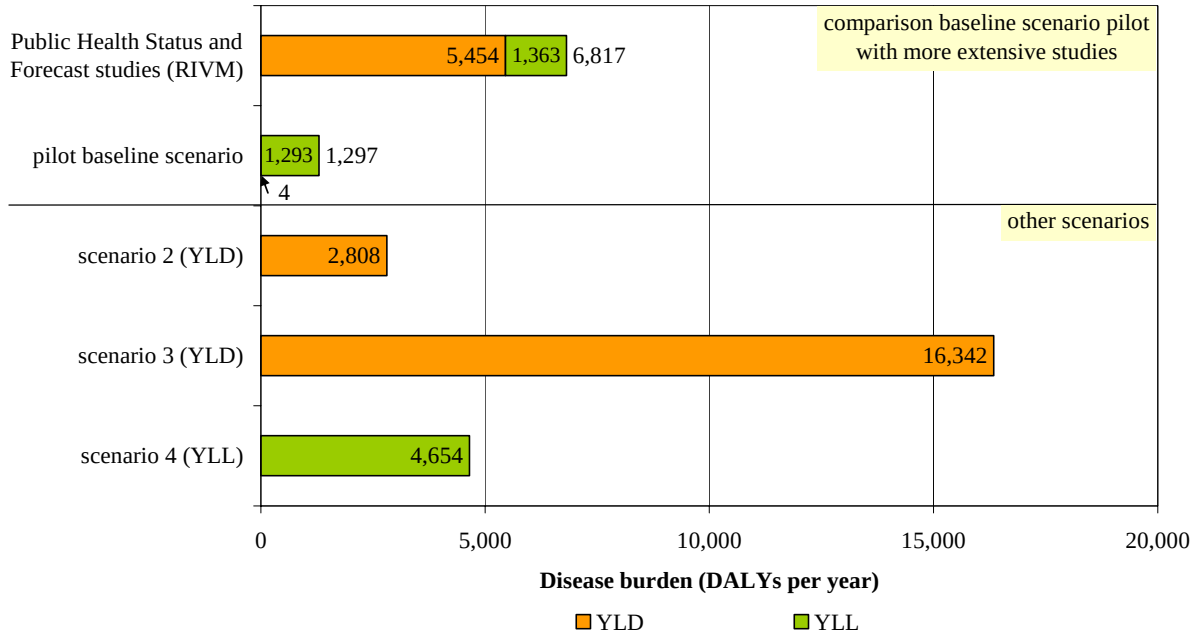


Figure 4.2 Scenario analysis influenza for the Netherlands

In scenario 3 the incidence was based on the assumption that the clinical attack rate of influenza during epidemics ranges from 10-20% in the general community.[43] In this scenario the lowest estimate of 10% has been used because in half of the cases the infection is subclinical. For the Netherlands the influenza incidence in scenario 3 was 1,628,178 cases per year (compared to 279,770 in scenario 2), the YLD estimate changes to 16,342. For the Netherlands the incidence in scenario 3 seems to be too high because it is considerably higher when comparing to scenario 2 which is probably closest to reality (based on sentinel data).

For the Netherlands Sprenger et al. estimated that in the period 1967-1989 the overall impact of influenza on mortality was greater than registered mortality by a factor of 3.6.[44] In scenario 4 the registered mortality in all age classes was therefore multiplied by 3.6, which resulted in a mortality estimate of 4,654 (compared to 1,293 in the baseline scenario). The number of deaths could have been overestimated this way because the influenza virus seems to be less virulent in the last years[41] and today vaccination coverage is considerably higher than in the period 1967-1989. Furthermore, YLL was probably overestimated because it is likely that people dying from influenza have un underlying disease and therefore a lower life expectancy. In the study of Sprenger et al. almost half of the non-registered influenza deaths were registered as deaths from heart disease, approximately 25% from lung disease and approximately 30% from other diseases.[44]

4.4 Discussion and recommendations

Based on scenarios 2 (YLD) and 4 (YLL) combined, the Dutch disease burden of influenza may have been underestimated in the baseline scenario by a factor of at least five. It is likely that the burden was also underestimated for other countries. The number of respiratory specimens tested positive for influenza is not suitable as incidence indicator for disease burden calculations, because testing is not general practice (this applies for all the selected diseases but for influenza in particular). Future morbidity estimates need to concentrate on scenario 2. EISS collects data on general practitioner visits because of influenza-like-illness in different countries. Besides the wide range of national case definitions, estimated consultation rates may differ between countries due to differences in consultation behaviour, estimation procedure, vaccination coverage and obligatory doctor visits for absence from work or school.[45, 46] The fraction of patients that visits their general practitioner and the proportion of influenza-like-illness that can be ascribed to influenza need to be determined for each of the countries.

An alternative mortality estimate could be the excess all-cause mortality during periods of high circulation of influenza,[39, 47] like the Dutch example in scenario 4. According to Armstrong et al. in people aged over 75 years the proportion of deaths attributable to influenza during periods of influenza for all cause mortality was 13,4% in unvaccinated people and 2.2% in vaccinated people.[48]

5. Measles

Worldwide measles is still an important cause of death among children below five years old and measles is the leading cause of vaccine preventable deaths in children.[28, 49] In many industrialized countries measles is now a rare disease but outbreaks still occur. Measles is one of the most contagious infectious diseases. The immunity degree of the population needed to prevent epidemic spread is very high, probably over 95%, which has not yet been achieved in all European countries. WHO aims to eliminate measles in the European region by 2010.[50, 51] According to the surveillance Community Network for Vaccine Preventable Infectious Diseases 82% of the reported measles cases with a known vaccination status occurred in unvaccinated children.[52] Measles is caused by a respiratory virus (a morbillivirus) and spreads through direct contact.[28]

5.1 Outcome tree

The outcome tree for measles is shown in Figure 5.1. Measles starts with high fever, coughing, runny nose, red eyes and small white spots inside the cheeks (Koplik spots). After several days a red rash develops (usually on the face and upper neck).[53, 50] Most important complications of measles are otitis media (5-10% of the cases), pneumonia (1-5% of the cases) and encephalitis (0.1% of the cases). A very rare complication is subacute sclerosing panencephalitis (SSPE), caused by persistent infection with measles virus, with nerves and brain tissue degeneration.[28] In children who previously had natural measles the risk of developing SSPE is between 0.6 and 2.2 per 100,000 measles infections.[54]

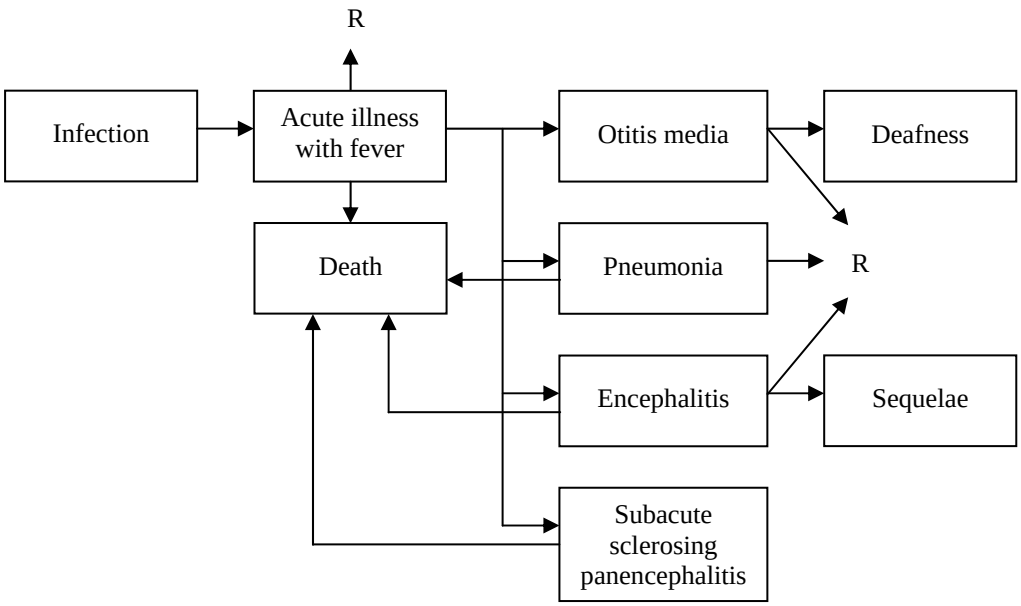


Figure 5.1 Outcome tree measles (R=recovery)

5.2 Baseline estimate of disease burden

Specific data sources and assumptions regarding mortality, incidence, duration and severity of the different outcomes in the outcome tree of measles are described in Appendix IV (Table IV.2 and IV.8). Based on this information the YLD, YLL and DALY for measles have been calculated (Table 5.1). Except for countries with a relatively high number of measles cases and therefore morbidity (especially France and Italy), the disease burden for measles is mainly dominated by mortality. Unfortunately, Italy is one of the countries where mortality data were not generally available. In the countries Portugal, Malta, Norway, Austria and the Netherlands the number of reported deaths is relatively high compared to the number of reported measles cases, while the number of deaths in France seems to be relatively low.

Table 5.1 Morbidity, mortality and disease burden (DALYs per year) for measles

	Morbidity				Mortality		DALY per year		
countries	incidence	YLD acute	YLD compl.	YLD total	deaths	YLL	DALY total	DALY per case	DALY per 100.000
Austria	41	0.2	0.3	0.5	4	187.3	187.9	4.6	2.3
Belgium	44	0.3	0.3	0.6	-	-	-	-	-
Cyprus[3]	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Czech Republic	16	0.1	0.1	0.2	0	0.0	0.2	0.0	0.0
Denmark	1	0.0	0.0	0.0	-	-	-	-	-
Estonia	1	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Finland	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
France[1,2]	7,454	45.4	53.0	98.4	4	247.1	345.5	0.0	0.6
Germany	560	3.4	4.0	7.4	5	227.0	234.4	0.4	0.3
Greece	43	0.3	0.3	0.6	0	0.0	0.6	0.0	0.0
Hungary	1	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Ireland	333	2.0	2.4	4.4	1	30.9	35.3	0.1	0.9
Italy	4,293	26.2	30.5	56.7	-	-	-	-	-
Latvia	0	0.0	0.0	0.0	0	0.0	0.0	-	0.0
Lithuania	1	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Luxembourg	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Malta	1	0.0	0.0	0.0	1	26.0	26.0	19.5	6.5
Netherlands	6	0.0	0.0	0.1	1	21.2	21.3	3.5	0.1
Poland	24	0.1	0.2	0.3	1	38.2	38.5	1.6	0.1
Portugal	5	0.0	0.0	0.1	4	227.5	227.6	42.7	2.2
Slovakia	1	0.0	0.0	0.0	-	-	-	-	-
Slovenia	0	0.0	0.0	0.0	0	0.0	0.0	-	0.0
Spain	98	0.6	0.7	1.3	3	115.8	117.1	1.2	0.3
Sweden[2]	7	0.0	0.0	0.1	0	0.0	0.1	0.0	0.0
United Kingdom	245	1.5	1.7	3.2	5	237.5	240.7	1.0	0.4
Iceland	0	0.0	0.0	0.0	0	0.0	0.0	-	0.0
Liechtenstein	-	-	-	-	-	-	-	-	-
Norway	5	0.0	0.0	0.1	1	35.8	35.9	7.2	0.8

Note
incidence = mean # of cases 2003-2005 (data Eurostat)
mortality = mean # of deaths 2003-2004 (data Eurostat/WHO)
- = no data available
[1] = incidence data 2003-2004 only
[2] = mortality data 2003 only
[3] = mortality data 2004 only

The incidence of measles based on reported cases may be underestimated because many persons do not seek medical attention,[55] however no alternative estimates were available. In scenario analysis the effect of an outbreak on the disease burden estimate have been studied (section 5.3).

5.3 Scenario analysis

There are considerable differences between disease burden estimates of the pilot baseline scenario and the Global Burden of Disease study (2002) (Figure 5.2). The differences between both estimates are mainly caused by differences in mortality and may be a random effect. Since measles mortality is rare, only one death more or less will have a considerable impact on disease burden (for example in the GBD estimate for the Netherlands the number of deaths in 2002 was 0, in the pilot there was 1 reported death in the period 2003-2004).

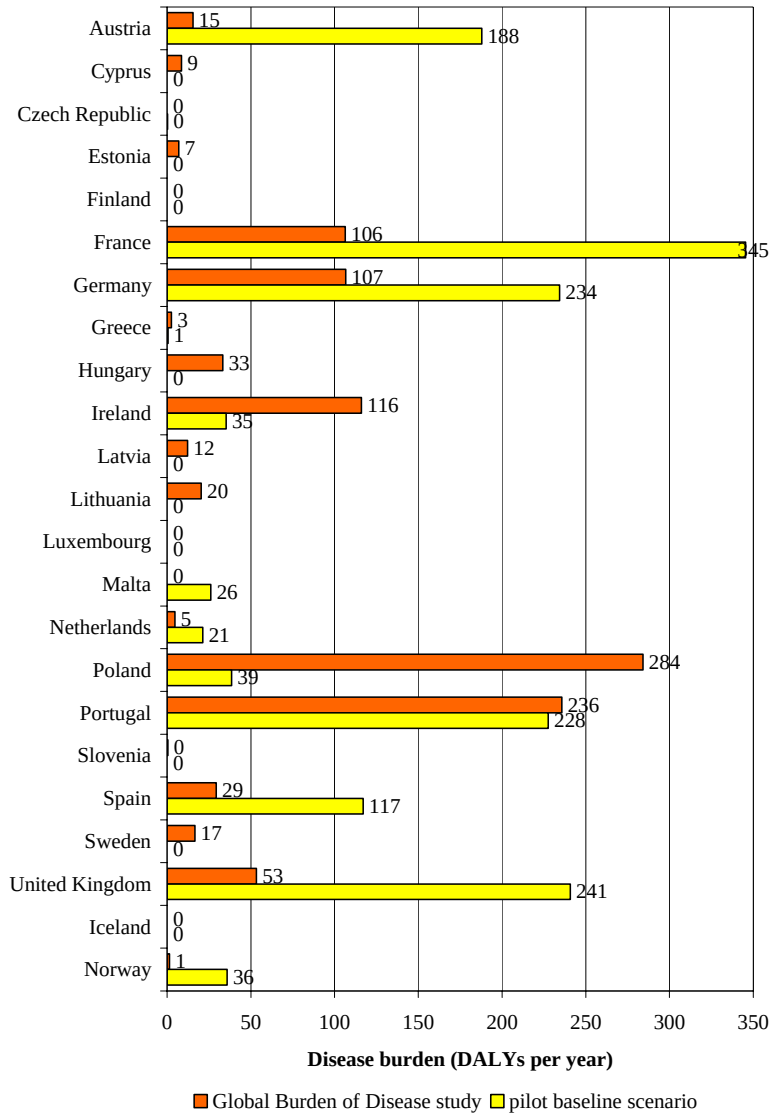


Figure 5.2 Comparison baseline scenario pilot for measles with Global Burden of Disease study

The difficulty with measles is that in most European countries there normally are very few cases and mortality is rare but there is always the risk of an outbreak situation which will lead to a sudden rise in incidence and therefore in disease burden. Scenario 2 provides another estimate for both morbidity and mortality (Figure 5.3). In this scenario the measles incidence and mortality data of a Dutch measles outbreak in 1999/2000 have been used. During this outbreak 3,292 measles cases and 3 deaths have been reported in the Netherlands[56] which leads to a disease burden estimate of 258 DALYs per year. Although the disease burden for measles in scenario 2 is still low compared to other diseases, the effect of an outbreak is substantial (mainly due to mortality). However, if the mean incidence and mortality over a period including several years is considered, the effect of an outbreak will be smaller.

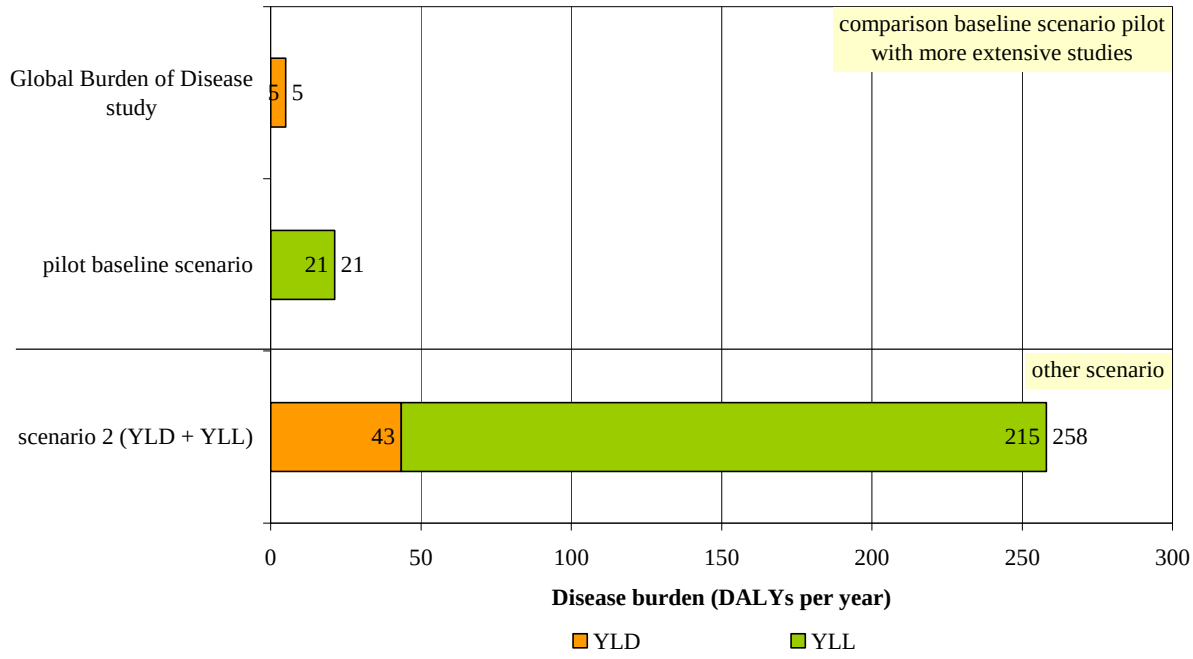


Figure 5.3 Scenario analysis measles for the Netherlands

5.4 Discussion and recommendations

The disease burden of measles is mainly dominated by mortality even though a number of complications (otitis media including deafness, pneumonia, encephalitis including sequelae and SSPE) were taken into account. Morbidity could have been underestimated due to underreporting of the “acute phase”. Studies in England/Wales and the USA have shown that the notification efficiency for measles rarely exceeds 40%, even in outbreak situations.[57, 58] However, even in the outbreak situation of scenario 2 the morbidity burden is just 17% of the total disease burden. The case-fatality ratio differs substantially between countries. There is no information on the degree of underreporting; in particular better data on measles-related mortality are important for disease burden estimates. In general the disease burden of measles is relatively low compared to other diseases but the effect of an outbreak is substantial. This demonstrates the importance of prevention efforts.

6. HIV-infection

There are indications that sexually transmitted infections are again on the rise in many countries in the European Union.[59] HIV-infection, caused by the Human Immunodeficiency Virus through contact with infected body fluids (sexual contact, blood, pre/perinatal or breast-feeding), is spread worldwide. At the end of 2005 an estimated 38.6 million (33.4 million – 46.0 million) people worldwide were living with HIV.[60] Rates of new HIV diagnoses vary greatly between countries in Europe. In general, the total number of reported HIV cases in Western and Central Europe is low compared to Eastern Europe.[22] In Eastern Europe a considerable number of new HIV-infections is acquired through intravenous drug use.[61]

6.1 Outcome tree

In Figure 6.1 the outcome tree for HIV-infection is shown. Primary infection with HIV can be accompanied by influenza-like symptoms for some days to weeks, which occurs in more than half of the cases. The diagnosis HIV is rarely made at this stage. The primary infection is followed by an asymptomatic period.[62] Without treatment, HIV-infection almost always leads to progressive immunosuppression (symptomatic infection) that can lead to Acquired Immunodeficiency Syndrome (AIDS) and death. Well known examples of opportunistic infection and malignancy related to AIDS are pneumonia caused by *Pneumocystis carinii* and Kaposi's sarcoma (cancer of connective tissue).[28] Tuberculosis is the most frequently diagnosed AIDS indicative disease.[22]

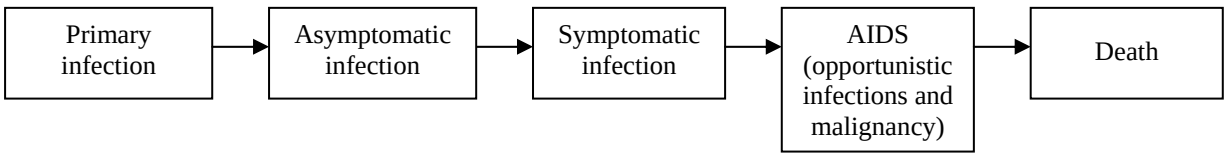


Figure 6.1 Outcome tree HIV-infection

Highly Active Anti-Retroviral Therapy (HAART), standard of care from 1996 onwards, can delay symptomatic infection and the onset of AIDS with years. Before the introduction of HAART most HIV-infected people progress to AIDS within 10 years of infection and to death in less than 2 years after AIDS diagnosis. As a result of the widespread use of HAART, the incidence of AIDS cases and AIDS related deaths in Europe have strongly declined.[63, 64, 65, 66] Possible complications of (long-term) usage of HAART are toxicities, metabolic changes and immune reconstitution disease.[61] In all countries of the European Union the access to HAART in 2005 is good (=over 75%). However in 2003 the access to HAART in Estonia, Latvia and Lithuania was only partial (10-70%).[67]

6.2 Baseline estimate of disease burden

Specific data sources and assumptions regarding mortality, incidence, duration and severity of the different outcomes in the outcome tree of HIV-infection are described in Appendix IV (Table IV.3 and IV.8). Based on this information the YLD, YLL and DALY for HIV have been calculated (Table 6.1). HIV-infection is one of the diseases for which both morbidity and mortality have a substantial impact on the disease burden. The disease burden of HIV-infection is relatively high in Portugal, Estonia, France and probably Italy and Spain.

Table 6.1 Morbidity, mortality and disease burden (DALYs per year) for HIV-infection

	Morbidity					Mortality		DALY per year		
countries	incidence HIV	incidence AIDS	YLD HIV	YLD AIDS	YLD total	deaths	YLL	DALY total	DALY per case	DALY per 100.000
Austria	449	88	605.0	89.0	693.9	52	1,879.1	2,573.1	5.7	31.5
Belgium	1,038	168	1,411.3	169.8	1,581.1	-	-	-	-	-
Cyprus[1,7]	31	-	29.2	-	-	1	16.6	-	-	-
Czech Republic	76	11	72.1	5.6	77.7	0	0.0	77.7	1.0	0.8
Denmark	284	48	386.3	48.2	434.5	-	-	-	-	-
Estonia	735	23	699.4	11.3	710.7	14	704.7	1,415.4	1.9	104.9
Finland	133	23	180.3	23.2	203.6	8	297.0	500.6	3.8	9.6
France[2,6]	5,493	1,463	7,474.1	1,478.8	8,952.9	1,044	37,043.1	45,996.0	8.4	74.0
Germany	2,200	1,058	2,992.8	1,069.1	4,061.9	505	17,335.3	21,397.2	9.7	25.9
Greece	485	101	660.3	102.1	762.4	18	651.1	1,413.5	2.9	12.8
Hungary	81	28	77.5	13.9	91.4	10	323.7	415.1	5.1	4.1
Ireland	358	48	486.3	48.9	535.1	15	638.3	1,173.4	3.3	28.8
Italy[3]	1,094	1,651	1,486.8	1,669.2	3,156.0	-	-	-	-	-
Latvia	342	75	325.5	37.8	363.3	14	568.5	931.8	2.7	40.3
Lithuania	122	13	116.0	6.7	122.7	7	261.4	384.2	3.2	11.2
Luxembourg	57	9	77.1	9.4	86.6	4	108.2	194.8	3.4	43.0
Malta[4]	18	2	17.2	1.0	18.2	2	47.7	65.8	3.7	16.4
Netherlands	1,361	243	1,849.7	245.6	2,095.3	86	2,956.6	5,051.9	3.7	31.0
Poland	639	162	608.5	80.9	689.4	122	5,194.9	5,884.3	9.2	15.4
Portugal	2,561	989	3,486.3	999.3	4,485.6	940	36,223.8	40,709.5	15.9	387.6
Slovakia	16	3	15.6	1.3	16.9	-	-	-	-	-
Slovenia	25	9	23.8	4.4	28.2	2	61.3	89.5	3.6	4.5
Spain	-	2,383	-	2,408.4	-	1,592	60,467.6	-	-	-
Sweden[6]	395	60	536.8	60.6	597.5	29	870.0	1,467.5	3.7	16.3
United Kingdom	7,757	898	10,549.5	907.7	11,457.2	228	8,652.8	20,109.9	2.6	33.6
Iceland	8	2	10.4	1.7	12.1	1	16.6	28.7	3.7	9.8
Liechtenstein	-	-	-	-	-	-	-	-	-	-
Norway[5]	225	39	306.1	39.4	345.5	20	623.1	968.6	4.3	21.1

Note
incidence = mean # of cases 2003-2005 (data EuroHIV)
mortality = mean # of deaths 2003-2004 (data Eurostat/WHO)
DALY per case = DALY per HIV-case
- = no data available
[1] = 40% HIV-cases were non-residents
[2] = incidence data HIV 2004 only, AIDS 2003-2004 only
[3] = incidence data HIV for seven regions only
[4] = incidence data HIV 2004-2005 only
[5] = incidence data HIV and AIDS 2003 only
[6] = mortality data 2003 only
[7] = mortality data 2004 only

Unfortunately, the disease burden in Italy and Spain could not be fully calculated because these countries have not yet implemented HIV case reporting at national level.[22] The disease burden per case is remarkably high in Portugal because the number of deaths is relatively high compared with other countries. Possibly, this can be explained by underreporting of new HIV-infections in Portugal.

ECDC states that the HIV-epidemic in Europe is not one but a multitude of diverse epidemics because the epidemic exhibits very different patterns in the different countries in terms of magnitude, trends and affected populations.[68] HIV-infection will lead to AIDS so the difference in the number of HIV- and AIDS-cases in Table 6.1 is noticeable: the AIDS incidence and number of deaths is much lower than the HIV-incidence (except for Italy but in this country the HIV-incidence is based on seven regions only). Most likely this is an effect of the introduction of HAART, by which the onset of AIDS and death is delayed.
The incidence of HIV-infection is difficult to determine because in many cases the diagnosis is not made in an early stage. Furthermore, the incidence data of EuroHIV were based on the year of reporting and not on the year of diagnosis. Finally, it must be noted that for AIDS this is not a true incidence approach because the new cases of AIDS in 2003-2005 are the result of older HIV-infections (not the result from HIV-infections in 2003-2005). However no alternative incidence estimates were available. Also, duration and severity weights of HIV/ AIDS used in the baseline estimate have been derived before the widespread use of HAART. In scenario analysis the effect of new estimates for duration and severity of HIV-infection, which take HAART into account, have been studied. Furthermore, a scenario has been calculated in which all new HIV-cases develop AIDS and die due to HIV (section 6.3).

6.3 Scenario analysis

For most countries the estimates of the pilot baseline scenario and the Global Burden of Disease study (2002) are in the same order of magnitude (Figure 6.2). For HIV-infection in the Netherlands the differences between the pilot study and more extensive studies as the Public Health Status and Forecast studies and the Global Burden of Disease study are not substantial (Figure 6.3). It must be noted however that in the Dutch Public Health Status and Forecast studies only AIDS has been taken into account.
Figure 6.3 also shows the results of a scenario analysis for the Netherlands. In the baseline scenario the implemented duration and severity weights for HIV and AIDS have been derived before the widespread use of HAART. In scenario 2 the same incidence and mortality data were included but new estimates for the duration and severity of HIV and AIDS were applied (based on person perceived health related quality of life; Table 6.2).[69] The morbidity estimate in scenario 2 is higher than in the baseline scenario, mainly due to the longer duration of the disease (see also Figure 6.4 for other countries).

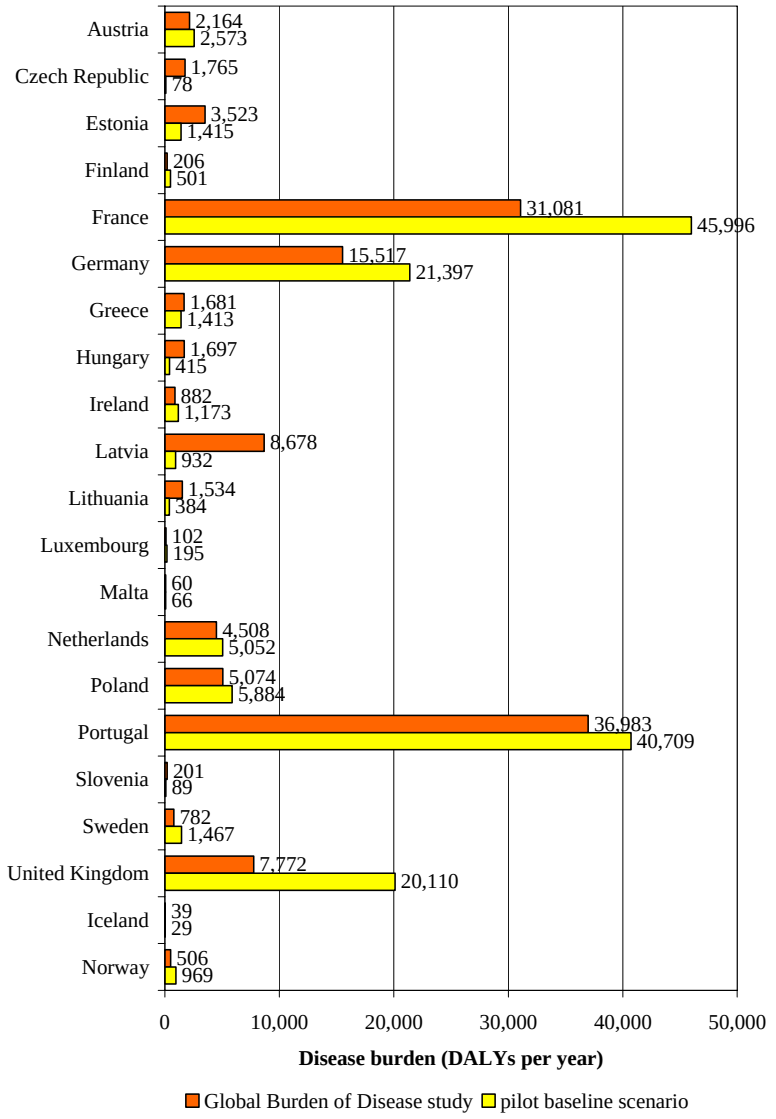


Figure 6.2 Comparison baseline scenario pilot for HIV with Global Burden of Disease study

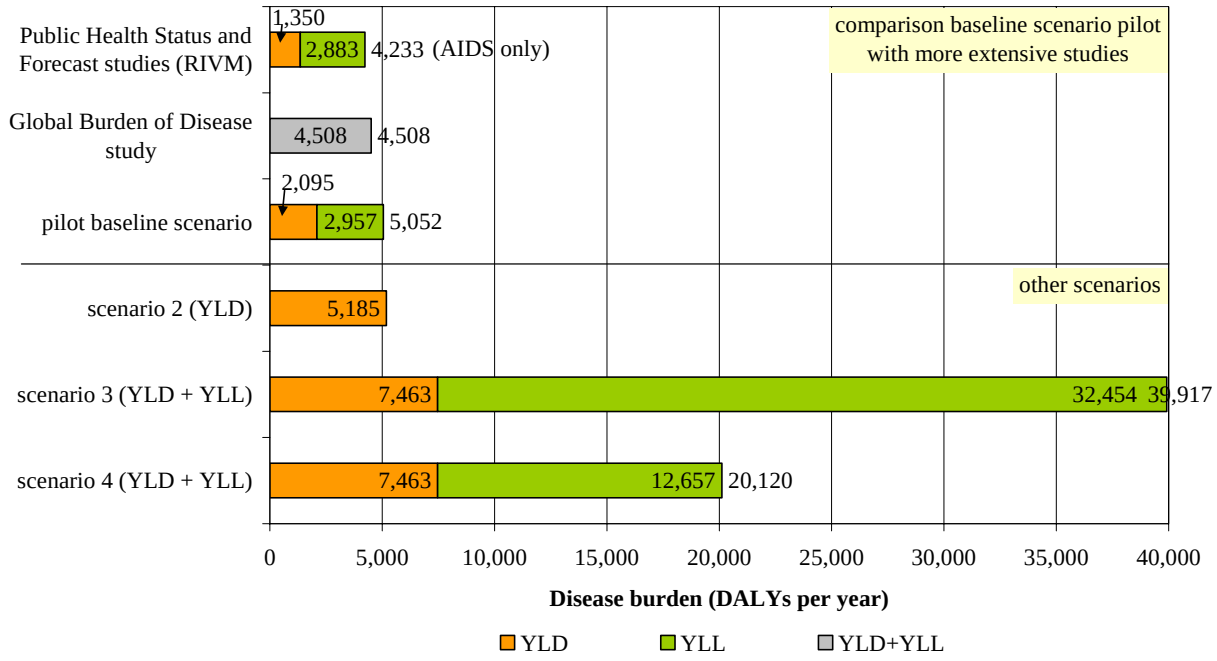


Figure 6.3 Scenario analysis HIV-infection for the Netherlands

Table 6.2 Duration and severity weights for HIV and AIDS in the different scenarios

	HIV		AIDS	
scenario	**duration**	**severity**	**duration**	**severity**
baseline scenario (prior to HAART)[23, 17]	10 year (EME) 7 year (FSE + MEC)	0.123 (00-14 year) 0.136 (15+ year)	2 year (EME) 1 year (FSE + MEC)	0.505
scenario 2/3 (HAART taken into account)[69]	17.20 year	0.20	5.36 year	0.38

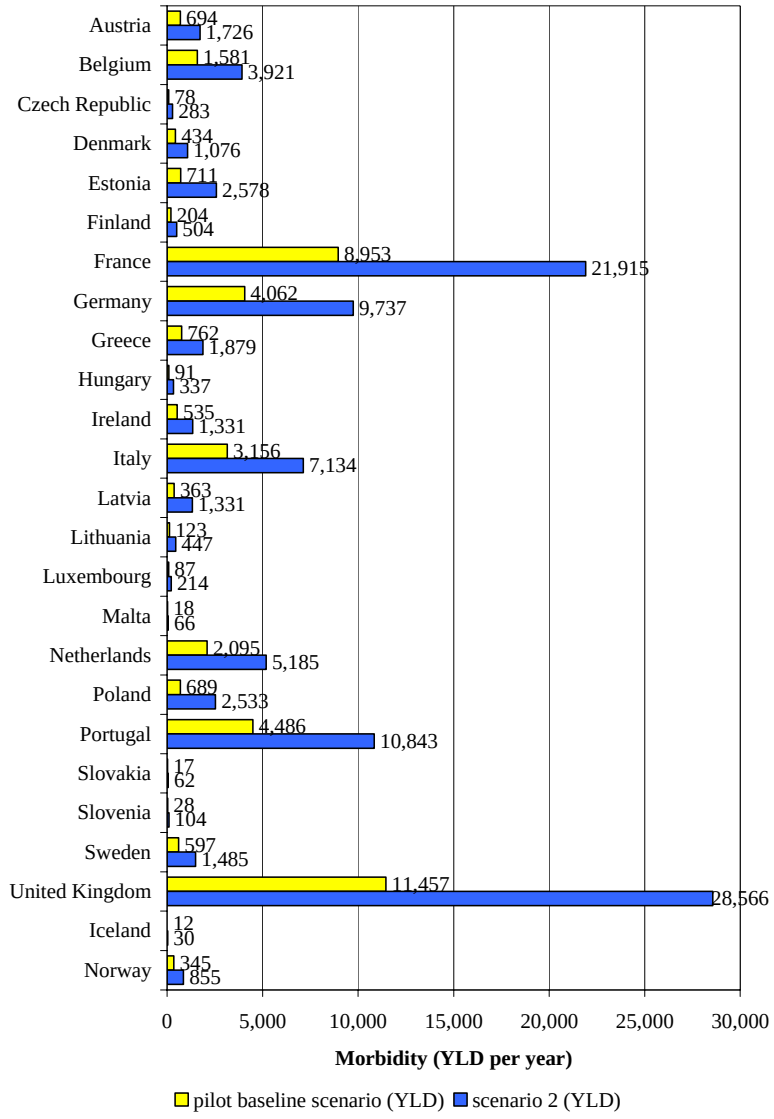


Figure 6.4 Comparison morbidity (YLD) baseline scenario pilot for HIV-infection with scenario 2

In scenario 3, the new estimates for duration and severity from Herida et al. were applied too, but reported incidence of AIDS and reported mortality was replaced by the assumption that **every** HIV-infected person lives 22.57 years (17.20 years with HIV and 5.36 years with AIDS[69]) and subsequently dies due to HIV/AIDS. In this scenario the disease burden is much higher (Figure 6.3) because the incidence of AIDS and mortality is estimated much higher (n=1,361) than the reported incidence of AIDS (n=243) and mortality (n=86) in the baseline scenario.

It must be noted that in scenario 3 mortality was overestimated because not all HIV-infected persons will die because of HIV/AIDS and with increasing survival, a growing part of patients with HIV/AIDS will die due to other causes. Among HIV-patients in the Netherlands the proportion of HIV-related causes of death declined from 76% in 1996 to 39% in 2005.[70] Scenario 4, in which we included only 39% of the years of life lost from scenario 3, seems to be more realistic even though we do not know if death due to other causes is spread evenly over different age categories.

6.4 Discussion and recommendations

Seeing the considerable differences between the scenarios we need to have better insight in the course of the disease, especially because there are remarkable differences in the ratio of HIV-cases, AIDS-cases and deaths between countries. Because of the long duration of the disease it does not seem right to combine incidence and mortality data from the same calendar years, especially because of the enormous effect of HAART. Furthermore, not all HIV-infected people will develop AIDS and die due to HIV-infection. Advanced mathematical modelling of the HIV epidemic is required to provide a better basis for disease burden estimation.

7. Campylobacteriosis

The most frequently reported zoonotic disease in humans in the European Union in 2004 is Campylobacteriosis, caused by thermophilic *Campylobacter* spp. Campylobacteriosis is often acquired through contaminated food or water.[71, 28] For unknown reasons, the incidence of *Campylobacter* infections in developed countries has been increasing for several years.[72] Although an overall decreasing trend has been observed in Europe in the period from 2001-2003, in 2004 the number of cases increased again.[71]

7.1 Outcome tree

The outcome tree for campylobacteriosis[9] is presented in Figure 7.1. *Campylobacter* infections may cause acute gastroenteritis (in most cases self-limiting within a few days to weeks). The disease may be fatal for few patients and may result in complications, of which Guillain-Barré syndrome (GBS), reactive arthritis (ReA) and inflammatory bowel disease (IBD) are the most significant.[9]

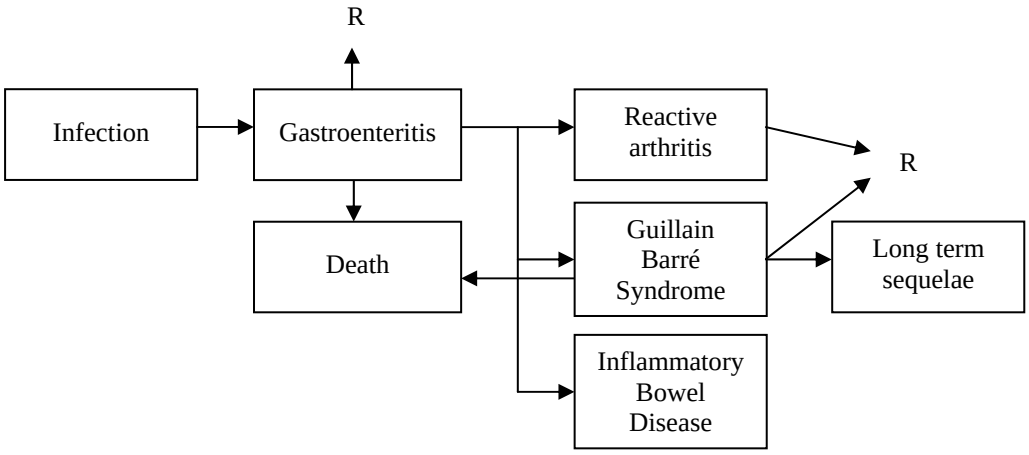


Figure 7.1 Outcome tree Campylobacter–associated gastroenteritis and sequelae (R=recovery)[9]

7.2 Baseline estimate of disease burden

Specific data sources and assumptions regarding mortality, incidence, duration and severity of the different outcomes in the outcome tree of campylobacteriosis are described in Appendix IV (Table IV.4 and IV.8). Based on this information the YLD, YLL and DALY for campylobacteriosis have been calculated (Table 7.1). The disease burden of campylobacteriosis is mainly dominated by morbidity, mortality is rarely reported. Especially in the Czech Republic, the disease burden due to campylobacteriosis is relatively high. There is no information on the degree of underreporting of campylobacteriosis. In scenario analysis two other incidence estimates have been taken into account (section 7.3).

Table 7.1 Morbidity, mortality and disease burden (DALYs per year) for campylobacteriosis

	Morbidity				Mortality		DALY per year		
countries	incidence	YLD acute	YLD compl.	YLD total	deaths	YLL	DALY total	DALY per case	DALY per 100.000
Austria	4,743	50.5	478.4	528.9	0	0.0	528.9	0.1	6.5
Belgium[1]	6,474	69.0	653.0	721.9	-	-	-	-	-
Cyprus[2,6]	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Czech Republic	25,274	269.3	2,549.1	2,818.4	0	0.0	2,818.4	0.1	27.6
Denmark	3,646	38.8	367.7	406.5	-	-	-	-	-
Estonia	115	1.2	11.6	12.9	0	0.0	12.9	0.1	1.0
Finland	3,588	38.2	361.9	400.1	0	0.0	400.1	0.1	7.7
France[3,5]	1,997	21.3	201.4	222.7	0	0.0	222.7	0.1	0.4
Germany	55,253	588.7	5,572.8	6,161.5	1	3.6	6,165.1	0.1	7.5
Greece	-	-	-	-	0	0.0	-	-	-
Hungary	8,551	91.1	862.4	953.5	0	0.0	953.5	0.1	9.4
Ireland	1,694	18.0	170.9	188.9	0	0.0	188.9	0.1	4.6
Italy	3	0.0	0.3	0.3	-	-	-	-	-
Latvia	0	0.0	0.0	0.0	0	0.0	0.0	0.1	0.0
Lithuania	703	7.5	70.9	78.4	0	0.0	78.4	0.1	2.3
Luxembourg	-	-	-	-	0	0.0	-	-	-
Malta	92	1.0	9.3	10.3	0	0.0	10.3	0.1	2.6
Netherlands[3]	2,205	23.5	222.4	245.9	1	18.9	264.7	0.1	1.6
Poland[4]	36	0.4	3.6	4.0	0	0.0	4.0	0.1	0.0
Portugal	-	-	-	-	0	0.0	-	-	-
Slovakia	1,697	18.1	171.1	189.2	-	-	-	-	-
Slovenia	1,014	10.8	102.2	113.0	0	0.0	113.0	0.1	5.7
Spain	5,854	62.4	590.4	652.8	0	0.0	652.8	0.1	1.5
Sweden[5]	6,723	71.6	678.1	749.7	0	0.0	749.7	0.1	8.3
United Kingdom	50,834	541.6	5,127.0	5,668.6	3	20.6	5,689.3	0.1	9.5
Iceland	127	1.4	12.8	14.2	0	0.0	14.2	0.1	4.9
Liechtenstein	-	-	-	-	-	-	-	-	-
Norway	2,393	25.5	241.4	266.9	0	0.0	266.9	0.1	5.8

Note

incidence = mean # of cases 2003-2005 (data Eurostat)

mortality = mean # of deaths 2003-2004 (data Eurostat/WHO)

- = no data available

[1] *= incidence data 2003-2004 only*

[2] *= incidence data 2005 only*

[3] *= incidence data 2003 only*

[4] *= incidence data 2004-2005 only*

[5] *= mortality data 2003 only*

[6] *= mortality data 2004 only*

7.3 Scenario analysis

Comparing the results of the pilot with more extensive studies at the RIVM,[9] it becomes clear that in these studies the disease burden estimate is almost a factor five higher than in the pilot (Figure 7.2). The higher mortality can be explained by the fact that in these more extensive studies mortality estimates were based on Danish cohort studies,[73] instead of on reported deaths (pilot). The morbidity in more extensive studies was based on data of the RIVM. According to these RIVM data the number of new campylobacteriosis cases in 2003 in the Netherlands was n=5,387 (corrected for the coverage of the system). The absolute number of reported cases to the sentinel laboratories was 2,805. According to Eurostat the number of cases in 2003 (2004-2005 not available) was n=2,205 instead of 2,805.

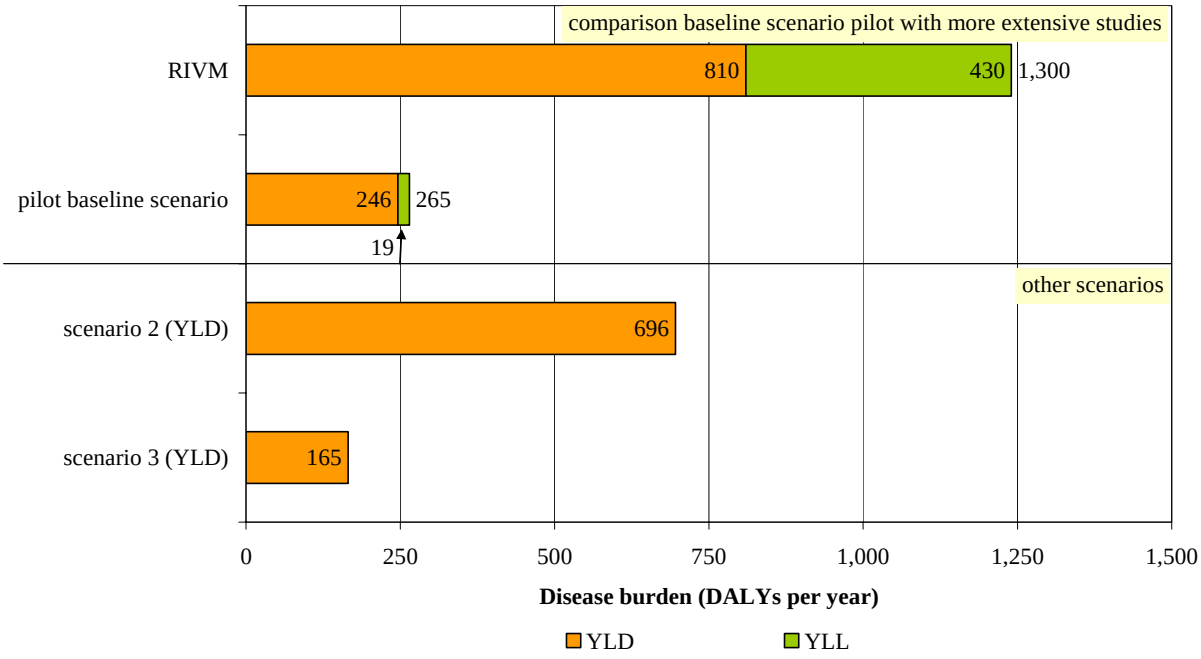


Figure 7.2 Scenario analysis campylobacteriosis for the Netherlands

Figure 7.2 also shows the results of a scenario analysis for the Netherlands. In scenario 2 the morbidity estimate (YLD) was based on RIVM data (mean incidence 2003-2005 n=6,241), which is more in line with more extensive studies of the RIVM. It is not clear why the Dutch data of RIVM and Eurostat are not identical and why recent data are lacking, but possibly this is also the case for other countries.

In scenario 3 the morbidity estimate is based on the incidence of campylobacteriosis derived from a study among Swedish travellers. In this study returning tourists were used as a sentinel population to identify the risk of campylobacteriosis. The estimated risk for the Netherlands was 9.1 per 100,000 travellers.[74] Applied to the average Dutch population of 2004 this results in an YLD estimate of 165. For the Netherlands this scenario does not seem very realistic compared to scenario 2 and more extensive studies in which morbidity is higher.

In Figure 7.3 the comparison for the baseline scenario and scenario 3 for other countries is shown. For some countries the morbidity (YLD) in scenario 3 is higher than in the baseline estimate but for other countries it is just the other way around.

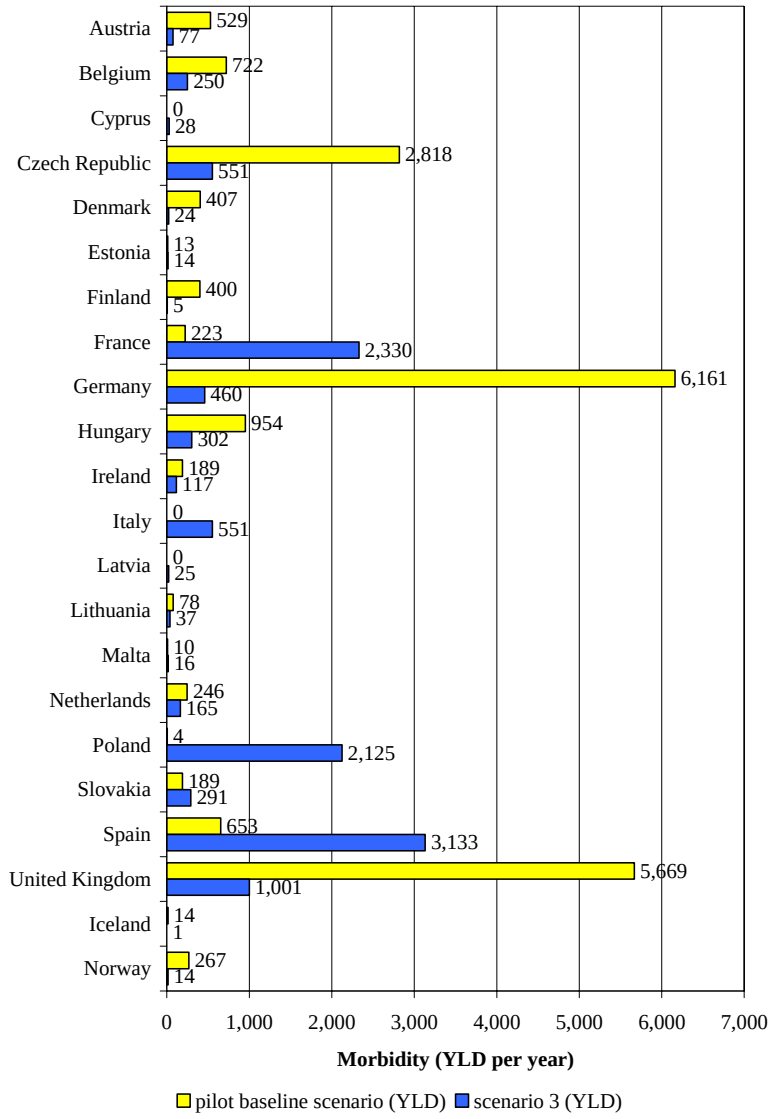


Figure 7.3 Comparison morbidity (YLD) baseline scenario pilot for campylobacteriosis with scenario 3

7.4 Discussion and recommendations

Based on scenario 2 and the more extensive studies of the RIVM, the disease burden of campylobacteriosis in the baseline estimate of this pilot was underestimated. Differences between national and Eurostat incidence data need to be sorted out and and Eurostat needs to take into account the coverage of the sentinel systems from which the data are derived. Data from Enter-net may be appropriate to include in the future, this needs to be investigated. Scenario 3 gives the idea that there are perhaps considerable differences between countries in the degree of underreporting which needs to be investigated. Furthermore, future estimates of disease burden of campylobacteriosis should include other mortality data than reported mortality.

8. EHEC-infection

While less frequently reported than *Campylobacter* and *Salmonella* infections, *E. coli* infection is one of the most severe zoonotic illnesses due to high morbidity and mortality in vulnerable populations and children.[71] Enterohaemorrhagic *Escherichia coli* (EHEC) produces toxins, known as verotoxins (or Shiga-like toxins because of their similarity to the toxins produced by *Shigella dysenteriae*). EHEC is primarily transmitted through consumption of contaminated food[28, 75] although increasingly direct animal contact and environmental transmission are reported.

8.1 Outcome tree

In Figure 8.1 the outcome tree for enterohaemorrhagic *Escherichia coli*[9] is shown. Mild and self-limiting gastroenteritis can occur after infection but particularly among children under five years of age there is also a probability of developing haemolytic-uraemic syndrome (HUS) which can result in end-stage renal disease (ESRD).[9]

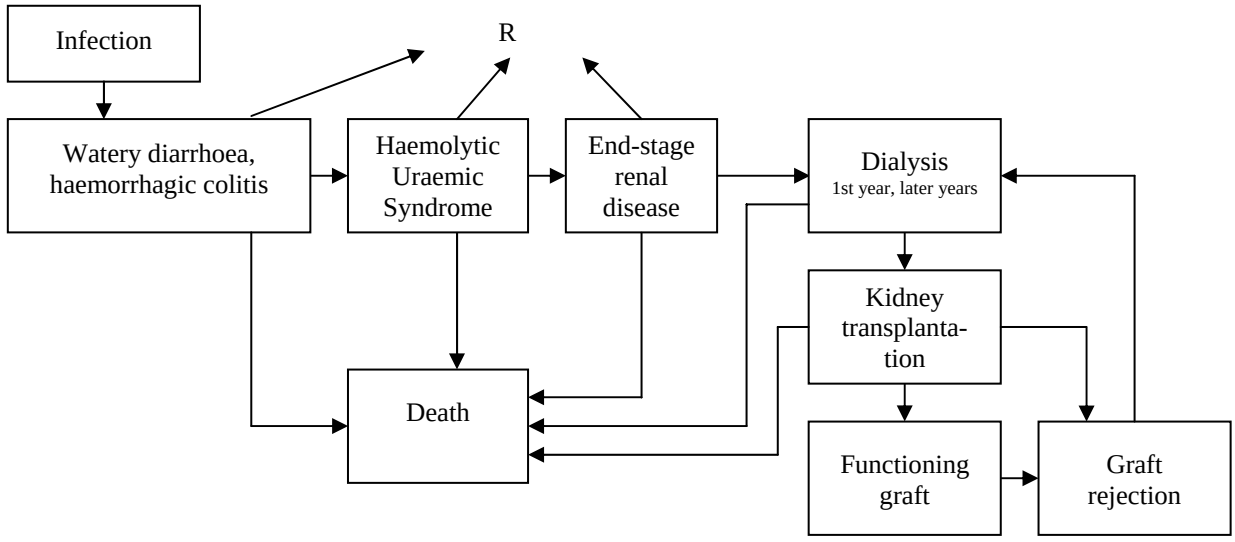


Figure 8.1 Outcome tree for infection with enterohaemorrhagic Escherichia coli (R=recovery)[9]

8.2 Baseline estimate of disease burden

Specific data sources and assumptions regarding mortality, incidence, duration and severity of the different outcomes in the outcome tree of EHEC-infection are described in Appendix IV (Table IV.5 and IV.8). Based on this information the YLD, YLL and DALY for EHEC-infection have been calculated (Table 8.1). Just like campylobacteriosis, the disease burden of EHEC-infection is mainly dominated by morbidity, mortality is seldom reported. Again, in the Czech Republic, the disease burden is relatively high. There is no information on the degree of underreporting.

Table 8.1 Morbidity, mortality and disease burden (DALYs per year) for EHEC-infection

	Morbidity				Mortality		DALY per year		
countries	incidence	YLD acute	YLD compl.	YLD total	deaths	YLL	DALY total	DALY per case	DALY per 100.000
Austria	17	0.1	9.1	9.2	1	3.6	12.8	0.7	0.2
Belgium	-	-	-	-	-	-	-	-	-
Cyprus[1,3]	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Czech Republic	1,678	10.1	877.8	888.0	0	0.0	888.0	0.5	8.7
Denmark	142	0.9	74.1	75.0	-	-	-	-	-
Estonia	35	0.2	18.5	18.7	0	0.0	18.7	0.5	1.4
Finland	15	0.1	8.0	8.1	1	30.9	39.0	2.5	0.7
France[2]	-	-	-	-	0	0.0	-	-	-
Germany	5,647	34.0	2,953.8	2,987.8	0	0.0	2,987.8	0.5	3.6
Greece	1	0.0	0.7	0.7	0	0.0	0.7	0.5	0.0
Hungary	184	1.1	96.4	97.5	0	0.0	97.5	0.5	1.0
Ireland	89	0.5	46.4	46.9	0	0.0	46.9	0.5	1.2
Italy	-	-	-	-	-	-	-	-	-
Latvia	15	0.1	7.8	7.9	0	0.0	7.9	0.5	0.3
Lithuania	150	0.9	78.3	79.2	0	0.0	79.2	0.5	2.3
Luxembourg	-	-	-	-	0	0.0	-	-	-
Malta	10	0.1	5.2	5.3	0	0.0	5.3	0.5	1.3
Netherlands	55	0.3	28.8	29.1	0	0.0	29.1	0.5	0.2
Poland[1]	1,430	8.6	747.9	756.6	0	0.0	756.6	0.5	2.0
Portugal	-	-	-	-	0	0.0	-	-	-
Slovakia	561	3.4	293.4	296.8	-	-	-	-	-
Slovenia	146	0.9	76.5	77.4	0	0.0	77.4	0.5	3.9
Spain	1,007	6.1	526.9	532.9	0	0.0	532.9	0.5	1.2
Sweden[2]	220	1.3	114.9	116.2	0	0.0	116.2	0.5	1.3
United Kingdom	995	6.0	520.4	526.4	0	0.0	526.4	0.5	0.9
Iceland	3	0.0	1.4	1.4	0	0.0	1.4	0.5	0.5
Liechtenstein	-	-	-	-	-	-	-	-	-
Norway	31	0.2	16.4	16.6	0	0.0	16.6	0.5	0.4

Note *incidence = mean # of cases 2003-2005 (data Eurostat)*

mortality = mean # of deaths 2003-2004 (data Eurostat/WHO)

- = no data available

[1] = incidence data 2005 only

[2] = mortality data 2003 only

[3] = mortality data 2004 only

8.3 Scenario analysis

When comparing the results of the pilot for EHEC-infection with more extensive studies of the RIVM,[9] it becomes clear that in the latter studies the disease burden estimate is over three times higher than in the pilot due to a higher mortality (Figure 8.2). This can be explained by the fact that in these more extensive studies mortality due to HUS and end-stage renal disease (ESRD) were taken into account.

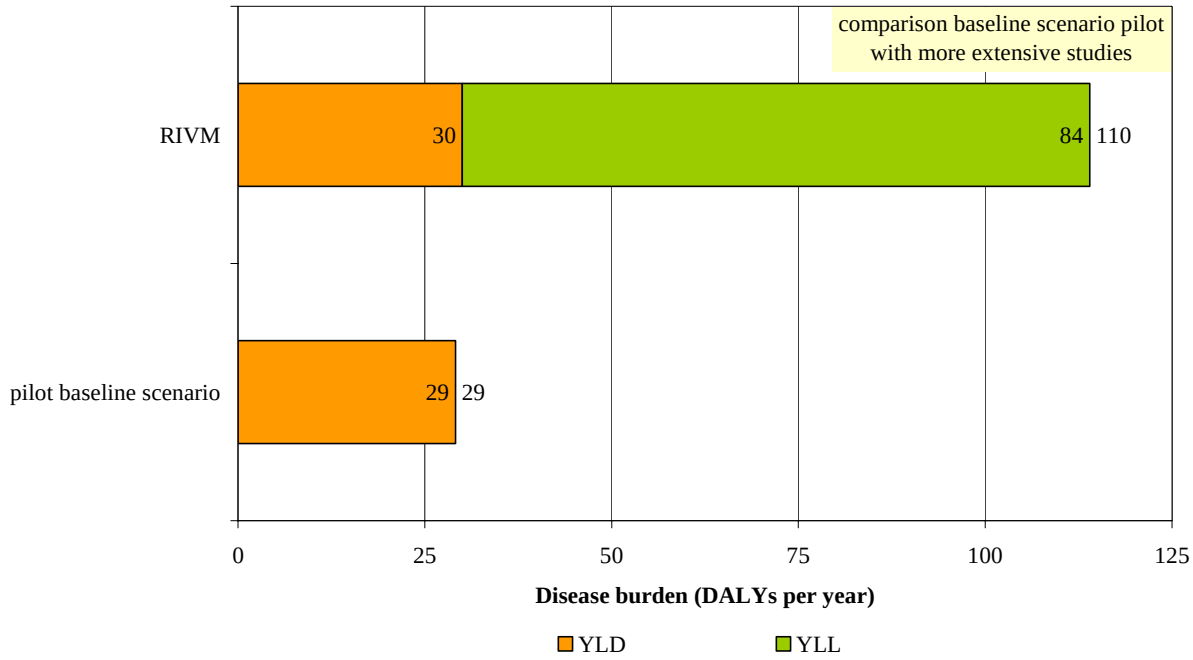


Figure 8.2 Comparison baseline scenario pilot for EHEC-infection with more extensive studies for the Netherlands

8.4 Discussion and recommendations

The disease burden of EHEC-infection in the baseline estimate of this pilot was underestimated. Future estimates of disease burden of EHEC-infection should include other mortality data than reported mortality. Data from Enter-net may be appropriate to include in the future, this needs to be investigated.

9. Salmonellosis

The second most frequently reported zoonotic disease in humans in the European Union in 2004 is *Salmonella* infection. The overall reported incidence of salmonellosis is slightly lower than of campylobacteriosis.[71] Salmonellosis is caused by bacteria of the genus *Salmonella* (in particular *S.* Enteritidis and *S.* Typhimurium) and is generally contracted through the consumption of contaminated food of animal origin.[76]

9.1 Outcome tree

The outcome tree for salmonellosis[9] is presented in Figure 9.1. *Salmonella* infections may cause acute gastroenteritis (in most cases self-limiting within a few days to weeks). The disease may be fatal for few patients and may result in complications, of which reactive arthritis (ReA) and inflammatory bowel disease (IBD) are the most significant. Sepsis is a rare complication and was therefore not taken into account.[9]

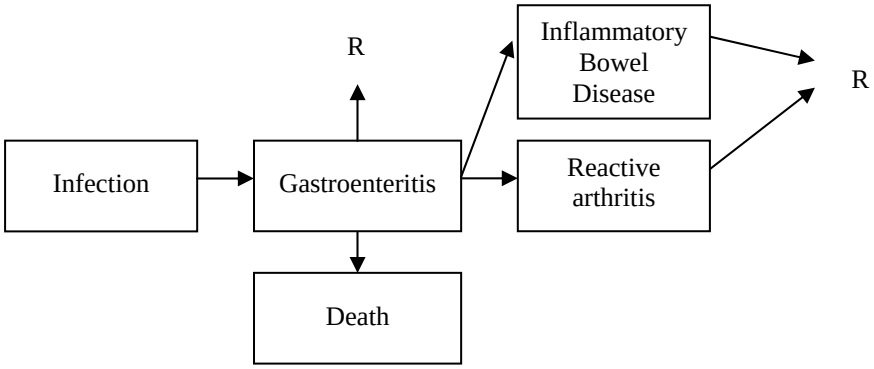


Figure 9.1 Outcome tree Salmonella–associated GE and sequelae (R=recovery)[9]

9.2 Baseline estimate of disease burden

Specific data sources and assumptions regarding mortality, incidence, duration and severity of the different outcomes in the outcome tree of salmonellosis are described in Appendix IV (Table IV.6 and IV.8). Based on this information the YLD, YLL and DALY for salmonellosis have been calculated (Table 9.1). The disease burden for samonellosis is mainly dominated by morbidity but reported mortality is less rare than for campylobacteriosis and EHEC-infection. Again, the disease burden is relatively high in the Czech Republic followed by Slovenia. There is no information on the degree of underreporting of salmonellosis. In scenario analysis two other incidence estimates have been taken into account (section 9.3).

Table 9.1 Morbidity, mortality and disease burden (DALYs per year) for salmonellosis

	Morbidity				Mortality		DALY per year		
countries	incidence	YLD acute	YLD compl.	YLD total	deaths	YLL	DALY total	DALY per case	DALY per 100.000
Austria	6,486	78.4	336.3	414.7	3	38.2	452.9	0.1	5.5
Belgium[1]	11,219	135.6	581.7	717.3	-	-	-	-	-
Cyprus[4]	74	0.9	3.8	4.7	0	0.0	4.7	0.1	0.6
Czech Republic	30,183	364.8	1,565.2	1,930.0	1	16.7	1,946.7	0.1	19.1
Denmark	1,675	20.2	86.9	107.1	-	-	-	-	-
Estonia	210	2.5	10.9	13.4	0	0.0	13.4	0.1	1.0
Finland	2,335	28.2	121.1	149.3	1	2.0	151.3	0.1	2.9
France[1,3]	8,319	100.5	431.4	531.9	15	152.7	684.6	0.1	1.1
Germany	57,419	694.0	2,977.5	3,671.5	54	577.2	4,248.7	0.1	5.1
Greece	1,290	15.6	66.9	82.5	1	18.9	101.3	0.1	0.9
Hungary	8,390	101.4	435.1	536.5	5	77.1	613.6	0.1	6.1
Ireland	404	4.9	21.0	25.9	0	0.0	25.9	0.1	0.6
Italy	9,756	117.9	505.9	623.8	-	-	-	-	-
Latvia	645	7.8	33.4	41.2	1	18.9	60.1	0.1	2.6
Lithuania	1,804	21.8	93.5	115.4	0	0.0	115.4	0.1	3.4
Luxembourg	319	3.9	16.5	20.4	1	2.0	22.4	0.1	4.9
Malta	116	1.4	6.0	7.4	0	0.0	7.4	0.1	1.8
Netherlands[2]	2,012	24.3	104.3	128.7	9	120.6	249.2	0.1	1.5
Poland	16,107	194.7	835.3	1,029.9	8	112.1	1,142.0	0.1	3.0
Portugal	553	6.7	28.7	35.4	1	11.5	46.8	0.1	0.4
Slovakia	12,936	156.3	670.8	827.1	-	-	-	-	-
Slovenia	2,904	35.1	150.6	185.7	1	8.3	194.0	0.1	9.7
Spain	7,373	89.1	382.3	471.4	23	291.5	763.0	0.1	1.8
Sweden[3]	3,609	43.6	187.1	230.7	1	24.5	255.2	0.1	2.8
United Kingdom	14,588	176.3	756.5	932.8	14	231.2	1,163.9	0.1	1.9
Iceland	112	1.3	5.8	7.1	1	3.6	10.7	0.1	3.7
Liechtenstein	-	-	-	-	-	-	-	-	-
Norway	1,529	18.5	79.3	97.7	1	13.2	111.0	0.1	2.4

Note
incidence = mean # of cases 2003-2005 (data Eurostat)
mortality = mean # of deaths 2003-2004 (data Eurostat/WHO)
- = no data available
[1] = incidence data 2003-2004 only
[2] = incidence data 2003 only
[3] = mortality data 2003 only
[4] = mortality data 2004 only

9.3 Scenario analysis

Comparing the results of the pilot with more extensive studies at the RIVM,[9] it becomes clear that in these studies the disease burden estimate is more than two and a half times higher than in the pilot (Figure 9.2). The higher mortality can be explained by the fact that in these more extensive studies mortality estimates were based on Danish cohort studies,[73] instead of on reported deaths (pilot). The morbidity in more extensive studies was based on data of the RIVM. According to this RIVM data the number of new salmonellosis cases in 2003 in the

Netherlands was n= 3,359 (corrected for the coverage of the system). The absolute number of reported cases to the sentinel laboratories was 2,142. According to Eurostat the number of cases in 2003 (2004-2005 not available) was n= 2,012 instead of 2,142.

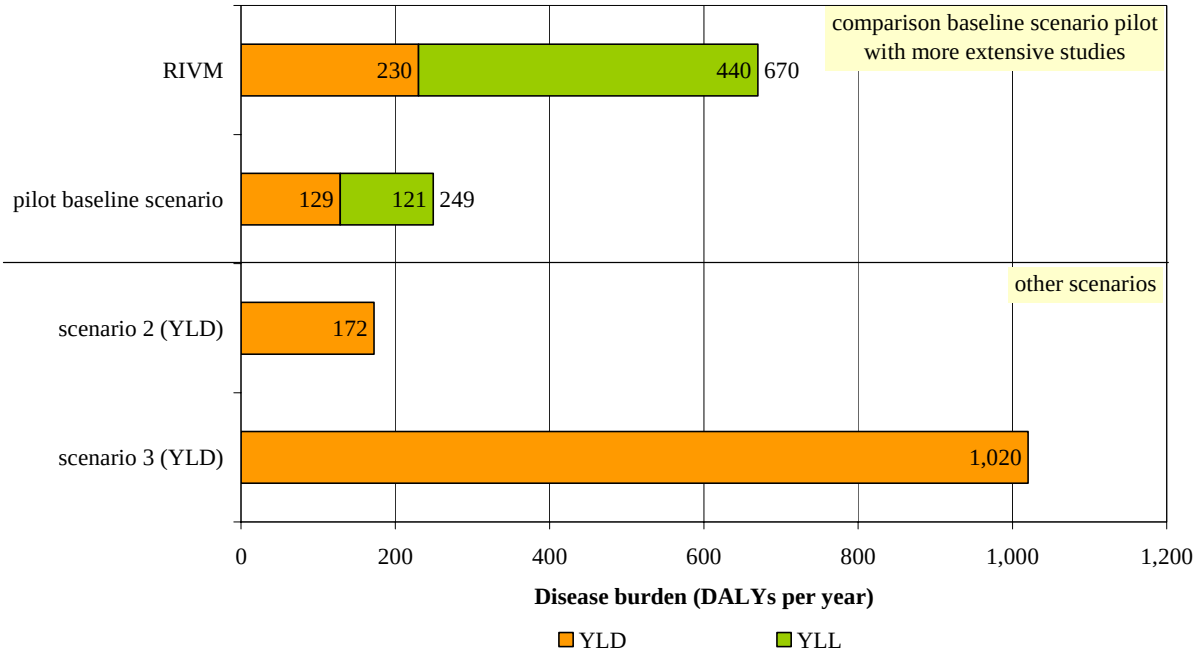


Figure 9.2 Scenario analysis salmonellosis for the Netherlands

Figure 9.2 also shows the results of a scenario analysis for the Netherlands. In scenario 2 the morbidity estimate (YLD) was based on RIVM data (mean incidence 2003-2005 n= 2,695), which is more in line with more extensive studies of the RIVM. It is not clear why the Dutch data of RIVM and Eurostat for salmonellosis are not identical and why recent data are lacking, but possibly this is also the case for other countries.
In scenario 3 the morbidity estimate is based on the incidence of salmonellosis derived from a study among Swedish travellers. In this study returning tourists were used as a sentinel population to identify the risk of salmonellosis. The estimated risk for the Netherlands was 98 per 100,000 travellers.[77] Applied to the average Dutch population of 2004 this results in an YLD estimate of 1,020. For the Netherlands this scenario does not seem very realistic compared to scenario 2 and more extensive studies in which morbidity is lower. In Figure 9.3 the comparison for the baseline scenario and scenario 3 for other countries is shown. In most countries the morbidity (YLD) in scenario 3 is considerably higher than in the baseline estimate.

9.4 Discussion and recommendations

Based on scenario 2 and the more extensive studies of the RIVM, the disease burden of salmonellosis in the baseline estimate of this pilot was underestimated. Differences between national and Eurostat incidence data need to be sorted out and Eurostat needs to take into account the coverage of the sentinel systems from which the data are derived. Data from Enter-net may be appropriate to include in the future, this needs to be investigated. Scenario 3 gives the idea that there are perhaps considerable differences between countries in the degree of underreporting which needs to be investigated. Furthermore, future estimates of disease burden of salmonellosis should include other mortality data than reported mortality.

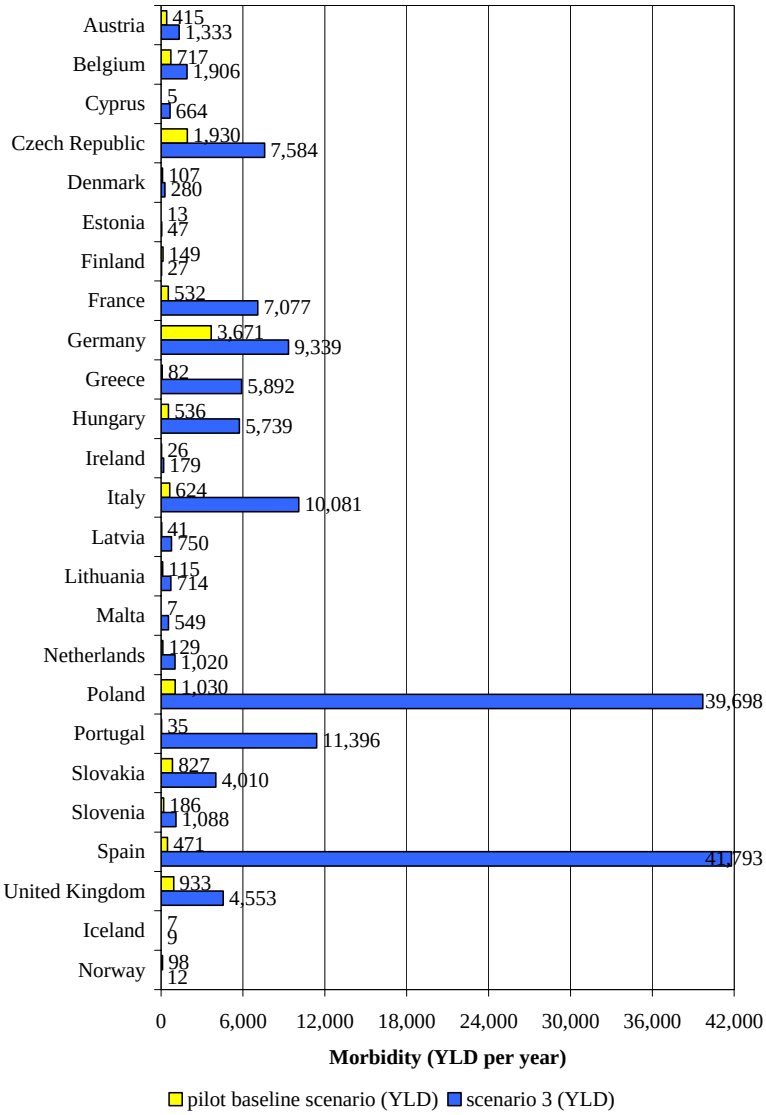


Figure 9.3 Comparison morbidity (YLD) baseline scenario pilot for salmonellosis with scenario 3

10. Tuberculosis

Tuberculosis is defined as an infection with bacteria of the *Mycobacterium tuberculosis*-complex and the infection spreads through the air.[28] In 2004 there were nine million new tuberculosis cases reported worldwide and approximately two million tuberculosis deaths. More than 80% of all identified tuberculosis patients live in sub-Saharan Africa and Asia.[78] In the European Union tuberculosis morbidity is concentrated in vulnerable groups (populations of foreign origin, elderly people, HIV infected patients).[79, 80] The incidence (per 100.00) is highest in the Baltic States (Estonia, Latvia and Lithuania) and Portugal.[81]

10.1 Outcome tree

In Figure 10.1 the outcome tree for tuberculosis is shown. The infection usually gives no symptoms. Approximately 10-15% of the infected persons is expected to develop active tuberculosis (pulmonary or extrapulmonary) during life, the majority within the first two years. The remainder may develop a latent infection. Reduced immunity, including ageing, can induce reactivation of a latent infection. Coughing, fatigue, fever, losing weight and night sweating are the most important symptoms of pulmonary tuberculosis. Without treatment tuberculosis will lead to premature death. Treatment of tuberculosis consists of long-term multiple drug medication (at least six months).[28, 82] Extrapulmonary tuberculosis occurs less frequently (30%) than pulmonary tuberculosis (70%).[43] Treatment failures can result in the emergence of multidrug-resistant tuberculosis (MDR-TB). In case of infection with MDR-TB, the duration of treatment can rise to two years and consists of a complicated combination of antibiotics, chemotherapeutics and incidentally surgery.[83, 82] Treatment and prognosis of these patients resemble malignancy more than infection. So far, MDR-TB is mainly confined to eastern European populations, but may spread in the near future. The emergence of extremely resistant TB strains (XDR-TB) threatens to increase the potential burden of infection substantially. So far, the incidence of XDR-TB in Europe is relatively low.[84] Because MDR-TB is an important problem which needs specific attention, it is included in the outcome tree. However, MDR-TB is more a specific form of tuberculosis rather than a true separate outcome (therefore a dotted line is used in the outcome tree).

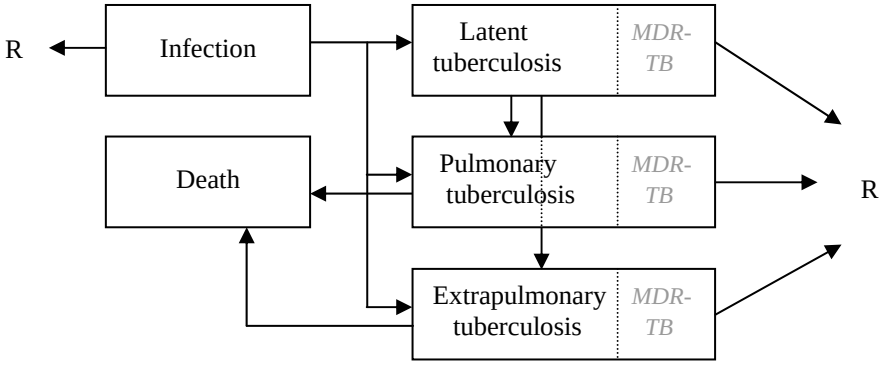


Figure 10.1 Outcome tree tuberculosis (R=recovery, MDR-TB = multidrug-resistant tuberculosis)

10.2 Baseline estimate of disease burden

Specific data sources and assumptions regarding mortality, incidence, duration and severity of the different outcomes in the outcome tree of tuberculosis are described in Appendix IV (Table IV.7 and IV.8). Based on this information the YLD, YLL and DALY for tuberculosis have been calculated (Table 10.1). The disease burden of tuberculosis is mainly dominated by mortality. The disease burden is relatively high in the Baltic States (Lithuania, Latvia and Estonia), Hungary, Portugal and Poland.

Table 10.1 Morbidity, mortality and disease burden (DALYs per year) for tuberculosis

	Morbidity				Mortality		DALY per year		
countries	incidence	YLD acute	YLD compl.	YLD total	deaths	YLL	DALY total	DALY per case	DALY per 100.000
Austria	998	67.5	-	67.5	45	702.2	769.8	0.8	9.4
Belgium	1,153	78.0	-	78.0	-	-	-	-	-
Cyprus[2]	34	13.7	-	13.7	3	102.8	116.5	3.4	15.7
Czech Republic	1,075	146.1	-	146.1	75	1,274.0	1,420.1	1.3	13.9
Denmark	401	27.1	-	27.1	-	-	-	-	-
Estonia	579	78.0	-	78.0	98	2,779.2	2,857.2	4.9	211.8
Finland	368	25.1	-	25.1	75	808.2	833.2	2.3	15.9
France[1]	5,662	383.0	-	383.0	959	10,412.0	10,795.0	1.9	17.4
Germany	6,584	446.1	-	446.1	470	6,979.8	7,425.9	1.1	9.0
Greece	720	49.0	-	49.0	91	1,222.7	1,271.6	1.8	11.5
Hungary	2,315	314.3	-	314.3	300	6,156.2	6,470.5	2.8	64.0
Ireland	433	29.2	-	29.2	37	491.2	520.5	1.2	12.8
Italy	4,292	290.0	-	290.0	-	-	-	-	-
Latvia	1,593	215.3	-	215.3	202	5,623.4	5,838.7	3.7	252.4
Lithuania	2,636	356.9	-	356.9	325	8,684.2	9,041.2	3.4	263.2
Luxembourg	41	2.7	-	2.7	1	17.2	19.9	0.5	4.4
Malta	16	6.6	-	6.6	1	7.0	13.5	0.8	3.4
Netherlands	1,274	85.8	-	85.8	75	1,011.9	1,097.7	0.9	6.7
Poland	9,632	1,306.8	-	1,306.8	897	19,057.3	20,364.1	2.1	53.3
Portugal	3,846	258.6	-	258.6	328	5,924.8	6,183.4	1.6	58.9
Slovakia	816	111.0	-	111.0	-	-	-	-	-
Slovenia	278	37.7	-	37.7	20	394.8	432.5	1.6	21.7
Spain	7,684	518.6	-	518.6	459	6,974.8	7,493.4	1.0	17.6
Sweden[1]	479	32.3	-	32.3	57	483.4	515.7	1.1	5.7
United Kingdom	7,765	522.7	-	522.7	478	7,962.4	8,485.2	1.1	14.2
Iceland	9	0.6	-	0.6	5	33.0	33.6	3.6	11.5
Liechtenstein	-	-	-	-	-	-	-	-	-
Norway	310	20.8	-	20.8	48	398.6	419.5	1.4	9.1

Note
incidence = mean # of cases 2003-2005 (data EuroTB)
mortality = mean # of deaths 2003-2004 (data Eurostat/WHO)
YLD compl. = multi-drug resistant tuberculosis (MDR-TB) not taken into account in baseline scenario
- = no data available
[1] = mortality data 2003 only
[2] = mortality data 2004 only

The incidence of tuberculosis is difficult to determine, tuberculosis cases are mostly underreported.[85] However no alternative estimates were available. In the baseline scenario multidrug-resistant tuberculosis was not included as complication. The duration and severity of MDR-TB were not available in other disease burden studies and the number of MDR-TB cases was only available for a limited number of countries. In scenario analysis the effect of MDR-TB has been addressed (section 10.3).

10.3 Scenario analysis

The disease burden in the pilot baseline scenario is close to the estimate of the Global Burden of Disease study (2002) (Figure 10.2). Another indication that the baseline scenario is a rather good estimate is that the Public Health Status and Forecast studies for the Netherlands estimated the Dutch disease burden for 2003 on 1,065 compared to 1,098 DALYs in the pilot baseline scenario.

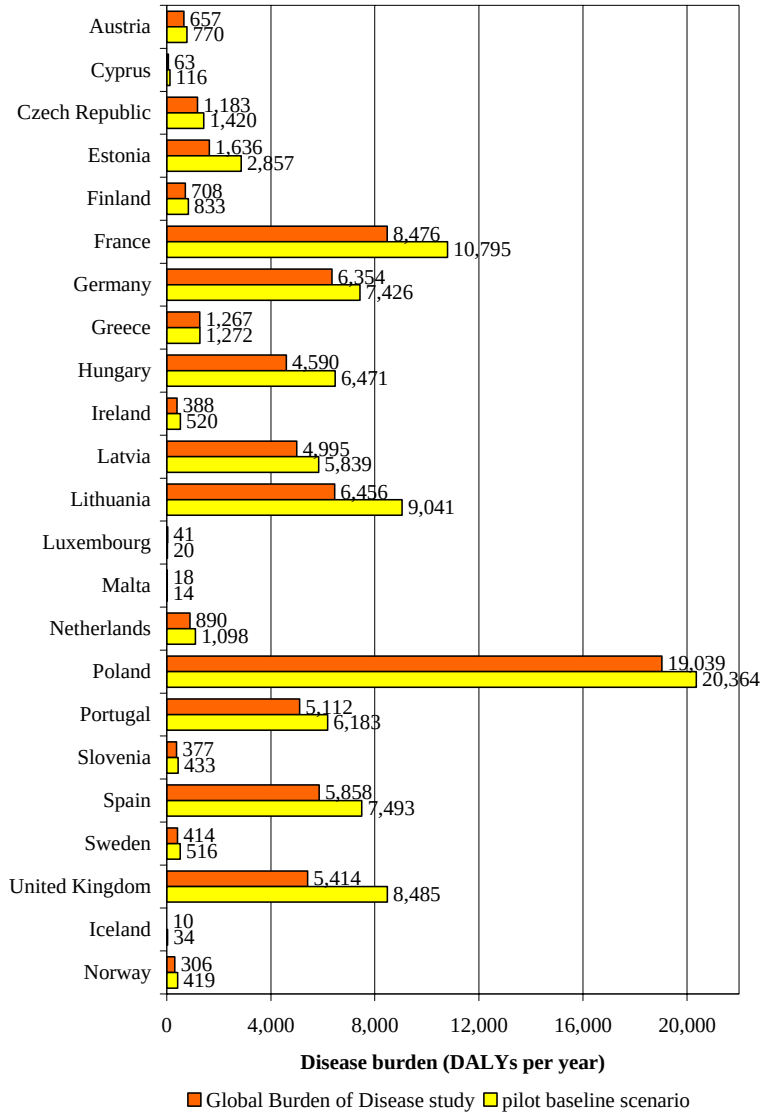


Figure 10.2 Comparison baseline scenario pilot for tuberculosis with Global Burden of Disease study

Figure 10.3 shows the results of a scenario analysis for the Netherlands. In scenario 2 multidrug-resistant tuberculosis has been included based on the assumption that the duration is two years and the severity can be compared with a terminal illness (severity weight = 0.93). The effect on the morbidity estimate is small because in the Netherlands the mean number of MDR-TB cases in the period 2003-2005 was small (n=5). In the Baltic States, where more MDR-TB cases are reported, the effect is more important (Figure 10.4). However the total disease burden for tuberculosis remains mainly dominated by mortality, even if multidrug-resistant tuberculosis is taken into account.

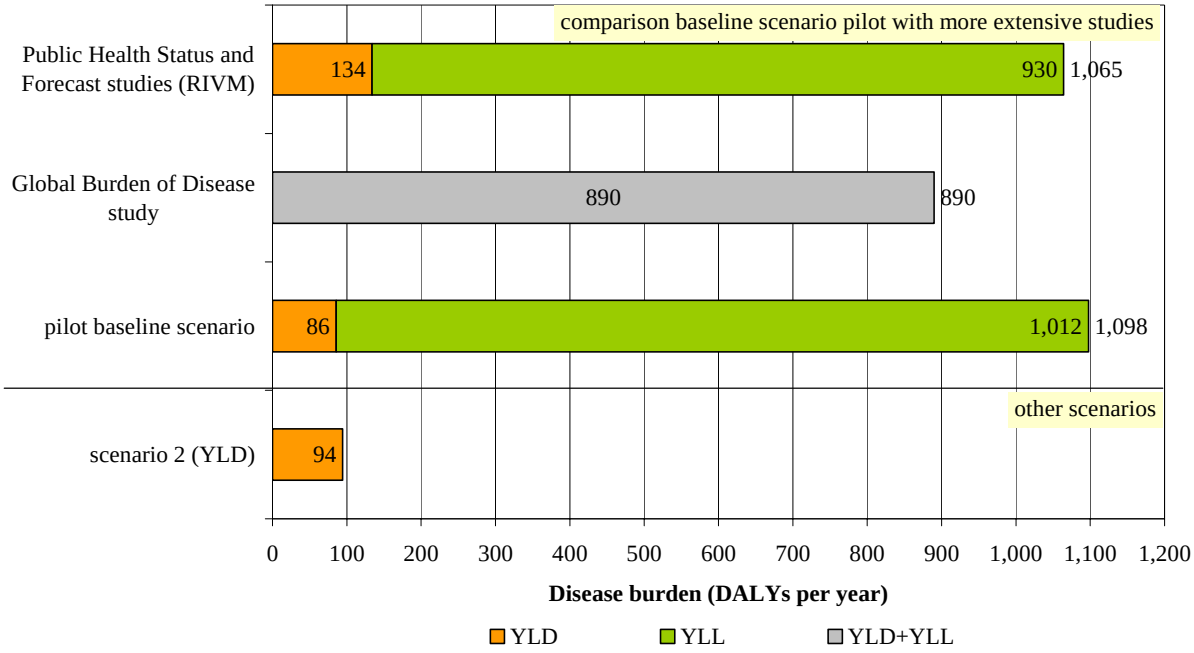


Figure 10.3 Scenario analysis tuberculosis for the Netherlands

10.4 Discussion and recommendations

The disease burden estimate of the pilot baseline scenario is comparable with results of other studies. Especially for countries with a considerable number of multidrug-resistant tuberculosis cases, MDR-TB should be included in the disease burden estimate of tuberculosis.

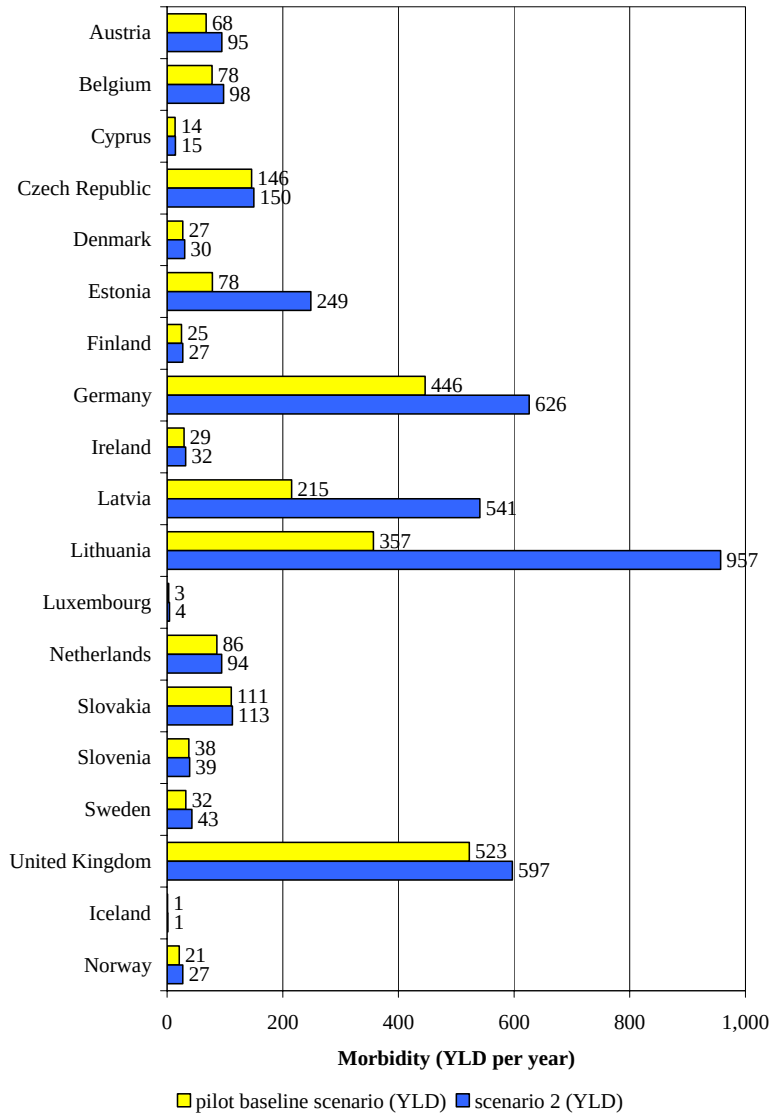
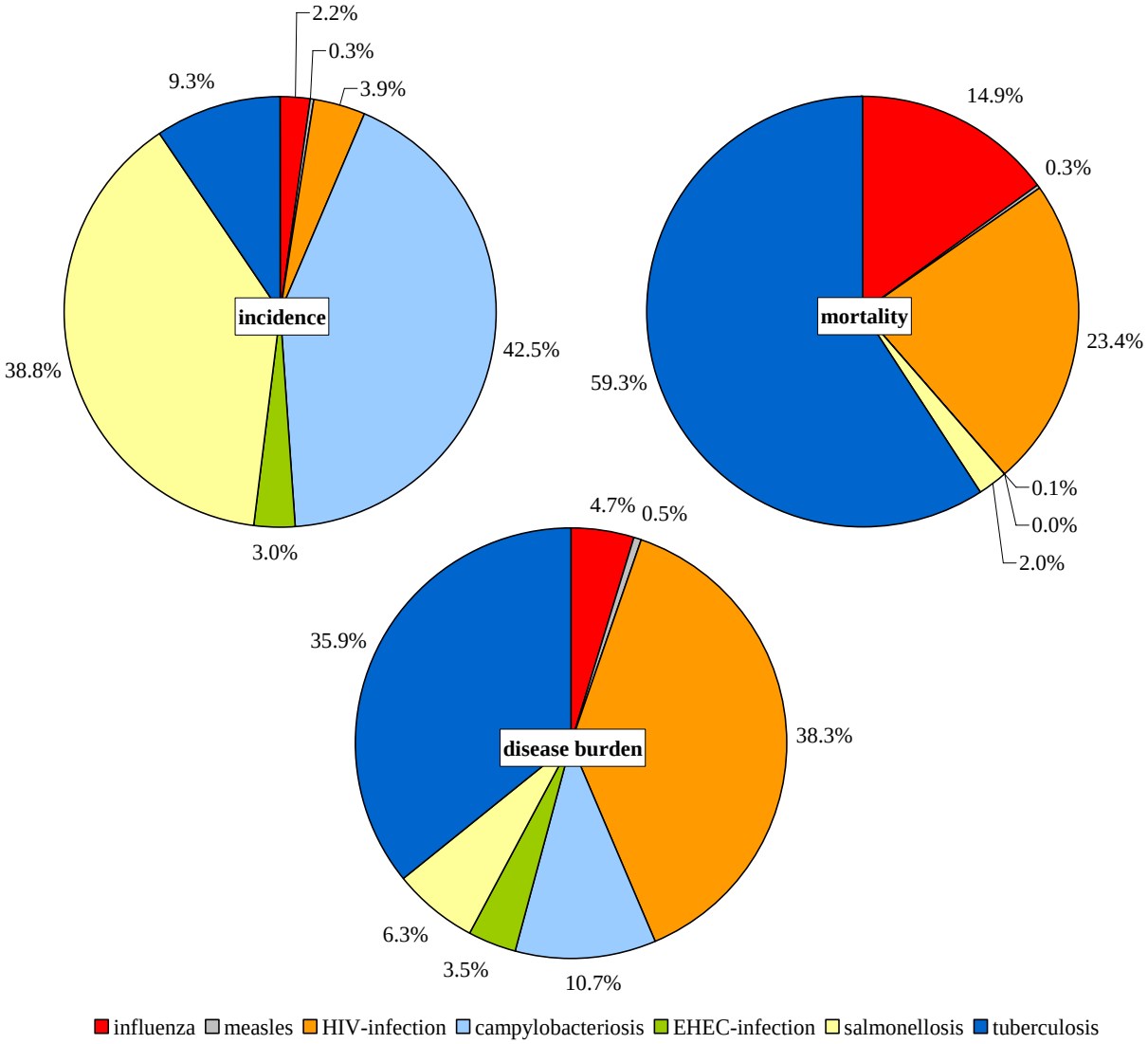


Figure 10.4 Comparison morbidity (YLD) baseline scenario pilot for tuberculosis with scenario 2

11. Comparison between diseases

Disease burden is a composite measure which includes not only incidence and mortality data but also the severity and duration of a disease. Figure 11.1 highlights the importance of taking disease burden estimates into consideration in guiding public health policy and actions. Based on incidence data individually, the foodborne diseases cause relatively the greatest burden, while mortality data indicate the relatively high burden of tuberculosis. Disease burden (DALYs) shows a quite different picture with a relative high burden for HIV-infection and tuberculosis.



Based on data for twelve countries (data available for all seven diseases):

Austria	Ireland	the Netherlands	Sweden
Czech Republic	Latvia	Poland	United Kingdom
Germany	Lithuania	Slovenia	Norway

Figure 11.1 Relative burden of the seven selected diseases based on different indicators:
- incidence (mean number of reported new cases per year in the period 2003-2005)
- mortality (mean number of reported deaths per year in the period 2003-2004)
- disease burden (DALYs per year based on above mentioned incidence and mortality)

In Figure 11.2 an estimate of the total disease burden per 100,000 population for the seven selected diseases is shown, for those countries for which YLD **and** YLL **and** DALY could be calculated. Because the number of countries for which the disease burden could be calculated, differs for each disease, a comparison between the diseases could be biased. However Figure V.1, based on the 12 countries for which the disease burden could be calculated for **all** diseases, shows a quite similar picture (see Appendix V). Figure V.2 (Appendix V) shows the same picture as Figure 11.2 but in this figure **all** components of the DALY were included irrespective if one component is missing (for example: for HIV Spain is not included in Figure 11.2 because the total disease burden could not be calculated, in Figure V.2 for Spain the YLD of AIDS and the YLL is included).

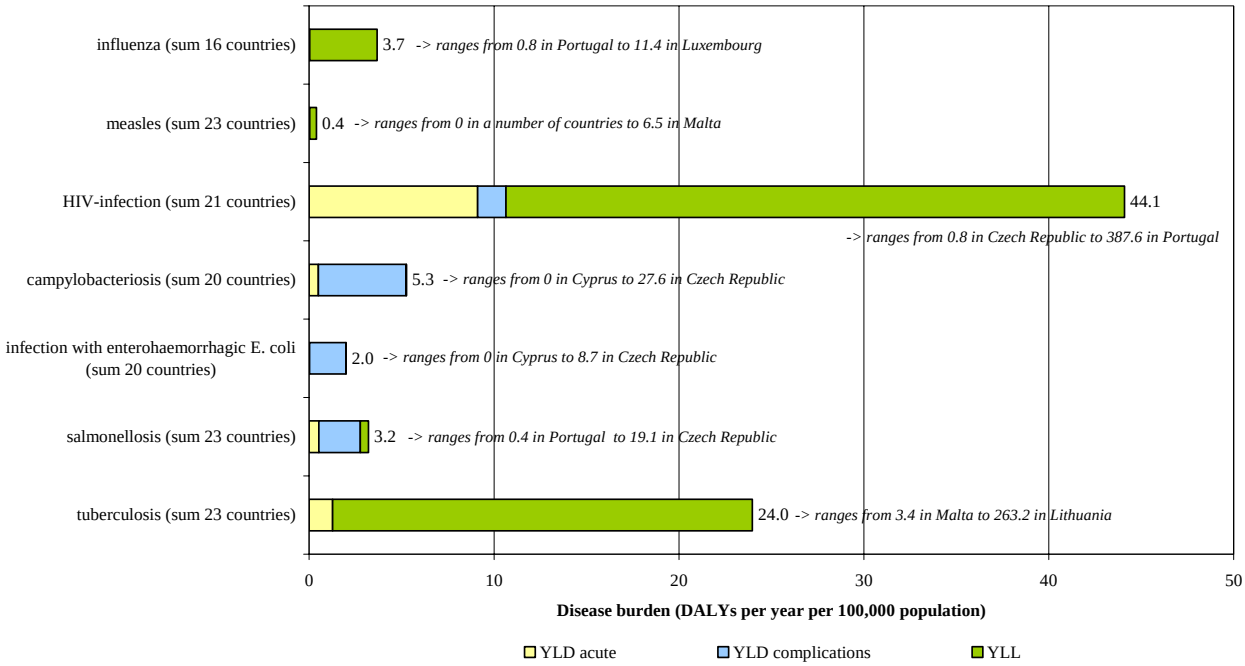


Figure 11.2 Sum of disease burden per 100,000 population of all countries for which data are available for at least one disease (for each disease number of countries is different) (Table 3.1 shows per disease which countries could not be included)

Although the absolute numbers in the three pictures are different, the ranking between diseases does not change. All three pictures show that HIV-infection and tuberculosis have the highest disease burden in Europe but scenario analysis suggested that the disease burden of influenza is seriously underestimated. Measles has the lowest disease burden. The results of this comparison need to be considered with care because of the limitations of both data availability as well as data quality that are described in Chapter 3.

Within each country the ranking can be different. However, in most countries HIV-infection and tuberculosis are responsible for the highest disease burden (in Western Europe HIV-infection is more often on top, in Eastern Europe tuberculosis) and measles for the lowest disease burden. For most diseases mortality has more effect on the disease burden estimate than morbidity, for the foodborne diseases morbidity (mainly complications) plays a more important role. However, scenario analysis has suggested that both morbidity and in particular reported mortality for foodborne diseases are likely to be underestimated.

12. General conclusions and recommendations

12.1 Conclusions

Potential of disease burden estimates for guiding public health policy and actions
This pilot study reports preliminary estimates of the disease burden of a number of infectious diseases in the Europe, based on generally available data. The study makes clear that the relative burden of diseases as measured by disease burden is quite different compared to the relative burden as measured by just incidence or mortality data. Taking into account the limitations of this pilot in data availability and quality, it was found that (based on data for 2003-2005 when available) the disease burden in Europe is estimated to be highest for HIV-infection and tuberculosis, followed by campylobacteriosis, influenza and salmonellosis, and was lowest for measles and EHEC-infection. Scenario analysis limited to the Netherlands suggested that this ranking is not likely to be affected by better data. However, the relative burden of influenza is likely to increase. These results are in line with the expectations in advance: because HIV-infection and tuberculosis are chronic diseases, the disease burden was expected to be higher compared to the disease burden of the more acute diseases (i.e. measles).

There are considerable differences between the burden of specific diseases across Europe. Most notable are a high disease burden (per 100,000 inhabitants) of HIV/AIDS in Portugal, Estonia and France (Spain had a high mortality burden but did not report the incidence of HIV-infections), of campylobacteriosis, EHEC-infection and salmonellosis in the Czech Republic, of salmonellosis in Slovenia and of tuberculosis in the Baltic States (Estonia, Latvia and Lithuania), Hungary, Portugal and Poland. This may partly be due to differences in reporting systems but will also be due to true differences in disease incidence between countries. If not corrected for underreporting, disease burden estimates are not very appropriate for comparison between countries and suffer from the same limitations as reported incidence.

Estimates in this pilot study for the burden of measles, HIV/AIDS and tuberculosis are similar to those presented by the Global Burden of Disease (GBD) Study (WHO) and the Dutch Public Health Status and Forecast (PHSF) studies. Other infectious diseases evaluated in this pilot were not included in the GBD study and therefore this pilot gives added value. The PHSF study provided a higher burden of influenza, mainly due to higher morbidity estimates. Special studies at RIVM on the enteric pathogens also presented higher estimates.

The current disease burden reflects the balance between threats and the effectiveness of preventive measures. A low burden stresses the need for the continued support of these strategies. A high burden indicates the need for additional interventions. Disease burden estimates provide an integrated representation of the burden of infectious diseases. However, for priority setting other factors, such as threats and trends, costs and perception should be taken into account as well. For example, a recent study in the Netherlands has shown that on a population of 16 million in 2004 the annual costs for campylobacteriosis were € 22.3 million, for salmonellosis € 8.8 million, for norovirus € 25.0 million and for rotavirus € 21.7 million.[9]

Exploration of data availability and quality

Considerable limitations with regard to both data availability and data quality were encountered. Major limitations in data availability were:

- inconsistent morbidity and/or mortality by some countries and/or for some years;
- very limited information on the age-distribution of morbidity for most diseases;
- no reporting of the incidence of complications and chronic sequelae;
- no consistent set of severity weights available.

Major limitations with regard to data quality were:

- no information on underreporting of morbidity and mortality;
- no information on possible variation between countries of the duration, severity and rate of complications and chronic sequelae;
- differences between reports from different sources (national, Eurostat and WHO).

The baseline results of this study were not adjusted for under-reporting. Scenario analysis has mainly focused on the limitations of incidence data. Based on Dutch results, it is concluded that the currently presented data may significantly underestimate the burden of infectious diseases in Europe. Underestimation is particularly a problem for:

- influenza due to underreporting of morbidity and to a lesser extent of mortality;
- HIV/AIDS due to incomplete information on the long-term outcomes of current infections;
- enteric diseases (campylobacteriosis, EHEC-infection and salmonellosis) due to underreporting of both morbidity and mortality.

Estimates of the burden of measles and tuberculosis appear to be less uncertain. Other data limitations were not evaluated in this pilot study due to limitations in time and resources.

12.2 Recommendations

Disease burden (DALYs) calculations should be extended to other infectious diseases as well, because this composite measure gives more insight in burden than incidence or mortality data on its own. A full burden of disease study is recommended and would benefit from an approach that combines and triangulates several methods of investigation, including epidemiological modelling. In this short term pilot pragmatic choices had to be made, a full study should include a systematic and critical review on other disease burden estimates and on aspects like most suitable data sources, extent of underreporting, severity weights, outcome trees etcetera for each of the diseases under study. Furthermore there needs to be general agreement on methodological issues discussed in Chapter 2 like using a standard life table instead of the European life expectancy (that changes over time) or showing both discounted and undiscounted results in the future. Where possible a full burden of disease study should join other international efforts in this field (i.e. the WHO update of the Global Burden of Disease for the year 2004). With regard to priority setting, besides disease burden other aspects such as economical costs or outbreak potential should also be taken into account.

In order to obtain better insight in the epidemiology of infectious diseases in general and in the disease burden in particular, the following recommendations are made:

- improve the completeness and consistency of reporting of the incidence of morbidity and mortality in Europe, including information on the age-distribution;
- conduct cohort studies on the incidence of complications and chronic sequelae, including possible variability between countries and factors associated with that variability;
- conduct studies addressing sources of underreporting of morbidity and mortality in order to calibrate the data and to decrease inconsistencies in reporting between countries;
- improve quantification of the mortality risks due to infectious diseases by cohort-studies;
- integrate mathematical modelling to better understand the current and future burden, in particular for the HIV/AIDS epidemic including the impact of HAART;
- promote standardized data collection on disease severity and duration across Europe;
- conduct studies on severity weights and obtain consensus on the protocols for such studies, including national differences;
- develop a standardized approach to value choices inherent in disease burden calculations.

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Appendix I List of communicable diseases for EU surveillance

Source:
ANNEX I of Commission Decision 2000/96/EC of 22 December 1999 on the communicable diseases to be progressively covered by the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Amended by Decision 2003/534/EC.

1. COMMUNICABLE DISEASES AND SPECIAL HEALTH ISSUES TO BE PROGRESSIVELY COVERED BY THE COMMUNITY NETWORK

1.1. For the diseases/health issues listed below, surveillance within the Community network will be performed by standardised collection and analysis of data in a way that will be determined for each disease/health issue when specific Community surveillance networks are put in place.

2. DISEASES

2.1. Diseases preventable by vaccination

1. Diphtheria
2. Infections with haemophilus influenza group B
3. Influenza
4. Measles
5. Mumps
6. Pertussis
7. Poliomyelitis
8. Rubella
9. Smallpox (added by Commission Decision No 2003/534/EC)
10. Tetanus (added by Commission Decision No 2003/534/EC)

2.2. Sexually transmitted diseases

11. Chlamydia infections
12. Gonococcal infections
13. HIV-infection
14. Syphilis

2.3. Viral hepatitis

15. Hepatitis A
16. Hepatitis B
17. Hepatitis C

2.4. Food- and water-borne diseases and diseases of environmental origin

18. Anthrax (added by Commission Decision No 2003/534/EC)
19. Botulism
20. Campylobacteriosis
21. Cryptosporidiosis
22. Giardiasis

23. Infection with enterohaemorrhagic E.coli
24. Leptospirosis
25. Listeriosis
26. Salmonellosis
27. Shigellosis
28. Toxoplasmosis
29. Trichinosis
30. Yersinosis

2.5. Other diseases

2.5.1. Diseases transmitted by non-conventional agents

31. Transmissible spongiform encephalopathies variant (CJD)

2.5.2. Air-borne diseases

32. Legionellosis
33. Meningococcal disease
34. Pneumococcal infections
35. Tuberculosis

2.5.3. Zoonoses (other than in 2.4)

36. Brucellosis
37. Echinococcosis
38. Q-Fever (added by Commission Decision No 2003/534/EC)
39. Rabies
40. Tularaemia (added by Commission Decision No 2003/534/EC)

2.5.4. Serious imported diseases

41. Cholera
42. Malaria
43. Plague
44. Viral haemorrhagic fevers

3. SPECIAL HEALTH ISSUES

45. Nosocomial infections
46. Antimicrobial resistance

4. EMERGING DISEASES

47. SARS
48. West-Nile virus
49. Avian influenza

Appendix II List of countries

The 25 EU Member States (situation 2006)*:

Austria	Estonia	Hungary	Luxembourg	Slovakia
Belgium	Finland	Ireland	Malta	Slovenia
Cyprus	France	Italy	the Netherlands	Spain
Czech Republic	Germany	Latvia	Poland	Sweden
Denmark	Greece	Lithuania	Portugal	United Kingdom

* Bulgaria and Romania joined the EU in January 2007 but are not included in this report

The EEA/EFTA Countries:

Iceland
Liechtenstein
Norway

Appendix III Life expectancy

Life expectancy at the average age of death within each age interval (used in this study)

		European life expectancy 2004*			Standard life expectancy West Level 26**	
Age (years)	Average age at death	Total	Males	Females	Males	Females
0	0.1	78.57	75.48	81.56	79.94	82.43
1-4	2.6	76.43	73.36	79.40	77.77	80.28
5-9	7.5	71.59	68.53	74.56	72.89	75.47
10-14	12.5	66.64	63.58	69.60	67.91	70.51
15-19	17.5	61.72	58.68	64.65	62.93	65.55
20-24	22.5	56.87	53.88	59.73	57.95	60.63
25-29	27.5	52.04	49.12	54.82	52.99	55.72
30-34	32.5	47.21	44.36	49.92	48.04	50.83
35-39	37.5	42.43	39.64	45.06	43.10	45.96
40-44	42.5	37.72	35.01	40.25	38.20	41.13
45-49	47.5	33.14	30.54	35.54	33.38	36.36
50-54	52.5	28.73	26.28	30.96	28.66	31.68
55-59	57.5	24.48	22.20	26.48	24.07	27.10
60-64	62.5	20.40	18.35	22.13	19.65	22.64
65-69	67.5	16.56	14.78	17.96	15.54	18.32
70-74	72.5	13.03	11.58	14.06	11.87	14.24
75-79	77.5	9.89	8.80	10.55	8.81	10.59
80-84	82.5	7.16	6.45	7.53	6.34	7.56
85+	90.0	4.01	3.63	4.20	3.54	4.25

Life expectancy at the beginning of the age interval

	European life expectancy 2004*			Standard life expectancy West Level 26**	
Age (years)	Total	Males	Females	Males	Females
0	78.63	75.54	81.63	80.00	82.50
1	78.00	74.93	80.97	79.36	81.84
5	74.07	71.00	77.04	75.38	77.95
10	69.11	66.05	72.08	70.40	72.99
15	64.16	61.10	67.11	65.41	68.02
20	59.28	56.27	62.19	60.44	63.08
25	54.45	51.50	57.28	55.47	58.17
30	49.62	46.74	52.37	50.51	53.27
35	44.80	41.99	47.48	45.57	48.38
40	40.05	37.30	42.63	40.64	43.53
45	35.38	32.72	37.87	35.77	38.72
50	30.89	28.35	33.22	30.99	33.99
55	26.57	24.20	28.69	26.32	29.37
60	22.38	20.20	24.26	21.81	24.83
65	18.42	16.49	19.99	17.50	20.44
70	14.71	13.08	15.92	13.58	16.20
75	11.36	10.09	12.19	10.17	12.28
80	8.42	7.52	8.92	7.45	8.90

* Calculation based on total mortality and average population EU-25 in 2004 (data Eurostat)

** Life expectancy used in Global Burden of Disease study

Appendix IV Data and assumptions baseline estimates of disease burden

Table IV.1 Influenza: incidence, duration and severity weight for each outcome (see section 4.1)

Outcome	Estimate	Source and assumptions
Acute illness with fever		
- incidence	reported cases	number of sentinel and non-sentinel respiratory specimens tested positive for influenza A or B based on annual reports of European Influenza Surveillance Scheme (EISS); mean number of the three influenza seasons 2002/2003[86], 2003/2004[87] and 2004/2005[27]
- duration	1 year	severity weight based on annual profile[24]
- severity weight	0.01	annual profile (1 year with 2 weeks influenza)[24]
Otitis media		
- incidence	0.65% of influenza cases	0.0065 * influenza incidence[31]
- duration	0.08 year	Global Burden of Disease[23]
- severity weight	0.023 (all ages)	Global Burden of Disease[17]
Deafness (due to otitis media)		
- incidence	0.3/5,067 otitis media cases	Global Burden of Disease[23]; 0.000059206 * otitis media incidence (in EME* incidence rate otitis media is 5,067 per 100,000 and incidence rate deafness due to otitis media is 0.3 per 100,000)
- duration	chronic	full life expectancy because age is unknown and otitis media occurs more often in children
- severity weight	00-04 year 0.175 05-14 year 0.169 15-44 year 0.168 45-59 year 0.168 60+ year 0.168	Global Burden of Disease[17]; if age unknown we choose severity weight 0.168 (same for ages 15 years and older)
Pneumonia		
- incidence	0.36% of influenza cases	0.0036 * influenza incidence[31]
- duration	EME* 0.02 year FSE** 0.02 year MEC*** 0.03 year	Global Burden of Disease[23]; duration of lower respiratory infections in general (pneumonia not available)
- severity weight	00-04 year 0.280 05-14 year 0.280 15-44 year 0.276 45-59 year 0.276 60+ year 0.280	Global Burden of Disease[17]; severity weight of lower respiratory infections in general (pneumonia not available); if age unknown we choose severity weight 0.278 (mean 0.276 and 0.280)

Table IV.2 Measles: incidence, duration and severity weight for each outcome (see section 5.1)

Outcome	Estimate	Source and assumptions
Acute illness with fever		
- incidence	reported cases	data Eurostat, mean 2003-2005
- duration	0.04 year	Global Burden of Disease[23]
- severity weight	0.152 (all ages)	Global Burden of Disease[17]
Otitis media		
- incidence	5-10% of measles cases	0.075 * measles incidence[28]
- duration	0.08 year	Global Burden of Disease[23]
- severity weight	0.023 (all ages)	Global Burden of Disease[17]
Deafness (due to otitis media)		
- incidence	0.3/5,067 per otitis media case	Global Burden of Disease[23]; 0.000059206 * otitis media incidence (in EME* incidence rate otitis media is 5,067 per 100,000 and incidence rate deafness due to otitis media is 0.3 per 100,000)
- duration	chronic	full life expectancy because in general measles incidence is highest in youngest age groups
- severity weight	00-04 year 0.175 05-14 year 0.169 15-44 year 0.168 45-59 year 0.168 60+ year 0.168	Global Burden of Disease[17]; if age unknown we choose severity weight 0.172 (mean 00-04 year and 05-14 year; in general incidence of measles is highest in the youngest age groups)
Pneumonia		
- incidence	1-5% of measles cases	0.03 * measles incidence[28]
- duration	EME* 0.02 year FSE** 0.02 year MEC*** 0.03 year	Global Burden of Disease[23]; duration of lower respiratory infections in general (pneumonia not available)
- severity weight	00-04 year 0.280 05-14 year 0.280 15-44 year 0.276 45-59 year 0.276 60+ year 0.280	Global Burden of Disease[17]; severity weight of lower respiratory infections in general (pneumonia not available), if age unknown we choose severity weight 0.280 (in general incidence of measles is highest in the youngest age groups)
Encephalitis		
- incidence	0.1% of measles cases	0.001 * measles incidence[28]
- duration	0.08 year	Global Burden of Disease[23]; duration bacterial meningitis (encephalitis not available)
- severity weight	00-04 year 0.616 05-14 year 0.616 15-44 year 0.613 45-59 year 0.613 60+ year 0.613	Global Burden of Disease[17]; severity weight of bacterial meningitis and Japanese encephalitis (encephalitis not available), if age unknown we choose severity weight 0.616 (in general incidence of measles is highest in the youngest age groups)
Sequelae encephalitis		
- incidence	0.255 per encephalitis case	0.255 * encephalitis incidence (mortality 10-20% and morbidity 20-40% of patients who recovered -> 0.255 per measles encephalitis case)
- duration	chronic	full life expectancy because in general incidence of measles is highest in the youngest age groups
- severity weight	00-04 year 0.334 05-14 year 0.334 15-44 year 0.334	Global Burden of Disease[17]; severity weight of motor deficit bacterial meningitis and neurological sequelae Japanese encephalitis (sequelae encephalitis not available), if age unknown we choose severity weight

	45-59 year 0.337 60+ year 0.390	0.334 (in general incidence of measles is highest in the youngest age groups)
Subacute sclerosing panencephalitis (SSPE)		
- incidence	0.6-2.2 per 100,000 measles cases	0.000014 * measles incidence[54]
- duration	0.75 year	duration of 9 months [88]
- severity weight	0.93 (all ages)	severity weight of terminal disease, end stage (SSPE not available)[24]

Table IV.3 HIV-infection: incidence, duration and severity weight for each outcome (see section 6.1)

Outcome	**Estimate**	**Source and assumptions**
Symptomatic infection		
- incidence	reported cases	data EuroHIV, mean 2003-2005
- duration	EME* 10 year FSE** 7 year MEC*** 7 year	Global Burden of Disease[23]; duration before introduction of HAART, in the age group 0-4 year average duration is less but there is no specific incidence information on this age group and the incidence in younger age groups is small
- severity weight	00-04 year 0.123 05-14 year 0.123 15-44 year 0.136 45-59 year 0.136 60+ year 0.136	Global Burden of Disease[17]; severity weight before introduction of HAART, if age unknown we choose severity weight 0.136 (incidence in younger age groups is small)
AIDS		
- incidence	notified cases EuroHIV	data EuroHIV, mean 2003-2005
- duration	EME* 2 year FSE** 1 year MEC*** 1 year	Global Burden of Disease[23]; duration before introduction of HAART, in the age group 0-4 year the average duration in FSE and MEC is 0.5 year
- severity weight	0.505 (all ages)	Global Burden of Disease[17]; severity weight before introduction of HAART

Table IV.4 Campylobacteriosis: incidence, duration and severity weight for each outcome (see section 7.1)

Outcome	Estimate	Source and assumptions
Gastroenteritis		
- incidence	reported cases	data Eurostat, mean 2003-2005
- duration	9.9 days = 0.027 year	weighted mean of duration for cases visiting GP (9.72 days) and hospitalized (14.39 days); assumption: the reported incidence = patients that at least have visited GP[9]
- severity weight	0.393	[9]
Reactive arthritis (ReA)		
- incidence	0.16 per case	Netherlands 2004: 1,000 cases per 6,285 laboratory-confirmed Campylobacteriosis cases[9, 89]
- duration	222 days = 0.61 year	[9]
- severity weight	0.14	weighted mean of severity weights for cases not visiting GP (0.127), visiting GP (0.21) and hospitalized (0.37) = 0.14[9]
Guillain Barré Syndrome (GBS), 1st year		
- incidence	0.009 per case	Netherlands 2004: 59 cases per 6,285 laboratory-confirmed Campylobacteriosis cases[9, 89]
- duration	1 year	[90]
- severity weight	0.25	weighted mean of severity weights (1st year) for mild and severe GBS = 0.25[90]
Guillain Barré Syndrome (GBS), following years (long term sequela)		
- incidence	0.009 per case	same as GBS 1st year[9]
- duration	29.26 year	weighted mean of duration mild and severe GBS = 30.26 year – 1 (first year) [90]
- severity weight	0.16	weighted mean of severity weights (following years) for mild and severe GBS (including full recovery) = 0.16[90]
Inflammatory Bowel Disease (IBD)		
- incidence	0.0035 per case	Netherlands 2004: 22 cases per 6,285 laboratory-confirmed Campylobacteriosis cases[9, 89]
- duration	44.36 year (total)	life long -> mean life expectancy based on age distribution cases visiting GP[9]
- severity weight	0.26	[9]

Table IV.5 EHEC-infection: incidence, duration and severity weight for each outcome (see section 8.1)

Outcome	Estimate	Source and assumptions
Watery diarrhoea (WD), haemorrhagic colitis (HC)		
- incidence	reported cases	data Eurostat, mean 2003-2005
- duration	5.6 days = 0.015 year	[7]
- severity weight	0.393	[9]
Haemolytic-uraemic syndrome (HUS), including end-stage renal disease (ESRD)		
- incidence	0.5 per case	Netherlands 2004: 21 cases[9] per 42 cases reported to Eurostat
- duration		model indicates 22.7 YLD for 21.7 cases -> 1.05 YLD per HUS case[91]
- severity weight		model indicates 22.7 YLD for 21.7 cases -> 1.05 YLD per HUS case[91]

Table IV.6 Salmonellosis: incidence, duration and severity weight for each outcome (see section 9.1)

Outcome	Estimate	Source and assumptions
Gastroenteritis		
- incidence	reported cases	data Eurostat, mean 2003-2005
- duration	11.2 days = 0.031 year	weighted mean of duration for cases visiting GP (10.65 days) and hospitalized (16.15 days); assumption: the reported incidence = patients that at least have visited GP[9]
- severity weight	0.393	[9]
Inflammatory Bowel Disease (IBD)		
- incidence	0.003 per case	Netherlands 2004: 7 cases per 2,573 laboratory-confirmed Campylobacteriosis cases[9, 89]
- duration	50.52 year (total)	life long -> mean life expectancy based on age distribution cases visiting GP[9]
- severity weight	0.26	[9]
Reactive arthritis (ReA)		
- incidence	0.18 per case	Netherlands 2004: 460 cases per 2,573 laboratory-confirmed Campylobacteriosis cases[9, 89]
- duration	0.61 year	222 days[9]
- severity weight	0.15	weighted mean of severity weights for cases not visiting GP (0.127), visiting GP (0.21) and hospitalized (0.37) = 0.15[9]

Table IV.7 Tuberculosis: incidence, duration and severity weight for each outcome (see section 10.1)

Outcome	Estimate	Source and assumptions
Latent tuberculosis		not taken into account because incidence, duration and severity is unknown
(Extra)pulmonary tuberculosis		
- incidence	reported cases	data EuroTB, mean 2003-2005; rough proxy of incidence: a proportion of the cases would have had tuberculosis in the past
- duration	EME* 0.25 year FSE** 0.50 year MEC*** 1.50 year	Global Burden of Disease[23]; no difference between pulmonary and extrapulmonary tuberculosis
- severity weight	00-04 year 0.294 05-14 year 0.294 15-44 year 0.264 45-59 year 0.274 60+ year 0.274	Global Burden of Disease[17]; no difference between pulmonary and extrapulmonary tuberculosis, if age unknown we choose severity weight 0.274
Multidrug-resistant tuberculosis		not taken into account in baseline estimate because duration and severity is unknown
- incidence	reported cases EuroTB	data EuroTB, mean 2003-2005 (limited number of countries)

Table IV.8 All diseases: mortality and life expectancy

All diseases	Estimate	Source and assumptions
- mortality	reported deaths	data Eurostat/WHO, mean 2003-2004 (2005 not yet available for many countries) ICD-10 codes: influenza (J10-J11), measles (B05+A81.1), HIV-infection (B20-B24), campylobacteriosis (A04.5), EHEC-infection (A04.3), salmonellosis (A02) and tuberculosis (A15-A19+B90); assumption 1: if a country has reported deaths for a specific year according to ICD-10 in general but the number of deaths for a specific disease is missing, we assumed that zero deaths have been reported for that specific disease; assumption 2: in case of differences between Eurostat and WHO, we used data Eurostat;
- life expectancy	life expectancy Europe 2004	data Eurostat European Union 2004 (25 countries); own calculation of European life expectancy 2004 based on total number of deaths and average population in Europe in 2004 (latest data available)

* EME = Established market economies (all other countries in the project than FSE and MEC, see below)
** FSE = Formerly socialist economies of Europe (Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia)
*** MEC= Middle Eastern crescent (Cyprus, Malta)

Appendix V Figures on comparison between diseases

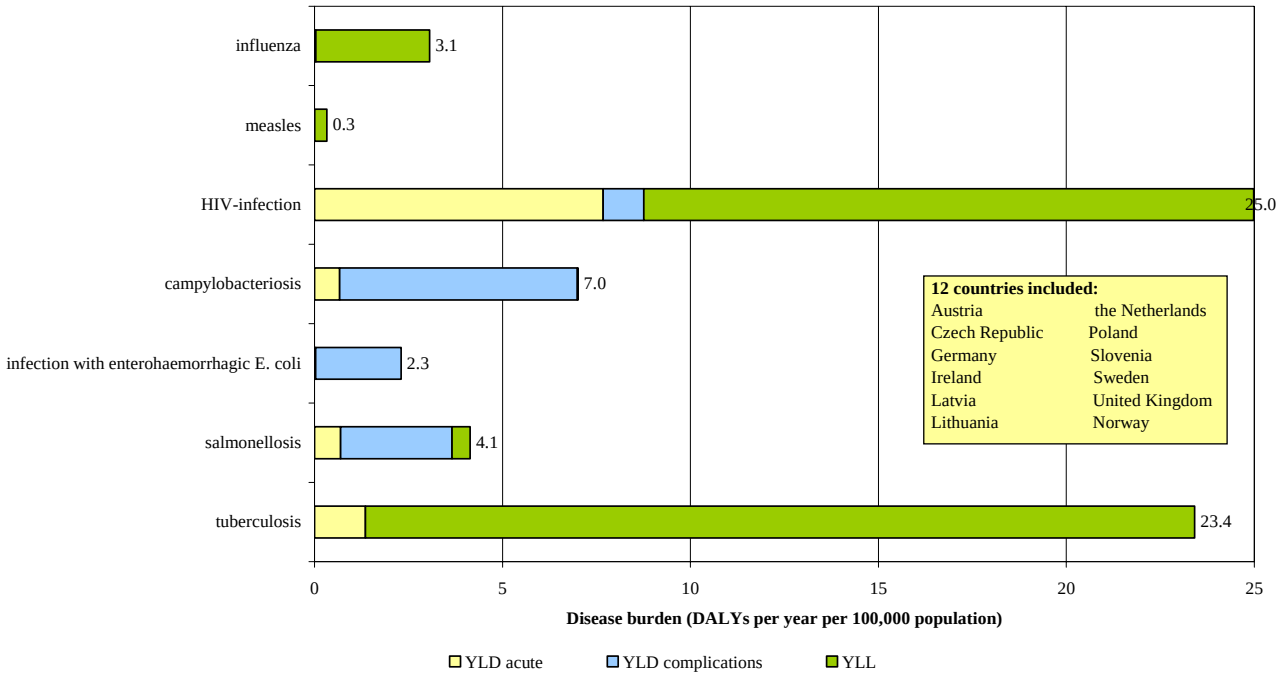

Figure V.1 Sum of disease burden per 100,000 population of 12 countries for which data is available for <u>all</u> diseases

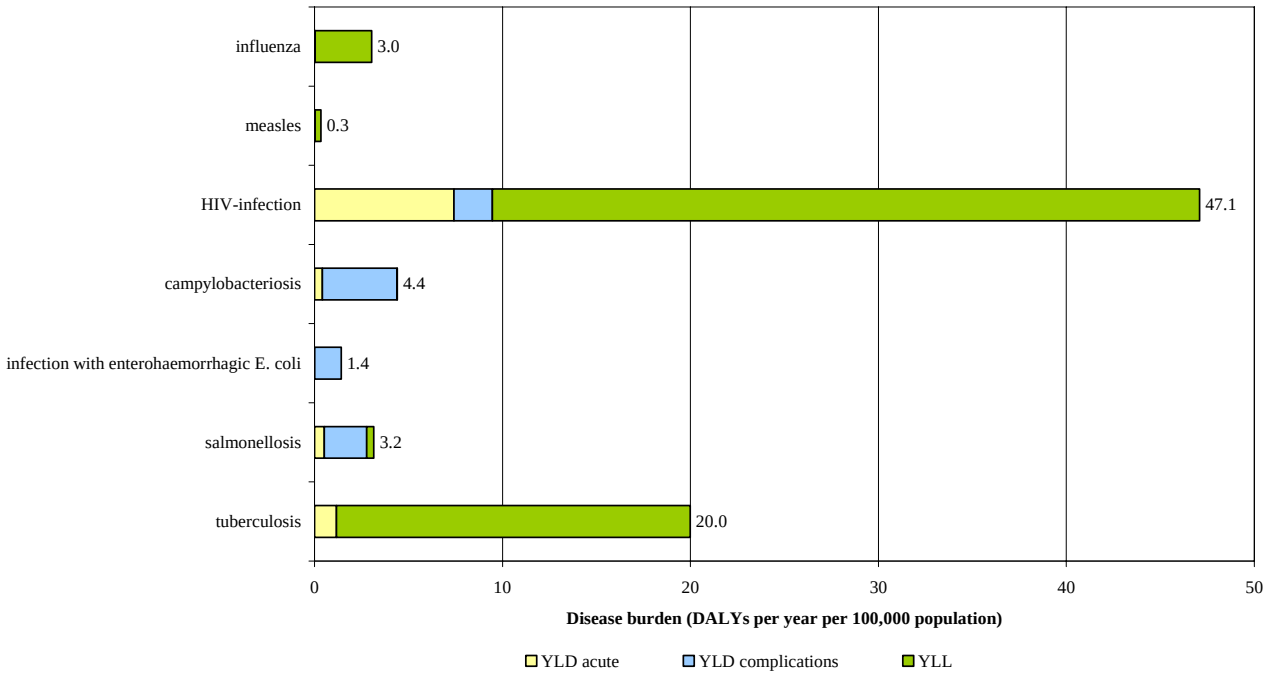

Figure V.2 Sum of disease burden per 100,000 population of all countries for which data is available, also for countries with missing DALY components