

## THE BURDEN OF INFECTIOUS DISEASES IN EUROPE: A PILOT STUDY

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The main objectives of this pilot study were to test the potential use of the disease burden concept in the field of infectious diseases, including data quality and availability; to recommend future studies; and to stimulate a debate. The disease burden of seven infectious diseases (influenza, measles, HIV, campylobacteriosis, infection with enterohaemorrhagic *Escherichia coli*, salmonellosis and tuberculosis) in Europe was estimated by calculating Disability Adjusted Life Years (DALYs), a composite measure that attempts to combine mortality, incidence and sequelae, taking duration and severity into account. The results show that the relative burden of diseases as measured by DALYs differs from that only measured by incidence or mortality. Several limitations regarding data availability and quality have been identified, resulting in an underestimation of the true burden of disease in this pilot. Notwithstanding these, HIV-infection, tuberculosis (TB) and influenza are estimated to cause the highest burden in Europe among the selected diseases. The burden of foodborne diseases (campylobacteriosis, infection with enterohaemorrhagic *Escherichia coli* and salmonellosis) and in particular of measles is lower. A consideration of the relative comparison of burden between diseases can be useful when tackling the difficult, sensitive but necessary task of identifying priority actions. A low burden stresses the need for continued support for prevention and control whereas a high burden indicates the need for additional interventions. Following this pilot project, a generalised burden of disease study for infectious diseases in Europe is recommended. Such a study would benefit from an approach that identifies and combines several methods of investigation, including epidemiological modelling, and it should be done in collaboration with other international efforts in this field.

### Introduction

Assessments of disease burden are often based on singular health metrics, such as incidence, prevalence or mortality data alone. However, as diseases and their consequences are heterogeneous in terms of morbidity and mortality it is difficult to get an overall estimate of disease burden. Composite health measures attempt to overcome this by combining mortality, incidence (and/or prevalence) and the sequelae associated with a disease. The Disability Adjusted Life Years (DALYs) is such a composite measure that could be helpful in prioritising diseases. Other priority-setting criteria are incidence, the severity of a disease, its potential to spread among the general population, its associated socioeconomic burden, its preventability, its potential to drive public health policy, the perception of risk related to the disease, changing patterns in time [1] and perceived outbreak potential.

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 [2]. As part of its work to fulfil this mandate, the ECDC has produced the first Annual Epidemiological Report on Communicable Diseases

in Europe [3]. This report provides a comprehensive overview of the threat of infectious diseases in the European Union (EU) in 2005. It analyses incidence trends and patterns of the 46 diseases under mandatory surveillance, as well as severe acute respiratory syndrome (SARS), avian influenza and West Nile virus. The trends identified give an indication of which diseases require priority action; additional indications would be given by including mortality, prevalence (only few data are available) and sequelae. The ECDC aims to evaluate whether a composite measure could be useful to inform its decision-making process. If so, it could be used to gain insight into the current burden and the expected trends of these 49 infectious diseases in order to guide public health policy and action. 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 a debate. This study was conducted by the Dutch National Institute for Public Health and the Environment (RIVM).

### Methods

The pilot study was performed between October and December 2006, to fit into the 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 include only generally available data, such as those of the Statistical Office of the European Communities (Eurostat), the World Health Organization (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 (TB). These diseases were mainly selected based on the availability of incidence and mortality data and previous experience with disease burden calculations at RIVM so that comparisons could be made.

The DALY methodology used in this study has been described by Murray and co-workers in the Global Burden of Disease (GBD) project, [4,5] using the following equation:

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

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:

$$\text{YLL} = \sum_i d_i \times e_i$$

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):

$$YLD = \sum_i n_i \times t_i \times w_i$$

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. Value choices, such as disability weighting, age-weighting and discounting, imply that life years are assigned different value depending on the age and the health state they are in. Disability weighting means that each outcome of a disease is assigned a different value (severity weight) on a scale from 0 (perfect health) to 1 (death), see Table 1 for some examples.

For this pilot project, taking into consideration its short duration, the following (value) choices were made in consultation with the ECDC:

- ▶ to use incidence rather than prevalence data;

**TABLE 1**

**Disability classes and severity weights according to the Global Burden of Disease study [6]**

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, heumatoid 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

**TABLE 2**

**Generally available data sources used for the disease burden pilot study, RIVM 2007 [10]**

YLL	D	= Number of fatal cases	Mean number of deaths 2003-2004 reported to Eurostat/WHO [11,12] CD-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)
	E	= Life expectancy at age of death	European life expectancy 2004 (calculation based on total mortality and average population data 2004 [11])
YLD	N	= Number of cases of illness	Mean incidence 2003-2005 reported to - EuroHIV [13] (HIV-infection) - EuroTB [14] (tuberculosis) - EISS [15,16,17] (influenza, mean 2002/2003-2004/2005) - Eurostat [18] (other diseases)
	T	= Duration of illness	Literature (mainly Global Burden of Disease study [19])
	W	= Severity weights	Literature (mainly Global Burden of Disease study [6])

YLL = number of years of life lost due to mortality

YLD = number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability

- ▶ to focus on all the relevant health outcomes that can be attributed to one particular infectious agent (an agent-based approach), rather than focussing on clinically defined categories of diseases (ICD-codes) irrespective of their cause (an outcome-based approach);

- ▶ which outcomes to include for each of the diseases;

- ▶ to use the European life expectancy rather than the life expectancy of a standard life table;

- ▶ not to apply discounting and age-weighting (both are debated [7,8,9]);

- ▶ to use severity weights based on period profile if available (in contrast to annual profile).

More detailed information on the background of the choices made is included in a full report published by the RIVM.10

Depending on data availability, as many as possible Member States of the European Union plus Iceland, Liechtenstein and Norway were included in the pilot study. The sources of generally available data are displayed in Table 2.

More detailed information on data and assumptions used for calculating baseline estimates of disease burden is included in the full RIVM-report [10]. Due to time limitations, a true sensitivity analysis could not be conducted. However, when alternative morbidity or mortality estimates or severity weights were available, other scenarios were calculated (=scenario analysis) to explore the uncertainty resulting from different limitations. Furthermore, the disease burden estimates were compared with those of previously published more detailed studies [20,21,22].

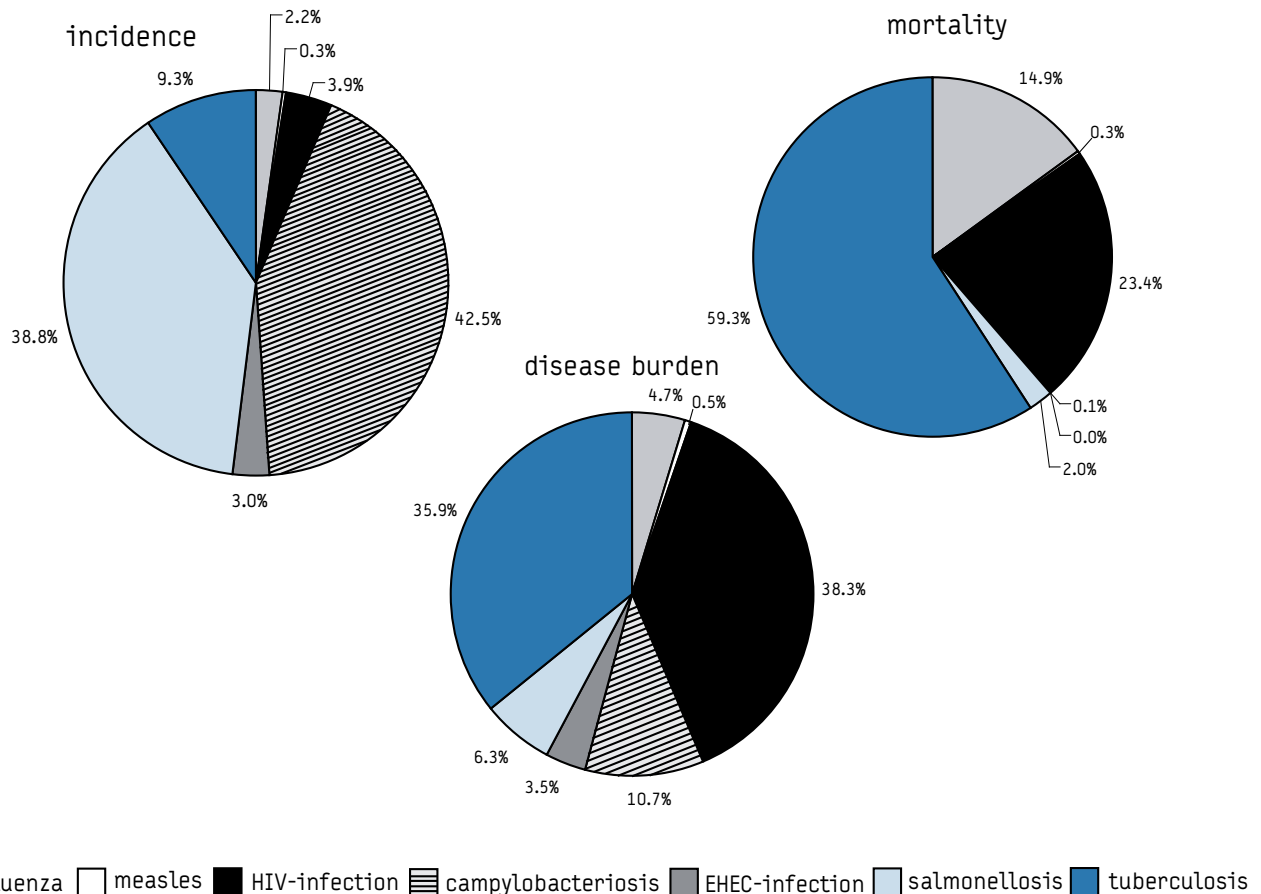
**Results**

The potential use of disease burden estimates in guiding public health policy and actions The relative burden of diseases as measured by disease burden is different to the relative burden as measured only by incidence or mortality data (Figure 1). Based on incidence data alone, foodborne diseases cause the greatest relative burden of the seven diseases studied, while mortality data demonstrate the relatively high burden of TB.

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), RIVM Study 2007<sup>10</sup>



Based on data for twelve countries (data available for all seven diseases): Austria, Czech Republic, Germany, Ireland, Latvia, Lithuania, the Netherlands, Poland, Slovenia, Sweden, United Kingdom, Norway

According to our study, disease burden based on DALYs shows a different picture, with a relatively high burden of HIV-infection and TB. Figure 2 shows an estimate of the total disease burden per 100,000 population for the seven selected diseases, for those countries for which DALYs could be calculated. An analysis based on 12 countries for which the disease burden could be calculated for all diseases shows a fairly similar picture. HIV-infection and TB have the highest disease burden in Europe, measles the lowest.

**Scenario analysis**

The scenario analysis focused primarily on the limitations of incidence data for the Netherlands. Figure 3 suggests that the disease burden of influenza is seriously underestimated (especially morbidity). 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 TB appeared to be more certain. The scenario analysis for influenza and

TB are discussed in more detail below. Further detailed information on the scenario analysis is included in the full RIVM-report [10].

**Influenza**

Figure 4 shows the baseline scenario for influenza in the Netherlands. In this scenario (scenario one), the number of respiratory specimens tested positive for influenza reported to the European Influenza Surveillance Scheme (the only generally available data at that moment) was used as an estimate of the influenza incidence. However, the disease is usually self-limiting and diagnoses are generally not laboratory-confirmed. Therefore, the true incidence of influenza is considerably higher.

In scenario two, the mean number of general practitioner (GP) visits because of influenza-like-illness in the seasons 2003/2004 to 2005/2006 [23] was used as the incidence estimate. This incidence was corrected on the assumption that only 30% of the influenza patients in the Netherlands visit their GP24 and only 32.2% of influenza-like-illnesses in the Netherlands can be ascribed to influenza [25] (based on laboratory confirmation for the

FIGURE 2

Disease burden per 100,000 population: total for countries for which data are available for at least one disease (for each disease the number of countries is different), RIVM Study 2007<sup>10</sup>

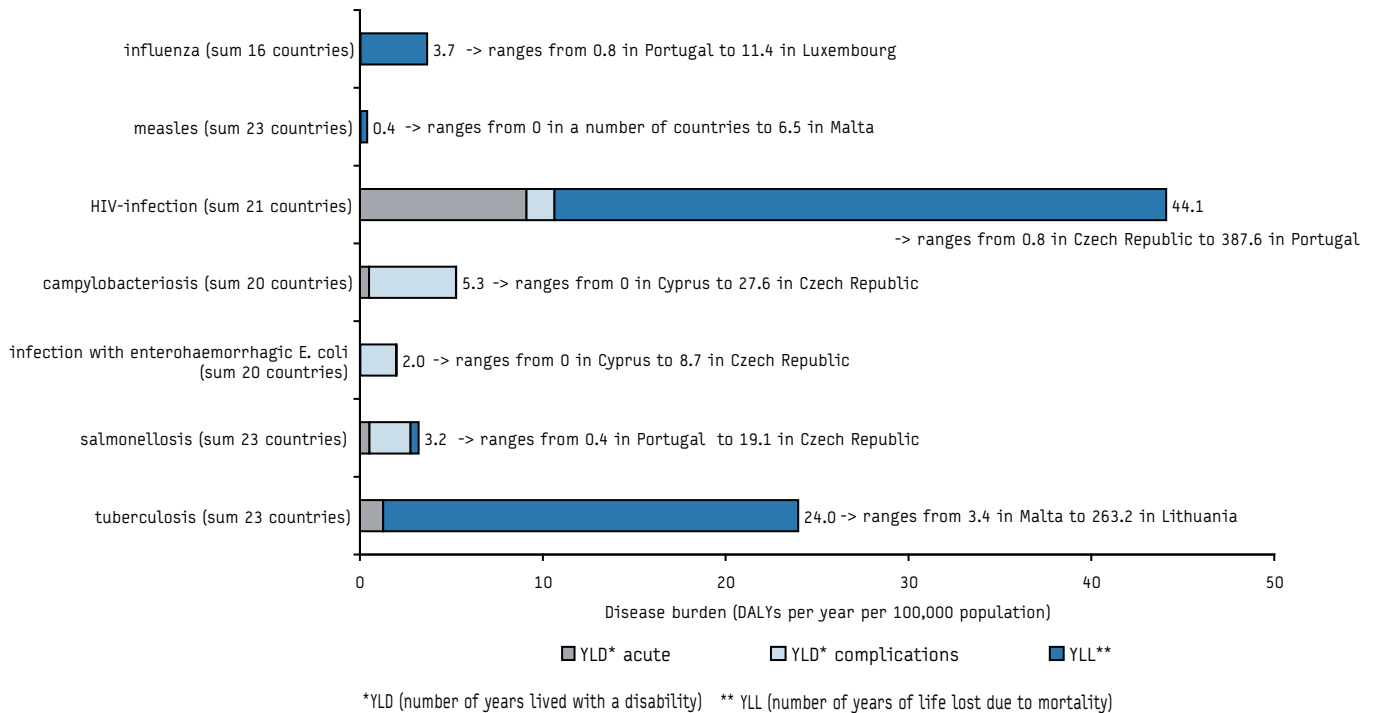
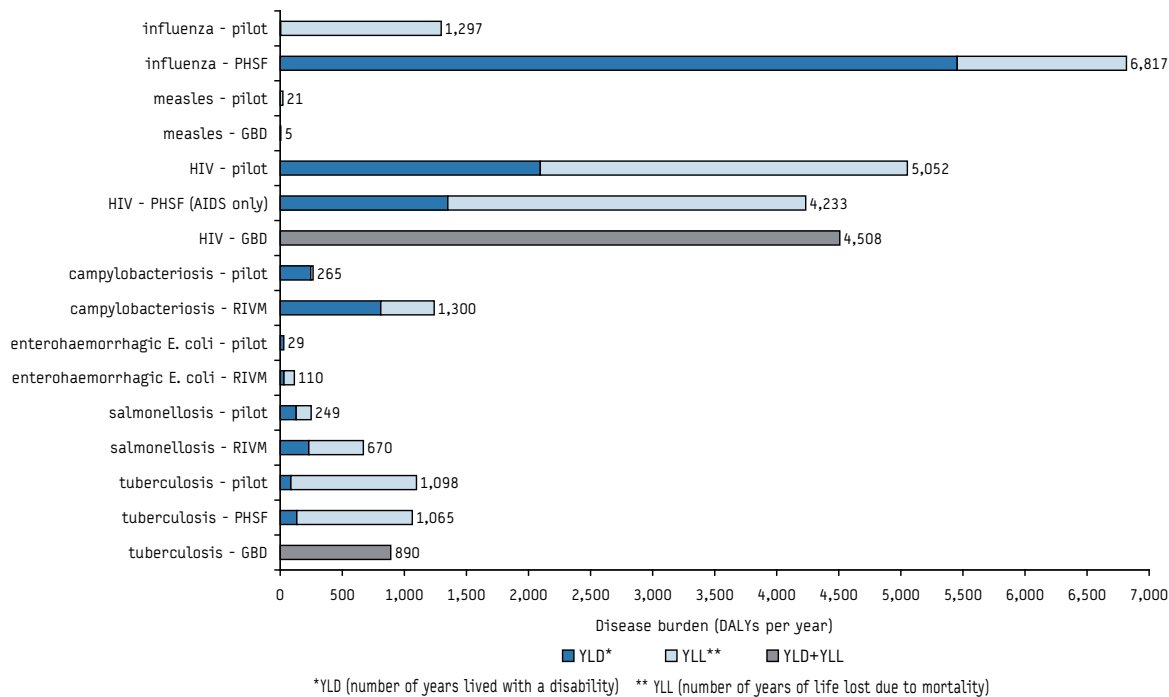


FIGURE 3

Disease burden of seven selected diseases in the Netherlands: comparison of results from the pilot study with previously published more extensive studies, RIVM Study 2007<sup>10</sup>



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)

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 difference has a considerable impact on the morbidity estimate that changes from four YLD in the baseline scenario to 2,808 YLD in scenario two. In England and Wales, approximately 800,000 GP consultations for respiratory illnesses each year are attributed to influenza [26], resulting in 8,030 YLD, compared to 20 YLD for the United Kingdom in the baseline scenario.

In scenario three, the incidence was based on the assumption that the clinical attack rate of influenza during epidemics ranges between 10-20% in the general community [27]. In this scenario, the lowest estimate of 10% was used because in half of the cases the infection is subclinical. For the Netherlands the influenza incidence in scenario three was 1,628,178 cases per year (compared to 279,770 in scenario two and 400 in the baseline scenario), whereas the YLD estimate was 16,342.

For the Netherlands, Sprenger et al. estimated that in the period 1967-1989 the overall impact of influenza on mortality was greater than the officially registered influenza mortality by a factor of 3.6 [28]. In scenario four the registered mortality in all age groups 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 may have been overestimated this way because the influenza virus seems to have been less virulent in recent years [25] and vaccination coverage today is considerably higher than it was between 1967 and 1989. Furthermore, YLL was probably overestimated because it is likely that people dying from influenza have an 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% were attributed to lung disease and approximately 30% to other diseases [28].

### Tuberculosis

In contrast with the disease burden estimate for influenza, the estimate for TB seems to be more certain. Figure 5 shows that results of this pilot are in line with the estimates of the WHO's Global Burden of Disease study (2002). However, multidrug-resistant TB should be taken into account in future disease burden estimates, especially for countries with a relatively high number of such cases (e.g. the Baltic States).

### Discussion

In this pilot study, considerable limitations with regard to both data availability and quality were encountered. Major limitations in data availability were: inconsistent data on morbidity and/or mortality reported 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.
- ▶ Major limitations with regard to data quality were:

FIGURE 4

Disease burden of influenza in the Netherlands: scenario analysis (description of scenarios in the text), RIVM Study 2007<sup>10</sup>

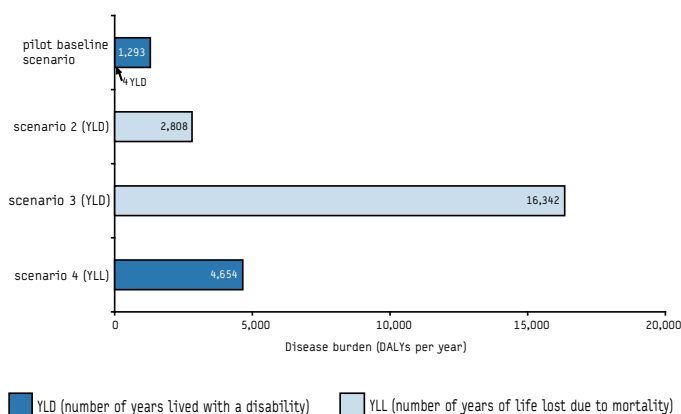
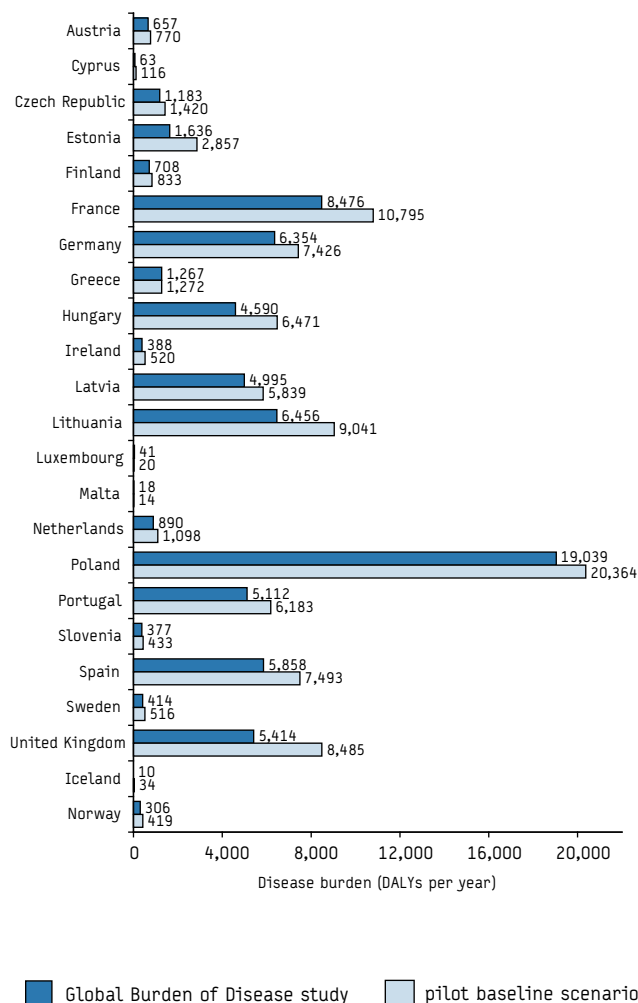


FIGURE 5

Disease burden of tuberculosis: comparison of results from the pilot study's baseline scenario with the Global Burden of Disease study (2002), RIVM Study 2007<sup>10</sup>



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

The authors are aware that the results of this preliminary study, based on generally available information, do not reflect the full disease burden of the selected infectious diseases in Europe, mainly due to potential underreporting in the available data on morbidity and mortality. Even the current relative comparisons of disease burden may be biased, as the extent of the potential underreporting varies between diseases and countries. Furthermore, not all relevant disease outcomes could be included in this preliminary assessment. Although it seems controversial to weigh health outcomes, a Dutch study on toxoplasmosis indicates that disease burden estimates are more affected by using different data sources than different severity weights [29]. Comparisons of the results of this pilot project with other more extensive studies could only be very general, since the methodological choices differed for each of the studies.

The relative burden of diseases as measured by disease burden is different from the relative burden as measured by incidence or mortality data alone. Based on data for 2003-2005 when available, the disease burden in Europe was estimated to be highest for HIV-infection and TB, followed by campylobacteriosis, influenza and salmonellosis, and 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.

Based on the presented scenarios two (YLD) and four (YLL) combined, the disease burden of influenza in the Netherlands may have been underestimated in the baseline scenario by a factor of at least five. It is likely that the disease burden of influenza was also underestimated for other countries. The number of respiratory specimens tested positive for influenza is not a suitable incidence indicator for disease burden calculations, because laboratory testing is not a general practice (this applies to all the selected diseases, but to influenza in particular). Future morbidity estimates for influenza should concentrate on GP consultation data in combination with virological data to estimate the percentage of influenza among influenza-like-illnesses (scenario two), which give a more reliable incidence estimate than laboratory data. An alternative mortality estimate could be the excess all-cause mortality during periods of high circulation of influenza [30,31], like the example in scenario four.

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. For priority-setting, however, other factors – such as threats and trends, costs and perception – should also be taken into account.

### Recommendations

It would be worthwhile to extend the calculation of disease burden (e.g. based on DALYs) to other infectious diseases as well, because this composite measure gives more insight into the burden of diseases than single incidence or mortality data. A complete burden of disease study for a wider range of diseases is recommended although it needs to be explored if this is relevant to all 49 diseases. The selection of relevant diseases should be part of a complete burden of disease study. Such a study would benefit from an approach that identifies and combines several methods of investigation, including epidemiological modelling. In this short-term pilot project, pragmatic choices had to be made; however, a more comprehensive study should include a systematic and critical review of other disease burden estimates and of issues such as the most suitable data sources, the extent of underreporting, severity weights, outcome trees etcetera for each of the diseases under study. Furthermore, there needs to be a general agreement on methodological issues, 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, other aspects besides disease burden should also be taken into account, such as economic costs or presumed outbreak potential.

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

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

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