Burden of infectious diseases in Europe: methodological challenges and opportunities for public health policy

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2023

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PhD thesis, Utrecht University, the Netherlands

ISBN:	978-90-393-7580-8
DOI:	https://doi.org/10.33540/1881
Author:	Alessandro Cassini
Cover design:	May-Kou Moroni
Layout:	Publiss | www.publiss.nli
Printing:	Ridderprint | www.ridderprint.nl

The author has not received any specific funding for the studies presented in this PhD thesis, which was done as part of routine work while the author was employed (mainly by the European Centre for Disease Prevention and Control). The decision to submit for publication was taken by the author, who has full access to all the data in the studies and had final responsibility for the decision to submit for publication.

Burden of infectious diseases in Europe: methodological challenges and opportunities for public health policy

Infectieziektenlast in Europa: Methodologische uitdagingen en kansen voor het volksgezondheidsbeleid
(met een samenvatting in het Nederlands)

Impacte des maladies infectieuses en Europe : défis méthodologiques et opportunités de santé publique
(avec un résumé en français)

Impatto delle malattie infettive in Europa: sfide metodologiche e opportunità di sanità pubblica
(con un riassunto in italiano)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

vrijdag 29 september 2023 des ochtends te 10.15 uur

door

Alessandro Cassini

geboren op 24 april 1976
te Etterbeek, België

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Nothing has such power to broaden the mind as the ability to investigate systematically and truly all that comes under thy observation in life.

Marcus Aurelius (121–180 AD) – Meditations, Chapter II.
In *Hoyt's New cyclopedia of practical quotations (1922)*

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CHAPTER 1

Introduction

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Among their tasks, epidemiologists collect and analyse data on diseases and health in order to provide the best available evidence to health decision-makers for setting public health priorities. However, there are numerous methods for summarising and communicating health information. Moreover, health data are often limited and of poor quality. Without comprehensive, representative and comparable data on the impact of diseases, decisions lack an evidence-based platform and can be disproportionally influenced by other factors such as political pressure, advocacy and public perception.

The term burden of disease generally describes the impact of a health problem. This can be measured by epidemiological and/or economic data and indicators. The burden of disease is also defined as the cumulative consequences of diseases and/or disabilities stemming from health problems, compared to an ideal health status.

1.1 Integrating epidemiological data: Summary measures of population health

The impact of diseases has traditionally relied on epidemiological measures such as incidence, prevalence and mortality. These are the most common measured and reported health metrics. However, these measures should be combined to provide a complete picture of the burden. Furthermore, they tend to shift the focus to the immediate impact of a disease and might favour short-term health policy decisions. Additionally, diseases might have different age- or sex-specific fatality patterns, or tend to generate lasting disabilities that impact significantly the well-being and productivity of people. The ensuing impact of short- and long-term disabilities, and of the years lost due to premature mortality is not measured by the traditional epidemiological metrics cited above. Moreover, the implications of preventive or mitigating interventions, as well as of the economic impact and opportunities, are less obvious. Summary measures of population health (SMPH) or composite health measures (CHM) enable summarising all epidemiological features of a disease into a single metric and compare the burden of very different diseases, across time, geographical areas and populations, as well as the preventive, therapeutic and economic impact of interventions. The resulting estimates are extremely valuable in providing a more precise picture of the disease burden and evidence for a more informed allocation of resources.

Two prominent SMPH are disability-adjusted life years (DALY) and quality-adjusted life years (QALY). Both measures reference an ideal health goal, DALYs measuring the gap due to disabilities and premature death and QALYs the quality of life gained by investing in better health. Therefore, the latter is more frequently used by health economists, particularly in high-income countries. However, DALYs have emerged as the most common metric used by epidemiologists and policy experts, especially those working on infectious diseases.

DALYs represent the sum of the number of life years lost due to premature death (YLL) and the number of life years lost due to disability (YLD). Hence, one DALY represents one year of healthy life lost because of illness, disability or early death. A simplified formula for DALYs can be (1):

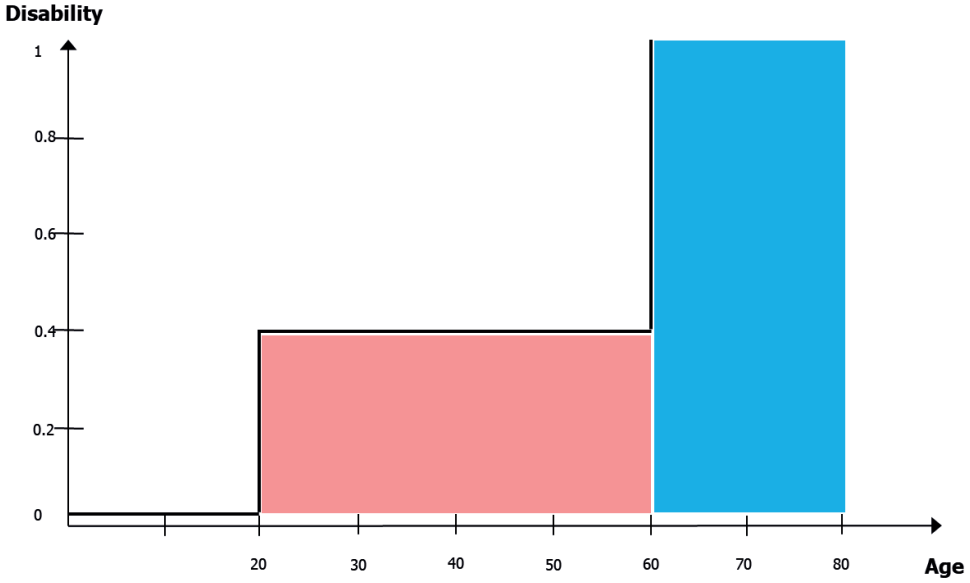
DALY = YLL + YLD

with

$YLL = \sum_{a=1}^{n} D_a * E_a$ and $YLD = \sum_{a=1}^{n} I_a * L * DW$.

Here D_a denotes numbers of deaths at age *a*, E_a the remaining life expectancy at age *a*, I_a the incidence of infection at age *a*, *L* the duration of disability, and *DW* the disability weight. Figure 1 provides a visualisation of the DALYs experienced by a fictional person who experienced a disabling disease at 20 years old lasting 40 years and a premature death at 60 years old considering 80 years old as the life expectancy, this person has lost 16 YLDs and 20 YLLs for a total of 36 DALYs.

Figure 1: DALYs experienced by fictional person who experienced a disabling disease at 20 lasting 40 years and premature death at 60.



1.2 DALYs take their first steps

DALYS made their breakthrough when introduced in the World Development Report in 1993 (2), commissioned by the World Bank and carried out by Chris Murray at Harvard University and Alan Lopez at the World Health Organization (WHO), in collaboration with a large global network of scientists. The methodology was further explained the following year (3) and results deepened in a comprehensive book in 1996 (4). In subsequent years, the methodology evolved, the 1990 and 2010 Global Burden of Disease (GBD) estimates were reviewed, and those for risk factors were refined (5-15). Since its inception, DALYs have been argued to be useful for health economic and cost-effectiveness studies (16, 17), and several modelling studies have been published since (18, 19). Throughout those years, the DALY methodology and its development were mainly driven by Professor Chris Murray and his

colleagues while at the World Health Organization (WHO), Harvard School of Public Health and, from its inception in 2007, at the Institute of Health Metrics (IHME), which is part of the University of Washington and funded by the Bill and Melissa Gates Foundation (BMGF).

Since their first publication, GBD estimates surprise policy makers who are traditionally used to common health measures such as mortality. The main focus of global health arenas on infectious diseases was immediately challenged by GBD findings, whereas mental health and road traffic accidents were placed as significant leading causes of disease burden.

1.3 The continuous evolution of global health estimates

Led by the WHO with collaboration from Murray and colleagues, global DALY estimates were also produced for other years between 1990 and 2010, either as stand-alone institutional reports (20) or as part, for example, of the 1999 WHO World Health Report (21) repeated until 2004. Other research groups have estimated DALYs across diseases in national studies (22, 23) or for specific diseases (24) across different countries (25), while estimating and applying population-specific disability weights (26). The reinforcement of the robustness of the estimations through their scientific improvement and institutional collaboration led to a platform for cost-effectiveness studies and analysis for setting priorities. The Disease Control Priorities Project (DCPP) was a scientific partnership between the WHO, the World Bank and the National Institutes of Health that provided an overview of priorities for health interventions in low income settings (27) and a renewed estimation of the GBD (28).

Paucity of data in many countries, particularly in low resourced settings, was highlighted since the very beginning as being a strong limitation to the acceptance and use of GBD data throughout countries. However, starting with the United National General Assembly adoption of the Millennium Development Goals (MDGs) in 2000 (29), a number of health targets were developed for countries to aspire to. This increased monitoring and surveillance of health data and international collaboration among UN agencies such as the Interagency Group on Child Mortality Estimation (UN-IGME) in 2004. Moreover, reporting on MDG progress entailed that the GBD focus shift on country-specific estimates, starting from GBD 2004. Consultations with countries intensified, funding reinforced national health information systems and collaborative initiatives were established, such as the Health Metrics Network which lasted until 2013 (30). Since 2013, the WHO regularly produced its Global Health Estimates (GHE) of DALYs by cause, age and sex, although the focus shifted towards monitoring of progress of MDGs and other country targets (31).

Estimations of the GBD within a collaborative framework with the WHO and the UN family faded little after the establishment of the IHME in 2007. GBD 2010 was sparked by the collaboration between IHME, several prominent academic institutions (Harvard University, Johns Hopkins University, University of Queensland), several scientific working groups and the WHO. However, experts from the WHO were concerned that access to methods and primary data were limited, and could not reconcile the differences with WHO statistics and

estimations (32). Ultimately, the WHO Director General praised the scientific contribution to global health estimates represented by GBD 2010 (33), but WHO as an institution did not endorse its findings and WHO experts decided to withdraw their authorship before the study was published in 2010 (32). Communication and scientific exchange continued between WHO and IHME (34), which in many cases led to improvements of estimations and tools for transparency such as the GATHER checklist (35). Another aim was consistency and harmonisation with other estimates and databases such as UNAIDS on HIV and the WHO Mortality Database.

In terms of GBD methods, a significant leap occurred in 2012 when the GBD 2010 study was published in the Lancet (14). The previous estimations for DALYs, deaths and prevalence increased from 107 diseases and ten risk factors in eight regions, to 291 diseases and injuries in 21 regions, included epidemiological trends from 1990 to 2010, and was topped by the assessment of 67 risk factors. During the course of this modelling effort, the IHME and collaborators built, and continue to expand, one of the largest databases on health data in the world. The database on cause of death, for example, includes millions of entries since 1950 occupying many terabytes and stemming from all known sources. Specific software, such as DisMod-MR, and innovative modelling approaches, such integrating correlation coefficients with machine learning (stacked generalisation), were developed, adapted and improved. These approaches aim at identifying, assessing and modelling the quality of the available data, particularly where its paucity undermines any meaningful estimation. Particularly for some diseases or low income settings, small surveys were the only source of reliable health data, which needed to be expanded and become proxies for other similar settings (36).

Clearly, GBD 2010 further underlined the urgent need to strengthen health surveillance such as vital registration systems in low income settings. Ultimately, GBD 2010 increased our knowledge on the availability and reliability of health data, triggering calls for increasing countries' capacity to collect harmonised, relevant and good quality health information (33).

Another important innovation triggered and nurtured by the GBD initiative has been international scientific collaboration. The GBD 2010 had 488 co-authors from 303 institutions in 50 countries (14); these numbers have continuously increased ever since in the major publications of the GBD. The growing cooperation is the result of the multi-disciplinary nature of undergoing burden of disease studies that encompass such a large number of diseases, risk factors, geographical areas and settings, as well as new modelling and statistical approaches. It also reflects the need to understand local data, how it is generated and what factors shape it.

1.4 Are DALYs challenging models or modelling challenges?

Throughout the years, the continuous evolution and adaptation of the DALY methodology has made comparisons across time and research groups difficult. This is good news as it reflects a healthy debate in the scientific community on the quality of the data on which

estimations are based, as well as the modelling methodologies for SMPH. However, this means that institutions, such as the IHME for example, systematically re-estimate past burden of disease studies according to the latest methodological decisions and superseding previous estimations for the sake of comparing time trends.

1.4.1 Mortality and estimation of YLLs

The computation of YLLs is based on mortality data. The estimation of the mortality for the WHO burden of disease estimates are based on WHO estimates of deaths by region, cause, age and sex being released in the Global Health Estimates (GHE) update (37). The WHO categorises the cause of death according to the International Statistical Classification of Diseases and Related Health Problems (ICD), version 10 for the latest 2019 estimates (37). The WHO estimates of deaths for their burden of disease estimates starts from the assessment of the availability and quality of death registration data and stored in the WHO Mortality Database. Rigorous and transparent quality inclusion criteria (defining if data are "usable") are applied to the database to identify countries with high-quality vital registration data on cause of death (short and detailed cause list). However, the countries with higher quality death registration data are a minority and the WHO must resort on using updated IHME single-cause analyses from the GBD studies.

The IHME approach to estimation of number and cause of deaths combines a number of different statistical and modelling strategies. Data sources span from official death registration databases to published surveys; the resulting information is subject to covariate regression modelling and countries with similar patterns in various health information are drawn together to exchange information by proxy (38).

Given that WHO and IHME estimate YLLs independently from YLDs, most methodologies to estimate the number and cause of death rely on existing surveillance data, with modelling to account for missing or so-called "garbage" codes. However, the availability is limited and quality varies extensively based on geography, disease, access to care, sex and age.

1.4.2 Prevalence versus incidence, estimation of YLD and of sequelae

In the computation of DALYs, modellers have the option to choose an incidence or prevalence approach to the estimation of YLDs, i.e. estimating the annual new number of cases or the number of cases in a specific time point, or a combination of both. Their choice typically will also trickle down to the estimation of mortality and, hence, of YLLs. Until GBD 2010, DALY estimates were computed using an annual incidence-based approach, where YLDs reflected the new number of cases of the disease under study for a given year, including the sequelae occurring that year. It was argued that: the approach was missing the burden of sequelae due to the onset of diseases occurring in previous years; that the data source generally being prevalence health data, there was an added uncertainty due to deriving incidence from prevalence; that the incidence-based approach improperly assigns the loss of health from

sequelae to younger age groups; and that adjusting for comorbidities is more complex with incidence-based DALYs. Consequently, GBD and WHO DALY estimates have been based on prevalence data since 2010 (39, 40).

Conversely, other studies contended that for some diseases, such as infectious diseases, failing to account for all chronic and long-term sequelae resulted in a vast underreporting of their burden and underestimation of the impact of interventions to prevent the infection at the start (41). Moreover, a prevalence approach would fail to recognise the role played by asymptomatic infections in developing future disabling conditions, a very relevant situation for some important diseases such as hepatitis B and C which might develop liver cancer and cirrhosis after many years from the initial infection. Murray et al. also sustained that incidence-based DALYs produced estimates that were more relevant for public health decision-making and that YLDs had a more coherent time frame with YLLs (4).

Regardless of the incidence versus prevalence approach, computation of YLDs require an assessment of the most reliable data sources. Descriptive epidemiological data and data reported to surveillance systems is limited by missing data, inconsistencies and methodological variations.

The GBD approach has consistently applied Bayesian meta-regression tools, which take into account a large number of data sources and re-distribute causes of disease, allowing for weighting of data source according to its quality, and culminating in the development of various improvements of DisMod software applications (42). This approach also includes back calculating from mortality rates and cross-validation between causes and their sequelae.

Another approach to computing YLDs is based on the assessment of official surveillance systems. Reporting of health data is fraught with a number of potential gaps, throughout the surveillance pyramid (43). The loss to reporting of people with a disease (symptomatic or not) who do not seek or access care, can be defined as under-ascertainment. The loss of information stemming from those who are incorrectly diagnosed or not reported to the surveillance system can be defined as under-reporting. Adding under-ascertainment and under-reporting constitutes the under-estimation of a disease to the surveillance system (43).

Disease sequelae have been either estimated based on the assessment of different health data sources or by representing diseases through disease progression models. Regardless of the methodology, a number of biases need to be considered, ranging from different case definitions, diagnostic technology or sampling strategies (13). One very relevant bias is selection bias, which is intrinsic to, for example, data stemming from hospital discharge reports where access to care can vary widely. Similarly to the approach for the estimation of excess mortality, prevalence and incidence, a meta-regression tool was specifically developed for the GBD, DisMod-MR (42).

On the other hand, outcome trees attempt to model the progression of a disease starting from the initial trigger condition (e.g., an infection) followed by short and long-term sequelae or complications, and ending into either death, recovery or life-long outcomes. According to Kretzschmar et al. (41) "an outcome tree gives a qualitative representation of the progression of disease in time by ordering all relevant health outcomes following infection and illustrating their conditional dependency."

1.4.3 Comorbidity

The disability(ies) experienced by a population has been related to specific outcomes due to diseases or conditions included in GBD studies. The expert group on Critical Ethical Choices convened for GBD 2010 shifted this paradigm and advised that disabilities are to be assessed at the individual level (39). This entails that, regardless of the cause, like disabilities are to be treated alike. Therefore, if a disability is exacerbated by a concomitant condition, disability weights should reflect this status. This approach also prevents multiple counting of the burden for the individuals with comorbidities.

The common approach has been to assume independence of conditions, i.e. two comorbid conditions result from the product of the single probabilities of developing each condition. This was criticised for overestimating the number of DALYs and alternatives were proposed to compute dependent comorbidity adjustments (44). However, the solutions proposed and applied still rely on population-level computation of DALYs and re-distribution at a second stage according to the prevalence of comorbid conditions. Researchers have proposed an individual-based modelling approach to adjust incidence-based burden for multimorbidity that allows for individual-level and time-adjusted computation of DALYs (45). This method relies on a multiplicative approach to computing disability weights for each individual experiencing a given condition, for a given amount of time. The multiplicative approach is argued to best reflect the quantitative assessment of the condition experienced as it results in a composite disability weight that is more adherent to the real disability experienced by the individual (measured by associating the predicted and observed morbid disability weight), is lower than the additive approach, but higher than the maximum limit approach (46).

Apart from the estimation of the prevalence, incidence and mortality of diseases, revisions of DALYs have triggered a number of revisions of four components that require value choices. Life expectancy tables and disability weights are essential for calculating DALYs. On the other hand, time discounting and age weighting are optional. These value choices have been extensively debated, to the extent that a panel of philosophers, ethicists and economists were convened for providing insight in the GBD 2010 methodological approach (39).

1.4.4 Life expectancy standard tables

DALYs are typically estimated per sex and age group, generally 19 or 20 groups starting from neonates (which can be split in early, late and post-neonates) and increasing every five years

until over 80 or 85 years old. A standard life expectancy (LE) is necessary at each age or age group. The LE can be adapted from observed statistics of a given population, can be applied based on the global highest life expectancies or can be based on a gold standard highest achievable LE. The first option, i.e. standard tables based on observed life expectancy in the population under study, has been argued to best reflect the impact of diseases on that specific population and avoid over-pessimistic findings (47). On the other hand, LE tables based on observed data would not capture the dynamic nature of life expectancy, which has been increasing particularly in low and middle income countries. Moreover, standard LE tables based on the highest observed life expectancy at the time of the modelled data as was done in several GBD studies before GBD 2010 would entail differences between males and females.

With the publication of GBD 2010, a new standard reference life table is introduced, based on the global lowest observed death rate for any age group in large countries. The underlying assumption is that the new table should reflect a gold standard aspiration of all individuals for a healthy lifespan. Hence, even elderly populations have a few years of life expectancy and, for example, people aged 105 years old have 1.63 years life expectancy (39). Moreover, the same table was applied to males and females as it was considered that there was no reason for males not to aspire to full healthy lives, as well as no demonstrated biological reason why males should die at younger ages. The resulting estimations would better identify the causes of diseases and risk factors for the higher burden in males.

However, the WHO technical experts producing the global burden of disease estimates argue that even where death rates are low, a small proportion of deaths are preventable, and that, for example, Japanese females already exceeded the GBD 2010 reference life expectancy table in 2013 (40). Therefore, the WHO chose to derive the standard life expectancy table from the projected mortality rates for 2050 (48).

1.4.5 Disability weights

Disability weights are an essential component of YLDs and measure the severity of a health state between 0 and 1, with 0 reflecting full health and 1 equivalent to death. In principle, they allow comparisons between health states, including acute and sequelae, across time, across different populations and cultures, and with YLLs. Therefore, in principle, the same disability weights for a disease reflect the burden of that health state regardless of the setting where the person is experiencing that given health state. The possibility of agreeing on a universal weighting of disabilities continues to be a subject of discussion (49, 50). The GBD 2010 and 2013 attempted to narrow the estimation of disability weights to the health status (through, for example, pair-wise comparisons and surveys in large general populations), regardless of losses in welfare and impact of the environment such as access to care (8).

Since the first GBD estimations (51), disability weights have played an crucial role, have been thoroughly debated and their methodological approach assessed and amended (52, 53). Several methodological choices can incur in establishing disability weights, although they are

all based on the preferences of a given population through the assessment of values from a panel of judges. The latter can be global (51) or specific to a geographical area (54), as well as vary in nature, from a restricted group of health experts to general populations. Until GBD 2010 and subsequent revisions (39, 55-57), most disability weights were based on panels of medical experts (52). Other variations include using policy-makers, patients or people with disabilities and patient proxies (58). Since GBD 2010, authors have shifted towards large populations (almost 70,000 respondents for GBD 2013 disability weights (55)) in several geographical areas in order to best reflect values of respondents from different geographic, cultural or socioeconomic backgrounds (59).

The number of health states for which disability weights are calculated also varies largely, from 3 to 483 (53). How they are described to the panel of judges varies and generally has evolved due to the shift towards reflecting values of a general population. Hence, lay disease-specific health state descriptions have been prioritised over more complex tools such as European Quality of Life instruments. Moreover, most estimations now are based on administration of household or web-based surveys to large populations (53). Time is an essential part of the description of a health state. The duration of a health condition is valued as much as the condition itself. Health conditions are generally either described as annual profiles (the course of the health state is described over a 1-year period) or as period profiles (assumes that the duration of the health state remains constant over time). Annual profiles are extremely difficult to consider by lay judges and are not appropriate for evaluating short, acute conditions such as infectious diseases (e.g. influenza) and chronic conditions with acute manifestations (e.g. epileptic seizure, asthma or acute myocardial infarction). Hence, it is not surprising that most published studies assessed period profiles instead (53).

Other methodological choices in developing disability weights focus on the statistical approach to capture and summarise preferences and values of the panel of judges. These are called valuation methods and include rating scales (e.g. visual analogue scaling or VAS) and trade-off methods (asking judges to make trade-offs in time, quality of life or risk of death against improving health: methods based on choice-based valuations): e.g. standard gamble (SG), time trade-off (TTO), willingness-to-pay (WTP), paired comparison (PC), population health equivalence (PHE), preference ranking (PR) and person trade-off or PTO) (53, 60). Studies find that absolute values for disability weights differ according to the valuation method (61), but ranking is generally unaffected (62). All valuation methods have inherent biases and limitations, and combinations of multiple valuation methods are preferred. This is reflected in the disability weight studies after 2012 where in most cases PC was used in combination with VAS techniques. PHE was sometimes also combined with the former, although often deemed too complex to be used in the general population (53).

1.4.6 Time discounting and age weighting

Time discounting is the principle for which the effects of a disability occurring at the observation time (time 0) lose value as time passes. Time discounting is a common option in economic modelling as it is assumed that the marginal utility of a currency declines with time and that there is the expectation that one will reach higher incomes in the future. The debate underpinning for or against time discounting in health assessment exercises are fundamentally two-fold: investments in health should not happen at the expense of current generations or health should not be considered to lose value in time. Arguments for applying time discounting are often based on paradoxes (16); in the example referenced here, Murray and Acharya argue that by not discounting time when assessing investments for interventions, such as eradication of a disease for example, would entail dedicating all currently available resources at the expense of those in need at time 0. On the other hand, ethical considerations dictate that a year of disability should weigh alike regardless of when it is experienced (63).

Until GBD 2010, DALYs were discounted for time with a 3% annual discount rate for future health, with optional results without discounting. However, the GBD ethics review board, which underpinned most value choices for GBD 2010, and the main authors concluded that there was no reason future health should be less important than current health (39). The authors added that time discounting anyway represents an artificial and unappealing solution: instead, other factors, such as equity and fairness, were the appropriate drivers of social choices to consider when interpreting the results of their burden of disease studies (63).

Age weighting entails introducing a different weight to each age (group) reflecting different, for example, values or productivity at different ages. To a certain extent, this debate resembles the one on inclusion of time discounting. In cost-effectiveness studies particularly, age weighting is inserted to reflect stages of life in which productivity is reduced or not measurable, or because individuals do not have developed life plans (64), hence, giving less weight to disabilities experienced in young and older ages. Furthermore, some authors argued that improving the health status of specific age groups could be beneficial to other age groups and more effectively to the rest of society as a whole (65).

There are ethical grounds for considering the value of life and health the same regardless of age. Moreover, once again such a construct seems artificial and unappealing, and should rather be discussed when considering DALYs in face of social priorities, choices and articulating some type of welfare interdependency (63).

Time discounting and age weighting were dropped in both the GBD studies after GBD 2010 and in the WHO DALY time series from 2012 onwards (39, 40), resulting in a substantial increase in the total number of DALYs computed from both institutions (40).

The debate around applying or not age weighting also includes arguments to count foetal loss (64). Many questions arise when exploring the possibility of counting foetal deaths: should it be counted separately or as part of disabilities for the mother (or even for the parents), from which gestation week should it be counted. Moreover, attribution to cause of death is also particularly challenging. GBD and other studies estimating DALYs have sometimes included the burden of foetal loss, particularly for some specific causes of death or stages (e.g. stillbirths) (66).

1.4.7 Uncertainty

As claimed by George EP Box, "All models are wrong, but some are useful" (67). Calculation of DALYs requires to quantify the uncertainty at each stage of the process. Each modelling step and component described above requires the propagation of uncertainty, and the final uncertainty values around a DALY estimation should reflect and summarise the uncertainties intrinsic to each step. This requires the introduction of methods to summarise added uncertainties. Given the number of diseases, the task is computationally intensive. Methodologies to propagate uncertainty are generally based on micro-simulation processes, such as Monte Carlo simulations, drawn at least 1,000 times and expressed as 95% uncertainty intervals.

Estimation of uncertainty at all levels of the data inputted in the models provide information on data gaps. This information is crucial evidence for epidemiologists and health policy-makers to call for better data availability and quality (68).

1.5 Estimating DALYs for infectious diseases

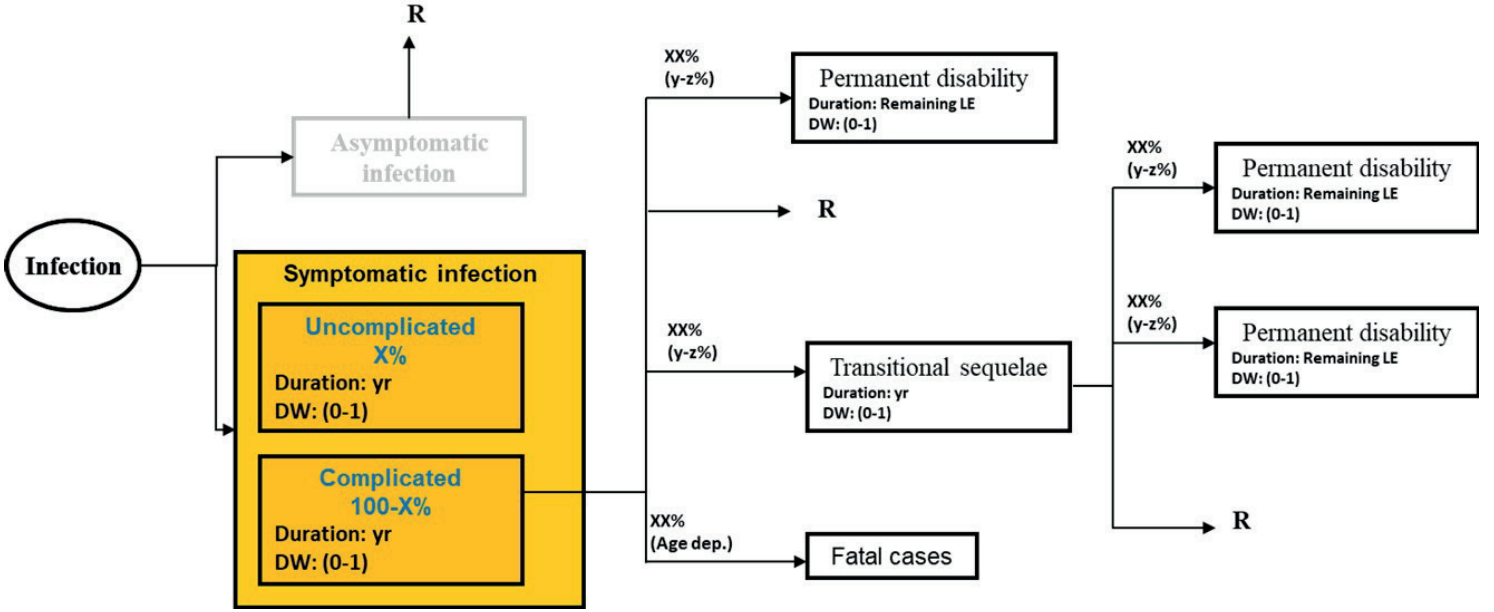
Estimation of the burden of disease and calculation of DALYs for infectious diseases is particularly relevant when assessing the impact of infectious diseases. Compared to incidence or mortality alone, DALYs provide a more precise picture of the disease burden and evidence for a more informed allocation of resources. Their burden has decreased in the past century, since antimicrobials have been discovered, vaccines have been routinely administered, and hygiene improved dramatically. However, there is increasing evidence on the infectious disease aetiology of many non-communicable diseases (NCDs) (69, 70), such as hepatitis B virus (HBV) leading to carcinoma of the liver. Evidence is also increasing on the long-term sequelae of infectious diseases such as Guillaume-Barre syndrome following campylobacteriosis (71) or neurological disorders following bloodstream infections (72). Moreover, the number and impact of emerging and re-merging infectious threats, from SARS-CoV-1, MERS-CoV and more recently SARS-CoV-2, have highlighted the need to generate evidence and measure the impact of infectious diseases (IDs). Finally, the increasing technological pressure of highly specialised and invasive tertiary healthcare has increased the risk of transmission to patients of opportunistic pathogens, in particular healthcare-associated infections (HAIs) and those with microorganisms resistant to antimicrobials (AMR).

The estimation of the prevalence or incidence of IDs include a number of challenges. Many IDs involve an asymptomatic phase that will then develop into diseases with disabilities or evolve into a chronic phase. Notable examples are infections with hepatitis B and C viruses which may progress into cirrhosis or liver cancer, or infection with human immunodeficiency virus (HIV) which requires a life-long treatment with antiretroviral therapy associated with adverse effects. Therefore, attribution to a pathogenic cause and the modelling of time are crucial components that need thorough consideration. Kretzschmar et al. have described this through time-age planes of Lexis diagrams (41). Another advantage of this approach is the inclusion of temporal fluctuations in the incidence of IDs, although this might require the inclusion of several incidence years (e.g. incidence of measles follows fluctuations that go beyond annual seasonality).

The application of the time-age planes to estimation of DALYs requires an incidence- and pathogen-based approach to describing and modelling of diseases (41). An outcome tree (see Figure 2) is the most comprehensive way to reflect the progression of diseases as it links all health outcomes to the incidence of a specific pathogen and describes its conditional dependency. The pathogen and incidence-based approach (41, 73) constitute the starting point for the methodological approach to the Burden of Communicable Diseases in Europe project.

Since its inception in 2005, the European Centre for Disease Prevention and Control (ECDC) has been tasked with the surveillance of 46 diseases (now more than 50) under mandatory notification in the European Union (EU) and European Economic Area (EEA). The first Director of ECDC was already concerned with the development of a coherent and composite approach to describing the burden of IDs (74). The purpose was to identify an approach and related evidence for allocation of funds and support to disease areas and interventions to control and prevent IDs. The ECDC tasked the Dutch National Institute for Public Health and the Environment (RIVM) to pilot a study on the burden of a few selected IDs (75). The pilot study identified a number of issues related to the availability and quality of epidemiological data, as well as methodological challenges related to adapting the calculation of composite health measures for IDs. Addressing these challenges in a comprehensive and coherent approach, producing DALYs for IDs in the EU/EEA and translating these into options for health policy decision-making was the incipit for the Burden of Communicable Diseases in Europe (BCoDE) project.

Figure 2: generic outcome tree for infectious diseases



The figure shows possible outcomes (boxes) with duration and disability weights, and transition probabilities (arrows). A few alternatives are possible, such as long-term disabilities related to asymptomatic infections (e.g., HBV, although these can also be categorised as chronic HBV infections).

The main objectives of the BCoDE project were to promote evidence-based methods in epidemiology, to facilitate planning and prioritization related to public health decision making, to identify gaps in surveillance data availability and quality (mainly of The European Surveillance System, TESSy), and to provide a comprehensive framework for communicating complex information to decision-makers.

Several landmark publications ensued: an improved methodology for estimating DALYs for IDs in 2012 (41), followed by the consolidation in 2013 of the incidence- and pathogen-based approach (73), in 2014 the proposal for innovative definitions and approaches to the under-estimation of reported epidemiological data under surveillance (43), the development of new disability weights that take into account the values of the European population and involve improved health state descriptions (52, 57), which ultimately served the global estimates (55), a proof of concept of the methodology based on the burden of measles in relation to national vaccination coverages (76), the application to national burden of ID studies (23, 24), and exploring the use of DALYs for economic analysis (17).

However, when attempting to calculate DALYs for all diseases and syndromes under surveillance at ECDC, researchers were faced with a heterogenous set of contested questions for each specific disease, ranging from modelling choices, sources of health information, what evidence to include, and data availability and quality. The objectives of the research presented in this thesis were to develop a standardised and accessible approach for estimating DALYs for IDs (**Chapter 2**), to apply the methodology and estimate the burden of diverse IDs such as influenza, HIV, HAIs and AMR (**Chapters 3**, **4** and **5**), and to provide ways to translate and communicate the results for decision-making in public health (**Chapter 6**, **7** and **8**).

This research thesis presents the evidence included for building outcome trees, based on literature reviews of the scientific literature, how this was summarised and the methods to solve data gaps. The thesis will also present the general computational framework that underpin the modelling and statistical properties to estimate DALYs. Furthermore, we will discuss challenges related to the limited availability and quality of routine surveillance data, and suggest tailored solutions for each ID based on general principles to estimate the incidence of IDs. The results presented in **Chapters 3** to **8** will be put into perspective in relation to other published epidemiological data, and to communication and messages necessary for their translation into health policy opportunities and decision-making.

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PART I

Estimation of the burden of infectious diseases in disability-adjusted life years

CHAPTER 2

Providing tools for estimating burden of infectious diseases: A Software Tool for Estimation of Burden of Infectious Diseases in Europe Using Incidence-Based Disability Adjusted Life Years.

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Published 20 January 2017. *PLoS One. 2017 Jan 20;12(1):e0170662. doi:10.1371/journal.pone.0170662*

Abstract

The burden of disease framework facilitates the assessment of the health impact of diseases through the use of summary measures of population health such as Disability-Adjusted Life Years (DALYs). However, calculating, interpreting and communicating the results of studies using this methodology poses a challenge. The aim of the Burden of Communicable Disease in Europe (BCoDE) project is to summarize the impact of communicable disease in the European Union and European Economic Area Member States (EU/EEA MS). To meet this goal, a user-friendly software tool (BCoDE toolkit), was developed. This stand-alone application, written in C++, is open-access and freely available for download from the website of the European Centre for Disease Prevention and Control (ECDC). With the BCoDE toolkit, one can calculate DALYs by simply entering the age group- and sex- specific number of cases for one or more of selected sets of 32 communicable diseases (CDs) and 6 healthcare associated infections (HAIs). Disease progression models (i.e., outcome trees) for these communicable diseases were created following a thorough literature review of their disease progression pathway. The BCoDE toolkit runs Monte Carlo simulations of the input parameters and provides disease-specific results, including 95% uncertainty intervals, and permits comparisons between the different disease models entered. Results can be displayed as mean and median overall DALYs, DALYs per 100,000 population, and DALYs related to mortality vs. disability. Visualization options summarize complex epidemiological data, with the goal of improving communication and knowledge transfer for decision-making.

Introduction

Summary measures of population health (SMPH) are composite indicators that facilitate comprehensive and comparable quantitative assessments of health-related phenomena. Several measures have been developed for this purpose based on different assumptions, models and parameters [1–4]. One of the most common and prominent SMPH is the disability-adjusted life years (DALY), which has been largely used for global comparisons of the overall impact of diseases, injuries and risk factors [5, 6]. DALY is a composite metric quantifying the health losses measured in years by adding the number of years of life lost due to disability (YLD) and the number of years of life lost due to premature death (YLL).

A principal goal of the Burden of Communicable Disease in Europe (BCoDE) project is to provide the European Union and European Economic Area Member States (EU/EEA MS) with a tool to estimate the impact of communicable diseases on population health expressed in DALYs. The main objectives are to promote evidence-based methods in epidemiology, to facilitate planning and prioritization related to public health decision making, to identify gaps in surveillance data availability and quality, and to provide a comprehensive framework for communicating complex information to decision-makers.

The use and interpretation of DALY estimates is often challenging due to the complexity of a composite health indicator and due to the underlying assumptions made. Also, calculation of the DALYs can be quite computationally intensive and time consuming since DALYs have typically been calculated using multiple and complex tools such as spreadsheets, macros, complemented with ad-hoc add-on software (such as @Risk). The BCoDE project addresses these issues by creating a flexible and user-friendly software (the BCoDE toolkit, available from http://ecdc.europa.eu/en/healthtopics/burden_of_communicable_diseases/Pages/Tool.aspx#sthash.9GmX1e3Q.dpuf) able to estimate DALYs for several communicable diseases, and to provide clear and understandable results for public health professionals and policy makers [7].

In this paper we describe the technical and computational characteristics of the BCoDE toolkit and how this represents an important step forward by providing a consistent computational framework across diseases and populations.

Design and Implementation

The BCoDE toolkit is a stand-alone Microsoft Windows1 32-bit desktop application written in C++ using Qt C++ framework version 4.8.7. The main factors taken into consideration when designing the tool were: simple deployment, performance and customization capabilities. For this purpose, a client-side architecture has been chosen. The dual objectives of execution speed with a small memory footprint led to choice of a compiled language (C++) rather than a scripting language (JavaScript, R, etc.) for the core of the toolkit. The BCoDE toolkit runs on both 32- and 64-bit editions of Windows XP and later (so XP, Vista, 7, 8, 10) and the minimal

requirements in terms of hardware are low: 1 GB of RAM, 1GHz CPU. No other operating system is currently supported (e.g., Android, OS X, Linux). The supported platform has been limited to Windows as the most widely spread operating system used by the potential clients in order to maximize the resources for features development and minimize maintenance burden. Additionally, sticking to the proven Win32 architecture maximally expanded the supported versions of Windows operating system (.Net, for instance, is a relatively new technology and requires an additional external software installed: .Net runtime). The toolkit is equipped with all the necessary external libraries included in the download package. The only dependency is the presence of Microsoft Excel OLE objects in the system which are usually installed together with the Excel application. This dependency is due to the fact that the majority of input data for the toolkit are stored in Microsoft Excel files format (Excel 97–2003 workbooks with extension ".xls") which are used for loading and saving files. The remaining external inputs to the toolkit are disease reports which are stored as HTML files and are rendered in the interface without any additional dependencies. The prerequisites for compilation of the toolkit are:

1. C++ compiler;
2. Qt 4.8.7 framework;
3. Boost C++ libraries;
4. Visual Leak Detector.

All other prerequisites are distributed with the toolkit, which itself does not require any administrative rights.

The application is a hybrid of a desktop C++ application and a web application. All core functionality and computationally intensive tasks, including generating Monte-Carlo samples and post-processing results, are managed by the calculation engine implemented in C++. This gives an overall efficiency and speed to the calculations. The implementation follows the object-oriented paradigm. However, the graphical user interface is implemented in a web browser component embedded in the application. This feature, on the other hand, gives substantial possibilities for customizability. This is particularly valuable in the implementation of a dynamic walkthrough, visualization of outcome trees with interactive elements and output results tables and charts with complex formatting.

The toolkit is essentially a web page connected by a thin software layer to the C++ calculation engine handling data exchange between both worlds. The interface utilizes JavaScript as the programming language to implement handling of user actions and display of results. For that reason the software makes use of open-access external C++ libraries such as Boost, Marray, muParser, as well as JavaScript libraries jQuery, SlickGrid, jsPlumb, Flot and Trip.js.

The BCoDE toolkit does not include any scripting capability in the sense that it does not provide an API for use by external programs. The current version indeed limits the interoperability possibilities as project resources were allocated rather to areas determining

the core functionality of the toolkit, and the scripting capability has not been seen as one. However, it should be stressed that the BCoDE toolkit implements a very generic calculation engine that is not restricted to any specific disease model. This single engine handles all implemented disease models. A specification of a disease model has been developed and each implemented model must be provided to the tool in accordance with this specification. This gives a possibility of extending the tool with new models in a relatively straightforward way and ongoing work is oriented on making this process even easier in the future versions. An additional advantage is the fact that only a single calculation engine must be tested and maintained, whereas multiple disease models are supported.

The license GNU General Public License v.3, under which the toolkit is released, was determined by ECDC. The various libraries and frameworks used internally vary in licensing, but have been on purpose selected to be quite permissive so that they can be used even in commercial, closed-source applications. This gives all range of possibilities for the licensing of the BCoDE toolkit, starting from more permissive (less restrictions) licence (e.g., MIT) to very restrictive (e.g., GPL). From the algorithmic point of view the toolkit executes calculations in the order defined by the outcome tree, starting from infection and traversing down the tree structure with the directions of transitions. Each entity in the outcome tree is able to retrieve inputs from the preceding entity, process this input data and expose outputs for the consecutive entity which will be picked up for further processing. Data exchanged between model components is organized into 2-dimensional matrix objects implemented using Marray library, a runtime-flexible multidimensional array. Similarly, all calculations are performed cell-wise at matrix level thanks to the implementation of arithmetic operators directly in the Marray library. This simplifies expressions as the usage of loops is limited.

Another aspect of the calculation engine is the need to deal with the optional stochastic nature of the disease models. Any input, or part of it, can be specified as a random variable or an expression including a random component. The toolkit gives an option to select the following probability distribution to draw samples from: Uniform, Pert, Beta, Gamma, LogNormal. Their sample generators are all based on the Boost random number generator with Mersenne Twister pseudorandom number generator as the generator of the underlying uniform sample. The standard implementation, MT19933, using 32-bit word length is utilized. In order to appropriately express uncertainty in the model outputs given the random nature of its inputs, Monte Carlo simulation methods are used. First, a representative sample of the inputs is generated from their respective probability distributions independently of each other. The sample size defaults to 1000, but can be overridden by the user. The algorithm repeats traversing the outcome tree in order to calculate outcomes for every value in the input sample. Sample size of the inputs also determines the number of repetitions. Eventually, the output sample is processed and various statistics, like mean value and 2.5, 50 and 97.5 percentiles, are computed and presented in the interface.

In order to provide a certain degree of freedom in setting the inputs, the toolkit includes a fast mathematical formula parser, muParser library. The user specifies mathematical expressions as an input value, rather than a constant or one of predefined values. The standard set of operators provided by the muParser library is very broad and was extended with a set of extra expressions for representing random number generators. The user, for instance, can specify the following expression as an input: "2 + sin(RandUniform(0, 1))". The toolkit will then generate a value that is a sinus of random value sampled from a uniform distribution on interval [0, 1] and increased by 2. We found the performance of this expression parser to be very good and rarely a single full model run time on a moderately performing computer system (Intel Core2 Duo class) exceeds one second.

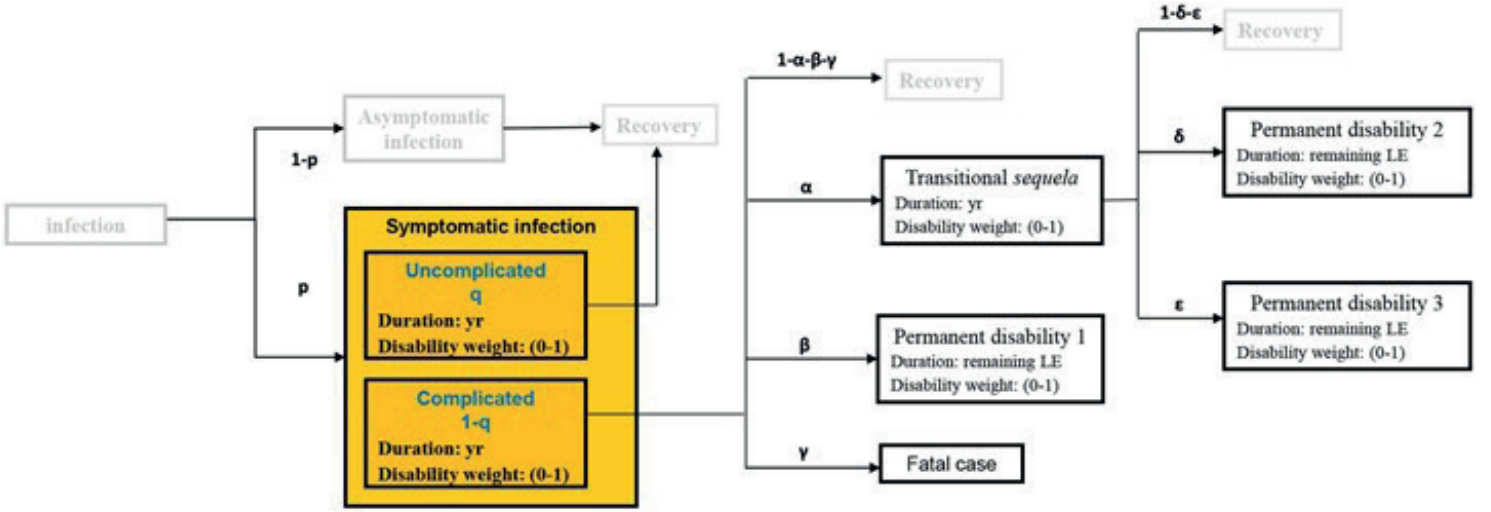
All calculations are executed with double-precision floating-point format used for variables.

Results

Disease models

Disease models (outcome trees) were created through a comprehensive literature review with the aim to describe the disease progression pathway of 32 selected communicable diseases and six healthcare-associated infections included in the project (Table 1, see S1 Document for details on the selection process) [7, 8]. Additional outcome trees were created whenever sex-specific or congenital/acquired forms of the disease lead to different health outcomes.
The outcome trees are shown in the BCoDE toolkit as graphical representations of disease progression. Detailed information on the modelling process are provided in S2 Document available from Mangen et al. [9]. In short, each box represents a distinct health outcome with a specific disability weight and a specific duration [10] (Fig 1).
Each arrow connecting various health outcomes is assigned a specific transition probability (probability for a case to move from one health outcome to the next, indicated by a Greek letter in Fig 1). The origin of each outcome tree is the infection (shown as a round box), and the entry point where the input data are entered, referring to the number of incident symptomatic cases and to the starting point of the modelling process, is shown in yellow. The end points in each outcome tree include death, recovery (R), and permanent disability. A health outcome can be further subdivided into health states according to different degrees of severity (see S2 Document). Each of these sub-boxes (health states) is assigned a specific disability weight, duration and proportion of cases that develop the health state out of the total number of cases that develop the overreaching health outcome.

Figure 1. A disease outcome tree linking infection and all sequelae.



"yr": years
"LE": life expectancy
"α", "β", "γ", "δ", "ε" = transitional probabilities
"p", "q" = proportions

Transition probabilities, durations of health outcomes, proportion of cases assigned to a certain health state within each health outcome (e.g., proportion of severe cases of acute symptomatic infection over the total number of acute symptomatic cases) were derived from literature reviews (a separate review of the literature was carried out for each of the 32 diseases and 6 healthcare-associated infections included in the tool) followed by rounds of disease experts' consultations in order to validate the proposed parameters' values.

Disease models have then been programmed in C++ and extensively tested by researchers with expertise in modelling disease progression. For application to specific diseases in different populations we conducted a pilot study covering four infectious diseases (salmonellosis, influenza, measles and hepatitis B) in four countries (Estonia, Germany, Italy, The Netherlands).

Results were compared per disease and per health state for all four countries [11]. After the pilot study led to satisfactory results for these countries, a national disease burden estimation was performed with a pilot version of the toolkit for all 32 infectious diseases [12].

Table 1. Diseases and healthcare-associated infections included in the BCoDE toolkit for DALYs calculation.

Diseases
Campylobacteriosis
Chlamydia
Congenital Toxoplasmosis
Cryptosporidiosis
Diphtheria
Giardiasis
Gonococcal infections
Hepatitis A
Hepatitis B
Hepatitis C
HIV/AIDS
Infection with STEC/VTEC
Influenza
Invasive Haemophilus influenza disease
Invasive meningococcal disease
Invasive pneumococcal infections
Legionnaires' disease
Listeriosis
Measles
Mumps
Pertussis
Poliomyelitis

Q fever
Rabies
Rubella
Salmonellosis
Shigellosis
Syphilis
Tetanus
Tick-borne encephalitis
Tuberculosis
Variant Creutzfeldt-Jakob disease
Healthcare-associated infections
Healthcare-associated Clostridium difficile infection (HA CDI)
Healthcare-associated pneumonia (HAP)
Healthcare-associated neonatal sepsis
Healthcare-associated primary bloodstream infection (HA primary BSI)
Healthcare-associated surgical site infection (HA SSI)
Healthcare-associated urinary tract infection (HA UTI)

Details of the outcome trees are shown in specific tabs within the BCoDE toolkit [7]. The outcome trees represented in the toolkit are interactive. Users can explore all parameters by clicking on boxes and arrows. Information on all disease model parameters and how default values were specifically obtained for each communicable disease is included in the disease reports which describe references and rationale behind all parameters chosen. The disease reports are available in text form for each disease as an integral part of the BCoDE toolkit (disease report tab, next to the outcome tree tab) and in the S3 Document. The disease models and default parameters implemented in the present version of the BCoDE toolkit represent the result of a thorough reviewing and validation process that was performed over a time period of around 5 years involving disease-specific experts from many countries and institutions.

However, since disease progression can be different in different populations (due to e.g. health care system, access to health care, social economic factors) and since default values within the toolkit outcome trees were chosen with the aim to reflect a European average, the software application enables the user to choose other than default parameter values and to include uncertainty in those parameters into the analysis. All disease model parameters can be thus edited by the user (see below).

The user become then responsible for the correctness of the assumptions made and of the validation. In fact, although we see this flexibility as a great advantage of this tool for carrying out tailored research, simulation exercises, scenario analyses and more accurate national and regional disease burden estimations taking into account geographical specificities and

other peculiarities of different populations, we also want to emphasize the importance for the user of always choosing parameters based on sound clinical and epidemiological evidence for the validity of the burden estimation.

The transition probabilities are of two types: lifetime transition probabilities (LTP) indicating a transition probability that applies once to all cases exiting the health outcome; and annual transition probabilities (ATP) which apply cyclically (i.e., annually) to all cases in the health outcome for the duration of the latter.

Results of BCoDE do not incorporate age-weighting, and are optionally shown with and without time discounting. The disability weights were obtained from European studies, involving more than 30,000 citizens, that applied elicitation methods (i.e. pairwise comparison) with the same methodology used by the Global Burden of Disease 2015 study but with disability weights tailored for the European population [13–15].

All parameter values can be specified according to 5-year age-group and/or sex if specific information is available. Moreover, each value can be entered as a constant or as an interval according to different distributions (Uniform, Pert, Beta, Gamma, LogNormal) by choosing the preferred option from a drop-down menu at the top of each input table.

BCoDE toolkit interface

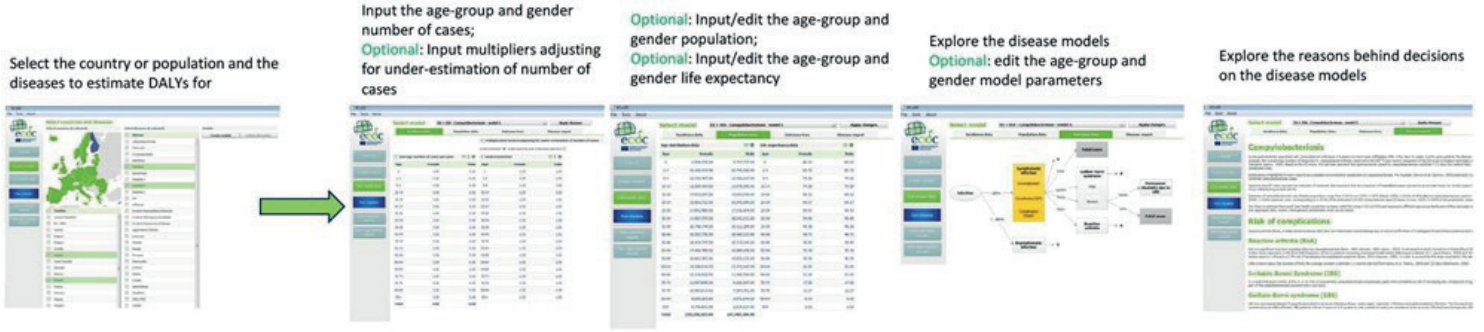
The user interface consists of various menu options on the left hand-side of the screen that link to different pages: “Tutorial”, “Create models”, “Edit model data”, “Run models”, “View detailed results” and “View aggregated results”. The tutorial guides the user through the BCoDE toolkit and is available in a static (pop-up window) and in a dynamic version with walk-through functionalities. The user selects the disease model(s) and the population from the “Create models” page. Multiple selections are possible for all the listed diseases and all the EU/EEA MS or custom populations. This permits estimation of the burden of the same disease across populations, or the burden of different diseases within the same population. Its application could be, for example, the estimation of the burden of several diseases within one EU/EEA MS as well as the ranking of the same disease across different population groups. Fig 2 shows more information on available input interfaces.

On the “Edit model” page, incidence data can be entered manually and all parameters can be viewed and edited. Data import from Microsoft Excel™ tables is also enabled. Four additional tabs are included on the page: “Case data”, “Population data”, “Outcome tree”, and “Disease report”. The most important input, the number of age-group and sex-specific annual symptomatic cases for each selected disease, is entered in the “Incidence data” tab. Data are entered as number of cases stratified by age-group and sex. Using this tab, adjustment for underestimation of the annual cases of symptomatic disease can be made, and a similar age- and sex-specific table can be populated with either a single or a combination of two multipliers, as described elsewhere [16]. Moreover, each value can be entered as a constant

or as parameters of an assumed [stochastic] distributional form by choosing the preferred option from a drop- down menu at the top of each input table. The user can move between disease models through a drop-down menu at the top of the screen. The “population data” tab shows the Eurostat 2014’s sex- and age-specific population distribution. This tab also shows the standard life expectancy table required for DALY calculation [17]. Both tables can be modified by the user. The “Outcome tree” tab presents the selected disease models. When the natural history is different between males and females (e.g., chlamydia infection) and/or between acquired and congenital syndromes (e.g., syphilis), more than one outcome tree is shown. The models are interactive and detailed information presented in the tables appears as pop-up windows when clicking on the transition probabilities or on the health outcomes. All default values can be edited and saved. The “Disease report” page shows detailed information on the selected disease model.

If edited, disease models can be saved and stored to be loaded again whenever necessary using the top-left hand corner menu under “File”. Age-weighting is not implemented in the toolkit and time discounting is optional and can be set by the user. Computation in the application consists of Monte Carlo simulations of disease progression models. Therefore, once all the necessary information is entered in the “Edit model data” page, the user will be able to choose the number of iterations (default number is 1,000), and if time discounting should be applied, the desired discount rate needs to be specified. This approach ensures that all uncertainty ranges included in the disease model parameters and incidence data are taken into account. Hence, results are provided with 95% uncertainty intervals (UI).

Figure 2. BCoDE toolkit: step-wise approach to disease model creation and data input.



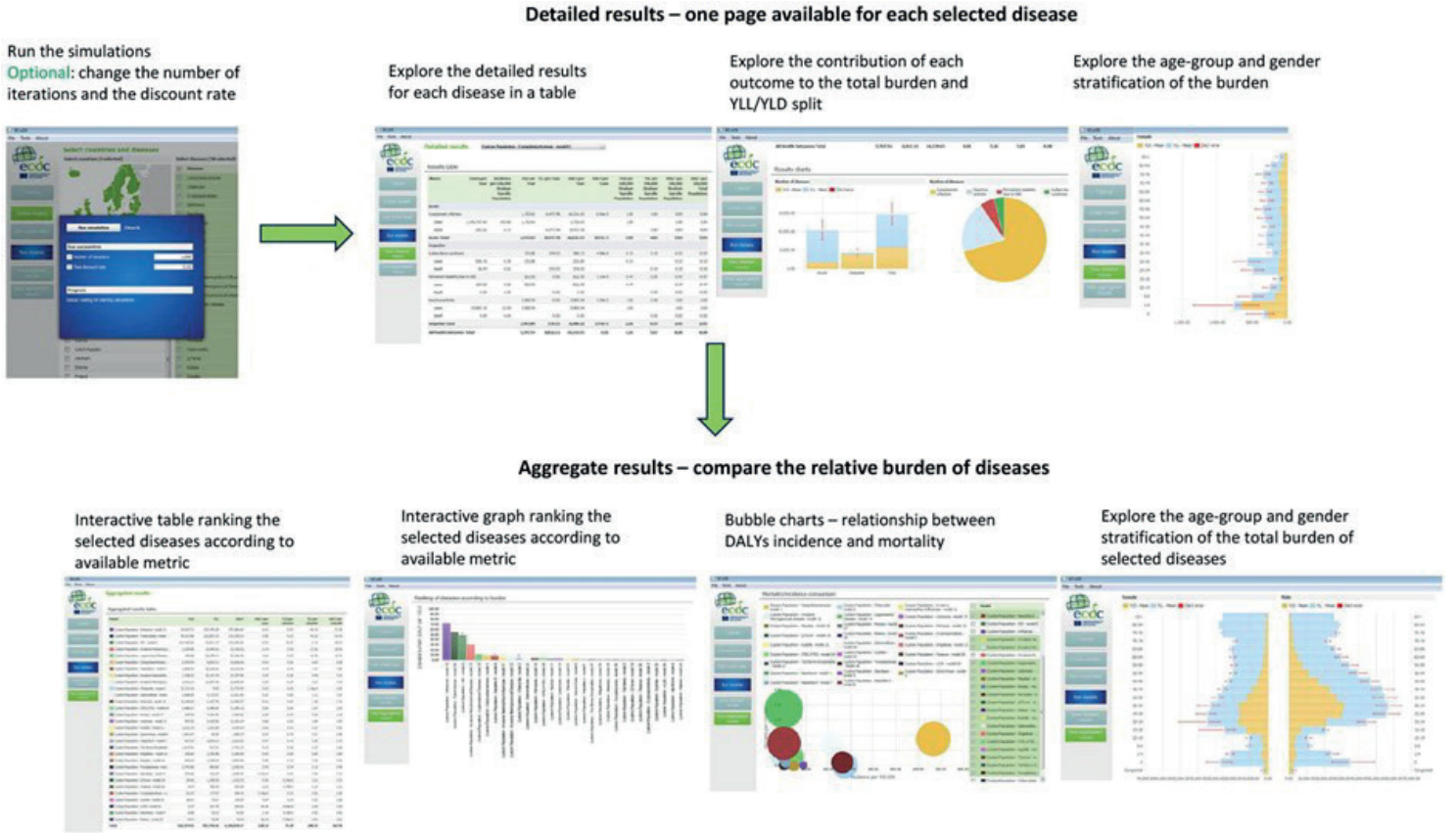
Outputs

In addition to a possibility of viewing the calculation outputs at outcome tree and disease model level, the user can explore results per individual sex/age category, outcome tree element (health state, transition), and type of sequela. The interface has been designed to give the user the option to view the output at various levels of aggregation, thus providing both a “birds-eye view” of the overall results, and a “zoomed-in” view of a specific health outcomes. It was a deliberate design choice of not exporting the actually generated sample as it is a vast data set even for a relatively simple disease model. A single unit of computation can be considered a 3D tensor (sex category x age category x sample size) occupying by default 39000 numeric cells (2 x 19 x 1000). Each health state requires three such tensors for storing its internal parameters (severity/duration/proportion) and two for outputs (number of cases, burden). Combining this with the model wide parameters (number of cases, underestimation, age distribution, life expectancy) and transition parameters would result in a substantial output dataset.

The BCoDE toolkit computes disease-specific results displayed as DALYs calculated for the selected set of disease models, and based on the incidence values entered by the user. Once the models are run, the results are presented as “Detailed results” separately for each disease model, and as “Aggregated results” comparing and ranking the various disease models according to their burden in DALYs (Fig 3).

The “Detailed results” page shows a summary table providing total and health outcome-specific results. This table shows the estimated number of cases and of deaths, incidence per 100,000 population, years of life lost due to disability (YLD), years of life lost due to premature death (YLL), DALYs, and DALYs per case as well as YLD per 100,000 population, YLL per 100,000 population, and DALYs per 100,000 population. DALYs per case represent the average burden of a disease experienced by each infected symptomatic case and it can be interpreted as a measure of average severity apart from those disease models where some of the burden comes also from asymptomatic infections (e.g., hepatitis B). The table is followed by a bar chart presenting results with the relative contribution of acute disease and sequelae, and a pie chart showing the contribution of the different health outcomes to the total burden. Finally, a series of interactive tables and bar charts complete the detailed description of the burden of each disease. Averages, medians and age- and sex-specific 2.5 and 97.5 percentiles are displayed for DALYs, DALY per case, DALY per 100,000 total population and DALY per 100,000 stratum specific population.

Figure 3. BCoDE toolkit: options for visualization of the outputs.



The final page “Aggregated results” compares the results of the selected disease models. An interactive table and a bar chart enables the user to rank the burden of disease by a selected metric from the ones listed above. Moreover, bubble charts are shown comparing different disease models, in which the size of each bubble corresponds to the magnitude of the burden of disease expressed in DALYs per 100,000 population. In the first graph the x-axis represents the estimated incidence per 100,000 of symptomatic disease, while the y-axis represents the estimated mortality per 100,000 population calculated through the disease model. The second graph differs only by showing DALYs per case on the y-axis. The “Aggregate results” page also shows interactive age-group and sex-stratified tables and bar charts similar to those described for the “Detailed results” page for the aggregate results of all diseases.

All results are printable and exportable in portable document format (PDF) and in Microsoft Excel™.

The BCoDE toolkit in practice

The BCoDE project employs an incidence- and pathogen-based DALY approach based on disease-specific models (outcome trees) [9,11,18]. For the estimation of healthcare-associated infections (HAIs), a syndromic approach was used based on different infection sites [19].

The BCoDE study summarized the 2009–2013 comparative impact of 31 infectious diseases [20,21] and the 2011/2012 impact of 6 HAIs [19] (Table 1) in DALYs across EU/EEA MS.

Within the BCoDE 2009–2013 study, the default starting point for the estimation of incidence, which is a necessary prerequisite of the underlying disease-specific models, was generally the cases notified to The European Surveillance System (TESSy) [22]. The assessment of how much notified cases underestimate the total number of symptomatic cases in the population was carried out through extensive literature review of previous studies addressing this specific issue, with a particular focus on studies carried out in EU/EEA MS [16].

The BCoDE toolkit has also been used for the assessment of an intervention comparing the burden of measles in EU/EEA Member States compared to the measles vaccination coverage [23].

Availability and future directions

The BCoDE toolkit is a user-friendly application to calculate DALYs for 32 communicable diseases and six HAIs. The interface and the layout are meant to facilitate utilization by public health professionals who are not necessarily familiar with the burden of disease methodology, and to enable more effective communication of ranking of infectious diseases in terms of disease burden within and across different populations. Moreover, this tool provides a standardized method for estimation of burden of infectious disease expressed

in DALYs in different settings. Since January 2016, it is available for download as a stand-alone software application, available from the ECDC's website: http://ecdc.europa.eu/en/healthtopics/burden_of_ communicable_diseases/Pages/Tool.aspx.

The BCoDE toolkit may be used by interested professionals from academia and EU/EEA national health institutes enabling the estimation of the burden of communicable diseases [24]. Until now (December 2016), the ECDC webpage hosting the link for downloading the BCoDE toolkit has had nearly 2,800 potential downloads. Furthermore, 44 public health experts from national public health institutes not limited to EU/EEA countries, as well as from academia, hospitals and international organizations, have downloaded the toolkit and subscribed to a newsletter reminding users when updates are available.

National experts will be able to estimate national and subnational burden of communicable diseases, or more generally to introduce DALYs to their epidemiological research. For example, the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment in the Netherlands (RIVM) has estimated the national burden of infectious diseases by adapting the BCoDE toolkit models to the Dutch epidemiological situation, using the BCoDE toolkit to calculate DALYs and communicating the results through the visualization options of the software [12]. Depending on their access to and understanding of local availability and quality of data, experts may be able to enter the most accurate incidence and outcome tree data for the setting under study. In the quantification of the actual occurrence of a symptomatic infection, national experts may have more detailed information on potential changes in the sensitivity of the data sources used due to contingent situation, such as outbreaks or changes in the surveillance system or laboratory testing, and may take this information into account when adjusting for underestimation. Notably, the BCoDE toolkit has been included in an European Food Safety Authority's (EFSA) Scientific Opinion on risk ranking tools and was recommended for use by European experts when developing risk ranking of biological hazards [25].

As with all epidemiological analyses, it is crucial to keep in mind that the quality of the output depends on the quality of the input. For many communicable diseases the notification data are not aimed at capturing the exact overall number of incident cases of disease; therefore alternative methods for obtaining incidence data (e.g., via modelling) or alternative data sources (e.g., from serological studies) should be considered. These decisions have to be made by the user who therefore needs to have an in-depth understanding of the quality of the disease incidence data available for the population of interest. Additionally, the incidence-based approach estimates the present and future burden based on the yearly incidence entered in the models. The starting point of the models is the new cases of symptomatic disease, hence, people affected with a chronic condition caused by a past infection do not contribute to the burden, ultimately underestimating the results. A planned improvement to the BCoDE toolkit is the optional inclusion of prevalence-based methodology for estimating the burden of these diseases.

Default disease model parameters were chosen from a literature review carried out with a European-wide perspective, rather than a national one, however, all parameters are modifiable by the user. Registered users will be informed about all updates of the software, which will be published regularly on the ECDC website. Conditional on funding, we are also planning to perform regular literature reviews on all disease models and parameters to keep the default disease models in the software up to date. An additional planned improvement will allow the user to create novel outcome trees (i.e., boxes and sub-boxes for health outcomes and states, and arrows for transitional probabilities). Related to this, an open access library where users can share new models is foreseen.

In conclusion, the BCoDE toolkit is a user-friendly software for estimating the burden of communicable diseases. The toolkit facilitates communication between data analysts and users through multiple visualization options, ultimately fostering its value in health policy communication. The use of the Toolkit could hopefully stimulate further improvements in epidemiological data availability and quality. Planned enhancement in the BCoDE methodology and toolkit should contribute to more effective and evidence-driven health policy decision-making.

Supplementary information

S1 Document. Criteria used when selecting pathogens/diseases.
https://doi.org/10.1371/journal.pone.0170662.s001
S2 Document. Defining health states in a pathogen and incidence-based DALY approach.
https://doi.org/10.1371/journal.pone.0170662.s002
S3 Document. Results from BCoDE 2015 study, Disease models—Outcome trees.
https://doi.org/10.1371/journal.pone.0170662.s003

Competing Interests

AC, EC and PK are employed by ECDC which funded the development of the BCoDE toolkit software. GM and AP were consultants with ECDC at the time of the design and development of the project. DL, self-employed by NextPage Software Daniel Lewandowski, is recipient of the project funding. This does not alter our adherence to PLOS ONE policies on sharing data and materials. No conflict of interest for MJJM, DP, SAM, AvL, JAH, MEK.

Authors' contribution

Conceptualization: AC EC PK MEK. Data curation: AC EC. Formal analysis: EC AC MJJM DP SAM AvL JAH GM MEK AP. Funding acquisition: AC EC MEK. Investigation: EC AC MJJM DP SAM AvL JAH GM MEK AP. Methodology: EC AC MJJM DP SAM AvL JAH GM MEK. Project administration: AC EC MEK. Resources: AC EC PK. Software: DL. Supervision: AC EC MEK PK. Validation: EC AC MJJM DP SAM AvL JAH GM MEK AP. Visualization: AC EC MEK. Writing – original draft: EC AC. Writing – review & editing: EC AC DL MJJM DP SAM AvL JAH GM MEK AP PK.

Funding

The European Centre for Disease Prevention and Control (ECDC), a publicly funded technical agency of the European Commission, funded the development of the BCoDE toolkit software through the framework contract ECDC/ 2013/020 "Maintenance and further development of the BCoDE software tool" with NextPage Software Daniel Lewandowski. DL, self-employed at NextPage Software Daniel Lewandowski, developed the BCoDE toolkit software but did not have additional roles in the study design, data collection and analysis and decision to publish. He contributed to the preparation of the manuscript concerning the BCoDE toolkit software development technical description. The funder (ECDC) also provided support in the form of salaries for authors EC, AC and PK, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Acknowledgments

We would like to thank for their valuable scientific input ECDC colleagues: Zero Akyol, Andrew Amato, Sabrina Bacci, Julien Beaute´, Ida Czumbel, Niklas Danielsson, Birgitta de Jong, Erika Duffell, Johan Giesecke, Karin Haar, Janusz Janiec, Csaba Ko¨dmo¨n, Piotr Kramarz, Otilia Mardh, Gordon Nichols, Taina Niskanen, Lucia Pastore Celentano, Pasi Pentinen, Anastasia Pharris, Emmanuel Robesyn, Ettore Severi, Gianfranco Spiteri, Johanna Takkinen, Lara Tavoschi, Wim Van Bortel, Marieke van der Werf, Eva Warns-Petit, Therese Westrell, Robert Whittaker, Herve Zeller.

Moreover, we would like to thank other members of the BCoDE consortium: Arie Havelaar (Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA); Cheryl L. Gibbons (Centre for Immunity, Infection and Evolution, Institute for Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom); G. Ardine de Wit (Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands; Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands); Eric Fèvre (Centre for Immunity, Infection and Evolution, Institute for Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom; International Livestock Research Institute, Nairobi, Kenya; Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom); Chiara de Waure (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy); Elisabetta Franco (Department of Public Health, University of Rome Tor Vergata, Rome, Italy); Taavi Lai (Department of Public Health, University of Tartu, Tartu, Estonia); Nikolai Mu¨hlberger (Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health and Health Technology Assessment, UMIT□University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria); Beate Jahn (Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health and Health Technology Assessment, UMIT—University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria; Division of Public Health Decision Modelling, Health Technology Assessment and Health Economics, Oncotyrol Center for Personalized Cancer Medicine, Innsbruck, Austria); Alexander Krämer (Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany); Silvia Longhi (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy); Ardo Matsi (National Institute for Health Development, Tallinn, Estonia); Laura Murianni (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy; Social & Enviromental Statistics Department, National Institute of Statistics, Rome, Italy); Paulo Pinheiro (Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany); Walter Ricciardi (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy); Kristi Ru¨u¨tel (National Institute for Health Development, Tallinn, Estonia); Uwe Siebert (Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health and Health Technology Assessment, UMIT—University for Health Sciences, Medical Informatics and Technology, Hall in Tirol,

Austria; Division of Public Health Decision Modelling, Health Technology Assessment and Health Economics, Oncotyrol Center for Personalized Cancer Medicine, Innsbruck, Austria; Institute for Technology Assessment and Department of Health Policy and Management, Harvard University, Boston, MA, USA); Russell John Brooke (Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands). Finally, we acknowledge the contribution of: Susan Hahne´, Mirjam Knol, Anita Suijkerbuijk, Corien Swaan, Nicoline van der Maas and Wilfrid van Pelt. We also acknowledge the work of Muna Abu Sin, Hans-Peter Blank, Tanja Ducomble, Tim Eckmanns, Sebastian Haller, Thomas Harder, Anja Klingeberg, Ute Preuß, Madlen Sixtensson, Edward Velasco, Bettina Weiß from the Robert Koch Institute, Berlin, Germany, for their work on the disease models of healthcare-associated infections.

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CHAPTER 3

Estimating the burden of infectious diseases in EU/EEA: Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013.

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Published 19 April 2018. *Eurosurveillance. 2018;23(16):pii=17-00454. https://doi.org/10.2807/1560-7917.ES.2018.23.16.17-00454*

Abstract

Background and aims: The Burden of Communicable Diseases in Europe (BCoDE) study aimed to calculate disability-adjusted life years (DALYs) for 31 selected diseases in the European Union (EU) and European Economic Area (EEA).

Methods: DALYs were estimated using an incidence-based and pathogen-based approach. Incidence was estimated through assessment of data availability and quality, and a correction was applied for under-estimation. Calculation of DALYs was performed with the BCoDE software toolkit without applying time discounting and age-weighting.

Results: We estimated that one in 14 inhabitants experienced an infectious disease episode for a total burden of 1.38 million DALYs (95% uncertainty interval (UI): 1.25–1.5) between 2009 and 2013; 76% of which was related to the acute phase of the infection and its short-term complications. Influenza had the highest burden (30% of the total burden), followed by tuberculosis, human immunodeficiency virus (HIV) infection/ AIDS and invasive pneumococcal disease (IPD). Men had the highest burden measured in DALYs (60% of the total), adults 65 years of age and over had 24% and children less than 5 years of age had 11%. Age group-specific burden showed that infants (less than 1 year of age) and elderly people (80 years of age and over) experienced the highest burden.

Conclusions: These results provide baseline estimates for evaluating infectious disease prevention and control strategies. The study promotes an evidence-based approach to describing population health and assessing surveillance data availability and quality, and provides information for the planning and prioritisation of limited resources in infectious disease prevention and control.

Introduction

Countries of the European Union (EU) and European Economic Area (EEA) increasingly face the challenge of how best to allocate limited resources for infectious disease prevention and control. Evidence to determine priorities is often limited and epidemiological data may be unavailable, of uncertain quality or difficult to communicate to decision makers. Burden of disease estimates, using composite health measures, provide clear and comprehensive information for transparent and accountable decision making and have the potential to play an important role in health policy formulation [1]. Numerous studies have addressed the challenge of estimating disease burden regionally, nationally and globally [2-8].

In high-income countries, the incidence of infectious diseases has decreased over the last century, but recent outbreaks of emerging and re-emerging diseases worldwide, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), measles, avian and pandemic influenza, chikungunya virus, Ebola virus disease (EVD) and Zika virus disease, have resulted in a renewed focus on infectious diseases [9-14]. In addition, the traditional boundaries between non-infectious diseases and infectious diseases have become blurred as increasing evidence of the aetiological role of the latter in triggering non-infectious conditions is available [15,16].

In 2006, the European Centre for Disease Prevention and Control (ECDC) commissioned a pilot disease burden study using seven selected infectious diseases in order to propose a methodology for a burden of disease study tailored towards infectious diseases and assess the feasibility of, and interest in, such an approach [17]. Based on this pilot, the Burden of Communicable Diseases in Europe (BCoDE) project was launched [18], funded by ECDC and implemented in collaboration with a European consortium led by the Dutch National Institute for Public Health and the Environment (RIVM) and consisting of academic and national health institutes from EU countries.

The main objective of the BCoDE project was to develop a methodology to assess the impact of infectious diseases on population health in EU/EEA countries. It also intended to promote an evidence-based approach to assess population health, foster analysis of surveillance data quality and availability, facilitate the communication of complex health information to decision makers, and provide a tool for the planning and prioritisation of infectious disease prevention, preparedness and control measures.

To achieve these objectives, a methodology was developed [19,20] that uses a composite health measure, the disability-adjusted life year (DALY) [21], to express the disease burden of an infectious disease in a single metric and is therefore suitable for comparing their relative burden.

In line with the overall objectives of the BCoDE project, the specific aim of the BCoDE 2009–2013 study described in this paper was to provide a baseline average annual estimate of the EU/EEA burden of selected infectious diseases surveyed by ECDC and measured in DALYs.

Methods

Outcome measure and disease models

The methodological framework of the BCoDE 2009-2013 study was based on the BCoDE project [19,20]. This methodology uses an incidence-based approach with a disease progression pathway to estimate DALYs, an outcome measure that describes the impact of years lived with disability (YLD) following the onset of a disease and of years of life lost due to premature mortality (YLL) compared with a standardised life expectancy [22]. The incidence-based approach acknowledges current and future sequelae of infections, and sets the baseline for estimating the impact of prevention and control interventions. The disease progression model (i.e. outcome tree) links possible sequelae to an initial infection and allocates that future burden to the time of infection.

To calculate DALYs, the incidence of acute, symptomatic disease is a key input variable. Besides the number of symptomatic infections, computation of DALYs requires several additional age group and sex-specific variables. These variables include the risk of developing short- and long-term complications (health outcomes), their duration, and weights reflecting their severity. These variables are described through disease models or outcome trees, which represent the progression of a disease over time by ordering relevant health outcomes following infection and illustrating their conditional dependency [19,20].

To determine the life expectancy at age of death, we used the same standard reference life table as the Global Burden of Disease Study 2010 (GBD 2010) [23]. Disability weights were selected from the set developed by the European disability weight project [24]. Outcome trees, their parameters and literature reviews for each disease included in this study are described in the BCoDE toolkit, version 1.2 [25] and are available in Supplement 1. No age-weighting and time-discounting was applied.

Selection of communicable diseases

Diseases for inclusion in the present BCoDE 2009– 2013 study were selected from those listed in Decision 2119/98/EC with amendments, which fall under the mandate of ECDC as part of its responsibilities for epidemiological surveillance in support of the identification, assessment and communication of threats to health due to communicable diseases in the EU/EEA countries [26]. The selection criteria were data availability, incidence, outbreak potential and whether the disease is preventable with widely used vaccines (Supplement 2). Final disease selections were made by an ad hoc working group of the ECDC Advisory Forum, a board of experts from EU/EEA countries advising the ECDC Director [27].

Study population and European Union/ European Economic Area countries included

Results represent the burden of infectious diseases in all of the EU/EEA countries, except for

Croatia, which joined the EU in 2012. However, due to the wide variability of data availability and/or quality across countries and in order to balance data quality and representativeness, for some diseases the estimation was based on a subset of countries. Details are available in Supplement 3. Reasons for excluding countries included data availability (e.g. countries not reporting surveillance data to ECDC) and data completeness (e.g. countries reporting only aggregate or sentinel-based surveillance data but with the denominator population being unreported or unknown). Age group and sex-specific demographic data were obtained from the Eurostat database, 2011 [28].

Estimation of annual number of cases

Cases of diseases notified to ECDC through The European Surveillance System (TESSy), a database of communicable diseases cases in EU/EEA countries, were used as the main data source for estimating incidence of acute infections. In order to remove the effect of large fluctuations in incidence data, for example that because of seasonality of disease or outbreaks, notified cases during five years, 2009 to 2013, were averaged to obtain an annual notified number of incident cases.

The annual number of cases was estimated in a step-wise approach, generally by multiplying the age group and sex-specific number of cases notified to ECDC by a multiplication factor adjusting for underestimation [29]. For full details see Supplement 3 and Table 1. In order to determine the most suitable multiplication factors, we reviewed the available TESSy data.

The first step involved determining the availability of notification data: which countries reported and for which years. Countries not reporting or reporting limited information on sex and age of cases data were excluded from the study. The second step involved reviewing annual notification rates separately for each country, and the third step involved comparing the average rates across different countries. During these steps, together with ECDC surveillance experts, we considered surveillance systems' characteristics, including case definition, case-based vs aggregate reporting, compulsory vs voluntary reporting, comprehensive vs sentinel surveillance and whether or not the surveillance system had national coverage. Notification rates were also reviewed in relation to epidemiological circumstances (e.g. outbreaks and disease exposure), reporting practices, healthcare providers' awareness, and healthcare system characteristics.

Table 1a. Annual notification rate, multiplication factors adjusting for under-estimation and countries included in the estimation of DALYs, EU/EEA countries, 2009–2013

Infectious disease	EU/EEA annual notification of confirmed cases per 100,000 population[a]					Multiplication factors adjusting for under-estimation[b,c]	EU/EEA population included in the estimation of DALYs	
	2009	2010	2011	2012	2013		Countries represented[d]	Percent of EU/EEA population (%)
Campylobacteriosis[e]	49.64	53.53	55.43	52.62	52.30	NA	Austria, Denmark, Finland, France, Ireland, Italy, the Netherlands, Poland, Romania and Spain	35
Chlamydia infection[f]	189.06	178.90	178.25	184.79	184.45	No multiplication factor for perinatal chlamydia NA for acquired chlamydia	All countries	100
Congenital toxoplasmosis[f,g,h]	10.04	7.87	6.18	4.16	6.23	NA	All countries	100
Cryptosporidiosis	2.77	2.36	2.02	3.19	2.32	8.2 to 13.9	Belgium, Finland, Germany, Hungary, Ireland, Latvia, Spain, Sweden and UK	46
Diphtheria	NS	NS	NS	0.01	NS	2	Belgium, Finland, France, Germany, Latvia, Lithuania, the Netherlands, Sweden and UK	50
Giardiasis	5.79	6.06	5.65	5.46	5.50	14 (4 to 49)	Austria, Belgium, Cyprus, Czech Republic, Estonia, Finland, Germany, Hungary, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Malta, Norway, Romania, Slovakia, Slovenia, Spain, Sweden and UK	51
Gonorrhoea	8.88	8.71	10.49	12.55	16.99	1.01 to 3.86 for acquired and congenital	Cyprus, Czech Republic, Denmark, Estonia, Finland, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Portugal, Romania, Slovakia, Slovenia, Sweden (and UK for acquired cases)	42 (acquired) 41 (congenital)
Hepatitis A	3.52	2.70	2.55	2.65	2.48	4.5 (3.7 to 5.6)	All countries except Bulgaria, Lithuania, Latvia and Poland	90

Infectious disease	EU/EEA annual notification of confirmed cases per 100,000 population[a]					Multiplication factors adjusting for under-estimation[b,c]	EU/EEA population included in the estimation of DALYs	
	2009	2010	2011	2012	2013		Countries represented[d]	Percent of EU/EEA population (%)
Acute hepatitis B	0.80	0.80	0.70	0.70	0.70	1 to 6.6	Austria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Norway, Romania, Slovakia, Slovenia, Sweden and UK	76
Acute hepatitis C	0.30	0.70	0.50	0.60	0.50	NA	NA	NA
Human immunodeficiency virus infection/AIDS[i]	6.60	6.50	6.50	6.60	6.30	1.01 to 1.59	All countries except Italy	89

DALYs: disability-adjusted life years; EU/EEA: European Union/European Economic Area; NA: not applicable; NAv: not available; NS: not specified (< 0.01); UK: United Kingdom.

[a] Except where indicated, based on the European Centre for Disease Prevention and Control (ECDC) surveillance atlas of infectious diseases (accessed 1 August 2016) [59].

[b] One number only corresponds to a point estimate, two numbers constitute a range and three numbers refer to a most likely value, lower and upper bound. See Supplement 3 for more details.

[c] Under-estimation is the combination of under-reporting, those cases that are not reported to the surveillance system, and under-ascertainment, those cases that did not access the healthcare system. See Gibbons et al. [29].

[d] All countries means all EU/EEA countries except for Croatia, which joined the EU in 2012.

[e] Estimation of incidence is based on a seroincidence study [60].

[f] Estimation of incidence is based on age and sex-specific incidence or prevalence from published literature.

[g] Notification rate per 100,000 < 1-year-of-age population.

[h] Acquired form is not notifiable to ECDC.

[i] Based on ECDC annual epidemiological reports [61].

[j] 2012 and 2013 notified data only as disease was not previously notifiable to ECDC.

[k] Notification of cases in meningo-encephalitic phase only; therefore, data are adjusted to estimate the number of symptomatic cases.

[l] Based on the ECDC/World Health Organization Regional Office for Europe report, Tuberculosis surveillance and monitoring in Europe 2015 [62].

Table 1b. Annual notification rate, multiplication factors adjusting for under-estimation and countries included in the estimation of DALYs, EU/EEA countries, 2009–2013

Infectious disease	EU/EEA annual notification of confirmed cases per 100,000 population[a]					Multiplication factors adjusting for under-estimation[b,c]	EU/EEA population included in the estimation of DALYs	
	2009	2010	2011	2012	2013		Countries represented[d]	Percent of EU/EEApopulation (%)
Influenza[f]	NAv	NAv	NAv	NAv	NAv	NA	All countries	100
Invasive *Haemophilus influenzae* disease	0.40	0.41	0.46	0.47	0.49	1.41 (1.35 to 1.52) forFrance2.27 (2.17 to 2.44) forall other countries	All countries except Belgium and Bulgaria	89
Invasive meningococcal disease	0.91	0.75	0.81	0.73	0.71	1.0 to 1.14	All countries except Bulgaria	99
Invasive pneumococcal disease	4.39[i]	5.17	4.88	5.04	5.01	Depending on country surveillance system sensitivity: 1 to 2.5	Cyprus, Czech Republic, Denmark, Finland, Iceland, Ireland, Lithuania, Malta, Norway, Slovakia, Slovenia and Sweden	11
Legionnaires' disease	1.10	1.16	0.88	1.06	1.06	Depending on country surveillance system sensitivity:1 to 3.031 to 7.691 to 60.24	All countries	100
Listeriosis	0.42	0.42	0.36	0.42	0.44	1.7 (1.1 to 2.3)for acquired and perinatal	Acquired listeriosis: all countries except Bulgaria and LithuaniaPerinatal listeriosis: Austria, Cyprus, France, Greece, Hungary, Italy, Latvia, the Netherlands, Poland, Romania, Slovakia, Sweden and UK	98 (acquired)67 (congenital)
Measles	13.91	68.59	63.00	22.18	20.96	1.5 for outbreak year to 2.5 for non-outbreak year	All countries	100
Mumps	4.90	3.32	3.50	5.40	5.86	4.57 to 6.99	All countries except Belgium, France and Germany	70
Pertussis[f]	5.80	4.44	5.50	11.65	5.92	NA	All countries	100
Poliomyelitis	0.00	0.00	0.00	0.00	0.00	NA	All countries	100

Infectious disease	EU/EEA annual notification of confirmed cases per 100,000 population[a]					Multiplication factors adjusting for under-estimation[b,c]	EU/EEA population included in the estimation of DALYs	
	2009	2010	2011	2012	2013		Countries represented[d]	Percent of EU/EEApopulation (%)
Q Fever[j]	0.88	0.35	0.20	0.16	0.17	5.04	All countries except Austria, Belgium, Bulgaria, Denmark and Italy	76
Rabies[i]	NS	NS	NS	NS	NS	NA	All countries	100

DALYs: disability-adjusted life years; EU/EEA: European Union/European Economic Area; NA: not applicable; NAv: not available; NS: not specified (< 0.01); UK: United Kingdom.

[a] Except where indicated, based on the European Centre for Disease Prevention and Control (ECDC) surveillance atlas of infectious diseases (accessed 1 August 2016) [59].

[b] One number only corresponds to a point estimate, two numbers constitute a range and three numbers refer to a most likely value, lower and upper bound. See Supplement 3 for more details.

[c] Under-estimation is the combination of under-reporting, those cases that are not reported to the surveillance system, and under-ascertainment, those cases that did not access the healthcare system. See Gibbons et al. [29].

[d] All countries means all EU/EEA countries except for Croatia, which joined the EU in 2012.

[e] Estimation of incidence is based on a seroincidence study [60].

[f] Estimation of incidence is based on age and sex-specific incidence or prevalence from published literature.

[g] Notification rate per 100,000 < 1-year-of-age population.

[h] Acquired form is not notifiable to ECDC.

[i] Based on ECDC annual epidemiological reports [61].

[j] 2012 and 2013 notified data only as disease was not previously notifiable to ECDC.

[k] Notification of cases in meningo-encephalitic phase only; therefore, data are adjusted to estimate the number of symptomatic cases.

[l] Based on the ECDC/World Health Organization Regional Office for Europe report, Tuberculosis surveillance and monitoring in Europe 2015 [62].

Table 1c. Annual notification rate, multiplication factors adjusting for under-estimation and countries included in the estimation of DALYs, EU/EEA countries, 2009–2013

Infectious disease	EU/EEA annual notification of confirmed cases per 100,000 population[a]					Multiplication factors adjusting for under-estimation[b,c]	EU/EEA population included in the estimation of DALYs	
	2009	2010	2011	2012	2013		Countries represented[d]	Percent of EU/EEApopulation (%)
Rubella	4.81	2.25	15.48	76.50	140.30	10 for acquired rubella2 to 3.57 for congenital rubella syndrome	Acquired rubella: Austria, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta,the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and UKCongenital rubella syndrome: all countries except Austria	68 (acquired)98 (congenital)
Salmonellosis[e]	26.34	24.67	23.53	23.19	21.37	NA	Austria, Denmark, Finland, France, Greece, Ireland, Italy, the Netherlands, Poland, Romania, Spain, Sweden and UK	62
Shigellosis	1.88	1.82	1.76	1.53	1.37	18.3 (2.9 to 39.5)	All countries except Bulgaria, Lithuania, Luxembourg and Poland	91
Shiga toxin/ verocytotoxin- producing *Escherichia coli* (STEC/ VTEC)[f]	0.84	0.84	2.20	1.28	1.37	26.68 (1.6 to 109.7)	All countries except Bulgaria, Lithuania and Italy	86
Syphilis	4.43	4.20	4.61	4.63	4.93	1.01 to 3.86 for acquired syphilis1 for congenital syphilis	Acquired syphilis: Czech Republic, Estonia, France, Ireland, Latvia, Lithuania, Malta, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia and SwedenCongenital syphilis: Bulgaria, Cyprus, Czech Republic, Estonia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and UK	31 (acquired)75 (congenital)
Tetanus	0.03	0.03	0.04	0.03	0.02	1.41 to 2.78	All countries except Finland and Germany	83

Infectious disease	EU/EEA annual notification of confirmed cases per 100,000 population[a]					Multiplication factors adjusting for under-estimation[b,c]	EU/EEA population included in the estimation of DALYs	
	2009	2010	2011	2012	2013		Countries represented[d]	Percent of EU/EEA population (%)
Tick-borne encephalitis[j]	NAv	NAv	NAv	0.54	0.71	3.33 to 5[k]	Austria, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden and UK	78
Tuberculosis	15.87	15.00	14.32	13.50	12.66	Country-specific depending on country surveillance system sensitivity[l]	All countries	100
Variant Creutzfeldt–Jakob disease	NS	NS	NS	NS	NS	NA	All countries	100

DALYs: disability-adjusted life years; EU/EEA: European Union/European Economic Area; NA: not applicable; NAv: not available; NS: not specified (< 0.01); UK: United Kingdom.

[a] Except where indicated, based on the European Centre for Disease Prevention and Control (ECDC) surveillance atlas of infectious diseases (accessed 1 August 2016) [59].

[b] One number only corresponds to a point estimate, two numbers constitute a range and three numbers refer to a most likely value, lower and upper bound. See Supplement 3 for more details.

[c] Under-estimation is the combination of under-reporting, those cases that are not reported to the surveillance system, and under-ascertainment, those cases that did not access the healthcare system. See Gibbons et al. [29].

[d] All countries means all EU/EEA countries except for Croatia, which joined the EU in 2012.

[e] Estimation of incidence is based on a seroincidence study [60].

[f] Estimation of incidence is based on age and sex-specific incidence or prevalence from published literature.

[g] Notification rate per 100,000 < 1-year-of-age population.

[h] Acquired form is not notifiable to ECDC.

[i] Based on ECDC annual epidemiological reports [61].

[j] 2012 and 2013 notified data only as disease was not previously notifiable to ECDC.

[k] Notification of cases in meningo-encephalitic phase only; therefore, data are adjusted to estimate the number of symptomatic cases.

[l] Based on the ECDC/WHO Regional Office for Europe report, Tuberculosis surveillance and monitoring in Europe 2015 [62].

For a number of diseases, i.e. campylobacteriosis, chlamydia infection, congenital toxoplasmosis, influenza, pertussis and salmonellosis, it was concluded that it was not possible to estimate the incidence from notified data and alternative methods were applied (see Supplement 3). In particular, no published large community study was found for influenza except for the results of the Flu Watch cohort study in the United Kingdom [30], which we chose as the main data source to model the incidence of influenza in EU/EEA countries.

All the approaches above were explored in order to estimate the incidence of acute hepatitis C virus (HCV) infection in the general population. However, only published serological studies based on limited populations at risk were found, which would have introduced an unmeasurable bias and uncertainty and would not have allowed to estimate the incidence in the total population. Therefore, we excluded HCV infection from our disease burden estimation as no reliable data on the annual incidence of acute HCV was identified.

Computational analysis and uncertainty

For each disease, a model was generated using the BCoDE toolkit. Within each model, the age group- specific and sex-specific annual number of cases, multiplication factors adjusting for underestimation and population were inserted in the software. Uncertainty intervals (UI) were expressed as Uniform (2 values) or Project Evaluation and Review Techniques (PERT) (3 values) distributions; we ran the models at 10,000 iterations of the Monte Carlo simulations, without time discounting and age-weighting. For each disease, results included DALYs per case and the following per 100,000 population: incidence, deaths, YLL, YLD and DALYs. For all the outputs, we showed the median and the 95% UI.

Ethics statement

The BCoDE 2009–2013 study used a combination of aggregate health information (i.e. without personal identifiers) notified to ECDC through TESSy and information stemming from the scientific literature; therefore, informed consent was not required. Other information included in the study was drawn from published literature.

Results

We estimated that between 2009 and 2013, the selected 31 infectious diseases accounted for 7,577 cases per 100,000 population per year (95% UI: 6,445–8,141) and there were 9.67 deaths per 100,000 population annually (95% UI: 8.47–10.3) (Table 2).

Considering the EU/EEA population in 2011, these numbers would correspond to 37,784,603 cases (95% UI: 32,139,602–40,597,130) and 48,222 deaths (95% UI: 42,238–51,364).

The annual burden of the infectious diseases included in our study was 275 DALYs per 100,000 population (95% UI: 249–299). The disease with the highest burden was influenza, with 81.8

DALYs per 100,000 population (95% UI: 76.9–86.5), followed by tuberculosis (TB), human immunodeficiency virus (HIV) infection/ AIDS and invasive pneumococcal disease (IPD) with 53.5 (95% UI: 52.5–54.4), 48.2 (95% UI: 44.5–51.9) and 30.1 (95% UI: 29.3–30.8 DALYs per 100,000 population respectively (Table 2, Figure 1). These four top-ranking infections accounted for 78% of the total burden of communicable diseases in EU/EEA countries.

Legionnaires' disease, campylobacteriosis and hepatitis B had a significantly lower burden compared to the four diseases discussed above. Invasive Haemophilus influenzae disease, invasive meningococcal disease, chlamydia, salmonellosis, pertussis and Shiga toxin/ verocytotoxin-producing *Escherichia coli* (STEC/VTEC) infection had an even lower burden. The remaining diseases were ranked with a significantly lower burden. YLL accounted for 71% of the total burden (Figure 2).

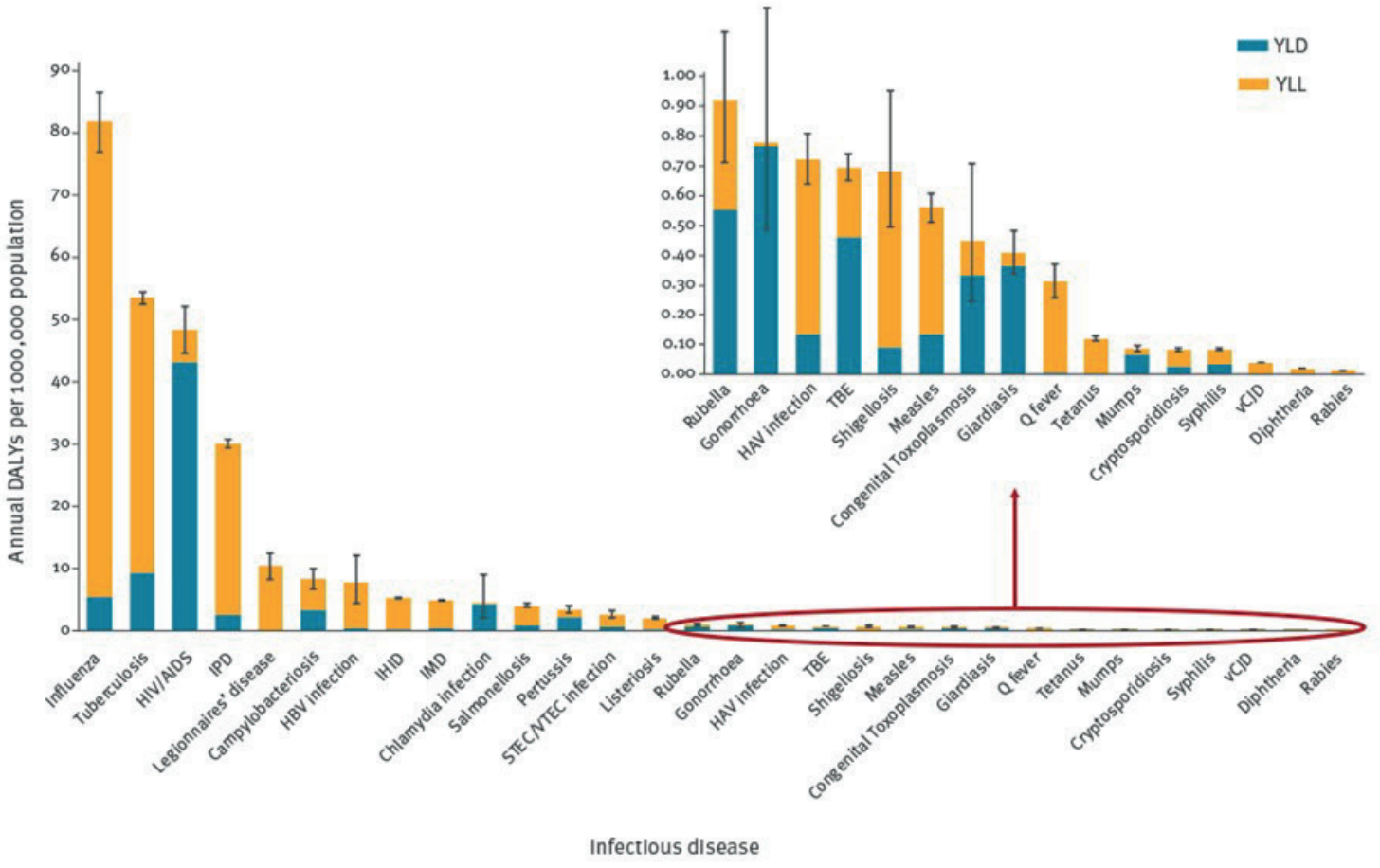


Figure 1. Median annual DALYs per 100,000 population for selected infectious diseases, EU/EEA countries, 2009–2013

EU/EEA: European Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IHID: Invasive Haemophilus influenzae disease; IMD: Invasive meningococcal disease; IPD: Invasive pneumococcal disease; STEC/ VTEC: Shiga toxin/verocytotoxin-producing *Escherichia coli*; TBE: Tick-borne encephalitis; vCJD: variant Creutzfeldt–Jakob disease; YLD: years lived with disability; YLL: years of life lost due to premature mortality. The error bars indicate the 95% uncertainty intervals.

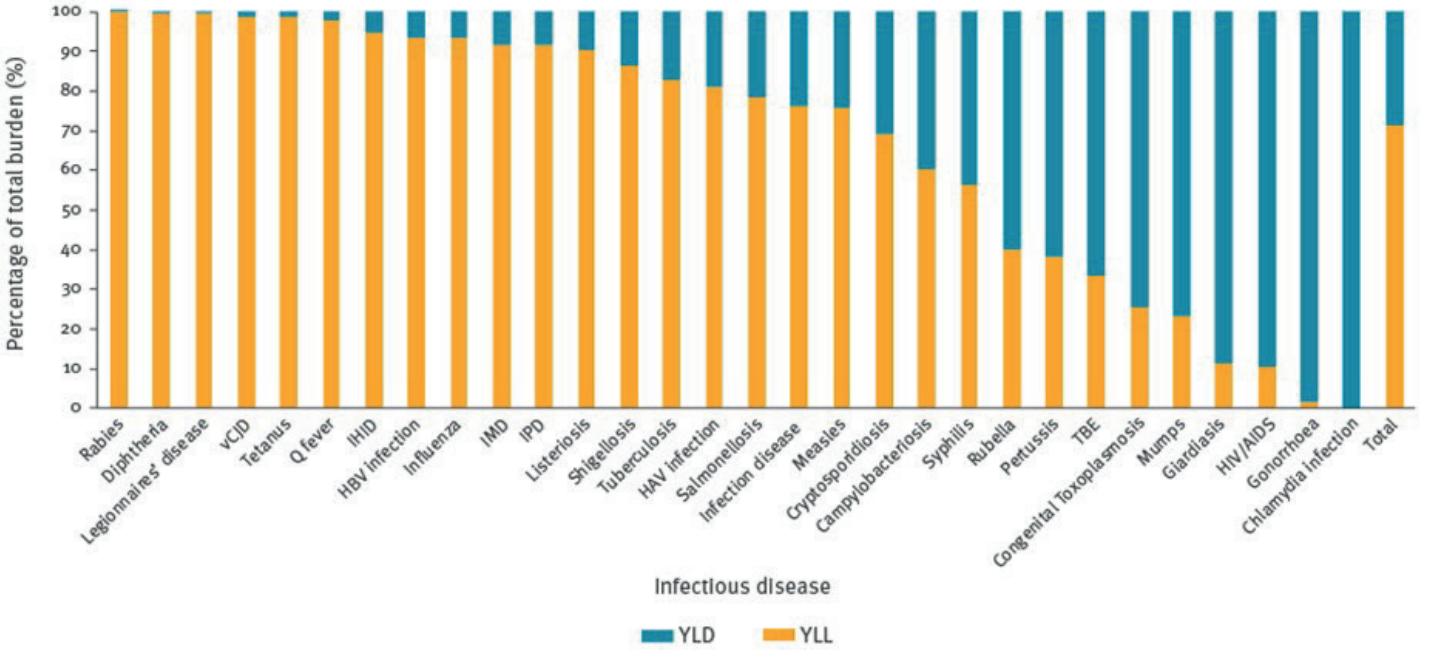


Figure 2. Relative contribution of YLL and YLD to the total burden of selected infectious diseases, EU/EEA countries, 2009–2013

EU/EEA: European Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IHID: Invasive Haemophilus influenzae disease; IMD: Invasive meningococcal disease; IPD: Invasive pneumococcal disease; STEC/ VTEC: Shiga toxin/verocytotoxin-producing *Escherichia coli*; TBE: Tick-borne encephalitis; vCJD: variant Creutzfeldt–Jakob disease; YLD: years lived with disability; YLL: years of life lost due to premature mortality.

Diseases with higher incidence and mortality as compared with other diseases were found to be influenza, campylobacteriosis and salmonellosis (Figure 3), although only the former has a high burden in DALYs. Pertussis and chlamydia have high incidence and low mortality, whereas TB, HIV/AIDS, IPD, Legionnaires' disease, hepatitis B virus (HBV) infection and invasive Haemophilus influenzae disease (IHID) had low incidence and high mortality.

Burden of congenital infections in newborns

In terms of burden of congenital infections in the newborns, almost all the burden (97%) was attributable to toxoplasmosis, listeriosis and rubella infections (Table 3).

Comparison of DALYs at the individual and population level

The diseases with the highest number of DALYs per case, which represents the individual burden and to a certain extent the severity of the disease, were rabies and variant Creutzfeldt–Jakob disease, which are ultimately fatal conditions. HIV/AIDS, invasive meningococcal disease, listeriosis, TB, IHID, Legionnaires' disease, HBV infection, IPD, congenital toxoplasmosis, tetanus and diphtheria followed, with DALYs per case ranging from 6.03 to 1.16. Diseases determined to have a high individual and population burden were Legionnaires' disease, IPD, HIV/AIDS and TB, while influenza was determined to have a low individual but high population burden (Figure 4).

DALYs by sex and age

Most DALYs, around 60%, were due to infections occurring in males. Considering more detailed results presented in Supplement 4, diseases such as TB, HIV/ AIDS, Legionnaires' disease, were found to impact mostly men while chlamydia and gonorrhoea had a higher burden in women.

When considering DALYs over the total population, 11% occurred in children less than 5 years of age, 15% in individuals less than 15 years of age and 24% in individuals aged 65 years and over (see Supplement 4); most DALYs were found in age groups between 25 and 49 year of age (Figure 5).

However, when considering the age group-specific DALYs per 100,000 population of the age group, those with the highest overall burden were infants under one year of age and individuals 80 years of age and over (Figure 6).

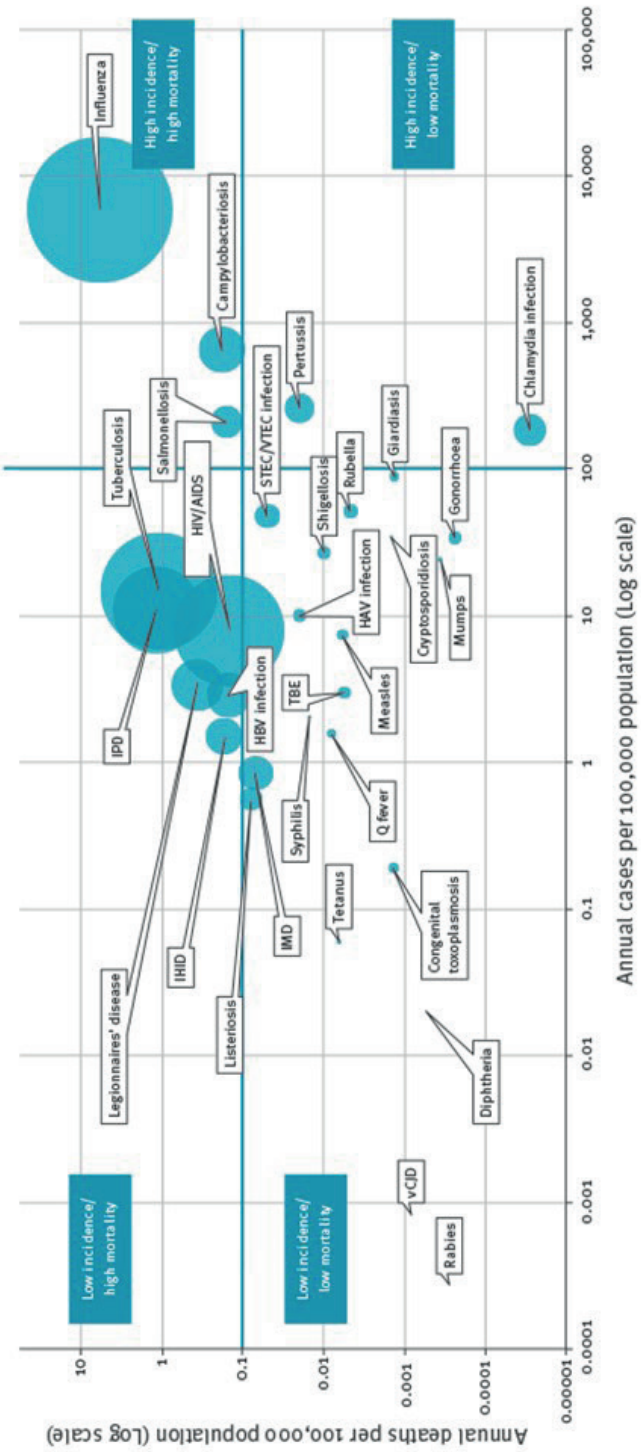


Figure 3. Bubble chart of the burden of selected infectious diseases in terms of mortality and incidence, EU/EEA countries, 2009–2013

EU/EEA: European Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IHID: Invasive Haemophilus influenzae disease; IMD: Invasive meningococcal disease; IPD: Invasive pneumococcal disease; STEC/ VTEC: Shiga toxin/verocytotoxin-producing *Escherichia coli*; TBE: Tick-borne encephalitis; vCJD: variant Creutzfeldt–Jakob disease. The diameter of the bubble reflects the number of DALYs per 100,000 population per year.

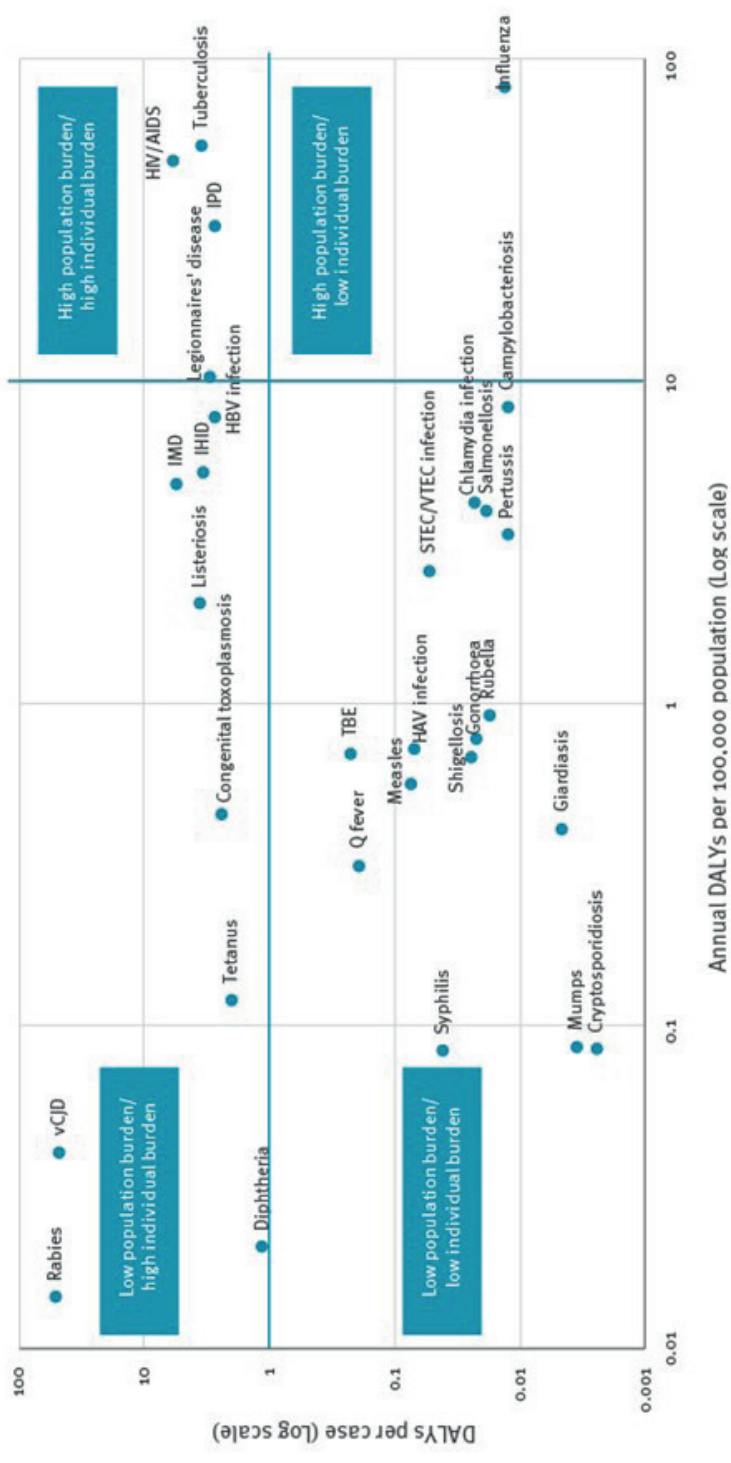


Figure 4. Scatterplot of the burden of selected infectious diseases in DALYs per case and DALYs per 100,000 population per year, EU/ EEA countries, 2009–2013

EU/EEA: European Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IHID: Invasive Haemophilus influenzae disease; IMD: Invasive meningococcal disease; IPD: Invasive pneumococcal disease; STEC/ VTEC: Shiga toxin/verocytotoxin-producing *Escherichia coli*; TBE: Tick-borne encephalitis; vCJD: variant Creutzfeldt–Jakob disease. Diseases were arbitrarily subdivided according to burden in DALYs per 100,000 population and DALYs per case.

Table 2. Ranking of selected infectious diseases according to annual DALYs per 100,000 population, EU/EEA countries, 2009–2013

Infectious disease	Median (95% uncertainty interval)[a]						% of total DALYs
	Incidence per 100,000 population	Deaths per 100,000 population	DALYs per case	YLD per 100,000 population	YLL per 100,000 population	DALY per 100,000 population	
Influenza	5,887(5,544–6,223)	5.89(5.54–6.22)	0.01	5.42(4.73–6.16)	76.3(71.9–80.7)	81.8(76.9–86.5)	29.8
Tuberculosis	14.9 (14.7–15.2)	1.10 (1.08–1.12)	3.58(3.55–3.62)	9.20(8.98–9.43)	44.3(43.5–45.1)	53.5(52.5–54.4)	19.5
Human immunodeficiency virus infection	7.99 (7.44–8.55)	0.15 (0.13–0.16)	6.03(5.86–6.20)	43.1(39.7–46.4)	5.13(4.53–5.64)	48.2(44.5–51.9)	17.5
Invasive pneumococcal disease	11.0 (10.7–11.2)	1.18 (1.15–1.21)	2.74(2.71–2.77)	2.49(2.25–2.73)	27.6(26.9–28.2)	30.1(29.3–30.8)	10.9
Legionnaires' disease	3.40 (2.77–4.01)	0.37(0.30–0.45)	3.04(2.73–3.36)	0.02(0.02–0.03)	10.3 (8.21–12.4)	10.3(8.23–12.4)	3.75
Campylobacteriosis	654 (599–707)	0.18(0.13–0.23)	0.01	3.25(2.73–3.87)	5.03(3.59–6.58)	8.28(6.68–10.0)	3.01
Hepatitis B	2.84 (2.29–3.40)	0.15(0.09–0.21)	2.79(1.46–4.45)	0.49(0.30–0.72)	7.37 (3.85–11.7)	7.86(4.19–12.2)	2.86
Invasive *Haemophilus influenzae* disease	1.52 (1.51–1.53)	0.17	3.43(3.39–3.47)	0.28(0.24–0.31)	4.94(4.88–5.00)	5.22(5.15–5.29)	1.90
Invasive meningococcal disease	0.85 (0.83–0.86)	0.07	5.64(5.59–5.70)	0.39(0.35–0.44)	4.39(4.31–4.48)	4.78(4.68–4.88)	1.74
Chlamydia infection	186 (124–259)	< 0.01	0.02(0.01–0.05)	4.62 (2.16–9.0)	Negligible	4.63(2.16–9.03)	1.68
Salmonellosis	211 (208–214)	0.16 (0.15–0.17)	0.02	0.86(0.74–1.01)	3.11 (2.85–3.36)	3.97(3.68–4.25)	1.44
Pertussis	263 (211–317)	0.02	0.01	2.04(1.59–2.56)	1.28 (1.14–1.45)	3.33(2.78–3.94)	1.21
Shiga toxin/verocytotoxin-producing *Escherichia coli* (STEC/VTEC) infection	48.1 (36.2–59.4)	0.05(0.04–0.07)	0.05(0.05–0.06)	0.62(0.49–0.76)	1.98(1.56–2.44)	2.59(2.05–3.21)	0.94
Listeriosis	0.56 (0.52–0.59)	0.08(0.08–0.09)	3.65(3.52–3.79)	0.20(0.15–0.25)	1.84 (1.74–1.94)	2.04(1.92–2.16)	0.74
Rubella	51.6	< 0.01	0.02(0.01–0.02)	0.55(0.39–0.74)	0.37(0.29–0.45)	0.92 (0.71–1.15)	0.33
Gonorrhoea	34.2 (24.4–44.2)	< 0.01	0.02(0.01–0.04)	0.77(0.49–1.24)	0.01(0.01–0.02)	0.78(0.50–1.26)	0.28
Hepatitis A	10.0 (9.67–10.4)	0.02	0.07(0.06–0.08)	0.14 (0.11–0.17)	0.58(0.51–0.66)	0.72(0.64–0.80)	0.26
Tick-borne encephalitis	3.00 (2.87–3.13)	< 0.01	0.23(0.22–0.24)	0.46(0.43–0.49)	0.23(0.22–0.25)	0.69(0.65–0.74)	0.25
Shigellosis	27.0 (23.4–30.7)	0.01(0.01–0.02)	0.03(0.02–0.03)	0.09(0.08–0.11)	0.59(0.41–0.82)	0.68(0.49–0.93)	0.25
Measles	7.46	< 0.01	0.08(0.07–0.08)	0.14 (0.11–0.17)	0.42(0.38–0.46)	0.56(0.51–0.61)	0.20
Congenital toxoplasmosis	0.19 (0.11–0.28)	< 0.01	2.42(1.92–3.05)	0.34(0.17–0.56)	0.12(0.06–0.19)	0.46(0.24–0.73)	0.17
Giardiasis	88.9 (75.0–104)	< 0.01	< 0.01	0.36(0.30–0.43)	0.05(0.04–0.06)	0.41(0.34–0.48)	0.15

Infectious disease	Median (95% uncertainty interval)[a]						% of total DALYs
	Incidence per 100,000 population	Deaths per 100,000 population	DALYs per case	YLD per 100,000 population	YLL per 100,000 population	DALY per 100,000 population	
Q fever	1.58	<0.01	0.20(0.16–0.23)	<0.01	0.31(0.25–0.36)	0.31(0.26–0.37)	0.11
Tetanus	0.06 (0.05–0.07)	<0.01	2.02(1.91–2.15)	<0.01	0.12 (0.11–0.13)	0.12 (0.11–0.13)	0.04
Mumps	24.2 (22.6–25.8)	<0.01	<0.01	0.07(0.06–0.07)	0.02	0.09(0.08–0.10)	0.03
Cryptosporidiosis	34.7 (32.3–37.1)	<0.01	<0.01	0.03(0.02–0.03)	0.06(0.05–0.06)	0.08(0.08–0.09)	0.03
Syphilis	2.04 (1.68–2.38)	<0.01	0.04(0.04–0.05)	0.04(0.03–0.04)	0.05	0.08(0.08–0.09)	0.03
variant Creutzfeldt–Jakob disease	<0.01	<0.01	48.6(48.4–48.8)	<0.01	0.04	0.04	0.01
Diphtheria	0.02	<0.01	1.16	<0.01	0.02	0.02	0.01
Rabies	<0.01	<0.01	52.1	<0.01	0.01	0.01	<0.01
Total	7,577 (6,445–8,141)	9.67(8.47–10.3)	NA	75.9(66.0–87.0)	196 (181–213)	273 (249–299)	100

DALYs: disability-adjusted life years; EU/EEA: European Union/European Economic Area; YLD: years lived with disability: YLL: years of life lost; NA: not applicable.
[a] Median and 95% uncertainty interval as estimated from the Burden of Communicable Diseases in Europe (BCoDE) toolkit (10,000 Monte Carlo simulations). Values < 0.01 are not specified. Uncertainties that deviate less than 0.01 from the median are not specified.

Table 3. Ranking of congenital diseases by DALYs and proportion among total congenital diseases per 100,000 newborn population, EU/EEA countries, 2009–2013

Disease	Median DALYs per 100,000 newborn population (95% uncertainty interval)[a]	DALYs due to congenital infections per 100,000 newborn population (%)
Congenital toxoplasmosis	43.6 (22.7–68.6)	35.1
Congenital rubella	42.5 (30.6–56.7)	34.6
Perinatal listeriosis	34.4 (26.2–43.4)	28.0
Congenital syphilis	2.73 (2.64–2.81)	2.22
Congenital chlamydia infection	0.09 (0.08–0.10)	0.08
Congenital gonorrhoea	<0.01	<0.01
Total	123 (82.2–172)	100

DALYs: disability-adjusted life years; EU/EEA: European Union/European Economic Area; YLD: years lived with disability: YLL: years of life lost. Values < 0.01 are not specified.
[a] Median and 95% uncertainty interval as estimated from the Burden of Communicable Diseases in Europe (BCoDE) toolkit (10,000 Monte Carlo simulations).

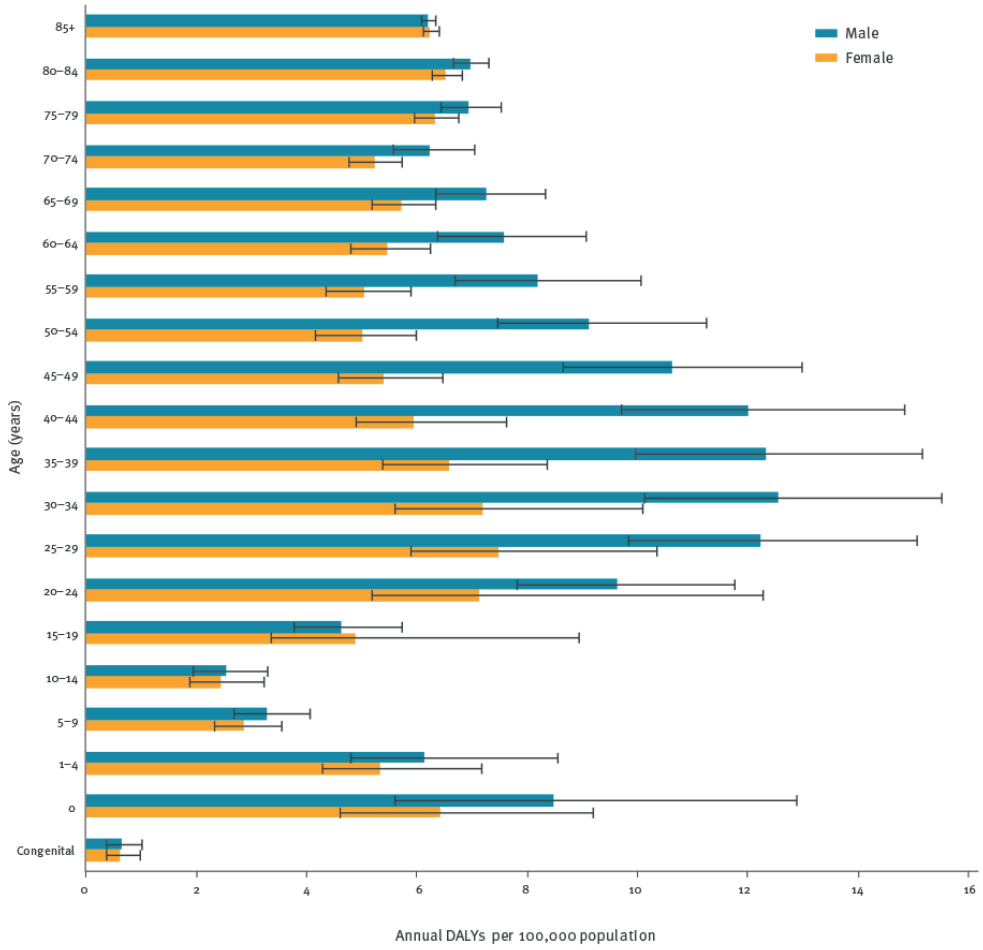


Figure 5. Annual total burden of selected infectious diseases by age group and sex, EU/EEA countries, 2009–2013

EU/EEA: European Union/European Economic Area. The error bars indicate the 95% uncertainty intervals.

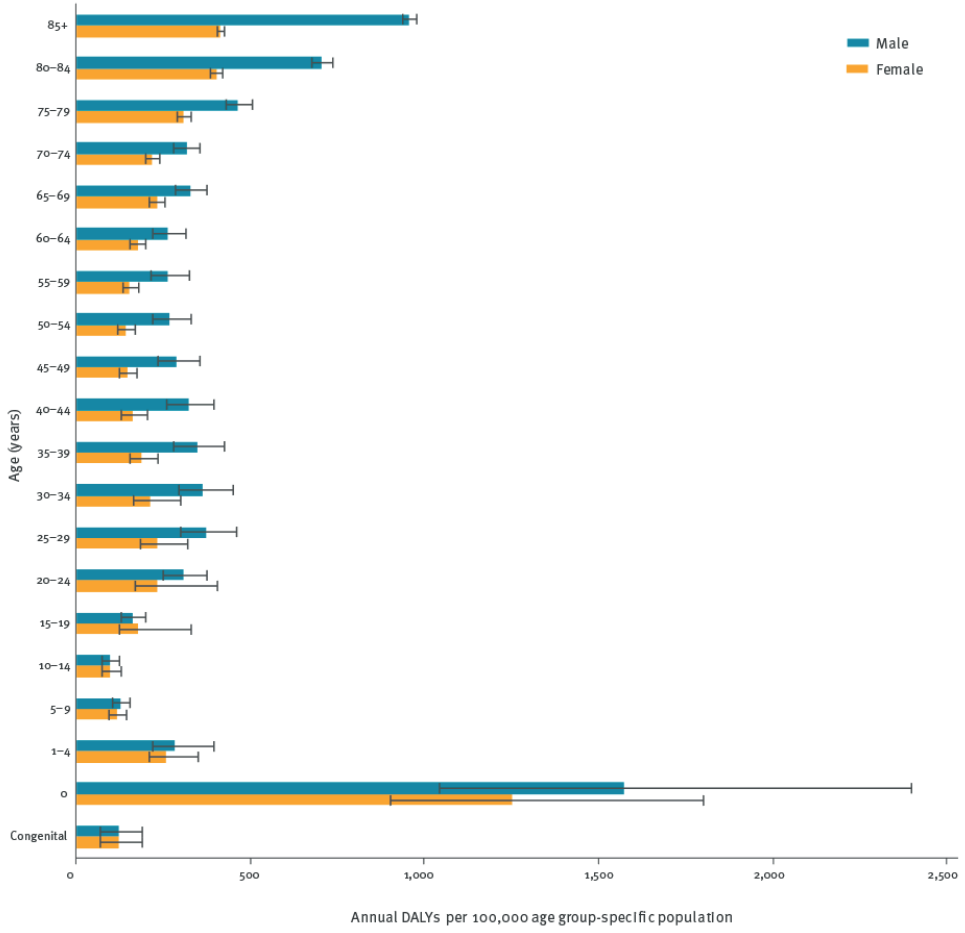
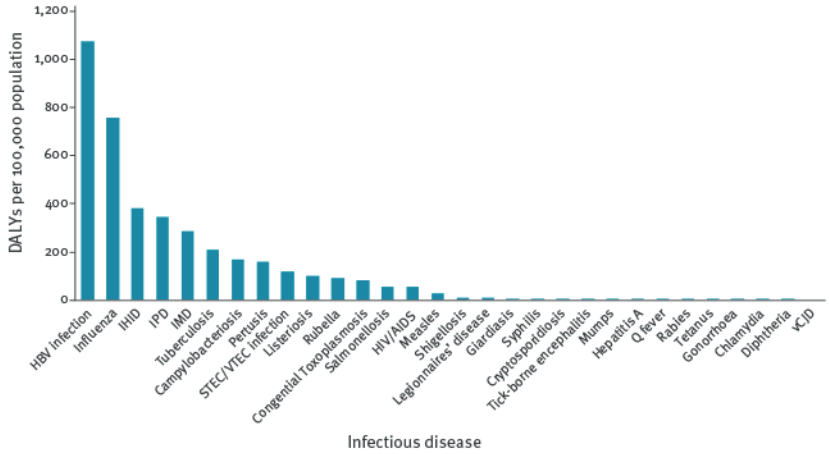


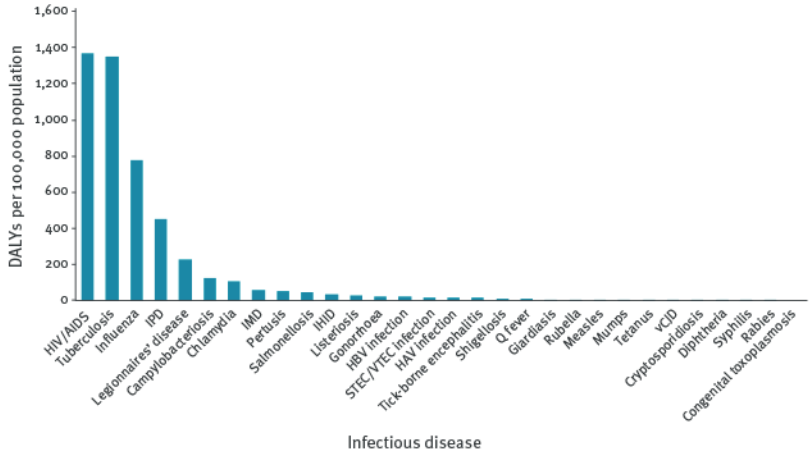
Figure 6. Annual age group-standardised burden of selected infectious diseases by age group and sex, EU/EEA countries, 2009–2013
EU/EEA: European Union/European Economic Area. The error bars indicate the 95% uncertainty intervals.

Figure 7. Annual age group-specific burden of selected infectious diseases by age groups < 15 years of age, 15–64 years of age and ≥ 65 years of age, EU/EEA countries, 2009–2013
EU/EEA: European Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IHID: Invasive Haemophilus influenzae disease; IMD: Invasive meningococcal disease; IPD: Invasive pneumococcal disease; STEC/ VTEC: Shiga toxin/verocytotoxin-producing *Escherichia coli*; TBE: Tick-borne encephalitis; vCJD: variant Creutzfeldt–Jakob disease.

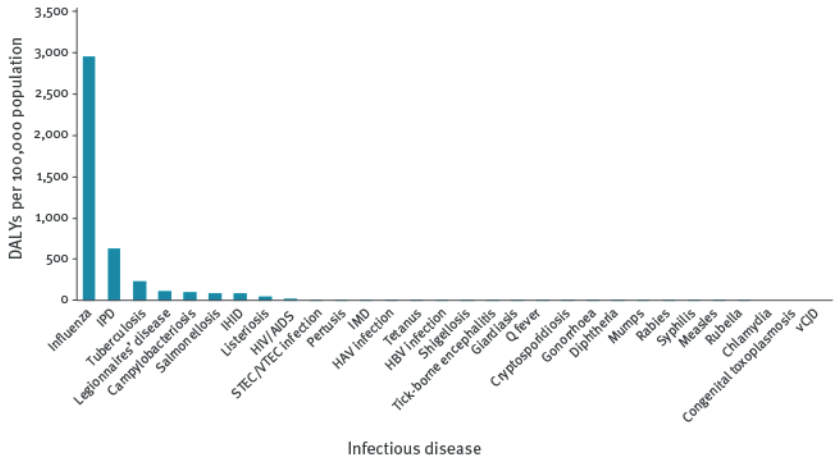
A. Burden <15 years of age



B. Burden ≥15 to <65 years of age



C. Burden ≥65 years of age



Compared with the age groups of between 15 and 64 years of age (adults) and 65 years of age and over (elderly population), the total burden of disease in the population under 15 years of age is lower (Figure 7). The diseases with the highest burden in the under 15 years age group are HBV infection, influenza, IHID, IPD and invasive meningococcal disease (IMD). HIV/AIDS, TB and influenza are the diseases with the highest burden in the adult population, whereas influenza, IPD and TB have the highest impact in the elderly population.

Contribution of the acute phase of the disease and of years of life lost due to premature mortality to disability-adjusted life years (DALYs)

The acute phase of diseases had the highest impact on the total burden (76%) (see Supplement 4). This was the result of the outcome trees that modelled case fatality proportions (CFP) as a direct risk to the acute infection. The high share of YLLs (72% of total DALYs, see Table 2) compared with YLDs was due to the limited amount of time lived with a disability, which is typical for infectious diseases.

Comparison of rankings

The final ranking of the burden of disease gives a new picture of the impact of infectious diseases when compared with notification data (Figure 8).

Discussion

This study presents the estimation of the burden of 31 selected infectious diseases in the EU/EEA in DALYs, adopting an incidence- and pathogen-based methodology and a consistent approach to surveillance and outcome data assessment. The results allow ranking of infectious diseases taking morbidity, disability and premature mortality resulting from acute infections and their sequelae into account.

The incidence-based approach chosen for this study allows for the effect of future long-term complications of a disease to be included in the calculation of DALYs, resulting in a more comprehensive estimate of the effect of prevention and control interventions [31]. Compared to a prevalence-based approach, in the incidence-based DALYs, the potential future burden avoided, for example, by vaccination as a possible intervention measure, is included [19,20,32].

We did not apply time discounting, which is generally applied in economic studies, because we did not consider there to be reasons justifying the decline of healthy life years over time. Similarly, age-weighting was also not applied because it was considered that a healthy life year should be valued equally, irrespective of the age at which it is lived or lost. Both choices are consistent with current methodologies used by the World Health Organization's (WHO) Foodborne Disease Burden Epidemiology Reference Group (FERG) and the Global Burden of Disease studies [23,33].

Access to healthcare varies across countries but is largely universal. Although healthcare and surveillance systems vary, incidence data included in this study is mainly based on cases of disease notified to national surveillance systems and reported to TESSy during years when the reporting procedures were considered to be consolidated. Surveillance in the EU/EEA differs in terms of purpose and systems for collecting data. This study enabled a thorough review of surveillance data availability and quality for each disease and each country. As a result, this study increases our knowledge and indicates areas for improving European infectious disease surveillance.

The averaging of annual number of cases over 5 years removed the effects of large fluctuations in incidence, i.e. flattened the effects of outbreaks. However, it could still be valuable to show the effect of an outbreak given that such can cause rankings to substantially change from the baseline. For example, the burden of disease was 35.5 DALYs per 100,000 Bulgarian population per year considering the 2010 measles outbreak of just under 22,000 cases [34]. This burden would have led to this outbreak ranking fourth in our results, between HIV/AIDS and IPD.

Our study ranked influenza as the infectious disease with the highest impact on population health in the EU/ EEA. Although the CFP chosen for the influenza disease model was low, the incidence was significantly higher than that of any other disease included in our study (Table 2). The main driver of the high burden of influenza is the contribution of premature mortality associated with the infection (YLL). Our study estimated a mortality of 5.89 per 100,000 population, slightly lower than the ECDC-estimated annual average influenza deaths in EU/EAA countries of 7.60 per 100,000 population (range: 1.07–15.5) within the same period based on the published figures of 38,500 deaths (range: 5,400 to 78,200) [35]. Similar mortality rates were published in national studies in the Netherlands: 3.69 to 18.8 per 100,000 population [36], 2.62 per 100,000 population [37] and 3.45 per 100,000 population [38]. Our estimated influenza mortality rates, based on the BCoDE outcome tree method, are reasonably consistent with other published rates.

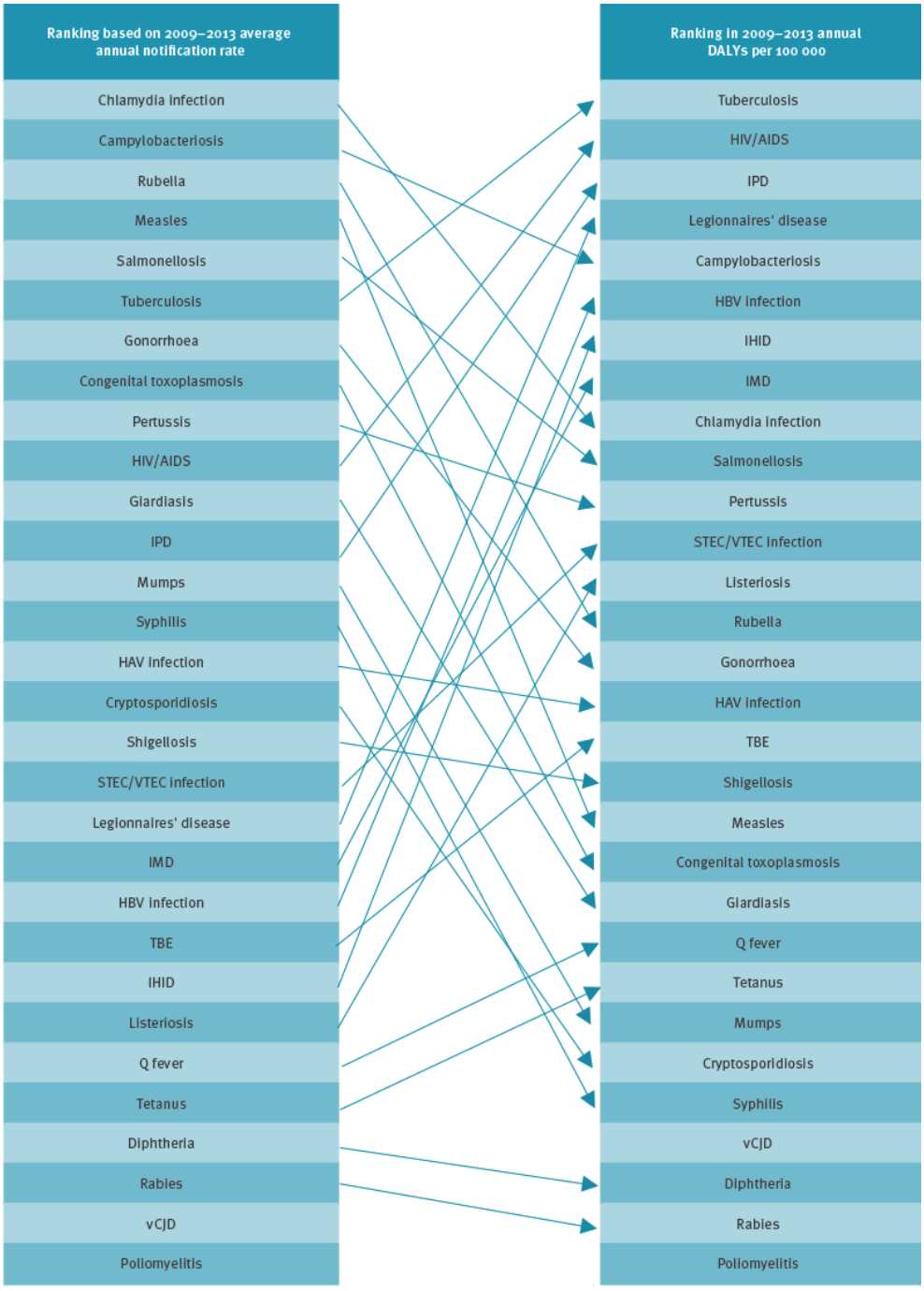


Figure 8. Comparison of ranking according to ECDC TESSy average annual notification rate and ranking according to estimated DALYs per 100,000 population, EU/EEA countries, 2009–2013

DALYs: disability-adjusted life years; ECDC: European Centre for Disease Prevention and Control; EU/EEA: European

Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IMD: Invasive meningococcal disease; IHID: Invasive Haemophilus influenzae disease; IPD: Invasive pneumococcal disease; STEC/VTEC: Verocytotoxigenic *Escherichia coli*; TBE: Tick-borne encephalitis; TESSy: The European Surveillance System; vCJD: variant Creutzfeldt–Jakob disease.

However, it is important to note the limitations of our estimation of DALYs for influenza, namely the single incidence data source, the Flu Watch cohort study in the United Kingdom, representing a limited geographical region [30] which may have a different epidemiological profile and vaccination coverage from other EU/EEA countries. However, the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance project (SHIVERS) in New Zealand found a very similar incidence of symptomatic influenza (personal communication, Sue Huang and Don Bandaranayake, July 2016). Moreover, the Netherlands national burden of disease study [5] estimated the incidence of influenza from the general practitioner sentinel system [37]. Using the 8,670 DALYs/year of the study and the Eurostat population in the Netherlands in 2009, we calculate an average annual burden of 52.6 DALYs per 100,000 population in the period 2007 to 2011, placing it in line with our findings.

Our results for influenza support the recommendations of the Council of the European Union [39], reiterated by the 2015 ECDC influenza vaccination report [40], to develop a national seasonal influenza vaccination action plan and to achieve target vaccination coverage for older population groups, people with chronic medical conditions, pregnant women and healthcare workers.

Our estimation of TB mortality rate was in line with national notified deaths of TB. For example, the Eurostat mortality for TB was 1.07 per 100,000 population in the 28 EU countries in 2011 [41], very much in line with our estimated rate of 1.10 per 100,000 population. Our findings reinforce the need for increasing efforts in EU/EEA countries to eliminate TB.

HIV/AIDS has a high burden of disease in Europe despite the low mortality risk compared with the pre- antiretroviral treatment era. This is reflected in the overwhelming contribution of YLD to the total DALYs (ca 90%). As significant HIV transmission continues in Europe [42] and the high associated burden found in our study highlights the need to strengthen prevention and testing efforts. This study estimated that 0.15 deaths per 100,000 population were due to HIV/AIDS. Given our incidence-based approach, one must consider that this estimation is a projection of future mortality rates for people being infected in the time-period analysed, i.e. 2009 to 2013. The Eurostat (EU 28 countries) notified standardised death rate from HIV/AIDS went from 1.2 per 100,000 population in 2002 to 0.74 per 100,000 population in 2013 [41]. In our model, we projected a lower fatality assuming further decrease in the future due to improved treatment options, increased testing/early ascertainment of cases and increased treatment compliance.

Published data on observed number of deaths of IPD are comparable to those in our study: in our study CFP was 11% (see Supplement 4) while in a European study in 17 countries, death was reported in 9.0% to 10.6% of cases and changed according to age [43], in line with the models used for our study. Similarly, published IPD incidence and mortality estimates in the

Netherlands based on sentinel surveillance and statistical estimation methods [44] reported incidence of 13.8 per 100,000 population and deaths of 1.6 per 100,000 population, which are very similar to those presented in our paper. Based on our study, most of the burden of IPD is experienced by adults over 55 years of age, although children aged under 5 years also significantly contribute to the total DALYs (see Supplement 4). These findings are relevant to discussions about vaccination strategies since, according to ECDC's report on invasive bacterial diseases in 2012, 'the majority of infections were caused by serotypes covered by the 13-valent pneumococcal conjugate vaccine PCV13' [45]. Ranking of diseases can be also tailored to specific age groups as illustrated in Figure 7. It is interesting to note that all five top ranking diseases among the less than 15 years of age group are preventable through vaccination. Within the adult population, further research on the main risk groups affected by HIV/AIDS and TB, which by far are the two infections with the highest impact, would be advantageous in order to better inform intervention strategies. The elderly population is mostly affected by respiratory diseases (influenza, IPD, TB and Legionnaires' disease) and gastro-intestinal diseases (campylobacteriosis and salmonellosis). Age-specific vaccination campaigns could help prevent the burden of influenza and IPD in particular.

Results from this study must be placed in a broader perspective. Recently, the burden of a six selected healthcare-associated infections (HAIs) was estimated in DALYs based on the BCoDE methodology [46]. Their cumulative burden of 501 DALYs per 100,000 population in that study was almost twice the one found in this one. These results imply that, among those surveyed by ECDC, HAIs represent the infections with the highest burden on European population. However, the methodological differences relating to the syndromic approach chosen for the burden of HAIs vs the pathogen-based approach of this study may limit comparing the results of the two studies. In particular, a number of diseases included in the current study may have been healthcare-associated (e.g. Legionnaires' disease, diseases attributable to *Streptococcus pneumoniae*), leading to some degree of double-counting [47,48]. However, this would likely be limited given that other diseases included in the present study may be uncommon causes of HAIs (e.g. infections due to Neisseria meningitidis, TB, hepatitis A and B and invasive meningococcal disease) [47,48].

The 2013 Global Burden of Disease Study (GBD 2013) estimated DALYs for a large number of diseases [7]. By downloading GBD 2013 country-specific estimates from the Global Health Data Exchange (GHDx) website and totalling the DALYs for 2013, we were able to estimate the EU/EEA burden of several infectious diseases included in our project. HIV/AIDS and TB overwhelmingly ranked higher than other infectious diseases in both studies. However, the GBD 2013 calculated prevalent DALYs, assuming a steady state and not taking into account the projected future burden, so comparisons must be made with caution.

The Ontario Burden of Infectious Disease Study (ONBOIDS) [4] used a comparable incidence-based DALY estimation approach as applied in our study. Similarly to our findings, the ONBOIDS found that infections caused by *Streptococcus pneumoniae*, HIV and influenza

virus had high burden. Differences in ranking of diseases might be explained by differences in, for example, case definitions and disability weights. Epidemiological differences should also be considered, as for example, the incidence of TB is higher in EU/EEA countries than in Ontario.

Another burden of disease study based on incidence is the World Health Organization (WHO) Foodborne Disease Burden Epidemiology Reference Group (FERG) [8,49]. Considering the overlapping diseases, the diseases with the highest burden based on the published results for WHO European Region EUR A of that study and the results of this study were campylobacteriosis, salmonellosis and listeriosis. The only difference, the burden of STEC/VTEC, might be due to the higher risk of developing haemolytic uraemic syndrome (HUS) and end-stage renal disease (ESRD) in the BCoDE toolkit disease progression model.

Strength and limitations

One strength of our study is that it is based on a rigorous assessment of national surveillance systems, which provided important information on sensitivity; where possible, notified data for a disease was adjusted specifically for each country. For example, country multiplication factors based on a self-reported survey of the national sensitivity towards IPD surveillance [50] were applied to the notification data and DALYs were estimated using the resulting cumulative number of cases. In other instances, such as for Legionnaires' disease, countries were grouped according to ECDC disease programme expert opinion into higher, intermediate and lower surveillance system sensitivity and different multiplication factors were then applied for each sensitivity group. The sensitivity of surveillance systems does not only depend on their intrinsic characteristics; systems are also prone to temporary changes, for example, during outbreaks, when increased awareness might also increase willingness and capacity to detect and report cases. For the estimation of the incidence of measles, for example, notification of cases from countries and years experiencing an outbreak were adjusted with a multiplication factor of 1.5 [51], as opposed to 2.5 for other countries and years [52,53].

Another strength of this study is that it captures the different risks of developing sequelae or death according to age group. Examples include the age group-specific risk of developing HUS after STEC/VTEC infection, a crucial step towards the estimation of its burden, and the redistribution of the CFP of salmonellosis, campylobacteriosis and influenza according to observed age-specific mortality data in order not to overestimate the number of deaths in younger age groups [25].

Disability weights included in the disease models are derived from a study performed in Europe and thus have the potential to better reflect the preferences and values of the EU/EEA population [24]. Most infectious diseases cause temporary mild disabilities; it is important to note that according to the methodology used to estimate disability weights, these may differ substantially for similar health states [54].

A further strength is that the freely accessible and transparent methodology, parameters and variables of this study allow for reproducing the estimates and making comparisons with results from similar studies. For example, the burden of infectious diseases in the Netherlands is a national study that was based on the BCoDE project methodology with national adaptations [5].

A number of limitations need to be taken into account when interpreting the results of this study. First, the selection of diseases was limited to those included in Decision 2119/98/EC with amendments. This list does not include other infectious diseases with a potentially significant burden in EU/EEA countries, such as infections with human papillomavirus (HPV), Helicobacter pylori, rotavirus, norovirus and human respiratory syncytial virus (HRSV).

Second, multiplication factors adjusting for underestimation of notified data were selected from information found in the literature. Few country-specific multiplication factors were available and ranges based on the limited number of published studies were applied consistently across EU/EEA countries. Moreover, multiplication factors were not adjusted for different age groups, although some diseases causing diarrhoea, such as salmonellosis for instance, had high notification rates in children. This may be due to a testing bias, i.e. children may be tested more often, or to their reduced immunity or to higher exposure. Regardless of the reason, this means that there is a risk that the results may be underestimated or overestimated.

Third, the disease models (outcome trees) in the BCoDE toolkit are based on several assumptions [55]. Variables for each model parameter represent the available information in the literature and the age-specific risk of developing a certain sequelae or death was often not available. Outcome trees were developed considering the incidence of disease and the risks of developing sequelae as currently observed in EU/EEA countries. Therefore, treatment and preventive measures were implicitly considered and this should be taken into account when interpreting the results. For example, vaccine-preventable diseases (VPDs) with high coverage had a lower burden of disease, but they had the potential to substantially increase their burden and their resulting position in the final ranking during outbreaks. In addition, the disease models included in this study are static and do not consider future infection transmissions. Dynamic models, such as SIR compartmental models for infection transmission, should be developed when assessing the impact of prevention and control interventions.

Fourth, the probability of developing sequelae or death were estimated based on the limited information in the literature, except in some cases where information was derived from surveillance data (Supplement 1), and considered the competing risks of dying or developing complications to the extent possible. At older ages, for example, co-morbidities may worsen the severity of a given infectious disease, suggesting modification of disability weights or the need to consider the attributable fraction due to the infections as opposed to the other underlying condition.

Fifth, the burden of HBV was based on the average annual number of acute infections but like other long-term disease progression pathways, other subsequent stages of the disease have an impact on population health. It would be beneficial to complement the incidence-based HBV results with prevalence studies given that our burden of HBV estimates do not consider prevalent long-term complicated cases.

The methodology and results in this study are based on a fully transparent and reproducible approach. We believe that the burden of disease methodology described in this study provides a clear and comprehensive view on the impact of infectious diseases on population health.

Conclusion

Calculation of DALYs through incidence-based disease progression models represents a comprehensive approach suitable for infectious diseases and provides useful information for prioritisation and planning in public health, among other purposes. For example, a recent Scientific Opinion by the European Food Safety Authority recommended using the BCoDE approach for ranking risks [56]. Another example is the Slovenian national estimation of the burden of tick-borne encephalitis that identified age groups with the highest DALYs in order to inform vaccination strategies [57].

However, as quantitative results alone might not fully encompass all unknowns, uncertainties and variability [58] other dimensions of health should be considered. Burden of disease measured in DALYs could be integrated with risk-ranking methodologies such as multi-criteria decision analysis (MCDA).

That being said, this study provides useful information for planning and prioritising surveillance strategies and intervention options aimed at preventing and controlling infectious diseases as the estimates provide a useful picture of the impact of infectious diseases in EU/EEA countries. The findings will help to inform assessment of the impact of epidemics and of public health interventions.

Supplementary information

Supplement 1. Disease models – Outcome trees.
https://www.eurosurveillance.org/docserver/fulltext/10.28071560-7917.es.2018.23.16.17-00454.sup1.pdf?expires=1677438630&id=id&accname=guest&checksum=60A0B408D2A-00283F086391A79D56269

Supplement 2. Criteria used when selecting pathogens/diseases.
https://www.eurosurveillance.org/docserver/fulltext/10.28071560-7917.es.2018.23.16.17-00454.sup2.pdf?expires=1677438588&id=id&accname=guest&checksum=8B813E70693F-7DE152618DFC2018FF5D

Supplement 3. Incidence of selected diseases.
https://www.eurosurveillance.org/docserver/fulltext/10.28071560-7917.es.2018.23.16.17-00454.sup3.pdf?expires=1677438647&id=id&accname=guest&checksum=7AB2A98A60FFEEFBAEE7D2AE6BBCFD5A

Supplement 4. Detailed results by disease
https://www.eurosurveillance.org/deliver/fulltext/10.28071560-7917.es.2018.23.16.17-00454.sup4.xlsx?itemId=%2Fcontent%2F10.28071560-7917.ES.2018.23.16.17-00454.sup4&mimeType=vnd.openxmlformats-officedocument.spreadsheetml.sheet

Competing Interests

None declared.

Authors' contributions

Conceived the project: AC, EC, PK, AH, MEK. Analysed the data: AC. Wrote the first draft of the manuscript: AC. Contributed to the writing of the manuscript: all authors. Developed disease models: AC, EC, AP, GM, MJM, DP, AvL, SM, AH, JAH, MEK. Developed incidence data estimation: all authors. ICMJE criteria for authorship read and met: all authors. Agree with manuscript results and conclusions: all authors.

Funding

None declared.

Acknowledgments

We are grateful to Prof. Johan Giesecke for his invaluable help in supporting and steering the BCoDE project throughout the years. We would also like to thank the following ECDC colleagues for their valuable scientific input: Zero Akyol, Andrew Amato, Sabrina Bacci, Julien Beauté, Ida Czumbel, Niklas Danielsson, Birgitta de Jong, Erika Duffell, Karin Haar, Janusz Janiec, Csaba Ködmön, Otilia Mardh, Gordon Nichols, Taina Niskanen, Lucia Pastore Celentano, Pasi Pentinen, Anastasia Pharris, Emmanuel Robesyn, Ettore Severi, Gianfranco Spiteri, Johanna Takkinen, Lara Tavoschi, Wim Van Bortel, Marieke van der Werf, Eva Warns-Petit, Therese Westrell, Robert Whittaker, Herve Zeller. We also acknowledge Mike Catchpole, Chief Scientist at ECDC, for his help in revising the manuscript.

We would also like to thank other members of the BCoDE consortium: Cheryl L. Gibbons (Centre for Immunity, Infection and Evolution, Institute for Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom); Ardine de Wit (Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands; Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven, the Netherlands); Eric

Fèvre (Centre for Immunity, Infection and Evolution, Institute for Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom; International Livestock Research Institute, Nairobi, Kenya; Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom); Chiara de Waure (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy); Elisabetta Franco (Department of Public Health, University of Rome Tor Vergata, Rome, Italy); Taavi Lai (Department of Public Health, University of Tartu, Tartu, Estonia); Nikolai Mühlberger (Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health and Health Technology Assessment, UMIT - University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria); Beate Jahn (Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health and Health Technology Assessment, UMIT - University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria; Division of Public Health Decision Modelling, Health Technology Assessment and Health Economics, Oncotyrol Center for Personalized Cancer Medicine, Innsbruck, Austria); Alexander Krämer (Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany); Silvia Longhi (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy); Ardo Matsi (National Institute for Health Development, Tallinn, Estonia); Laura Murianni (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy; Social & Environmental Statistics Department, National Institute of Statistics, Rome, Italy); Paulo Pinheiro (Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany); Walter Ricciardi (Institute of Public Health, Catholic University of the Sacred Heart, Rome, Italy); Kristi Rüütel (National Institute for Health Development, Tallinn, Estonia); Uwe Siebert (Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health and Health Technology Assessment, UMIT - University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria; Division of Public Health Decision Modelling, Health Technology Assessment and Health Economics, Oncotyrol Center for Personalized Cancer Medicine, Innsbruck, Austria; Institute for Technology Assessment and Department of Health Policy and Management, Harvard University, Boston, United States); Russell John Brooke (Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands). We also acknowledge the contribution of: Susan Hahné, Mirjam Knol, Anita Suijkerbuijk, Corien Swaan, Nicoline van der Maas and Wilfrid van Pelt (all National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands).

Finally, we would like to thank the ECDC Advisory Forum members who scored the selection criteria for the diseases to include in the study: Darina O'Flanagan (Ireland), Claudia Stein (WHO Geneva), Kåre Mølbak (Denmark), Jean-Claude Desenclos (France), Mike Catchpole (United Kingdom), Preben Aavitsland (Norway), Silvia Villanueva (European Commission) and Roel Coutinho (Netherlands).

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CHAPTER 4

Estimating the burden of healthcare-associated infections: Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study.

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Published 18 October 2016. *PLoS Medicine 2016 Oct 18;13(10):e1002150. doi:10.1371/journal.pmed.1002150*

Abstract

Background

Estimating the burden of healthcare-associated infections (HAIs) compared to other communicable diseases is an ongoing challenge given the need for good quality data on the incidence of these infections and the involved comorbidities. Based on the methodology of the Burden of Communicable Diseases in Europe (BCoDE) project and 2011–2012 data from the European Centre for Disease Prevention and Control (ECDC) point prevalence survey (PPS) of HAIs and antimicrobial use in European acute care hospitals, we estimated the burden of six common HAIs.

Methods and Findings

The included HAIs were healthcare-associated pneumonia (HAP), healthcare-associated urinary tract infection (HA UTI), surgical site infection (SSI), healthcare-associated Clostridium difficile infection (HA CDI), healthcare-associated neonatal sepsis, and healthcare-associated primary bloodstream infection (HA primary BSI). The burden of these HAIs was measured in disability-adjusted life years (DALYs). Evidence relating to the disease progression pathway of each type of HAI was collected through systematic literature reviews, in order to estimate the risks attributable to HAIs. For each of the six HAIs, gender and age group prevalence from the ECDC PPS was converted into incidence rates by applying the Rhame and Sudderth formula. We adjusted for reduced life expectancy within the hospital population using three severity groups based on McCabe score data from the ECDC PPS.

We estimated that 2,609,911 new cases of HAI occur every year in the European Union and European Economic Area (EU/EEA). The cumulative burden of the six HAIs was estimated at 501 DALYs per 100,000 general population each year in EU/EEA. HAP and HA primary BSI were associated with the highest burden and represented more than 60% of the total burden, with 169 and 145 DALYs per 100,000 total population, respectively. HA UTI, SSI, HA CDI, and HA primary BSI ranked as the third to sixth syndromes in terms of burden of disease. HAP and HA primary BSI were associated with the highest burden because of their high severity. The cumulative burden of the six HAIs was higher than the total burden of all other 32 communicable diseases included in the BCoDE 2009–2013 study. The main limitations of the study are the variability in the parameter estimates, in particular the disease models' case fatalities, and the use of the Rhame and Sudderth formula for estimating incident number of cases from prevalence data.

Conclusions

We estimated the EU/EEA burden of HAIs in DALYs in 2011–2012 using a transparent and evidence-based approach that allows for combining estimates of morbidity and of mortality in order to compare with other diseases and to inform a comprehensive ranking suitable for prioritization. Our results highlight the high burden of HAIs and the need for increased efforts for their prevention and control. Furthermore, our model should allow for estimations of the potential benefit of preventive measures on the burden of HAIs in the EU/EEA.

Introduction

Healthcare-associated infections (HAIs) are associated with increased morbidity and mortality and excess costs, and because a significant proportion of them are preventable, they are considered to be a marker of quality of patient care [1]. Many studies have attempted to estimate the number of cases of HAIs and of deaths attributable to these infections [2–6]. Such studies have used descriptive methods, modelling approaches, or a combination of the two.

There is a well-established methodology for estimating the burden of diseases that takes into account not only the incidence of the disease but also disabilities associated with their complications and the years of life lost, resulting in a composite health measure, the disability-adjusted life year (DALY) [7]. However, this methodology has not been applied to estimate an overall burden of HAIs. This prevents comparisons of the burden of HAIs to that of other infectious and non-infectious diseases, which would be particularly useful for healthcare professionals, policy makers, and the public.

One of the challenges in the estimation of the burden of HAIs is their special nature. Patients with an HAI are or have recently been hospitalised or were subject to a surgical intervention and have comorbidities that, beside the HAI, also contribute to morbidity and mortality. For this reason, it is essential to study patient outcomes that are specifically attributable to the HAI and not to the underlying disease. This includes calculating the expected individual life years at the age of death for patients with HAI. Moreover, administrative hospital discharge data that are commonly used to estimate the burden of other diseases do not accurately reflect the burden of HAIs, making it necessary to identify other sources of data [8].

We calculated the DALYs aiming at describing the burden of HAIs in acute care hospitals of the European Union and European Economic Area (EU/EEA) using the methodology of the Burden of Communicable Diseases in Europe (BCoDE) project [9,10] and the results of the European Centre for Disease Prevention and Control (ECDC) point prevalence survey (PPS) of HAIs and antimicrobial use in European acute care hospitals [6].

Methods

Ethics Statement

This study was based on health information collected and published during the 2011–2012 PPS of HAIs in acute care hospitals within the EU/EEA [6] and did not require informed consent from participants. Reported infectious disease data were provided in aggregate form by specific age and gender strata, without any personal identifiers.

Study Design

The methodology of the present study was adapted from the BCoDE project [10]. Specifically, the burden of selected HAIs in acute care facilities was expressed through a composite health

measure reflecting the burden of disabilities and premature deaths against a prespecified ideal. The approach is incidence-based in order to best express current and future consequences of infections, as well as the effect of future prevention and control interventions.

The present study used a syndrome-based approach and not the pathogen-based approach used for other BCoDE-related outputs, with the exception of C. difficile. A vast array of pathogens cause HAIs, which can be split according to recognizable and similar syndromes. Moreover, the syndrome approach has more significant public health relevance both in terms of surveillance and in terms of hospital infection prevention and control.

Selection of syndromes was primarily based on availability of incidence data, systematic literature reviews, and discussion within a European panel of experts. The HAIs included in the present study were healthcare-associated urinary tract infection (HA UTI), healthcare-associated primary bloodstream infection (HA primary BSI), healthcare-associated neonatal sepsis, healthcare-associated C. difficile infection (HA CDI), surgical site infection (SSI), and healthcare-associated pneumonia (HAP), as defined by the EU/EEA case definitions [11].

Outcome Measure

The DALY is a composite health measure estimating years lived with disabilities (YLDs) following the onset of a disease and of years of life lost due to pre-mature mortality (YLLs) compared to a standardized life expectancy [12]. YLDs include the length of time lived with disabilities (duration) multiplied by disability weights reflecting the ill health incurred. In our study, the latter were derived from the European disability weight project [13–15].

Data on life expectancy were obtained from the Global Burden of Disease 2010 (GBD 2010) standard reference life table with the same life expectancy for males and females, based on the lowest observed death rate for any age group [12].

Disease Models and Correction for Comorbidities

Since HAIs occur in the context of comorbidities, adjustment for the effect of these comorbidities was necessary. In order to take into account all possible health consequences of HAIs, disease models or outcome trees were developed based on several systematic reviews of the literature, focusing on the attributable risk of complications, death, and length of stay due to the HAI [16,17]. An outcome tree represents the progression pathway of a disease over time, starting with the infection and ending with either recovery, a permanent disability, or death. Health outcomes can include short-term complications (health states within a health outcome) and long-term sequelae. Each health outcome is related to the other outcomes by a transitional probability and includes a duration and a disability weight. The authors critically reviewed each outcome tree stemming from a systematic review of the literature and discussed and agreed on each parameter. The consensus-building procedure entailed four separate stages performed between February and December 2015. The results

from the systematic review [17] were reviewed independently by the two authors (AC and DP) and the structure and parameters for the final outcome tree indicatively selected during this first stage. During the second stage, shared views were discussed and their reasons analysed in order to confirm a common rationale. Disagreements were solved by discussion. The third stage included another expert and author (CS), and disagreements were further analysed and discussed until consensus was reached. The final and fourth stage entailed a final review by the head of the HAI programme at ECDC and author of the present study (DM). The final HAI outcome trees were published in the BCoDE toolkit on the ECDC website in December 2015. The disease model parameters are described in detail in the BCoDE toolkit [18] and are available in S1 Models.

Comorbidities also affect the life expectancy of hospitalised patients. Therefore, we categorized the affected hospitalized population according to the McCabe score [19] that was recorded for every patient enrolled in the ECDC PPS. The McCabe score gives an indication of the life expectancy of a patient according to the severity of their underlying disease. Patients are classified in three categories based on whether the underlying disease is nonfatal (McCabe

score 1, expected survival of more than 5 y), ultimately fatal (McCabe score 2, expected survival between 1 and 5 y), or rapidly fatal (McCabe score 3, expected survival less than 1 y). The incidence of each HAI was therefore divided into three groups based on McCabe score: McCabe score 1 (standard average life expectancy), McCabe score 2 (3 y average life expectancy), and McCabe score 3 (0.5 y average life expectancy) [19].

SSI incidence and severity vary widely depending on the site and nature of the surgical intervention and the depth of the infection. One way to deal with this variability could have been to focus the systematic review of the literature on SSIs following hip and knee joint replacements and following coronary artery bypass grafts (CABGs), as examples of operations with predominantly acute (CABG) or chronic (joint replacement) infectious complications. However, the results would only partially cover the full range of SSIs. Therefore, as a final decision for the SSI outcome tree, a different approach was chosen: only the acute phase of the disease and the attributable mortality were included based on data on overall SSI outcomes [20].

Study Population and Incidence

Estimates of the incidence of the selected HAIs were derived from the ECDC PPS, which was conducted in 2011–2012 in 29 EU/EEA Member States and Croatia, and included data from a total of 273,753 patients in 1,149 hospitals [6]. Since only acute care hospitals participated in this ECDC PPS, other healthcare facilities such as long-term care facilities were not included in our study.

The results of the ECDC PPS represent the EU/EEA Member States, with more that 510 million citizens according to 2011 Eurostat data. Five percent of the population was under

5 y old, and 18% was 65 y and over. In the EU/EEA, there were 2,719,634 available beds in hospitals [21], of which 1,840,514 were in acute care with 13,090 discharges of inpatients per 100,000 inhabitants in 2011 [22].

The gender-specific and age-group-specific yearly number of cases of HAIs (further referred to as "patients with HAIs") was calculated from the rate of new cases of HAI per 100 admissions using the 2011 Eurostat data on the number of inpatient hospital discharges and general population (see S1 Input) [22].

The rate of new cases of each type of HAI per 100 admissions was estimated for each gender, age group, and McCabe score category by converting the stratum-specific prevalence rate from the ECDC PPS into an incidence rate using the Rhame and Sudderth formula, $I = P \times LA/(LN - INT)$. I (incidence) is the rate of new patients with HAIs per 100 admissions, P (prevalence) is the percentage of patients with HAIs on the day of the PPS, LA is the length of stay of all hospitalized patients (irrespective of the presence of an HAI), LN is the length of stay of patients with an HAI, and INT is the length of stay before the onset of the HAI [23]. LN—INT, representing the length of stay of patients with HAIs from HAI onset until discharge, was derived from the median number of days from HAI onset until the day of the PPS. This choice was based on the fact that the average length of stay for all patients (as derived from the hospital data) in the ECDC PPS was best correlated with the median length of stay of patients included on the day of the PPS [6], as patients with a longer stay are overrepresented in any PPS sample. The country-specific average length of stay of all hospitalized patients (LA) was extracted from the ECDC PPS.

Under-reporting is a significant parameter affecting burden of disease estimates [24]. This is also true for the reporting of HAIs in the ECDC PPS, in which a small validation study indicated an average under-reporting factor of 1.25. This validation study was only performed in four EU/EEA Member States and was therefore not deemed indicative of under-reporting of HAIs in the whole EU/EEA. In the present study, we did not apply any correction factor adjusting for underestimation of HAI incidence.

Computational Analysis and Uncertainty

The final designs of the HAI outcome trees, including their model parameters and uncertainties, were inserted in the BCoDE toolkit [18]. For each type of HAI, three models were generated, and population and life expectancy data were customized to cover all EU/EEA populations according to their McCabe score category. Successively, the gender-specific and age-group-specific yearly numbers of cases of HAIs and uncertainties were inputted relatively to each McCabe score category. Where applicable, inputs for disease model parameters and HAI incidence data included uncertainty intervals, which were incorporated in the calculations as uniform (two variables) or Project Evaluation and Review Techniques (PERT) (three variables) distributions [25]. See S1 Input for detailed age-group- and sex-specific tables inputted in the BCoDE toolkit.

To calculate uncertainty intervals, the BCoDE toolkit models were run at 1,000 iterations of the Monte Carlo simulations with and without a 3.5% annual time discount rate. The option of discounting may allow for possible future comparisons with cost-effectiveness studies on, for example, interventions to prevent HAIs [26].

For each type of HAI, the outputs included the annual number of cases of HAIs, the HAI incidence, the number of deaths attributable to HAIs, and the DALYs per case, as well as the number and the rate per 100,000 population of YLLs, YLDs, and DALYs. For each output, the median and the 95% uncertainty interval (95% UI) based on the input uncertainties were calculated.

Results

Based on data from 2011–2012, we estimated that 2,609,911 (95% UI: 2,451,235–2,778,451) new cases of HAI occur every year in the EU/EEA. These HAIs accounted for a total of 2,506,091 DALYs (95% UI: 2,163,850–2,877,574) annually in the EU/EEA, corresponding to 501 DALYs per 100,000 general population (95% UI: 429–582). These DALYs consisted of 2 million YLLs (75% of total DALYs) and 681,400 YLDs.

When applying a 3.5% annual time discount rate, HAIs accounted for 1,335,159 DALYs (95% UI: 1,153,291–1,536,343), corresponding to 261 DALYs per 100,000 general population (95% UI: 226–301). The reduction of DALYs when applying time discounting occurred mainly within the McCabe score 1 category.

For each type of HAI, the relationship between the incidence of HAIs, the number of deaths attributable to HAIs, and the total burden of HAIs in DALYs per 100,000 general population depends on the severity of disease and its long-term complications. This is illustrated by the bubble chart presented in Fig 1.

As shown in this figure, HA primary BSIs, even with a relatively low incidence, generated a high burden of disease due to their high attributable mortality, whereas SSIs that have a higher incidence were associated with a lower burden of disease. More generally, the figure illustrates how the ranking of HAIs may differ depending on which indicator is used for measuring their health burden and therefore gives more detailed information on how different types of HAIs compare in their burden on population health.

More than 60% of the total burden of the six selected HAIs was accounted for by HAP and HA primary BSIs. When only considering the population at risk for HA neonatal sepsis, i.e., newborns (derived from the 2011–2012 average Eurostat number of births in the EU/EEA) instead of the general population, the burden of HA neonatal sepsis rose from 16.8 DALYs per 100,000 general population to 1,592 DALYs per 100,000 newborns. Over 60% of the total DALYs were due to the acute phase of the six HAIs, while the remaining DALYs were due to the sequelae, regardless of time discounting.

The estimates of the burden of the six selected types of HAIs are presented in Table 1. The detailed results for each type of HAI (without time discounting) are shown in S1 Output.

Fig 2 summarizes the burden of the six types of HAI expressed in annual DALYs per 100,000 general population, distributed between YLLs and YLDs.

A total of 91,130 deaths (95% UI: 76,117–107,883) each year in the EU/EEA were attributable to the six selected HAIs. Fifty-six percent of the estimated attributable deaths were attributable to HAP and HA primary BSIs (Table 1). Sixty-five percent of the deaths attributable to HAIs occurred in patients in the McCabe score 1 category, twenty-five percent in the McCabe score 2 category, and ten percent in the McCabe score 3 category. This distribution was mainly due to the large number of HAIs that occurred in patients with a McCabe score of 1 compared to patients in other McCabe categories.

Table 2 describes the relative burden on female patients, patients aged less than 5 y, and patients aged 65 y and above for each HAI and overall (including and excluding HAI neonatal sepsis).

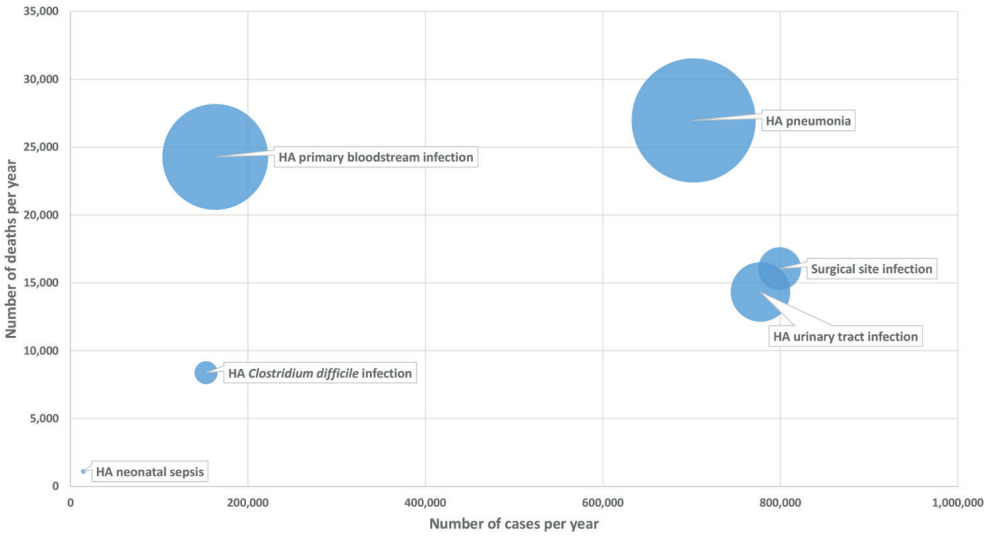

Figure 1. Six healthcare-associated infections according to their number of cases per year (x-axis), number of deaths per year (y-axis), and DALYs per year (width of bubble), EU/EEA, 2011–2012 (time discounting was not applied).
DALY, disability-adjusted life year; HA, healthcare-associated.

Table 1. Estimated annual burden of six healthcare-associated infections, EU/EEA, 2011–2012 (time discounting was not applied).

Healthcare-Associated Infections	Median (95% Uncertainty Interval)							% Total DALYs
	Cases per Year	Incidence (per 100,000 Population)	Deaths per Year	DALYs per Case	YLDs per 100,000 Population	YLLs per 100,000 Population	DALYs per 100,000 Population	
HA Pneumonia	702,315	138 (130–145)	26,972	2.2 (1.9–	67.0 (59.7–74.0)	103 (85.7–121)	169 (149–192)	33.7
	(664,764–		(21,859–	2.4)				
	744,419)		32,541)					
HA Primary	163,216	32 (28.4–35.7)	24,284	8 (7.2–	21.2 (17.9–24.9)	123 (104–142)	145 (123–166)	28.9
Bloodstream	(145,012–		(20,824–	8.8)				
Infection	182,059)		27,755)					
HA Urinary Tract	777,639	152 (145–161)	14,334	0.8 (0.7–	24.8 (20.8–29.0)	56.4 (47.1–66.5)	81.2 (69.0–94.2)	16.2
Infection	(737,820–		(11,768–	0.9)				
	820,228)		17,162)					
Surgical Site	799,185	156.5 (150–163.7)	16,049	0.5 (0.5–	0.8 (0.7–0.8)	57.5 (55.0–59.8)	58.2 (55.7–60.6)	11.6
Infection	(762,721–		(15,249–	0.6)				
	835,448)		16,893)					
HA *C. difficile*	152,905	30 (26.3–33.9)	8,382	1.7 (1.3–	1.4 (1.1–1.8)	29.8 (22.4–39.6)	31.2 (23.6–41.1)	6.23
Infection	(134,053–		(6,034–	2.2)				
	173,089)		11,152)					
HA Neonatal	14,651 (7,466–	2.9 (1.5–4.7)	1,109 (383–	12.1 (7.6–	6.9 (3.9–11.0)	9.9 (4.0–18.1)	16.8 (8.9–27.6)	3.35
Sepsis	23,873)		2,380)	16.9)				
Overall	2,609,911	512 (480–545)	91,130	25.1	122 (105–143)	380 (318–447)	501 (429–582)	100
	(2,451,235–		(76,117–	(19.0–				
	2,778,451)		107,883)	31.5)				

Abbreviations: YLDs, years lived with disability; YLLs, years of life lost due to premature mortality.

Table 2. Percentage of burden of healthcare-associated infections (% DALYs) in female patients, children (<15 y old), and the elderly (65 y old), EU/EEA, 2011–2012 (time discounting was not applied).

Healthcare-Associated Infections	Female Patients (% DALYs)	<15 y old (% DALYs)	>65 y old (% DALYs)
HA Pneumonia	36.5	22.3	23.7
HA Primary Bloodstream Infection	44.3	41.2	11.6
HA Urinary Tract Infection	59.4	13.1	29.6
Surgical Site Infection	45.1	6.3	48.7
HA *C. difficile* Infection	53.3	17.8	31.9
Overall, without HA Neonatal Sepsis	**30.5**	**24.5**	**24.1**
HA Neonatal Sepsis	61.4	N/A	N/A
Overall	**40.8**	**27.2**	**23.3**

Abbreviations: N/A, not applicable.

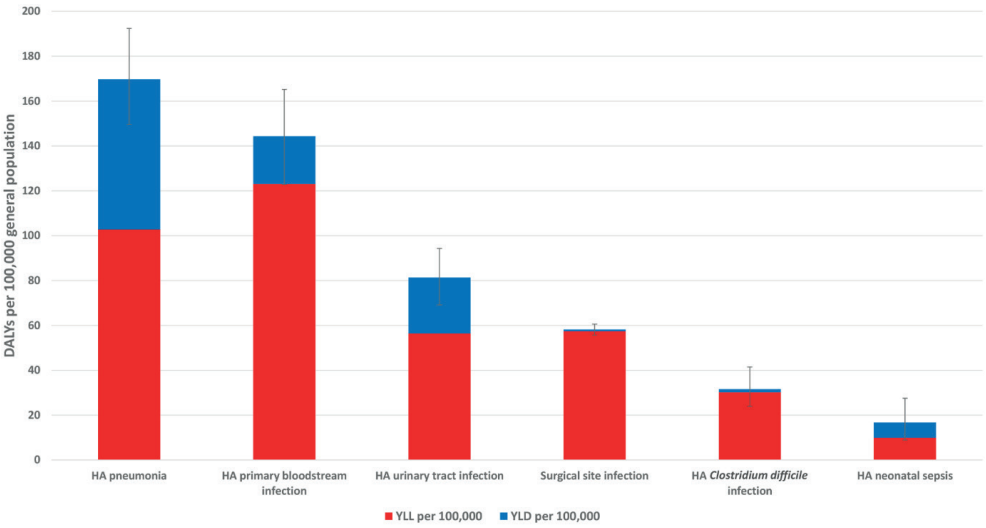

Figure 2. Estimated annual burden of six healthcare-associated infections in DALYs per 100,000 population (median and 95% uncertainty interval), split between YLLs and YLDs, EU/EEA, 2011–2012 (time discounting was not applied).

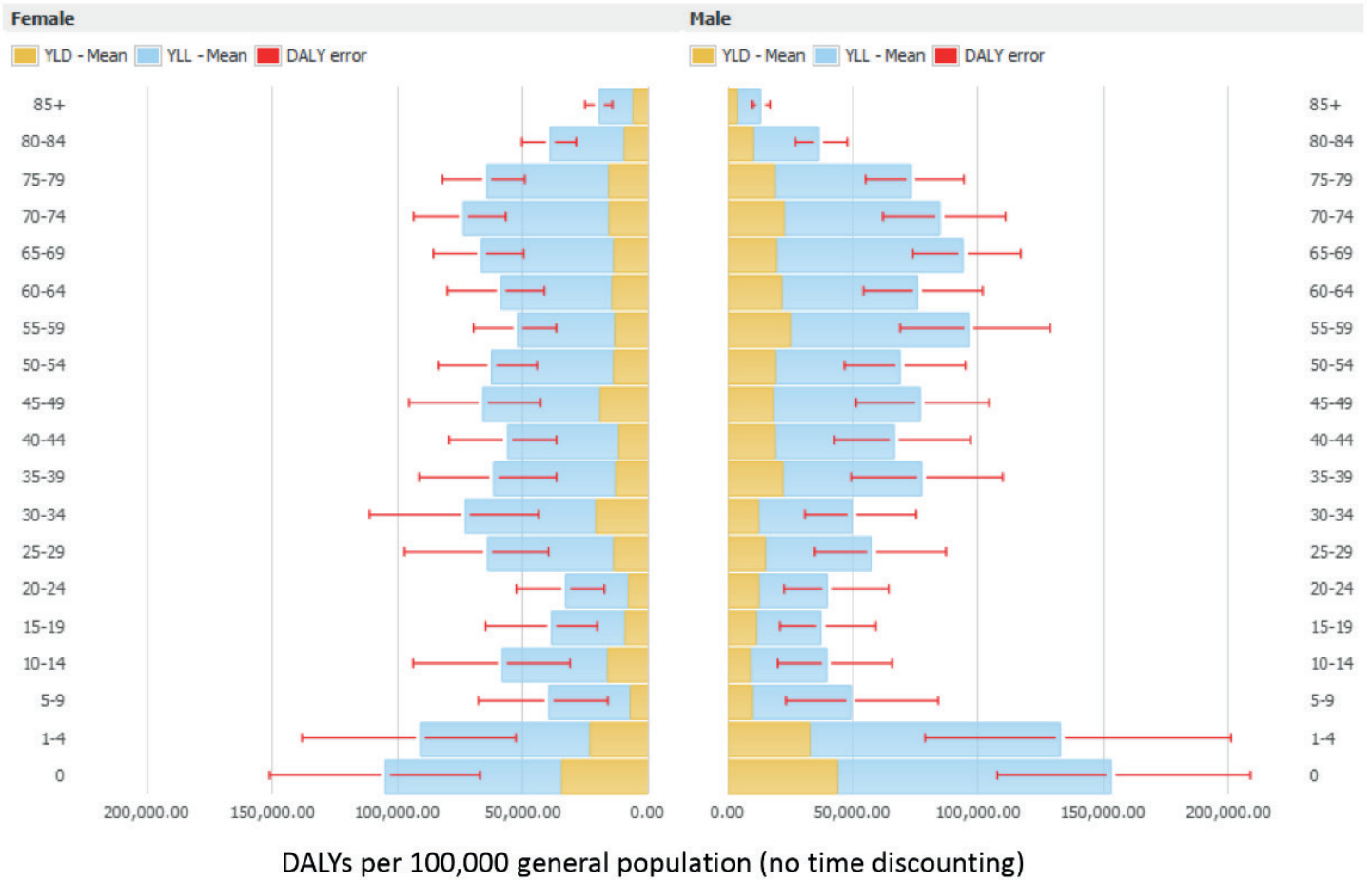

Figure 3. Estimated annual burden of six healthcare-associated infections in DALYs per 100,000 general population (median and 95% uncertainty interval) by gender and age group, split between YLLs and YLDs, EU/EEA, 2011–2012 (time discounting was not applied).

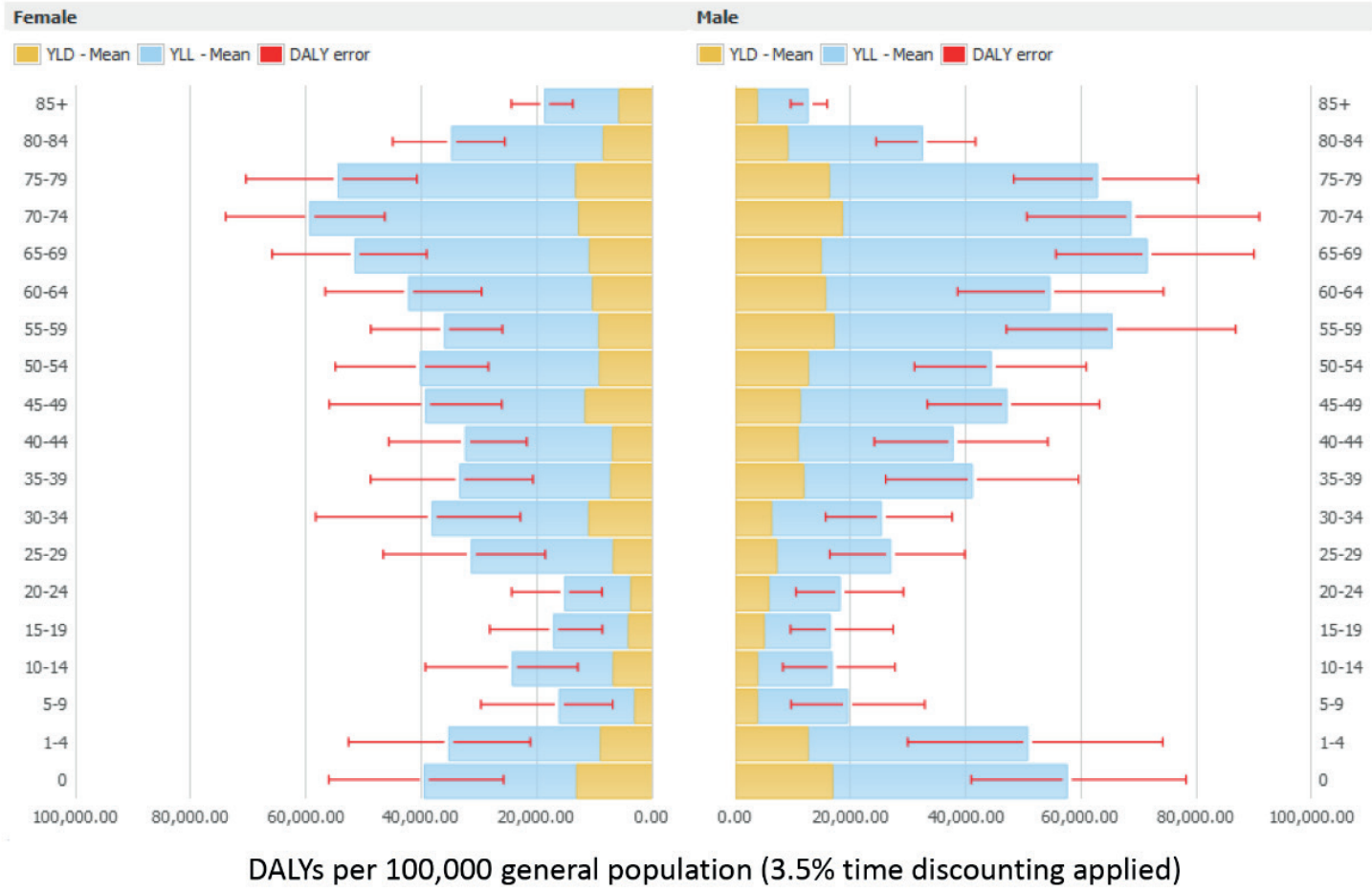

Figure 4. Estimated annual burden of six healthcare-associated infections in DALYs per 100,000 general population (median and 95% uncertainty interval) by gender and age group, split between YLLs and YLDs, EU/EEA, 2011–2012 (3.5% annual time discounting applied).

Figs 3 and 4 present the distribution of the burden of HAIs in DALYS per 100,000 total population by gender and by age group, without and with time discounting, respectively.

S1 Output provides detailed results for each HAI, as well as sensitivity analysis exploring the effect of lower values of ranges for each disease model.

Discussion

To our knowledge, this study represents the first attempt to estimate the burden of HAIs expressed in DALYs. Estimation of the burden of disease expressed in DALYs is a comprehensive and evidence-based approach to evaluate the burden of a disease that can be used to inform policy making in public health. The DALY is a composite measure that accounts not only for the number of cases but also for the associated mortality and short-term and long-term disabilities that result from a disease. DALYs provide a more comprehensive view of the burden of a disease, and the ranking of diseases according to DALYs is often different from the ranking based on incidence (Fig 5).

Rank	Healthcare-associated infections	Inccidence per 100,000
1	Surgical site infection	157
2	HA urinary tract infection	152
3	HA pneumonia	138
4	HA primary bloodstream infection	32.0
5	HA *Clostridium difficile* infection	30.0
6	HA neonatal sepsis	2.90

Rank	Healthcare-associated infections	DALYs per 100,000
1	HA pneumonia	170
2	HA primary bloodstream infection	145
3	HA urinary tract infection	81.2
4	Surgical site infection	58.2
5	HA *Clostridium difficile* infection	31.2
6	HA neonatal sepsis	16.8

Figure 5. Ranking of six healthcare-associated infections according to their median incidence per 100,000 population and median DALYs per 100,000 population, EU/EEA, 2011–2012 (time discounting was not applied).

Despite the fact that the population at risk for HAIs was limited to hospitalised patients, our estimated total burden of HAIs in the EU/EEA of 501 DALYs per 100,000 general population was significantly higher than that of other communicable diseases as estimated by the BCoDE 2009–2013 study [27]. In comparison, the total burden of all other communicable diseases included in the BCoDE 2009–2013 study was 260 DALYs per 100,000 general population, including influenza (71.2 DALYs per 100,000 general population) and tuberculosis (53.5 DALYs per 100,000 general population).

The syndromic approach that we selected for estimating the burden of HAIs may partly explain this observation, and one should be cautious when making comparisons between infection syndromes and infections caused by specific microorganisms. However, this comparison is indicative of the relative burden of HAIs on population health and on the use of healthcare resources. Although HAIs are caused by various microorganisms and are associated with a number of risks and causation pathways, the specific syndromes are well defined, and a substantial proportion of HAI cases are preventable by common infection prevention and control measures.

HAP, including ventilator-associated pneumonia, and HA primary BSI were the HAIs with the highest health burden measured in DALYs, representing 60% of the total burden of HAIs under study. This is the result of a large number of cases combined with the severity of these HAIs. HA UTIs and HA SSIs represented almost 30% of the total burden of HAIs under study. The fact that more than half of the cases of these four types of HAI are considered preventable [1] and that the four cumulatively represent 90% of the burden of HAIs under study is an indication that lowering the burden of HAIs in the EU/EEA should be an achievable goal.

HA neonatal sepsis accounted for 1,592 DALYs per 100,000 newborns (852–2,580), 12 times the DALYs of the congenital infections (congenital toxoplasmosis, congenital chlamydia infections, congenital gonorrhoea, perinatal listeriosis, congenital rubella, and congenital syphilis) included in the BCoDE 2009–2013 study.

YLLs represented almost 75% of the total DALYs, and over 60% of the DALYs were due to the acute phase of the HAIs. This is due to the high in-hospital attributable mortality of HAIs that occurs mostly in the acute phase, while long-term consequences of HAIs are comparatively less significant and less well defined. The latter may also be due to the relative lack of available evidence.

Our estimates of the burden of HAIs in the EU/EEA must be placed in a broader perspective. The 2013 Global Burden of Disease (GBD 2013) estimated DALYs for a number of syndromes other than HAIs [28]. By downloading GBD 2013 country-specific estimates from the Global Health Data Exchange (GHDx) website and adding the number of DALYs in 2013, we were able to estimate the EU/EEA burden of cardiovascular diseases (5,097 DALYs per 100,000 general population), lower respiratory tract infections (LRTIs) (392 DALYs per 100,000), neonatal sepsis (11.4 DALYs per 100,000), and diarrhoea (37 DALYs per 100,000). Our estimate of the burden of HAP (169 DALYs per 100,000) was more than one third of the GBD 2013 burden of all LRTIs. Our estimate of the burden of HA neonatal sepsis was 1.5 times higher than that of neonatal sepsis reported by GBD 2013. However, GBD 2013 was a prevalence-based study, and its results did not account for the projected future burden of disease. When discounting our estimates, thus reducing the burden of long-term sequelae, we found that HA neonatal sepsis from our study was almost half of that of neonatal sepsis in GBD 2013.

The Ontario Burden of Infectious Disease Study (ONBOIDS) used a methodology comparable to that of our study and estimated the burden of several syndromes including pneumonia, septicaemia, and UTIs, but it did not limit itself to HA cases [29]. The resulting ranking of infections according to their burden was similar to our study, with pneumonia and septicaemia ranking first in terms of number of health-adjusted life years (HALYs), followed by UTIs.

Moreover, as in our study, YLLs accounted for the largest part of the burden of disease, and the number of HALYs for C. difficile was surprisingly similar (27.2 HALYs per 100,000 general population in ONBOIDS versus 31.2 DALYs per 100,000 in our study).

Among the studied types of HAI, HA neonatal sepsis and HA primary BSI had the highest number of DALYs per case (12.1 and 8.0 DALYs per case, respectively), reflecting the severity of these infections for each affected patient. By comparison, in BCoDE 2009–2013, HIV/AIDS had 6.0 DALYs per case, invasive meningococcal disease had 5.6 DALYs per case, and tuberculosis had 3.6 DALYs per case.

In general, the burden of HAIs was higher in men, except for HA neonatal sepsis, HA UTI, and HA CDI, for which a higher proportion of the burden affected women. The fact that the incidence of HA CDI was higher in female patients is consistent with another study [30] and may be related to the higher incidence of HA CDI in elderly inpatients, a group in which female patients predominate. HAP, HA UTI, HA CDI, and, in particular, SSI had a higher burden on hospitalized patients aged 65 y and above, whereas HA primary BSI had a higher burden in paediatric patients aged less than 5 y. When including HA neonatal sepsis, almost half of the total burden of HAIs occurred in these more vulnerable population groups.

The present study was limited to HAIs in acute care settings. However, other studies indicate that, when long-term care facilities are included, the total number of HAIs each year approximately doubles [31]. Therefore, our results likely represent an underestimate of the total burden of HAIs on healthcare systems in the EU/EEA.

One strength of this study is the availability of data from the ECDC PPS to estimate the number of cases of HAIs in the EU/EEA. These data represent the most comprehensive assessment to date of the epidemiology of HAIs in the EU/EEA. An additional strength is the use of systematic literature reviews to determine attributable mortality, attributable length of hospital stay, and attributable short-term and long-term complications of HAIs. Lastly, the use of the McCabe score allowed adjustment of life expectancy, as a significant number of hospitalised patients have decreased life expectancy compared to the general population.

A number of limitations need to be taken into account when interpreting the results of this study. The outcome trees were developed based on systematic literature reviews and expert group consultations. The quality of evidence used to calculate the transitional probabilities varied as displayed in single study quality appraisals. For HA neonatal sepsis, we demonstrated by applying the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology that confidence in transitional probability estimates was also heterogeneous [16]. Variability in the estimates of HAI outcomes, and especially the attributable fraction of death associated with HAIs, was reflected in the range of the model parameters. Moreover, all outcome trees, except the one developed for SSI, were not adjusted for age-specific risks, assuming common transition probabilities for all subgroups.

Outcome trees were built on available published evidence, and the resulting disease progression pathway may not always fully reflect the definition of a case of HAI. However, while acknowledging that this might be a source of imprecision, the outcome trees were the best available approximation.

In the case of HA UTI, the outcome tree was based on studies of catheter-associated UTI in critically ill patients [32,33]. The diagnosis of HA UTI in these studies relied on bacteriuria.

However, according to the surveillance definition for HA UTI used in the ECDC PPS [11], only symptomatic bacteriuria is considered a UTI. We estimated the transitional probability from symptomatic UTI to bacteraemia/urosepsis assuming that bacteraemia/urosepsis is more common in patients with symptomatic UTI and using data on the probability of development of symptomatic UTI in patients with catheter-associated bacteriuria [34]. This led to a four times higher burden compared to the use of transitional probabilities from bacteriuria to bacteraemia/sepsis and illustrates the challenges of devising transitional probabilities for the estimation of disease burden. A minor change of the interpretation of the source literature resulted in a significant change of the result. The case fatality proportion estimated for the HA UTI model of 0.5% to 4% indicates a 10-fold range of probability. This is reflected in the large UIs around the results for the burden of HA UTI, as shown in Table 1.

An additional limitation is the uncertainty of using the Rhame and Sudderth formula for estimation of the incidence of HAI from prevalence data. The Rhame and Sudderth method was designed for and has been applied specifically to HAI surveillance [35–37]. Although both under- and overestimation have been described with the use of this method, it is the most commonly used formula for this purpose, and its use therefore allows for comparisons with the results of similar studies.

Furthermore, we used Eurostat data for discharges of inpatients to calculate the total number of cases of HAI for each age group. Eurostat data are not fully comparable across EU/EEA Member States because of differences of healthcare provision and of inclusion of various types of healthcare facilities. However, for the majority of the countries, psychiatric, rehabilitation, and long-term care facilities are not included, and the number of hospital discharges mainly represent acute care hospitals. Thus, the inpatient population as defined in the Eurostat hospital discharges database is similar to the population of acute care hospitals studied in the ECDC PPS.

We only studied six selected types of HAI. These were chosen because of their severity, perceived burden, and availability of data. Other less frequent types of HAI—such as HA central nervous system infections or HA head-and-neck infections, which represented 22% of HAIs in the ECDC PPS—were not included. This may be a factor leading to an underestimation of the total burden of HAIs in the EU/EEA.

We did not address the burden of HAIs specifically associated with antimicrobial resistance, although multidrug-resistant microorganisms are often responsible for HAIs. The fraction of the burden of HAIs attributable to antimicrobial resistance is currently unknown but is expected to vary between EU/EEA Member States because of the large intercountry differences in antimicrobial resistance percentages [38]. Higher antimicrobial resistance percentages likely

lead to increased morbidity and mortality due to inappropriate and ineffective treatment. In addition, the current increasing trends in antimicrobial resistance in bacteria responsible for HAI such as *Klebsiella pneumoniae* or *Acinetobacter* spp. combined with the lack of new antibiotics active against these bacteria likely contribute to increasing an already high burden of HAIs in the EU/EEA.

The present study highlights the substantial burden of HAIs in the EU/EEA, compared to other communicable diseases under surveillance in the EU, and the need for intensified efforts to prevent and control these infections, ultimately making European hospitals safer places.

Supplementary information

S1 Input. Annual number of age-group- and sex-specific cases per HAI and McCabe score.
https://doi.org/10.1371/journal.pmed.1002150.s001
S1 Models. Disease outcome trees.
https://doi.org/10.1371/journal.pmed.1002150.s002
S1 Output. HAI detailed results and sensitivity analysis.
https://doi.org/10.1371/journal.pmed.1002150.s003

Competing Interests

MEK is a member of the Editorial Board of PLOS Medicine.

Authors' contributions

Conceptualization: AC DP CS. Data curation: AC DP. Formal analysis: AC DP. Investigation: AC DP. Methodology: AC DP CS MAS HPB TD TE SH TH AK MS EV BW PK DLM MEK. Project administration: AC. Software: AC DP. Supervision: CS DLM MEK. Validation: AC DP CS MEK DLM. Visualization: AC. Writing original draft: AC DP. Writing – review & editing: AC DP CS MAS HPB TD TE SH TH AK MS EV BW PK DLM MEK.

Funding

The authors received no specific funding for this work.

Acknowledgments

We acknowledge Benedetta Allegranzi, World Health Organization; Philipp Deindl, University Medical Center Hamburg-Eppendorf; Maria Deja, Charite-Universitätsmedizin Berlin; Mathias Pletz, Jena University Hospital; and Walter Zingg, University Hospitals of Geneva, for their invaluable help and expertise. We also acknowledge the national Point Prevalence Survey coordination teams and participating hospitals. Finally, we acknowledge Mike Catchpole, Chief Scientist at ECDC, for his help in revising the manuscript.

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CHAPTER 5

Estimating the burden of antimicrobial resistance: Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis.

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Published online 5 November 2018. *Lancet Infectious Disease. 2019 Jan;19(1):56-66. http://dx.doi.org/10.1016/S1473-3099(18)30605-4*

Abstract

Background

Infections due to antibiotic-resistant bacteria are threatening modern health care. However, estimating their incidence, complications, and attributable mortality is challenging. We aimed to estimate the burden of infections caused by antibiotic-resistant bacteria of public health concern in countries of the EU and European Economic Area (EEA) in 2015, measured in number of cases, attributable deaths, and disability-adjusted life-years (DALYs).

Methods

We estimated the incidence of infections with 16 antibiotic resistance–bacterium combinations from European Antimicrobial Resistance Surveillance Network (EARS-Net) 2015 data that was country-corrected for population coverage. We multiplied the number of bloodstream infections (BSIs) by a conversion factor derived from the European Centre for Disease Prevention and Control point prevalence survey of health-care-associated infections in European acute care hospitals in 2011–12 to estimate the number of non-BSIs. We developed disease outcome models for five types of infection on the basis of systematic reviews of the literature.

Findings

From EARS-Net data collected between Jan 1, 2015, and Dec 31, 2015, we estimated 671 689 (95% uncertainty interval [UI] 583 148–763 966) infections with antibiotic-resistant bacteria, of which 63.5% (426 277 of 671 689) were associated with health care. These infections accounted for an estimated 33 110 (28 480–38 430) attributable deaths and 874 541 (768 837–989 068) DALYs. The burden for the EU and EEA was highest in infants (aged <1 year) and people aged 65 years or older, had increased since 2007, and was highest in Italy and Greece.

Interpretation

Our results present the health burden of five types of infection with antibiotic-resistant bacteria expressed, for the first time, in DALYs. The estimated burden of infections with antibiotic-resistant bacteria in the EU and EEA is substantial compared with that of other infectious diseases, and has increased since 2007. Our burden estimates provide useful information for public health decision-makers prioritising interventions for infectious diseases.

Introduction

Infections due to antibiotic-resistant bacteria are a threat to modern health care and have triggered the development of coordinated and comprehensive national, European, and global actions plans.[1,2] As outlined in these action plans, monitoring and evaluating interventions requires robust information on the incidence of infections with antibiotic-resistant bacteria and their effect on the health of populations; however, such information is scarce.[3] This information would also be useful to set priorities, across and within countries, and model future scenarios.[4]

Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) are relevant when monitoring trends in the EU and European Economic Area (EEA), but do not give the full epidemiological picture, in particular for monitoring the effect of the European action plan.

There are several challenges when estimating the burden of disease associated with infections due to antibiotic-resistant bacteria. For example, sampling and microbiological procedures for testing of the isolates, data collection processes, and the structures of surveillance systems might vary between and within countries. Furthermore, knowledge of the clinical and public health consequences of infections with antibiotic-resistant bacteria in humans is still scarce. In particular, scientific debate is ongoing on the appropriate epidemiological study design and statistical inference methods to measure reliable estimates of untoward clinical outcomes attributable to infections with antibiotic-resistant bacteria.[3,4]

Previous studies estimating the burden of infections with antibiotic-resistant bacteria were restricted by the number of included bacteria or type of infections.[5] In this study, we aimed to estimate the burden of infections due to selected antibiotic-resistant bacteria of public health importance in the EU and EEA in 2015, based on a country-specific evaluation of available surveillance data and on scientific evidence on attributable clinical outcomes (deaths, length of stay, risk of developing sequelae and their duration, attributable to the infections [yes or no]). We measured burden as the number of cases of all types of infections with antibiotic-resistant bacteria, the number of deaths attributable to these infections and, for the first time, the resulting number of disability-adjusted life-years (DALYs).

Methods

Overview

The study focused on the eight bacterial species frequently isolated from blood or cerebrospinal fluid (invasive isolates) in the EU and EEA in 2015 and reported to the EARS-Net. Other criteria considered were inclusion in the European Centre for Disease Prevention and Control (ECDC) point prevalence survey of health-care-associated infections and antimicrobial use (2011–12) and inclusion in the list of EU antibiotic resistance policy indicators in the ECDC, European Food Safety Authority, and European Medicines Agency Joint Scientific Opinion, and consideration of emerging threats (eg, colistin resistance).[6]

The included antibiotic resistance-bacterium combinations were colistin-resistant, carbapenem-resistant, or multidrug-resistant *Acinetobacter* spp; vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*; colistin-resistant, carbapenem-resistant, or third-generation cephalosporin- resistant *Escherichia coli*; colistin-resistant, carbapenem-resistant, or third-generation cephalosporin-resistant *Klebsiella pneumoniae*; colistin-resistant, carbapenem-resistant, or multidrug-resistant *Pseudomonas aeruginosa*; meticillin-resistant *Staphylococcus aureus* (MRSA); and penicillin-resistant and macrolide-resistant *Streptococcus pneumoniae*. Full details are provided in the appendix (p 197). We included all five types of infection: bloodstream infections (BSIs), urinary tract infections, respiratory tract infections, surgical site infections, and other infections.

Study design and population

We adapted this study from the Burden of Communicable Diseases in Europe (BCoDE) project,[7] which aimed to estimate DALYs and was specific to bacterium, type of antibiotic resistance, type of infection, and was based on incidence. We used the Global Burden of Disease 2010 (GBD 2010) standard life expectancy table.[8] Years lived with disabilities (YLD) include the length of time lived with disabilities (duration) multiplied by disability weights reflecting the ill health incurred; the latter were derived from the European disability weight project.[9]

We downloaded data in aggregate format by specific age and sex strata, without any personal identifiers, and did not require informed consent from participants. The checklist from the Guidelines for Accurate and Transparent Health Estimates Reporting is shown in the appendix (pp 219–21).

We developed a four-step approach to estimate the incidence of infections with antibiotic-resistant bacteria for five types of infection and in each of the 30 countries in the EU and EEA (appendix pp 191–211). Greece did not report data on *S pneumoniae* isolates to EARS-Net.

Disease models and attributable mortality

To account for all notable disabilities related to infections with the selected antibiotic-resistant bacteria, we developed disease models (or outcome trees) on the basis of published evidence. The baseline models for the five types of infection were expounded from a previous study that aimed to estimate the burden of health-care-associated infections,[10] with improvements such as the inclusion of the effect of comorbidities on long-term sequelae (appendix, pp 168–90).

We did a systematic review of peer-reviewed publications on the attributable case fatality and attributable length of stay of infections with antibiotic-resistant bacteria for each selected antibiotic resistance-bacterium combination and each type of infection. The literature search focused on the effects attributable to these infections compared with a matched non-infected population or to a population infected with susceptible isolates of the same bacteria. Full details on the methodology, search strategy, results, and extraction tables are given in the appendix (pp 3–141).

The results of the literature review were critically reviewed by five authors (AC, DP, CS, LDH, and AH) who scored the publications according to a defined set of applicability criteria (appendix pp 142–67). Two authors (AC and DP) discussed and agreed on the best summary estimate for each outcome parameter (mortality and length of stay; appendix pp 3–141). The final health outcome parameter values of each of the disease models are summarised in the appendix (p 176).

Estimation of incidence

First, using data reported to EARS-Net, we extracted the age-specific and sex-specific annual number of infections with antibiotic-resistant bacteria in 2015 in each EU and EEA country. For each antibiotic resistance-bacterium combination, unknown age and sex data were re-distributed by imputation.

Second, the ECDC National Focal Points for antimicrobial resistance and for health-care-associated infections were asked to report on the estimated country population coverage (including its uncertainties [appendix pp 198–99]) for each bacterium, reflecting the estimated national population coverage. We applied these country coverage correction factors to the number of cases reported to EARS-Net to estimate the total number of BSIs due to each selected combination of antibiotic resistance and bacterium.

Third, we adjusted the country coverage-corrected number of BSIs from EARS-Net with a multiplier reflecting the ratio of BSIs to non-BSIs for each antibiotic resistance–bacterium combination and derived from the ECDC point prevalence survey 2011–12.11 For each antibiotic-resistant bacterium, we applied the BSIs to non-BSIs ratio to the numbers from step two to estimate the number of urinary tract infections, respiratory tract infections, surgical site infections, and other infections. Finally, we deducted the percentage of secondary BSIs from each of the non-BSIs.

The same method used for the present study was also applied to the European Antimicrobial Resistance Surveillance System data for 2007. Information on 2007 self-reported country coverage was retrieved from the authors of the ECDC–EMEA 2009 report[12] on the burden of multidrug-resistant bacteria in the EU and EEA. For comparison, the 2015 results were adjusted to include the same antibiotic resistance–bacterium combinations and countries, and by standardising the populations according to the Eurostat revised standard population.[13]

Computational analysis and uncertainty

We inserted the final designs of the outcome trees into a custom version of the BCoDE modelling toolkit.[14] For each antibiotic-resistant bacterium, five models (one for each type of infection) were made, resulting in 80 disease models that repeated for each EU and EEA country, totalling 2400 models. We entered the sex-specific and age group-specific annual number of cases of infection with the selected antibiotic-resistant bacteria in each model.

Disease model parameters are given with 95% uncertainty intervals (UIs), which were included in the calculations as uniform distribution (two parameters; minimum and maximum) or PERT distribution (three parameters; minimum, maximum, and most likely).[15] To calculate 95% uncertainty intervals, each model was run at 10 000 iterations of Monte Carlo simulations. We did not use time discounting and age weighting.

Modelling outputs included the annual number of cases and incidence rate, the number of attributable deaths and attributable mortality rate, the number of DALYs (including years of life lost [YLLs] and YLDs), and DALY rate. We calculated values per 100 000 population. For each output, we calculated the median estimate and 95% UI on the basis of the input uncertainties. We standardised country-specific results by age group according to the Eurostat revised standard population.[13]

Attribution to health care and analysis of MRSA

We estimated the proportion of infections with health-care-associated antibiotic-resistant bacteria on the basis of various assumptions and epidemiological data (appendix pp 216–17). We further analysed results for MRSA infections to explore the apparent contradiction between the declining proportions of MRSA among *S aureus* infections as reported to the European Antimicrobial Resistance Surveillance System and EARS-Net between 2007 and 2015, and the results of this study (appendix pp 218–19).

Role of the funding source

No specific funding was allocated for this study, which was done as part of routine work of ECDC and participating institutions. The decision to submit for publication was taken by AC (employed by ECDC). The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From EARS-Net data collected between Jan 1, 2015, and Dec 31, 2015, we estimated that 671 689 (95% UI 583 148–763 966) cases of infections with selected antibiotic-resistant bacteria occurred in 2015 in the EU and EEA (table 1). These infections accounted for 33 110 (28 480–38 430) attributable deaths and 874 541 (768 837–989 068) DALYs. These estimates corresponded to an incidence of 131 (113–149) infections per 100 000 population and an attributable mortality of 6.44 (5.54–7.48) deaths per 100 000 population, causing 170 (150–192) DALYs per 100 000 population. YLLs accounted for 85.3% (145 of 170) and BSIs for 71.7% (122 of 170) of total DALYs, suggesting that the attributable mortality estimates affect the final results the most, in particular for BSIs.

67.9% (115 of 170) of the total DALYs per 100 000 were caused by infections with four antibiotic-resistant bacteria with the largest effect on health in our study: third-generation

cephalosporin-resistant *E coli*, MRSA, carbapenem-resistant *P aeruginosa*, and third-generation cephalosporin-resistant *K pneumoniae* (table 1). Infections with colistin-resistant or carbapenem-resistant bacteria accounted for 38.7% (65.9 of 170) of the total DALYs per 100 000. A greater proportion of the estimated total number of DALYs occurred in men (535 032 [61.2%] of 874 541) than in women (table 1), ranging from 43.6% (2006 of 874 541) for colistin-resistant *E coli* to 72.3% (2396 of 874 541) for colistin-resistant *Acinetobacter* spp in men.

Figure 1 shows the association between the number of cases, the number of attributable deaths, and the DALYs for each antibiotic resistance combination. The ranking of infections with antibiotic-resistant bacteria might differ depending on which indicator is used for measuring their health burden. Despite its relatively low incidence, carbapenem-resistant *K pneumoniae* had a high burden of disease because of its high attributable mortality, whereas vancomycin-resistant *E faecalis* and *E faecium* (which had a similar incidence to carbapenem-resistant *K pneumoniae*) was associated with a low burden of disease. The total burden of infections with selected antibiotic-resistant bacteria was highest in infants (aged <1 year), followed by those aged 65 years or older (figure 2).

We estimated that 63.5% (426 277 of 671 689) of cases of infections with antibiotic-resistant bacteria were associated with health care, resulting in 72.4% (23 976 of 33 110) of attributable deaths and 74.9% (127 of 180) of DALYs per 100 000 population. This finding suggests that the health effects of infections with antibiotic-resistant bacteria predominantly occur in hospitals and other health-care settings.

Italy and Greece had a substantially higher estimated burden of antibiotic-resistant bacteria than other EU and EEA countries, with carbapenem-resistant or colistin-resistant bacteria causing a larger proportion of the total burden in Greece than it did in Italy (figure 3). In 2015, in addition to a substantial burden due to infections with carbapenem-resistant or colistin-resistant bacteria, Portugal and Malta had a substantial burden due to MRSA infections. In Ireland, vancomycin-resistant E faecalis and E faecium caused a higher proportion of the total burden than in other countries. In Spain and Slovenia, a higher proportion of their burden estimates were due to antibiotic-resistant *S pneumoniae* infections than in other countries.

Table 1. Estimated annual burden of infection with antibiotic-resistant bacteria of public health importance, by decreasing number of DALYs per 100 0000 population, EU and European Economic Area, 2015

Antimicrobial-resistant bacteria	Median no. infections (95% UI)	Median no. attributable deaths (95% UI)	Median no. DALY per 100,000 population (95% UI)	Median percentage of total DALYs	Median percentage of DALYs in females	Median percentage of DALY per 100,000 population due to BSI
Third-generation cephalosporin-resistant *Escherichia coli* *†	297,416 (255,377-341,064)	9,066 (7,787-10,607)	37.2 (32.8-41.8)	21.9 (37.2/170)	46.0 (87,937/191,127)	80.5 (29.9/37.2)
Meticillin-resistant *Staphylococcus aureus*	148,727 (131,757-166,361)	7,049 (6,308-7,863)	32.6 (29.8-35.6)	19.2 (32.6/170)	38.0 (63,715/167,767)	63.9 (20.9/32.6)
Carbapenem-resistant *Pseudomonas aeruginosa* ‡	61,892 (53,210-70,984)	4,155 (3,398-5,087)	27.2 (23.0-32.0)	16.0 (27.2/170)	37.2 (52,007/139,832)	44.1 (12.0/27.2)
Third-generation cephalosporin-resistant *Klebsiella pneumoniae* *†	68,588 (61,459-76,068)	3,687 (3,370-4,031)	22.5 (20.8-24.3)	13.2 (22.5/170)	35.3 (40,820/115,546)	78.0 (17.5/22.5)
Carbapenem-resistant *Acinetobacter* spp ‡	27,343 (24,064-30,794)	2,363 (1,947-2,810)	14.0 (12.0-16.2)	8.24 (14.0/170)	35.6 (25,687/72,062)	77.9 (10.9/14.0)
Carbapenem-resistant *Klebsiella pneumoniae* ‡	15,947 (13,473-18,478)	2,118 (1,795-2,473)	11.5 (9.87-13.2)	6.75 (11.5/170)	34.8 (20,518/58,992)	92.9 (10.7/11.5)
Colistin-resistant *Klebsiella pneumoniae*	7,450 (6,223-8,715)	1,635 (1,362-1,922)	8.57 (7.19-10.0)	5.04 (8.57/170)	31.7 (13,947/44,035)	95.5 (8.19/8.57)
Vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*	16,146 (13,206-19,334)	1,081 (891-1,292)	5.49 (4.68-6.47)	3.23 (5.49/170)	37.3 (10,538/28,223)	91 (5.00/5.49)
Multidrug-resistant *Pseudomonas aeruginosa* *§	9,028 (7,736-10,425)	572 (456-703)	3.14 (2.60-3.76)	1.85 (3.14/170)	41.4 (6,681/16,142)	43.1 (1.35/3.14)
Colistin-resistant *Escherichia coli*	7,156 (6,107-8,241)	621 (518-751)	2.57 (2.22-2.95)	1.51 (2.57/170)	54.4 (7,182/13,209)	92.2 (2.37/2.57)
Penicillin-resistant *Streptococcus pneumoniae* ¶	2,836 (2,581-3,119)	172 (160-185)	1.54 (1.42-1.68)	0.91 (1.54/170)	30.1 (2,387/7,919)	49.1 (0.76/1.54)
Penicillin- and macrolide-resistant *Streptococcus pneumoniae* ‖	2,013 (1,776-2,252)	172 (141-206)	0.91 (0.76-1.06)	0.53 (0.91/170)	41.2 (1,922/4,664)	77.4 (0.70/0.91)
Multidrug-resistant *Acinetobacter* spp. **	2,181.5 (1,942.8-2,449)	100 (89.5-113)	0.90 (0.79-1.05)	0.53 (0.90/170)	56.4 (2,595/4,601)	30.6 (0.27/0.90)

Antimicrobial-resistant bacteria	Median no. infections (95% UI)	Median no. attributable deaths (95% UI)	Median no. DALY per 100,000 population (95% UI)	Median percentage of total DALYs	Median percentage of DALYs in females	Median percentage of DALY per 100,000 population due to BSI
Carbapenem-resistant *Escherichia coli* ‡	2,619.0 (2,269.0-2,961)	141 (119-165)	0.80 (0.68-0.92)	0.47 (0.80/170)	33.9 (1,390/4,101)	89.0 (0.71/0.80)
Colistin-resistant *Acinetobacter* spp.	1,084.7 (926.0-1,246)	94.5 (73.9-114)	0.64 (0.53-0.77)	0.38 (0.64/170)	27.7 (918/3,314)	78.1 (0.50/0.64)
Colistin-resistant *Pseudomonas aeruginosa*	1,261.9 (1,043.4-1,476)	84.5 (65.5-108)	0.59 (0.46-0.72)	0.34 (0.59/170)	42.0 (1,264/3,007)	44.0 (0.26/0.59)
Overall	671,689 (583,148-763,966)	33,110 (28,480-38,430)	170 (150-192)	100	38.8 (339,510/874,541)	71.7 (122/170)

Data are median number (95% uncertainty interval) or % (n/N). Data are not age-standardised. DALYs=disability-adjusted life-years. BSI=bloodstream infection. *Excluding isolates also resistant to colistin or carbapenem. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88.6%) and *K pneumoniae* (85.3%) isolates reported to EARS- Net produced an extended-spectrum β-lactamase.[9] ‡Excluding isolates also resistant to colistin. §Resistance to three or more antibiotic groups as marker of multidrug resistance. ¶Excluding isolates also resistant to macrolides. ||Excluding isolates only resistant to penicillins. **Aminoglycoside-resistant and fluoroquinolone-resistant as marker of multidrug resistance.

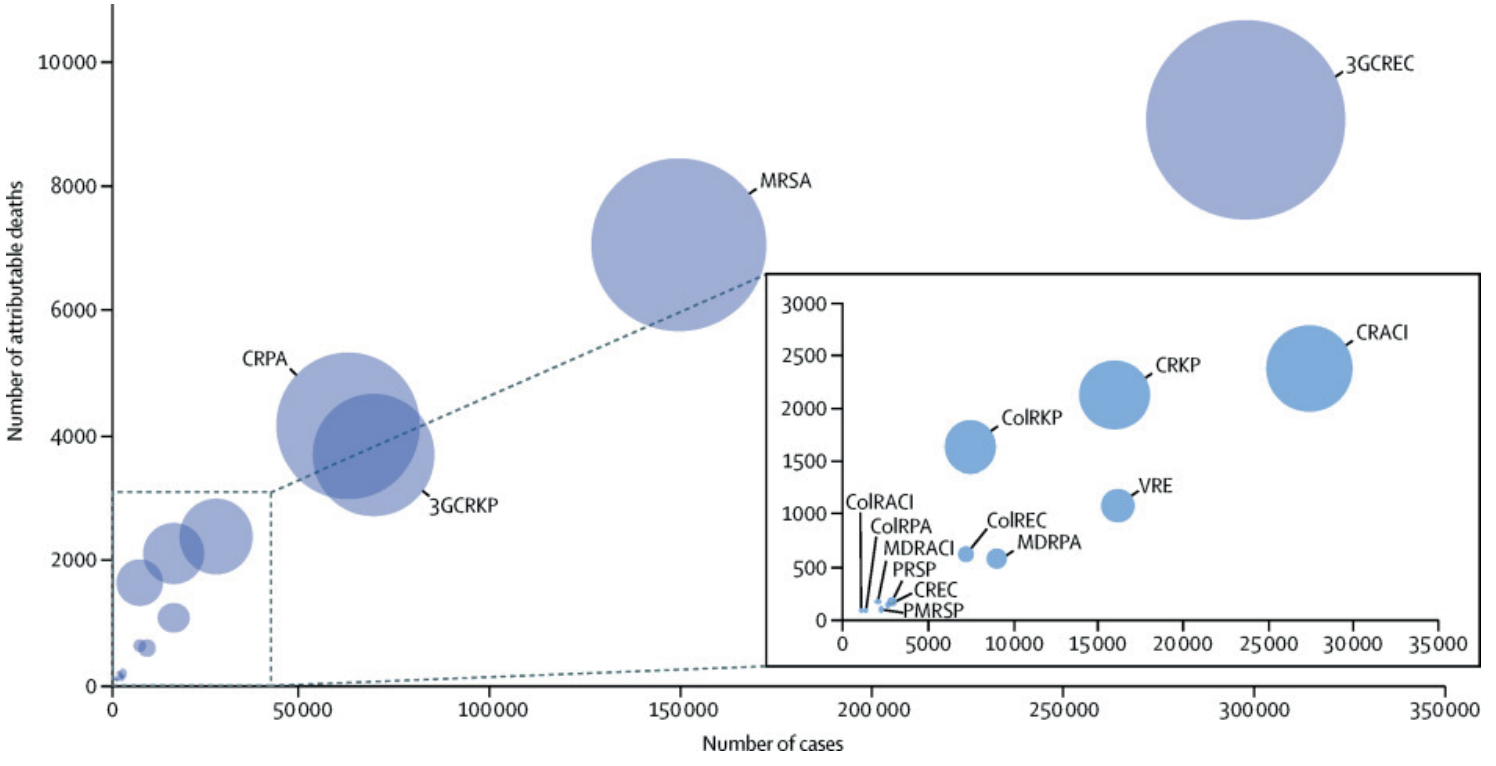

Figure 1. Infections with antibiotic-resistant bacteria, EU and European Economic Area, 2015

Diameter of bubbles represents the number of disability-adjusted life-years. ColRACI=colistin-resistant *Acinetobacter* spp. CRACI=carbapenem-resistant *Acinetobacter* spp. MDRACI=multidrug-resistant *Acinetobacter* spp. VRE=vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. ColREC=colistin-resistant *Escherichia coli*. CREC=carbapenem-resistant *E coli*. 3GCREC=third-generation cephalosporin-resistant *E coli*. ColRKP=colistin-resistant *Klebsiella pneumoniae*. CRKP=carbapenem-resistant *K pneumoniae*. 3GCRKP=third-generation cephalosporin-resistant *K pneumoniae*. ColRPA=colistin-resistant *Pseudomonas aeruginosa*. CRPA=carbapenem-resistant *P aeruginosa*. MDRPA=multidrug-resistant *P aeruginosa*. MRSA=meticillin-resistant *Staphylococcus aureus*. PRSP=penicillin-resistant *Streptococcus pneumoniae*. PMRSP=penicillin-resistant and macrolide-resistant *S pneumoniae*.

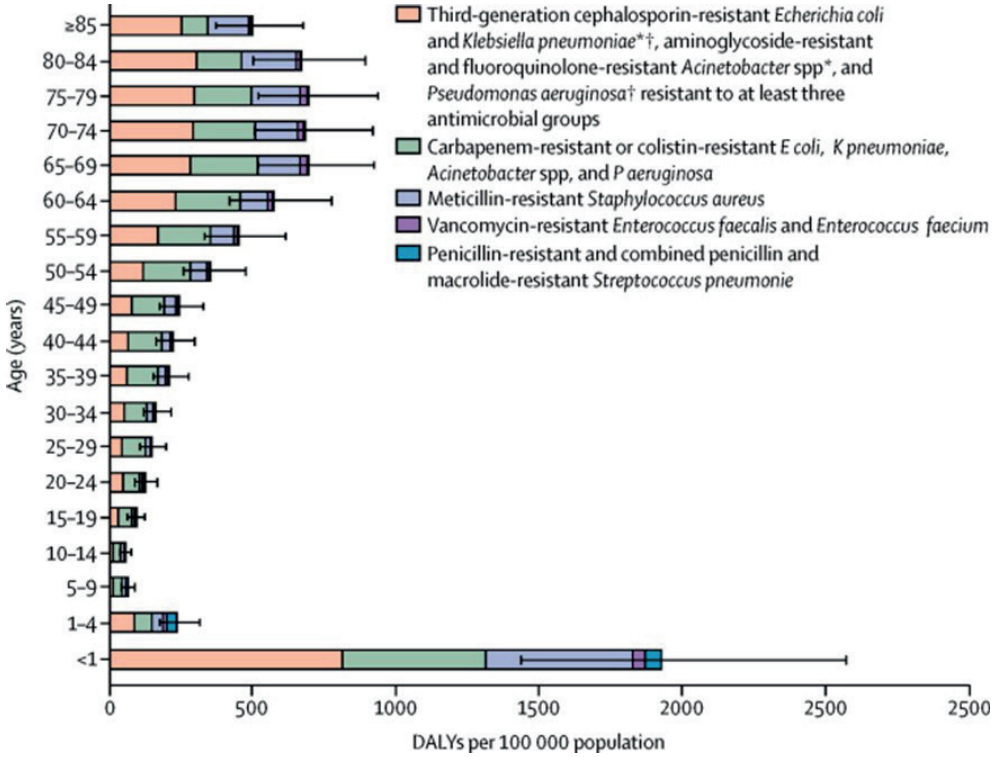

Figure 2. Model estimates of the burden of infections with antibiotic-resistant bacteria of public health importance in DALYs, by age group, EU and European Economic Area, 2015

Error bars are 95% uncertainty intervals. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88.6%) and *K pneumoniae* (85.3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.[9]

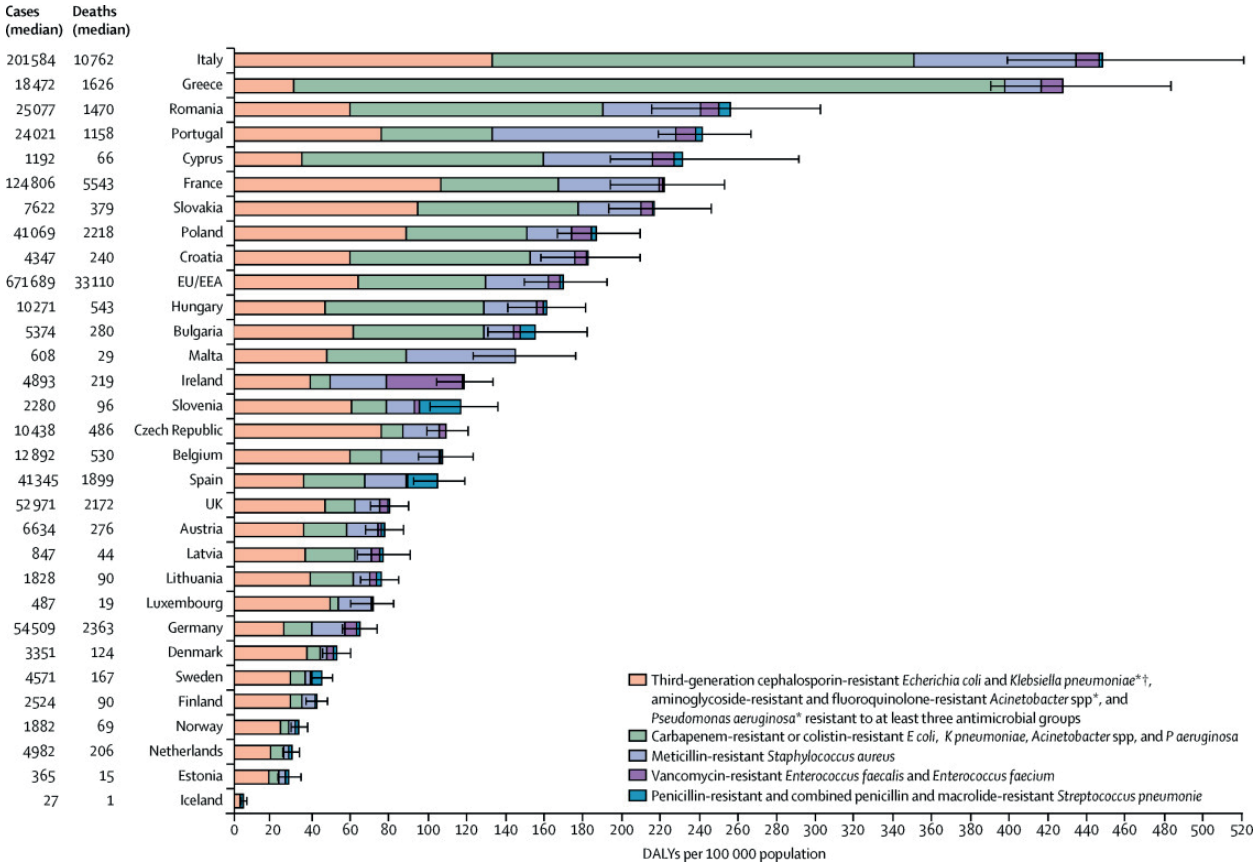

Figure 3. Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015

Error bars are 95% uncertainty intervals. Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALY rates are age-standardised to limit the effect of demographic differences across countries; numbers of cases and deaths are not age-standardised. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88.6%) and *K pneumoniae* (85.3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.[9]

Table 2. Estimated annual burden of infections with selected antibiotic-resistant bacteria of public health importance, age-group standardised, EU and European Economic Area, 2007–15

Antimicrobial-resistant bacteria	Median no. infections (95% UI)		Median no. attributable deaths (95% UI)		Factor increase in attributable deaths between 2007 and 2015
	2007	2015	2007	2015	
Third-generation cephalosporin-resistant *Escherichia coli* *†	70,276 (63,113-77,778)	285,758 (246,318-328,828)	2,139 (1,901-2,420)	8,750 (7,505-10,262)	4.12 (3.29-5.13)
Meticillin-resistant *Staphylococcus aureus*	112,782 (103,186-122,006)	143,947 (127,592-161,158)	5,340 (4,952-5,723)	6,810 (6,096-7,559)	1.28 (1.11-1.47)
Carbapenem-resistant *Pseudomonas aeruginosa*	17,972 (15,685-20,170)	59,529 (51,237-68,238)	1,216 (1,000-1,469)	4,008 (3,235-4,898)	3.29 (2.41-4.46)
Third-generation cephalosporin-resistant *Klebsiella pneumoniae* *†	16,474 (15,097-17,825)	64,980 (58,360-72,048)	891 (830-950)	3,508 (3,197-3,824)	3.95 (3.51-4.43)
Carbapenem-resistant *Klebsiella pneumoniae*	2,535 (2,125-2,952)	15,910 (13,352-18,377)	341 (288-404)	2,094 (1,779-2,460)	6.16 (4.78-8.04)
Vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*	8,277 (6,699-9,950)	15,917 (12,900-19,092)	538 (452-652)	1,065 (874-1,283)	1.95 (1.47-2.58)
Multidrug-resistant *Pseudomonas aeruginosa* ‡	5,603 (4,796-6,430)	8,749 (7,470-10,044)	357 (281-439)	556 (447-681)	1.55 (1.11-2.17)
Penicillin-resistant *Streptococcus pneumoniae* §	2,183 (2,033-2,355)	2,817 (2,552-3,104)	134 (126-143)	171 (159-184)	1.28 (1.15-1.42)
Penicillin- and macrolide-resistant *Streptococcus pneumoniae* ¶	1,916 (1,782-2,075)	2,386 (2,173-2,648)	118 (110-126)	145 (135-158)	1.25 (1.12-1.40)
Carbapenem-resistant *Escherichia coli*	543 (442-647)	2,616 (2,283-2,960)	29.2 (22.2-37.6)	141 (118-163)	4.76 (3.51-6.90)
Overall	239,238 (215,544-262,951)	602,609 (524,237-686,497)	11,144 (9,999-12,407)	27,249 (23,544-31,471)	2.46 (1.01-3.00)

Data are median (95% uncertainty interval) and are age-standardised. Note that only bacteria under surveillance in both 2007 and 2015 are included in this analysis. *Excluding isolates resistant to colistin or carbapenems. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88.6%) and *K pneumoniae* (85.3%) isolates reported to EARS-Net produced an extended-spectrum β-lactamase.[9] ‡Resistance to three or more antibiotic groups as marker of multidrug resistance. §Excluding isolates resistant to macrolides. ¶Excluding isolates resistant to penicillins, but not to macrolides.

The burden of infections with antibiotic-resistant bacteria was focused in the southern and eastern part of the EU and EEA (figure 4). In Croatia, Bulgaria, and Hungary more than 40% of the burden was due to infections with carbapenem-resistant or colistin-resistant bacteria, but the total burden in these countries was similar to the EU and EEA average. More detailed information on results per country is shown in the appendix (pp 222–55).

The estimated age-standardised number of cases of infections with antibiotic-resistant bacteria was 239 238 (95% UI 215 544–262 951) in 2007, which increased to 602 609 (524 237–686 497) in 2015 (table 2). The median number of attributable deaths increased from 11 144 (9999–12 407) in 2007 to 27 249 (23 544–31 471) in 2015. The burden of carbapenem-resistant *K pneumoniae* increased the most (by 6.16 times) in terms of number of infections and number of deaths, followed by carbapenem- resistant *E coli*, third-generation cephalosporin-resistant *E coli*, and third-generation cephalosporin-resistant *K pneumoniae*. The number of deaths attributable to third-generation cephalosporin-resistant *E coli* infections increased by 4.12 times during 2007–15, increasing to 8750 (7505–10 262).

Although the EU and EEA population-weighted proportion of MRSA among *S aureus* isolates reported to EARS-Net decreased from 26.6% in 2007 (Diaz Högberg L, European Centre for Disease Prevention and Control, personal communication) to 16.8% in 2015, our study found that the estimated incidence of MRSA infections increased by 1.28 times (95% UI 1.11–1.47). The estimated age-specific incidence of MRSA in 2007 and 2015 showed that incidence mainly increased in infants and in people aged 55 years or older; appendix p 217). In adults, the estimated incidence decreased during 2007–15, although this decrease was not significant.

Discussion

To our knowledge, this study is the first to estimate the burden of all types of infections with antibiotic-resistant bacteria expressed in DALYs. We aimed to provide reliable data for population health indicators, through a comprehensive and evidence-based approach, for planning, prioritisation, and to inform policy for control and prevention of this increasing public health threat. Moreover, DALYs allow for comparisons with the burden of other diseases and our incidence-based approach helps to assess the effect of future prevention and control interventions.[16]

Our findings show that all age groups are affected by infections with antibiotic-resistant bacteria, although their burden is significantly higher among infants than in any other age group. Among adults, the burden increases with age, suggesting that the ageing EU and EEA population could result in an increasing burden. In adults and young adults, a higher proportion of the burden was caused by infections with carbapenem-resistant and colistin-resistant bacteria. This finding might be due to a lower risk of complications after an infection in this age group in general, except for patients who are often admitted to hospital and have difficult-to-treat infections because of carbapenem or colistin resistance.

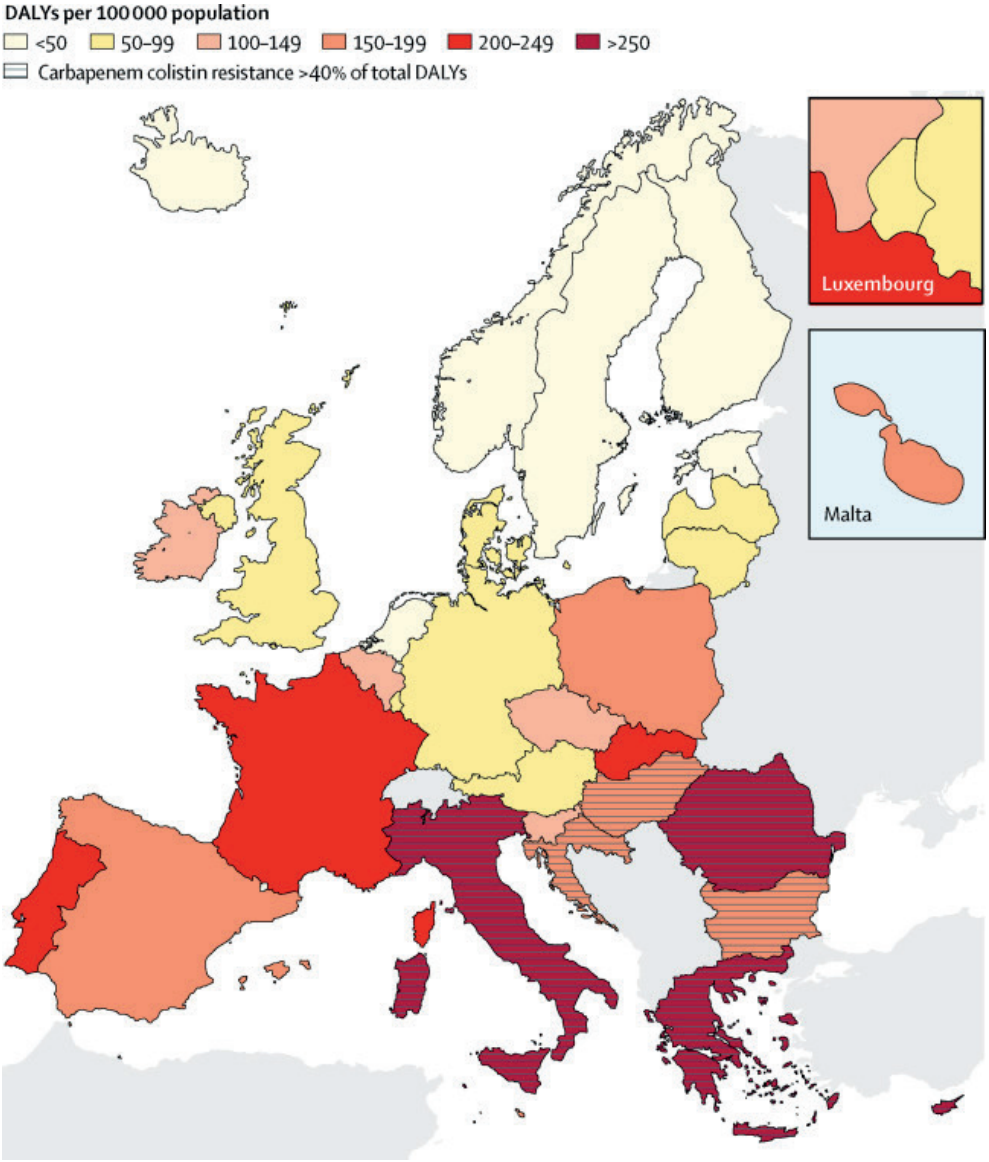

Figure 4. Model estimates of the burden of infections with selected antibiotic-resistant bacteria of public health importance in DALYs per 100000 population, EU and European Economic Area, 2015
Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALYs=disability-adjusted life-years.

Our finding of 170 DALYs per 100 000 population is similar to the combined burden of three major infectious diseases (influenza, tuberculosis, and HIV), which was 183 DALYs per 100 000 population.[17] We estimated that about 75% of the total burden of infections with antibiotic-resistant bacteria in EU and EEA countries (ie, 127 DALYs per 100 000 population) were associated with health care.

This estimation would mean, if compared with a previous study on the burden of health-care-associated infections in the EU and EEA,10 that 25% (127 of 501 DALYs per 100 000) of the burden of health-care-associated infections is due to such infections with antibiotic-resistant bacteria selected for our study. However, given the differences in the data sources and methods used to estimate the incidence of infections, this comparison should be considered with caution.

In 2013, the US Centers for Disease Control and Prevention published the first estimates of the burden of infections with antibiotic-resistant bacteria in the USA, based on 2011 national surveillance data.[18] Our study estimated a 2.6 times higher incidence of infections with antibiotic-resistant bacteria (131 cases per 100 000 population), although attributable mortality was only 1.22 times higher in our study. This increase is due to our conservative approach when defining case fatality of infections with antibiotic-resistant bacteria. The structures and resources that are available for the prevention and control of infections with antibiotic-resistant bacteria might have also caused differences, particularly in health care.

In 2016, a study[19] estimated the morbidity and mortality associated with antibiotic-resistant bacteria in France based on 2012 EARS-Net data. We used a similar methodology and found a similar incidence for France. Nevertheless, we estimated fewer MRSA infections, which can partly be explained by the decreasing trends in MRSA infections in France between 2012 and 2015, and much fewer carbapenem-resistant *P aeruginosa* infections (fewer than 50% of the number in the French study). We also estimated half the number of attributable deaths as in the French study, because of the reduced case fatality proportion stemming from our literature review.

Between 2007 and 2015, the burden increased for all antibiotic-resistant bacteria. The proportion of the DALYs due to all carbapenem-resistant bacteria combined increased from 18% (56 150 of 311 715) in 2007 to 28% (185 421 of 678 845) in 2015, and the proportion of the DALYs due to carbapenem-resistant *K pneumoniae* and carbapenem-resistant *E coli* combined doubled from 4.3% (13 515 of 311 715) in 2007 to 8.79% (57 536 of 678 845) in 2015, reflecting the emergence and rapid increase of carbapenem-resistant *K pneumoniae* infections in the EU and EEA during this period.

We were initially surprised to find that the incidence of MRSA infections increased between 2007 and 2015, given that the proportion of MRSA over meticillin-susceptible *S aureus* had decreased. This increase could be because of the increased reporting of *S aureus* BSI overall from 30 027 cases in 2007 to 45 364 cases in 2015. Further analysis of the age group-specific incidence of MRSA infections in 2007 and 2015 showed that the increase was mainly seen in infants and people aged 55 years or older (appendix p 217). The elderly population is more vulnerable to MRSA infections[20] and this population has grown since 2007; the improvement of neonatal services, leading to an increased survival of at-risk infants, might have also contributed to further increasing the size of the population at risk for MRSA infection. Studies

in Sweden,[21] Finland,[22] and Norway,[23] have also found that incidence of MRSA did not decrease in these countries.

Italy and Greece have the greatest burden of infections due to antibiotic-resistant bacteria or a combined 21.3% (171 899 of 874 541) of the EU and EEA total DALYs per 100 000 population and 36.2% (319 019 of 874 541) of EU and EEA DALYs per 100 000 population due to carbapenem-resistant or colistin-resistant bacteria. Even if one considers its large and ageing population, it is notable that about a third of the deaths due to infections with antibiotic-resistant bacteria in the EU and EEA were in Italy. Italy has published its National Action Plan on Antimicrobial Resistance 2017–20,[24] which includes targets for the reduction of antibiotic use and the control of health-care-associated infections. Greece published its National Action Plan (known as Procrustes) in 2010, which outlined the best practices for monitoring and preventing infections due to carbapenem-resistant Gram-negative bacteria.[25] Given that, in 2015, most of the burden in Greece was due to infections with carbapenem-resistant or colistin-resistant bacteria (overall case fatality proportion of 8.80), there is an urgent need to expand the measures to contain carbapenem-resistant bacteria in this country.

Our results are consistent with the European survey on carbapenemase-producing Enterobacteriaceae, which highlighted the geographical heterogeneity of carbapenemase-producing Enterobacteriaceae in the EU and EEA, and the endemic situation in Italy and Greece,[26] where the incidence of such infections per 100 000 patient-days was the highest of all EU and EEA countries.[27] Grundmann and colleagues[27] reported a ratio of 11 to one for *K pneumoniae* to *E coli* carbapenemase-producing bacteria; our study also found a higher number of carbapenem-resistant *K pneumoniae* than carbapenem-resistant *E coli* (ratio six to one).

Considering that, in our study, a large proportion of the burden was due to health-care-associated bloodstream, respiratory tract, or surgical site infections, and that more than half of health-care-associated infections are considered preventable,[28] reducing the burden of antibiotic-resistant bacteria in the EU and EEA through enhanced infection prevention and control measures could be an achievable goal. ECDC recently published guidance on infection prevention and control measures and tools for the prevention of the spread of carbapenem-resistant Enterobacteriaceae in hospitals or other health-care settings.[29] Stewardship interventions can be successful at safely reducing unnecessary use of antibiotics in hospitals.[30]

A substantial proportion of the burden of infections with antibiotic-resistant bacteria in the EU and EEA in 2015 was estimated to have been due to community-associated infections. This finding suggests that antimicrobial stewardship targeting prescribers and infection prevention and control interventions in primary care would also be necessary to reduce the burden of these infections in the EU and EEA.

Our study has several limitations. The disease models were based on the data retrieved from systematic literature reviews, which varied in availability, quality, and representativeness of evidence. We did not grade the strength of evidence supporting each parameter estimate on the basis of the statistical analysis methods used in the clinical outcome studies. Moreover, death from an infection with antibiotic-resistant bacteria is the result of many factors that are related to the pathogen, patient, and therapy, in particular regarding the delay in the administration of appropriate antibiotic therapy.[4] We did not adjust our models for age-specific risks, co-infections, appropriateness of antibiotic therapy, or for type of care, assuming common transition probabilities for all subgroups. However, to cover uncertainties related to the different patient case-mix, we considered studies focusing on specific populations for inclusion in the parameters of the disease models (appendix pp 168–90), and included when pertinent.

In the appendix (p 203), we list the limitations related to the method of estimating the incidence of infections from EARS-Net data, including frequency of susceptibility testing and representativeness of participating laboratories (geographical, type of hospital, and case-mix of patients). ECDC is currently working with countries in the evaluation of all factors affecting the EARS-Net country coverage. We also list limitations related to the factors used for converting the number of BSIs to other types of infection (appendix p 203), including the different time span of the ECDC point prevalence survey (2011–12) and EARS-Net, application of data from the point prevalence survey to community-associated infections, dependence of health-care-associated infections on the day of measurement, and estimation of non-BSIs (might have been affected by the case-mix of patients and could differ between hospitals). Finally, we defined multidrug-resistant isolates (appendix p 196) on the basis of antibiotic groups frequently used for empirical treatment of BSI as included in EARS-Net. Nevertheless, our definition might not reflect the available options for treatment in each individual case.

The strength of this study is the high quality of the surveillance data sources. EARS-Net and ECDC point prevalence survey 2011–12 are the most comprehensive, standardised, multi-country surveillance initiatives to date for antibiotic-resistant bacteria and health-care-associated infections. Another strength was the use of systematic literature reviews to determine the best available estimates of attributable mortality, attributable length of stay, and attributable short-term and long-term complications of infections.

To our knowledge, this study estimated for the first time the burden of five types of infection with antibiotic-resistant bacteria in the EU and EEA expressed in DALYs and provided reliable EU and EEA and country-specific profiles for 2015 data.

The estimated burden of infections with antibiotic-resistant bacteria in the EU and EEA is substantial compared with that of other infectious diseases, and has increased since 2007. Strategies to prevent and control antibiotic-resistant bacteria require coordination at EU and EEA and global level. However, our study showed that the contribution of various antibiotic-resistant bacteria to the overall burden varies greatly between countries, thus highlighting the

need for prevention and control strategies that are tailored to the needs of each country in the EU and EEA. Our study also showed that most of the burden of infections with antibiotic-resistant bacteria in the EU and EEA was health care associated, thus emphasising the need to urgently address antimicrobial resistance as a patient safety issue and the need for alternative treatment options for patients with such infections who have comorbidities or are otherwise vulnerable (eg, because of their poor immune system or age).

Future studies should include estimates of the burden of infections due to other antibiotic-resistant bacteria of public health importance, such as drug-resistant *Mycobacterium tuberculosis*, drug-resistant *Salmonella* spp, and drug-resistant *Neisseria gonorrhoeae*, to give a more comprehensive estimate of the burden of antimicrobial resistance. In the long term, research should be done to better understand the factors underlying the estimations of EARS-Net country coverage, such as catchment population, patient case-mix, laboratory capacity, and the appropriateness and frequency of collection of blood cultures.

Supplementary information

Supplementary appendix:

- Literature review report
- Literature selection grids
- Final disease outcome trees
- Methodology protocol to estimate incidence
- GATHER checklist and further analysis on MRSA and attribution as healthcare-associated infections
- Country specific results

https://www.thelancet.com/cms/10.1016/S1473-3099(18)30605-4/attachment/84c40198-ad78-4322-a158-cdf215c37dfc/mmc1.pdf

Competing Interests

ATA reports consultancy fees from Xellia Pharmaceuticals and Fidelta in the 36 months before submission of this manuscript. DŻ reports a grant from the Ministry of Health of the Republic of Poland for the National Program for Antibiotic Protection. KGK reports that Landspitali University Hospital received grants from GlaxoSmithKline Vaccines to study the effects of pneumococcal vaccination in Iceland. GLD reports grants from Pfizer and Gilead Sciences, and honoraria from Pfizer, Achaogen, MSD, and Rempex, outside the submitted work. GAP reports personal fees from Angelini Pharmaceuticals, outside the submitted work. All other authors declare no competing interests.

Authors' contributions

AC, DLM, LDH, and DP conceived the study. AC, LDH, DP, AQ, AH, GSS, MC-C, MEK, BD, MC, DAO, TCO, MJS, CS, and DLM designed the study. All authors acquired and analysed the data. AC, LDH, DP, AQ, AH, GSS, MC-C, MEK, BD, MC, DAO, TCO, MJS, CS, and DLM interpreted the findings. AC wrote the first draft of the manuscript. AC, LDH, DP, AQ, AH, GSS, MC-C, MEK, BD, MC, DAO, TCO, MJS, CS, and DLM drafted subsequent versions. All authors critically reviewed this report and approved the final version.

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Funding

European Centre for Disease Prevention and Control. No specific funding was allocated for this study, which was done as part of routine work of ECDC and participating institutions. The decision to submit for publication was taken by AC (employed by ECDC). The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

MC, DAO, and TCO alone are responsible for the views expressed in this Article; these views do not necessarily represent the views, decisions, or policies of the Organisation for Economic Co-operation and Development (OECD). We acknowledge the work done by the staff at the participating clinical microbiology laboratories and at the national health-care services that provided data to EARS-Net. We thank all of the hospitals that participated in the ECDC point prevalence survey 2011–12 and, in particular, the hospital staff that collected, validated, and entered the data during the survey, and the national teams that coordinated the survey in each participating country. We also thank Victoria Simpkin (OECD, Paris, France) for help during the initial literature reviews; Annalisa Pantosti (Istituto Superiore di Sanità, Rome, Italy), Maria Luisa Moro (Regional Agency for Health and Social Care of Emilia-Romagna, Bologna, Italy), José Campos Marqués, Jesús Oteo Iglesias (Instituto de Salud Carlos III, Madrid, Spain), Ines Noll, and Marcel Feig (Robert Koch Institute, Berlin, Germany) for their advice on the quality of EARS-Net data; and Ole Heuer for his support and work in shaping the EARS-Net surveillance network.

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PART II

Applying burden of disease estimates for policy-making

CHAPTER 6

Estimating the annual burden of tick-borne encephalitis to inform vaccination policy, Slovenia, 2009 to 2013.

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Published 20 April 2017. *Eurosurveillance. 2017 Apr 20;22(16):30509. http://dx.doi.org/10.2807/1560-7917.*

Abstract

With an annual incidence between 8 and 15 per 100,000 population in the period from 2009 to 2013, Slovenia has one of the highest notified incidences of tick-borne encephalitis (TBE) in Europe. TBE vaccination coverage remains at about 7.3%. To inform vaccination policy, we used surveillance data from 2009 to 2013 to calculate the overall and age- and sex-specific mean annual TBE incidence. We estimated disability-adjusted life years (DALYs) with 95% uncertainty intervals (UI), using the Burden of Communicable Diseases in Europe approach from the European Centre for Disease Prevention and Control. The mean annual incidence was 11.6 per 100,000 population, peaking in older age groups (50– 74 years: 18.5/100,000) while relatively lower among children (5–14 years: 10.2/100,000). We estimated an overall 10.95 DALYs per 100,000 population per year (95% UI: 10.25-11.65). In contrast to the TBE incidence, the disease burden in children aged 5–14 years was higher than in adults aged 50–74 years: 17.31 (95% UI: 14.58–20.08) and 11.58 (95% UI: 10.25–12.91) DALYs per 100,000 stratum-specific population, respectively. In a limited resource setting where prioritisation of TBE vaccination strategies is required, vaccination programmes targeting children may have a higher impact on disease burden.

Introduction

Tick-borne encephalitis (TBE) is a vector-borne disease caused by the TBE virus [1]. It typically presents as a two-phased illness [2-4]. The first phase is associated with symptoms such as fever, fatigue, headache, myalgia and nausea. The second phase involves the nervous system with symptoms related to meningitis and/or encephalitis. Life-long sequelae can have an important impact on the quality of life of those affected [5]. TBE cases notified in Europe have surged in the last three decades with an estimated increase of 193% [6-8].

In Slovenia, notification of TBE is mandatory and based on the European Union (EU) standardised case definition [9]. Only cases with central nervous system involvement (meningoencephalitic TBE) and laboratory confirmation are notified. Slovenia is one of the countries with the highest notified incidence in Europe, ranging from 8 to 15 per 100,000 in the period from 2009 to 2013, with cases occurring throughout the country [10]. Data for the past 20 years show a non-homogenous age distribution with higher incidence in older age groups (> 40 years) [10]. Preventive measures include the use of repellents, appropriate clothing and daily inspection of the skin to remove ticks [11]. The most effective method of preventing TBE is vaccination [11-13]. Mandatory vaccination against TBE was introduced in Slovenia in 1986 for those at risk of occupational exposure, and in 1990 for students at risk of exposure during curricular training, while the rest of the population needs to pay for the vaccination themselves. TBE vaccination coverage in Slovenia remains low: by 2007, the proportion of the general population reporting to ever have been vaccinated against TBE was 12.4% [14].

In a context where limited resources prevent universal TBE vaccination free of charge, data are needed to identify those groups most affected by the disease so that vaccination can be targeted in order to yield the greatest benefit on population health. Countries have used incidence data to guide vaccination strategies towards specific age groups and geographical areas [15-17]. Estimation of the TBE burden in the form of disability-adjusted life years (DALYs), a summary measure of population health, is better suited to express the overall and age group-specific impact of the disease in the population while taking into account the effects of acute illness and its sequelae on mortality and morbidity [18]. The objective of this study was to estimate the overall and age- and sex-specific annual burden of TBE in Slovenia in order to inform vaccination policy in a setting with limited resources.

Methods

Model

To estimate the burden of TBE we used the pathogen-based incidence approach developed by the European Centre for Disease Prevention and Control (ECDC) Burden of communicable diseases in Europe project (BCoDE) [18-20]. The burden was expressed in DALYs. DALYs have two components: years of life lost due to premature death (YLL) and healthy years of life lost due to disability (YLD) [21].

We used a disease model (outcome tree) based on the current knowledge of the disease progression pathway, linking all health outcomes related to TBE with the initial infection. Starting with the infection a case moved through the outcome tree transitioning into different health outcomes according to different conditional transition probabilities (i.e. probability of occurrence of each health outcome), exiting the tree with a resolved infection, with a life-long disability or with a fatal outcome. In order to measure YLL, life expectancy was based on the standard reference life table developed within the Global Burden of Disease 2010 project [22]. To measure YLD, each health outcome was characterised by a disease duration and a disability weight. Disability weights quantify health losses to reflect the disability experienced by someone living with a health issue. Based on the severity of the disease, they range from 0 (full health) to 1 (death). The disability weights were generated for BCoDE and the Global Burden of Disease study (GBD) 2013 through elicitation methods [23,24]. The outcome tree for TBE used in our model (Figure 1) was based on a thorough review of published studies and on the opinion of ECDC experts [25]. All parameters included in the outcome tree, conditional transition probabilities, durations and disability weights were based on published studies and entailed a certain level of uncertainty. The uncertainty was modelled by incorporating ranges using either uniform or Pert distributions [26] and quantified by performing Monte Carlo simulations with 10,000 iterations to obtain 95% uncertainty intervals (UI). In order to assess age groups of interest for vaccination strategies, we compared the median DALYs and their 95% UIs.

Input data

The ECDC BCoDE toolkit was used for DALY estimation [25]. Input data for the model were the mean annual numbers of meningoencephalitic TBE cases notified to the Slovenian national surveillance system for communicable diseases from 2009 to 2013. They were stratified by 5-year age groups and by sex. For those calculations where a population estimate was required, we used the 2011 population data for Slovenia obtained from Eurostat [27]. The main type of input data for TBE in the BCoDE toolkit was the number of symptomatic infections (first phase of the disease); to obtain this, surveillance data were multiplied by the appropriate transitional probabilities as specified by the TBE outcome tree. No time discounting was applied, thus future and present disabilities were weighted equally.

Results

From 2009 to 2013, a total of 1,190 cases (58% males) of TBE in their meningoencephalitic phase were notified in Slovenia, with a mean of 238 cases/year. The median age at diagnosis was 51 years (range: 1–86 years). The mean annual incidence of meningoencephalitic TBE was 11.6 per 100,000 population (9.6/100,000 for females and 13.6/100,000 for males). Incidence was higher in older individuals (50–74 years: 18.5/100,000) than in children (5–14 years: 10.2/100,000). Data by 5-year age groups and by sex are presented in Figure 2.

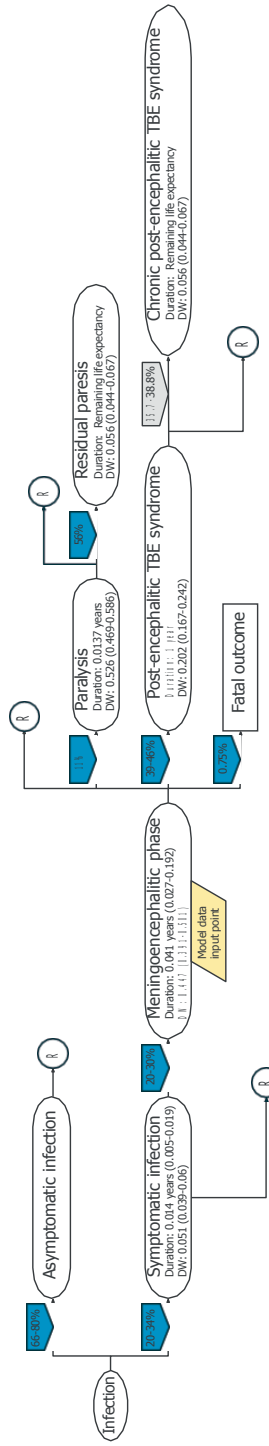

Figure 1. Outcome tree for tick-borne encephalitis virus infection
DW: disability weight; R: resolution of infection; TBE: tick-borne encephalitis.

The estimated DALYs per year were 224.52 (95% UI: 210.14-238.84), corresponding to 10.95 DALYs per 100,000 per year (95% UI: 10.25-11.65). Each case of TBE accounted for an average of 0.23 DALYs (95% UI: 0.22–0.24) In the Table, DALYs and their components (YLL and YLD) are presented for all health outcomes related to TBE. YLDs per year accounted for 67% of the total disease burden. Late sequelae, following the meningoencephalitic phase of the disease, contributed to 63% of the DALYs per year.

The group of 50–54-year-old women and the group of 25–29-year-old men had the highest point estimates of DALYs per year with 10.56 (95% UI: 7.34–14.03) and 13.02 (95% UI: 9.25–17.49) DALYs per year respectively. When looking at both sexes together, the 50–54 and 55–59-year-olds accounted for the highest number of DALYs, 21.08 (95% UI: 14.91–28.40) and 20.48 (95% UI: 14.48–27.70), respectively.

In terms of DALYs per 100,000 stratum-specific population, the highest burden point estimate was among the 5–9-year-olds: 19.29 DALYs per 100,000 stratum-specific population per year (95% UI: 15.41–23.90) with16.62 DALYs (95% UI: 11.48–22.51) and 21.69 DALYs per 100,000 per year (95% UI: 15.12–29.28) for girls and boys, respectively. Data by 5-year age groups and by sex are presented in Figure 3.

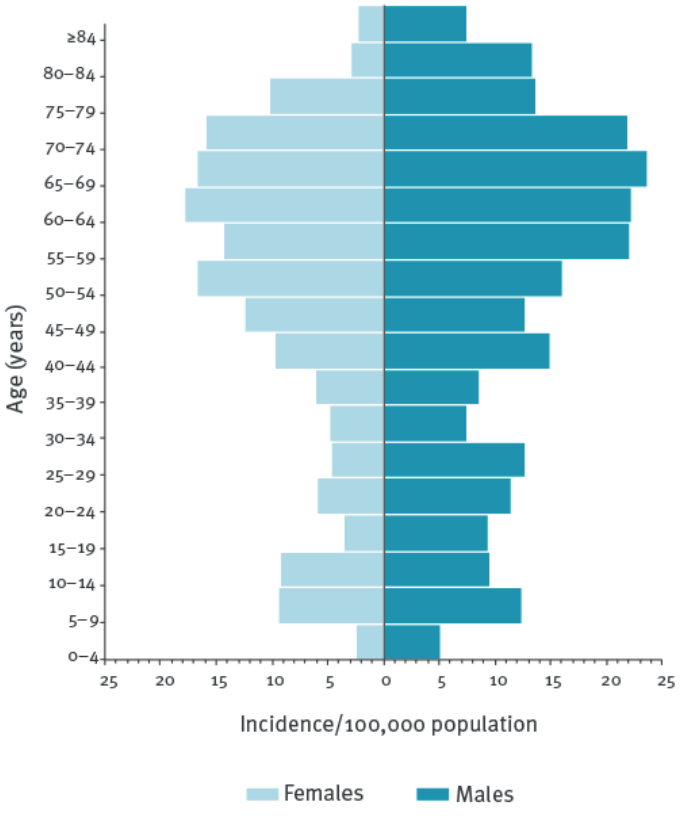

Figure 2. Mean annual incidence per100,000 of tick-borne encephalitis, by age and sex, Slovenia, 2009–2013 (n = 1,190)

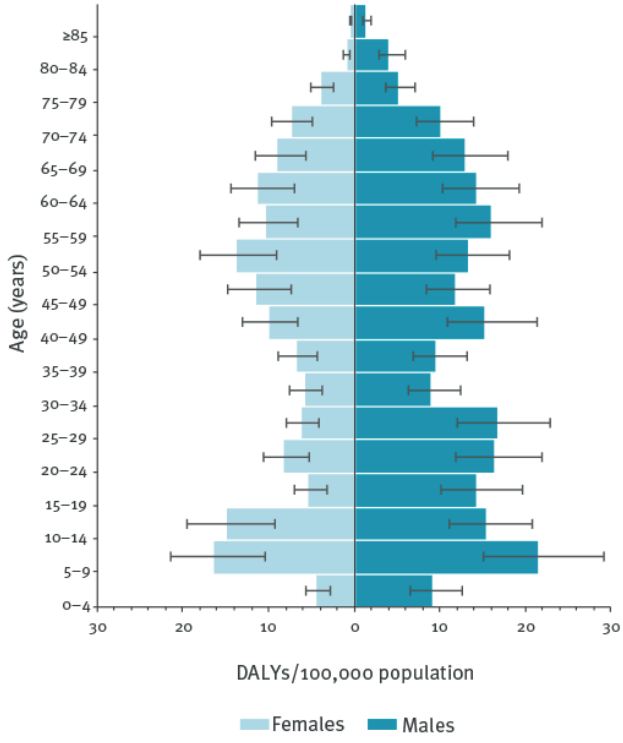

Figure 3. Estimated mean annual disability-adjusted life years per 100,000 stratum-specific population due to tick-borne encephalitis, by age and sex, Slovenia, 2009–2013
DALYs: disability-adjusted life years. The whiskers represent 95% uncertainty intervals.

The group of 50–74-year-olds had a lower TBE burden estimate of 11.58 (95% UI: 10.25–12.91) DALYs per 100,000 stratum-specific population per year in com- parison to the 5–14-year-olds with a burden of 17.31 (95% UI: 14.58–20.08) DALYs per 100,000 stratum-specific population per year (Figure 4).

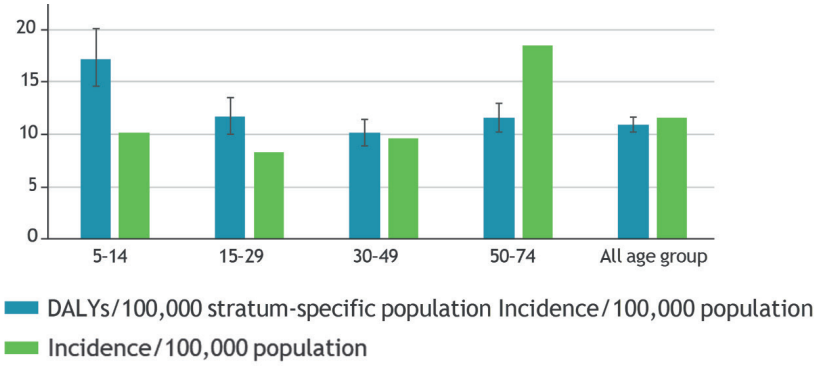

Figure 4. Figure 4. Estimated mean annual incidence per 100,000 and mean annual disability-adjusted life years per 100,000 stratum-specific population due to tick-borne encephalitis, by age group, Slovenia, 2009–2013
DALYs: disability-adjusted life years. The whiskers represent 95% uncertainty intervals.

Discussion

In this paper we present the overall and the age- and sex-specific annual burden of TBE in Slovenia expressed in DALYs. The use of DALYs integrates mortality and morbidity from TBE in a single composite health metric, giving a comprehensive estimate of the impact of this disease on population health.

An analysis of notified TBE cases in the 5-year period from 2009 to 2013 confirms Slovenia as one of the countries, together with the Baltic states and the Russian Federation, where reported incidence per 100,000 is the highest in Europe [11,28]. With an estimate of 10.95 DALYs per 100,000 per year (95% UI: 10.25-11.65), TBE has an important impact on the health of the Slovenian population. In accordance with input incidence data, we found consistently higher burden point estimates in male persons across all ages. According to the BCoDE 2009–13 study, the estimated burden of TBE in Slovenia was nine times higher than the corresponding estimated burden of TBE measured in DALYs per 100,000 population per year for the EU and European Economic Area (EEA) for the same time period [29]. Moreover, the impact of TBE on the Slovenian population is comparable to that of healthcare-associated neonatal sepsis (16.8 DALYs/100,000) according to a recent study on healthcare-associated infection in the EU/EEA [30].

Table 1. Tick-borne encephalitis annual burden estimates, Slovenia, 2009–2013

	DALYs/year (95% UI)	DALYs/100,000 (95% UI)	YLL/yea (95% UI)	YLD/year (95% UI)
Symptomatic infection	0.67 (0.61–0.73)	0.03 (0.03–0.04)	0	0.67 (0.61–0.73)
Meningoencephalitic phase	81.94 (76.77–87.15)	4.00 (3.74–4.25)	74.88 (70.14–79.56)	7.06 (5.92–8.36)
Post-encephalitic TBE syndrome	21.36 (19.87–22.91)	1.04 (0.97–1.12)	0	21.36 (19.87–22.91)
Paralysis	0.20 (0.18–0.21)	< 0.001	0	0.20 (0.18–0.21)
Residual paresis	34.32 (31.98–36.73)	1.67 (1.56–1.79)	0	34.32 (31.98–36.73)
Chronic post-encephalitic TBE syndrome	86.04 (79.87–92.31)	4.20 (3.90–4.50)	0	86.04 (79.87–92.31)
Total	**224.52 (210.14–238.84)**	**10.95 (10.25–11.65)**	**74.88 (70.14–79.56)**	**149.64 (139.67–159.75)**

DALYs: disability-adjusted life years; TBE: tick-borne encephalitis; UI: uncertainty interval; YLD: healthy years of life lost due to disability; YLL: years of life lost.

Looking at incidence data alone, older age groups (50–74-year-olds) appeared most affected by TBE in Slovenia. However, the use of DALYs identified children (5–14-year-olds) as the group with a higher burden. This difference in impact of TBE would not have been detected, if we had limited our assessment to incidence data, ignoring the combined effects of morbidity, short- and long-term sequelae and mortality. Other countries with a similar TBE incidence

profile as Slovenia could profit from this approach to identify groups with important burden, particularly when informing decision makers about the allocation of limited resources for targeted public health interventions (i.e. vaccination).

Vaccination is regarded as the most effective preventive measure for TBE [11]. Studies have shown a 96–99% field effectiveness in persons receiving three doses following the recommended schedule [12,13]. In neighbouring Austria, an estimated 88% of the general population are vaccinated with at least one dose, while 58% are vaccinated regularly following the advised schedule [13]. Austria has managed to reduce the number of TBE cases by 90% by increasing its vaccination rate from 6% in 1980 to its current level [13]. Despite the fact that vaccination has been recommended in Slovenia for decades, only 12% of the population was vaccinated with at least one dose by 2007 and only 7.3% get vaccinated regularly following the advised schedule [31].

TBE vaccination remains a self-paid expense for the majority of the population. The costs are covered by the mandatory insurance system or by the employer only in case of occupational exposure or exposure during education or training. Data from 2007 show that only 4.6% of the population paid themselves for TBE vaccination [14]. A recent study from Šmit et al., estimating DALYs of TBE in Slovenia using the GBD project methodological approach, supports the need for a public health strategy aimed at increasing the national vaccination coverage [32]. Multiple factors influencing the decision to get vaccinated against TBE (knowledge, trust, accessibility, cost) should be considered when planning strategies aimed at increasing vaccination coverage [33]. Projections, however, show that the impact of a vaccine subsidy, making the vaccine free of charge, could alone increase coverage by 45%, and even more in low-income households [34].

Increasing TBE vaccination coverage should be considered as an option for intervention to reduce the impact of TBE [10,32]. In the presence of limited resources, the implementation of such a measure could be difficult in the short term. Our results suggest that effective prevention of TBE in children would have the highest impact in terms of DALYs of TBE averted. This novel insight in the distribution of TBE burden should be considered when prioritising access to TBE vaccination and could improve previous recommendations originating from incidence data alone, where the focus was mainly on older age groups [10].

Prioritising vaccination in children could be easier thanks to the well-functioning Slovenian national childhood immunisation programme. It is also important to take into account the need for booster doses of the TBE vaccine. In the age groups of interest, a three-dose primary vaccination schedule with a first booster dose after 3 years and further boosters every 5 years is recommended to maintain seropositivity [35]. A recent study showed that a schedule that includes the first booster dose yields a high and long-lasting (> 5 years) immune response, thus suggesting that subsequent TBE booster intervals could be extended beyond the current recommendation [36]. Considering the financial implications of lifelong

booster doses (and the different schedules that apply at different ages), age-specific cost-effectiveness studies are needed to inform decisions on the extent to which TBE vaccine can be subsidised in order to achieve the highest level of immunopersistence and impact on TBE burden in a cost-effective manner.

We considered prioritising the most affected areas or regions as an alternative approach. Although some regions in Slovenia are more affected than others, TBE occurs throughout the country. Considering the epidemiological situation of TBE in Slovenia, the country`s relatively small area and population size, as well as the mobility of the population between regions, we consider this approach could be potentially misleading and lead to health inequalities. Other countries where restricted areas or regions are affected could consider a modelling approach stratified by region.

This study has certain limitations. The outcome tree describing the progression pathway of the disease assumes no differences in disease progression between different age groups. Lifelong sequelae make an important contribution to the overall burden, especially in the younger age groups. The disease in children is commonly regarded as mild, but evidence is increasing for the relevance of severe acute disease and long-term sequelae of TBE in children, as well as for the lack of knowledge around the matter [5,37-46]. The uncertainty around the disease progression, over- all and for different age groups, can lead to an over- or underestimation of the burden overall and in different age groups. Future study of the disease progression of TBE in different age groups is needed and could improve the accuracy of the model. Another limitation of our study is that the data set used for input in the model was not corrected for underestimation (due to under-reporting and under-ascertainment) of the surveillance system [47]. At the moment of writing, data on underestimation of TBE notification were not available. However, taking into consideration the structure of the morbidity surveillance pyramid [47], we can assume that the notified data were still underestimating the true incidence of disease, thus leading to an underestimation of our burden estimates.

DALYs are a composite health metric highly dependent on the assumptions made; it is commonly used for ranking the relative burden of diseases within the same study, in cost-effectiveness analyses or evaluations of interventions (e.g. DALYs averted). The differences in absolute values between our results and the recent study from Šmit et al. [32] are probably due to differences in underlying assumptions and disease modelling approaches. Šmit et al. used data from a single year that had more cases than the 5-year annual average we used; they used an underestimation coefficient (4.5) for the number of cases of meningoencephalitic TBE, but we did not find enough evidence to make such assumptions; they modelled all neurological sequelae as lifelong. Moreover, Šmit et al. used higher transitional probabilities (in the age groups older than 15 years) and higher disability weights when modelling mild sequelae. Taking this into consideration, a direct comparison is not valid. Our focus on the distribution of the TBE burden across different age groups enabled us to suggest efficient options for vaccination.

Conclusion

We identified a higher burden of TBE among children aged 5–14 years than among adults aged 50–74 years despite a lower TBE incidence. Incidence data alone do not fully reflect the disease impact and should not be the only indicator to inform vaccination policy. In a limited resource setting where prioritisation of TBE vaccination strategies is required, vaccination programmes targeting children should be considered as possibly having a higher impact on disease burden. Our data could be used for future cost-effectiveness studies.

Supplementary information

None.

Competing Interests

None declared.

Authors' contributions

MF and AC were responsible for the conception and design of this study. MF drafted the first study protocol, and AC, EC, IK, MM contributed to further drafts. MF and MG collected and assembled the data. MF undertook the primary data analysis in collaboration with AC. All authors had an opportunity to contribute to the interpretation of the results. MF wrote the first draft of the manuscript, and all other authors contributed to further drafts.

Funding

None declared.

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CHAPTER 7

Impact of food and water-borne diseases on European population health.

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Published 18 June 2016. *Current Opinion in Food Science 2016 Dec;12:21–29. http://dx.doi.org/10.1016/j.cofs.2016.06.002*

Abstract

Composite health measures are increasingly applied in studies aiming at describing the burden of diseases, and food and water-borne diseases (FWDs) are no exception. The Burden of Communicable Diseases in Europe (BCoDE) is a project led and funded by the European Centre for Disease Prevention and Control (ECDC) with the purpose of encouraging and empowering public health experts in the estimation of the impact of communicable diseases expressed in Disability Adjusted Life Years (DALYs). Calculation of DALYs and a critical assessment of burden of disease outputs require a thorough consideration of a number of methodological and epidemiological decisions ranging from modelling (e.g. incidence versus prevalence), disease model parameters (e.g. risks of developing complications or death) and the data feeding the number of cases.

Burden of disease studies produce useful results for public health decision-making, in particular when they aim at informing preventive strategies. For this purpose, we attributed FWDs results from the BCoDE 2015 study to different exposure routes. We discuss these in the more general perspective of generating burden of disease evidence for planning and prioritisation, including the potentials and limitations of its methodology.

Introduction

Determining the public health impact of food and water-borne diseases (FWDs) poses a number of challenges. Attempts to estimate such burden include reporting of infections [1,2,3], incidence and mortality [4]. However, severity, duration and mortality related to FWDs vary widely; therefore, a more coherent and consistent approach is needed to enable comparison between the overall impact of diseases. Disability-adjusted life years (DALYs), a summary measure of population health developed by the Global Burden of Disease (GBD) study [5], match these requirements and are increasingly utilised to inform evidence-based health policy decision making [6,7,8,9,10,11].

In 2006, the European Centre for Disease Prevention and Control (ECDC) commissioned a pilot estimation of seven selected infectious diseases (IDs) in order to explore the interest in and feasibility of a burden of infectious disease study and to layout its methodology [12,13]. Based on this pilot investigation, the Burden of Communicable Diseases in Europe (BCoDE) project was launched. Funded by an ECDC grant and implemented in collaboration with a European Consortium led by the Dutch National Institute for Public Health and the Environment (RIVM), the project included Europe- an experts from academic centres and national health institutes.

A consistent methodology for calculating the burden of infectious diseases expressed in DALYs, pathogen and incidence-based, was developed [14,15]. Results of the burden of selected FWDs on European Union and European Economic Area (EU/EEA) Member States, amongst others, were recently presented at the 2015 European Public Health Conference [16] and represent the findings of the BCoDE 2015 study [17]. Using the BCoDE 2015 study as a reference point, we provide an overview of, and a comparison with other methodological frameworks and options for burden of disease studies. With the purpose of informing risk assessment, we attributed the FWD disease- specific DALYs stemming from BCoDE 2015 to different exposure routes as an example illustrating how burden of disease outputs help inform public health planning and decision-making. Finally, we discuss how findings of burden of disease studies compare and how these are useful in providing scientifically sound information to risk managers and their decision making process.

Methodologies for estimating burden of foodborne and waterborne diseases

DALY is a composite metric quantifying the health losses measured in years. It was first developed as a composite health measure by the Global Burden of Disease project within the World health Organization (WHO) [18] and has evolved in time [5]. DALYs are calculated by adding years of life lost due to premature mortality (YLL) and years of life lived with a disability (YLD), associated with a specific disease. The former is based on the number of deaths associated with a disease, where deaths are stratified by age and multiplied by remaining life expectancy by age at death. YLDs are the sum of all outcomes' durations multiplied by their dis-

ability weights and the number of cases experiencing that outcome. Therefore, DALYs express the impact of the acute phase of diseases and their related short and long-term outcomes.

ECDC has the objective of surveillance and providing scientific advice on a number of communicable diseases (CDs) according to Decision 1082/2013/EU of the Euro- pean Parliament and of the Council [19], which are subject to mandatory notification by EU/EEA countries to The European Surveillance System (TESSy) [20]. Within the master list of all communicable diseases, a selection of diseases were integrated in the BCoDE toolkit [21], a stand-alone software application for calculation of DALYs. The diseases were selected by an ad hoc working group of the ECDC Advisory Forum based on based on data availability, perceived incidence, outbreak potential and if the disease is vaccine-preventable with widely used vaccines [22].

The GBD 2010 and 2013 studies utilised prevalence data sources [23,24] whereas the BCoDE project modified this methodology and suggested an incidence-based and pathogen-based approach [14,15]. The effect of an incidence approach is to acknowledge future sequelae of infections on top of the disabilities due to the acute phase of the disease. The incidence-based estimation of burden also sets the baseline information for estimating the impact of prevention and control interventions in a com- prehensive way by accounting for the short and long-term effects of interventions [25]. The pathogen approach assigns the disease burden to a causal or associated event. In practice, symptomatic infections are linked to out- comes through a disease progression model and visually described in outcome trees such as those displayed in the BCoDE toolkit [21]. It is important to note that, as shown by Schroeder [26], if DALYs are calculated with- out time discounting (see below), the choice of a prevalence versus an incidence approach has a minimal impact on the final results in a trend steady state situation [27].

Outcome tree parameters can be based on literature reviews, observed clinical outcome data, or a mix of the two. The BCoDE toolkit [21], for example, utilises the latter approach and case fatality proportions extracted from literature reviews were age-specifically modelled according to notified deaths by age groups, through enhanced surveillance data reported to TESSy.

Disability weights quantify health losses relating to non- fatal outcomes. Several sets of disability weights are available, all based on different elicitation methods [28]. The BCoDE toolkit utilises disability weights stemming from the European disability weights study [29,30]. Other methodological choices that need to be considered include time discounting and age weighting. The BCoDE toolkit users have the option to calculate DALYs with or without time discounting, as well as choosing the annual rate. Time discounting is particularly used in economic assessments and burden of disease studies aiming at estimating the economic impact of a disease or an intervention. For the BCoDE 2015 study, time discounting was not included as the purpose of the study was to estimate the impact of infectious diseases on the health of European citizens and not on its economy. In that sense, it was considered that there

were no particular reasons why future health effects should be valued less: utilities associated to healthy life years were assumed not to decline over time [31]. Similar considerations are valid for age weighting, which has been suggested as a way to account for societal priorities. The BCoDE methodology proposes an approach aiming at measuring the impact of infectious diseases on health. Moreover, if societal priori- ties were to be measured when calculating DALYs, age weighting would provide incomplete and biased information. Therefore, it was decided to exclude age weighting from the BCoDE toolkit. In conclusion, for the BCoDE 2015 study, disabilities and healthy life were treated equally regardless of age and time.

Ranges of values reflecting variability and uncertainty can be defined within all parameters of the BCoDE toolkit. DALYs are then calculated through Monte Carlo simulations for which the number of iterations is set by the user. The resulting 95% uncertainty intervals (UI) are dis- played in the results.

Choice of data sources: striking a very thin balance

When choosing the data source for determining incidence, researchers strive to balance data availability and quality with representativeness of the population under study. As a secondary objective, the BCoDE 2015 study aimed at exploring and describing the features of the ECDC surveillance system. Therefore, TESSy was chosen as the default data source. In principle, the approach consisted in exporting age-group and sex specific annual number of cases from TESSy's case-base data- base. EU/EEA MSs were considered according to data availability (i.e. if cases were reported to TESSy) and to characteristics of their surveillance system (e.g. compulsory versus voluntary, comprehensive versus sentinel, national coverage). In conclusion, differences of MS reporting patterns need to be considered in light of the European heterogeneity with regards to the surveillance system, reporting qualities and epidemiological situations.

When estimating a baseline burden of disease, annual epidemiological variations are particularly relevant due to seasonality and outbreaks for example. Including several years of surveillance data and averaging these to obtain the annual number of cases, spreads the peak effect over several years. For example, the BCoDE 2015 study aver- aged cases notified to TESSy between 2009 and 2013 and the Dutch Burden of infectious disease study averaged reported cases between 2006 and 2013 [9].

Notification data are of good quality in Europe although as usual prone to a varying degree of underestimation. Underestimation stems from a combination of underreporting (infected individuals whose disease is misdiagnosed, misclassified or not reported to the national surveillance system) and underascertainment (infected individuals who never seek healthcare) [32]. Moreover, the nature and the extent of the under-estimation effect varies across countries and, at times, across epidemiological years [33]. For the BCoDE 2015 study, extensive literature reviews were undergone for each disease in order to estimate multipliers adjusting for under-estimation of reported data.

About 5.69 cases per 100,000 population of giardiasis were reported in the EU/EEA which were multiplied by 14 (with a range from 4 to 49) [7,34]. The hepatitis A average reporting rate of 2.78 per 100,000 population was multi- plied by 4.5 (3.7–5.6) [35]. For listeriosis, a factor 1.7 (1.1– 2.3) was applied to the average notification rate of 0.41 per 100,000 population [7], for shigellosis the notified cases of 1.67 per 100,000 population were multiplied by 18.3 (2.9–39.5) [7,36] and notified rates of verocytotoxigenic *Escherichia coli* (STEC/VTEC) (1.31 per 100,000 population) were multiplied by 26.68 (1.6–109.7) [7,34,37].

When notification data is scarce or unavailable, alternative methods should also be considered, such as capture-recapture studies, analysis of attack rates and serological studies. For example, underestimation of notified campylobacteriosis and salmonellosis symptomatic cases was estimated based on serological studies [1,38,39]. These sero-incidence studies have determined the rate of infection in several EU Member States, which provides important information on the circulation of the infection. For example, it was estimated that Salmonella cause 0.06–0.61 infections per person-year, respectively in Sweden and Spain. These findings should not be con- fused with symptomatic diseases. However, assuming that the disease-to-infection rate is constant across countries, sero-incidence studies are able to provide useful information. In the BCoDE 2015 study, for the estimation of symptomatic campylobacteriosis and salmonellosis sero-incidence results of three EU Member States (for Salmonella; two for Campylobacter) were anchored to community based studies performed in the same countries [38]. Each anchoring provided a conversion factor between infections and diseases, which were applied to the other countries. The range of estimated incident symptomatic cases was used to estimate the burden in DALYs.

Another example describing a situation where notification data is unavailable is the estimation of the incidence of symptomatic congenital toxoplasmosis. A literature re- search provided a range of 7.3-29 cases per 100,000 births to which no multiplier adjusting for under-estimation was applied.

In the BCoDE 2015 study, age-group and sex specific incident cases and, where applicable, multipliers adjusting for under-estimation of notified cases were inserted in the BCoDE toolkit. No time discounting was applied and 1000 Monte Carlo simulations were chosen. No modifications to the BCoDE toolkit outcome tree parameters were applied and estimated DALYs were exported into tables and graphs.

Ranking risks according to impact on health measured in DALYs

The BCoDE 2015 found that campylobacteriosis was the disease with the highest burden in the EU/EEA with 8.20 (UI: 6.68–10.01) DALYs per 100,000 population, followed by salmonellosis with 3.96 (UI: 3.68–4.26) and infection with Shiga toxin-producing *E. coli* (STEC) with 2.08 (UI: 2.59–3.21). These diseases represent more than 75% of the burden of the FWDs under study and it was estimated that slightly over 2000 deaths are associated with FWDs in the EU/EEA every year. Moreover, congenital infections (congenital toxoplasmosis and perinatal listeriosis),

although rare, have a considerably high burden in new- born population, suggesting the need to continue and improve the existing preventive efforts in this vulnerable population.

As a composite health measure, DALY provides a com- prehensive overview of the impact of diseases as it encompasses the relative disabilities and mortality, sustained both during the acute phase and related to the short and long-term complications of diseases. These are the reasons underlying the European Food Safety Authority's (EFSA) recommendation on using the BCoDE toolkit, and the BCoDE methodological approach, as part of the risk ranking toolbox for the Panel on Biological Hazards (BIOHAZ) [40], in particular as a top-down method to rank pathogens.

The bubble chart in Figure 1 illustrates how the resulting DALYs per 100,000 for each disease relate to their incidence and estimated deaths. For example, the high burden of campylobacteriosis is a result of both high incidence and number of associated deaths. The burden of listeriosis is mainly due to its mortality, as opposed to giardiasis. This bubble chart shows more clearly that the choice of indicator affects very much the final ranking of diseases and the ensuing interpretation of the impact on population health.

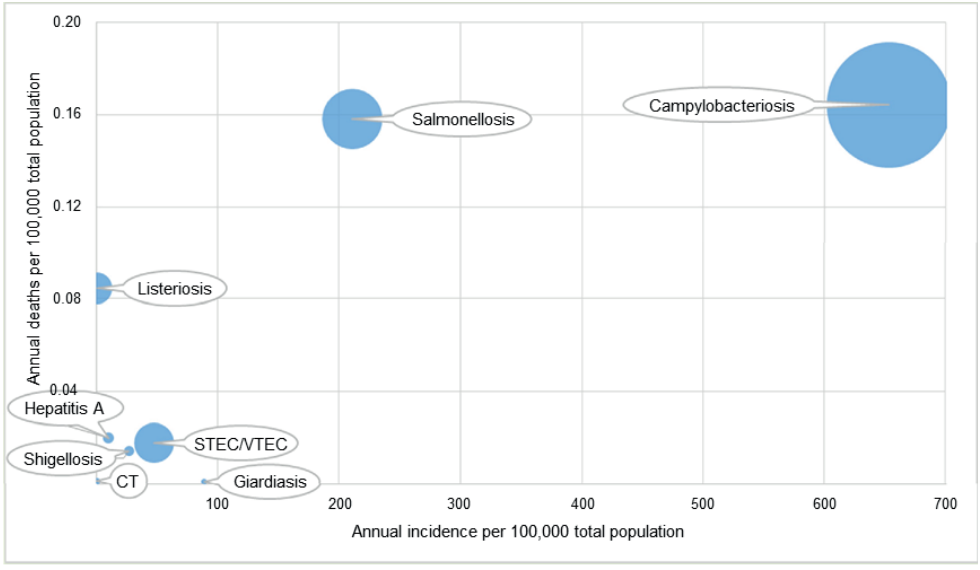

Figure 1. Bubble chart plotting the DALYs per 100,000 (diameter of bubble) with incidence per 100,000 total population and estimated deaths per 100,000 total population from the BCoDE toolkit disease models
CT = congenital toxoplasmosis; vCJD is not visible given the low burden

Several burden of disease studies have estimated DALYs for FWDs at the national level [41,42] and comparing the same FWD across different countries [43]. Studies with a similar methodology to the BCoDE 2015 study include the Ontario Burden of Infectious Disease Study (ONBOIDS) [44] and the World Health Organization (WHO) Foodborne Disease Burden Epidemiology Reference Group (FERG) [45,46]. Whilst comparing the same diseases, the former found an overall burden of 3.28 DALYs per 100,000 population in contrast to our finding of 18.76. Estimated incidence was similar in both studies (475–832 cases per 100,000 population in BCoDE 2015 versus 726 in ONBOIDS), as well as risks of developing complications. However, the ONBOIDS study estimated 0.33 annual deaths attributable to Campylobacter enteritis, resulting in a case fatality proportion (CFP) of 0.0004% while BCoDE 2015 was set a CFP of 0.001– 0.05%. As an effect, YLLs for campylobacteriosis was higher in the BCoDE 2015 study, representing 40% of the total burden against 15% in ONBOIDS. In terms of ranking, however, campylobacteriosis and salmonellosis consistently ranked as the foodborne diseases with the highest burden.

A global study of FWDs, the WHO FERG endeavour, offers results of burden of pathogens in different WHO subregions [45,47]. For comparison with our findings we considered EUR A region and found a higher burden of all comparable FWDs from the FERG study compared to BCoDE 2015: 26.62 (UI: 22.03–40.80) versus 19.14 (UI: 16.20–22.67) DALYs per 100,000 population. Main differences, both in terms of ranking and DALY per 100,000, are related to non-typhoidal Salmonella enterica (ranked first in the FERG study with 12 (UI: 7–18) DALYs per 100,000 population) and to Shiga toxin-producing *E. coli* (ranked 5th with 0.6 (95% UI: 0.2–1) DALYs per 100,000 population).

Incidence of STEC is similar across the two studies which both apply a set of multiplication factors adjusting for underestimation to notification data [48]: FERG applied the factor of 36 (with a range of 7.4–106.8) [49] whereas BCoDE 2015 chose the factor of 26.68 (with a range of 1.6–109.7) [7,34,37]. Moreover, the FERG study used the regional incidence of STEC incidence in the EUR A region of 47.1 cases per 100,000 population, not very dissimilar to our finding of 35 cases per 100,000 population. When comparing the STEC disease model (outcome tree) of BCoDE present in the ECDC BCoDE toolkit software application [21] with that of the FERG study, they appear to include the same outcomes, except renal transplantation present in BCoDE. However, risk of developing haemolytic uraemic syndrome (HUS) and end-stage renal disease (ESRD) is higher in BCoDE 2015 than in the FERG study (age dependent interval of 0.94–1.25% [21] against 0.03–0.8% [49] for HUS and 2.9–10.5% [21] against 3% (ranging from 0% to 30%) [49] for ESRD, respectively).

Differences in the salmonellosis results between the two studies seem more complex and possibly related to a combination of three factors. The FERG study inputted a higher incidence (301.5 per 100,000 population versus 216 per 100,000 population in BCoDE 2015 study), a higher proportion of moderate diarrhoea (25% against 15% [44], respectively) and a higher disability weight applied to the diarrhoeal event (0.202 taken from GBD 2010 against 0.149

applied in BCoDE 2015). Moreover, one substantial difference, which might explain the higher burden in FERG study, is related to choices concerning the CFP. The ECDC BCoDE mortality per 100,000 upper range is lower (0.17 against 0.40 DALYs per 100,000 population) although median values are the same (0.16 against 0.15 DALYs per 100,000 population). However, the BCoDE disease model applied an age- group re-distribution of the CFP (stemming from enhanced surveillance information from TESSy) where nearly 70% of the deaths occur in people older than 70 years, resulting in lower YLLs from death associated to salmonellosis.

Attribution of infection to exposure routes Attribution of the BCoDE 2015 FWDs to different exposure pathways was based on a recent global elicitation study, funded by the World Health Organization (WHO), within the framework of the Foodborne Disease Burden Epidemiology Reference Group (FERG) [50]. Major transmission routes were through food, animal contact (domestic and wild), human to human transmission, water, soil or other. For the present study, we only considered median values and 95% uncertainty intervals results for WHO subregion EUR A (European Region, Stratum A).

Figure 2 presents the attribution of the burden of FWDs to different exposure groups. As expected, estimation of DALYs by different exposure routes shows that most of the burden was attributed to food as the main cause of transmission, 77% (uncertainty ranging from 40% to 100%), suggesting the need to strengthen efforts to control and prevent FWDs through interventions in the food chain. For example, campylobacteriosis is the most commonly reported FWD and its trend has been increasing in the past years [3,4]. Recent studies also show that in some European countries up to 80% of the population are infected with Campylobacter every year, although not all develop a symptomatic disease [2]. EFSA has estimated that 50–80% of human Campylobacter infections can be attributed to the chicken as a reservoir, warranting appropriate prevention measures to be applied along the poultry food chain [51]. In 2012, EFSA has published options for interventions at poultry meat inspection with the aim to reduce the public health risk for Campylobacter, Salmonella and ESBL/AmpC gene-carrying bacteria [52].

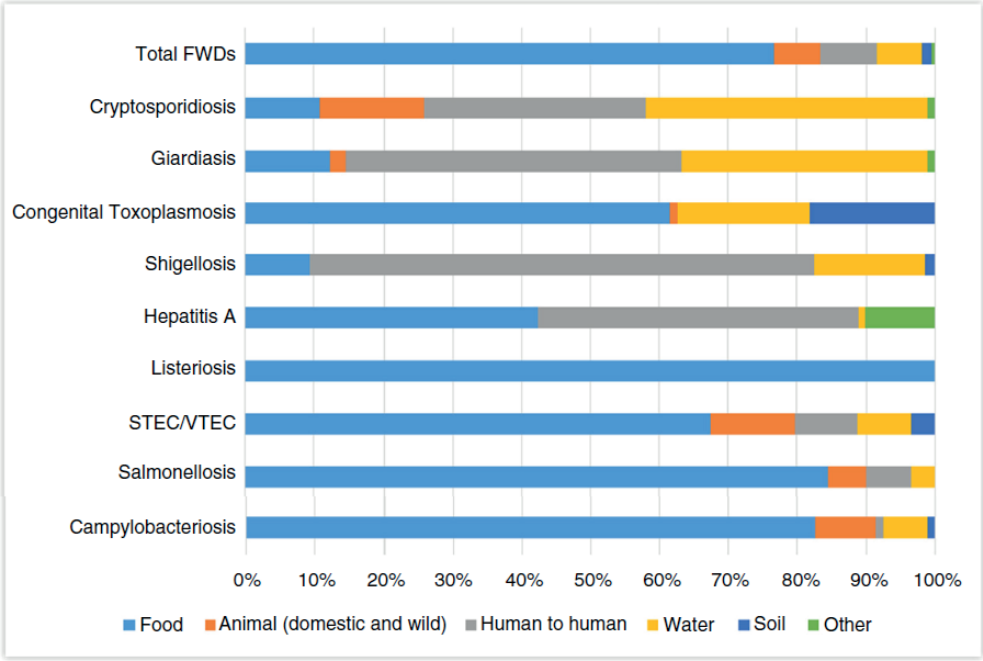

Figure 2. Percentage of DALYs from the BCoDE 2015 study attributed to different exposure routes according to WHO FERG expert elicitation (subregion EUR-A).

This information is potentially useful for improving prevention strategies in EU/EEA countries, especially in light of the planned further work on specific food sources/categories (personal communication, Tine Hald). However, the FERG study did not specifically explore the differential exposures according to age groups. Figure 3 clearly illustrates that young children under 5 years of age are the age group at highest risk for FWD. Infection pathways in this age category might differ, which might undermine the effectiveness of interventions aiming at preventive efforts.

Burden of disease studies for planning and prioritisation

Estimation of incidence, involving critical assessments of data quality and degrees of under-estimation of reported surveillance data, is a crucial factor in the calculation of burden of disease in DALYs. Likewise, assumptions and decisions underlying the choice of incidence to input in the disease models are decisive in the interpretation of the results. As discussed above, all parameters of the disease models will also play a fundamental role in the DALY results, along with modelling decisions. These assumptions have to be accounted for when interpreting and communicating outcomes from burden of disease studies, in particular for planning and prioritisation purposes during which communication of limitations and uncertainties become a complex but necessary task.

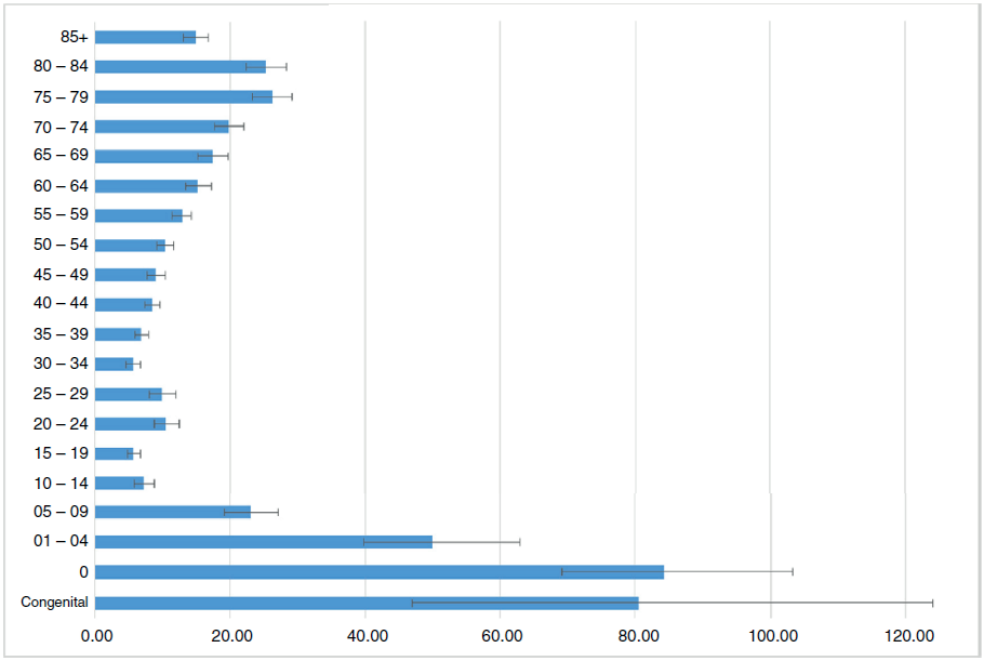

Figure 3. Age group specific burden of food and water-borne diseases from BCoDE 2015 study: 2009–2013 DALYs per 100,000 stratum specific population (median and 95% uncertainty intervals).

For this reason, integrative methods of risk ranking and prioritisation are highly recommended. Examples under- taken from National Health Authorities include prioritisation exercises for surveillance purposes in Germany and Sweden [53e,54]. Both studies report that infections from *Campylobacter* spp., *Salmonella* spp. and Shiga-toxin producing *E. coli* should be placed in the highest priority group. This is consistent with our findings, which ranked the diseases resulting from those infections as those with the highest burden. Moreover, listeriosis was consistently ranked as being in the high priority group. The remaining infections move between high and medium priority group depending on the study.

ECDC continues working on risk ranking methodologies [55e] and is developing a framework for emerging threats impact assessment based on multi-criteria decision analysis (MCDA) methodologies [56,57]. The underlying rationale is that quantitative methods alone, such as burden of disease outputs in DALYs, do not fully encompass all unknowns, uncertainties, variability and other 'softer' criteria such as public perception. On the other hand, MCDA risk ranking methods are subject to a certain degree of subjectivity, which may bias results.

DALY estimates of disease burden provide valuable information to be taken into account during public health decision-making for prevention strategies. Efforts aiming at improving surveillance data availability and quality will increase the precision and reliability of DALY estimates, and of infectious disease modelling efforts in general. Finally, DALYs can be one of the key inputs in comprehensive tools for risk ranking such as multi-criteria decision analysis.

Supplementary information

Appendix A: https://ars.els-cdn.com/content/image/1-s2.0-S2214799316300741-mmc1.pdf

Competing Interests

None declared.

Authors' contributions

AC wrote the first draft of the manuscript. All authors helped conceive the opinion and contributed to writing the manuscript.

Funding

None declared.

Acknowledgments

We would like to acknowledge our colleagues Therese Westrell and Mike Catchpole (ECDC) for their valuable input. We also acknowledge Marie- Josee Mangen (Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands) and Arie Havelaar (University of Florida, Gainesville, Florida, United States of America) for their contributions related to the BCoDE project.

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CHAPTER 8

Associated deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in Switzerland 2010-2019.

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Eurosurveillance. 2023;28(20):2200532.
https://doi.org/10.2807/1560-7917.

Abstract

Background

Cassini et al. (2019) estimated that, in 2015, infections with 16 different antibiotic-resistant bacteria resulted in ca 170 disability-adjusted life- years (DALYs) per 100,000 population in the European Union and European Economic area (EU/EEA). The corresponding estimate for Switzerland was about half of this (87.8 DALYs per 100,000 population) but still higher than that of several EU/EEA countries (e.g. neighbouring Austria (77.2)).

Aim

In this study, the burden caused by the same infections due to antibiotic-resistant bacteria ('AMR burden') in Switzerland from 2010 to 2019 was estimated and the effect of the factors 'linguistic region' and 'hospital type' on this estimate was examined.

Methods

Number of infections, DALYs and deaths were estimated according to Cassini et al. (2019) whereas separate models were built for each linguistic region/hospital type combination.

Results

DALYs increased significantly from 3,995 (95% uncertainty interval (UI): 3;327–4,805) in 2010 to 6,805 (95% UI: 5,820–7,949) in 2019. Linguistic region and hospital type stratifications significantly affected the absolute values and the slope of the total AMR burden estimates. DALYs per population were higher in the Latin part of Switzerland (98 DALYs per 100,000 population; 95% UI: 83–115) compared with the German part (57 DALYs per 100,000 population; 95% UI: 49–66) and in university hospitals (165 DALYs per 100,000 hospitalisation days; 95% UI: 140–194) compared with non-university hospitals (62 DALYs per 100,000 hospitalisation days; 95% UI: 53–72).

Conclusions

The AMR burden estimate in Switzerland has increased significantly between 2010 and 2019. Considerable differences depending on the linguistic region and the hospital type were identified - a finding which affects the nationwide burden estimation.

Introduction

Estimates of the impact of infectious diseases are needed for an accurate risk assessment, as well as for planning and prioritising public health resources. Disability-adjusted life-years (DALYs) [1] are a widely used measure of the overall disease burden accounting for healthy life years lost because of premature mortality and years lost living with disabilities for each condition or disease. Cassini et al. estimated that ca 672,000 infections, 33,100 deaths and 875,000 DALYs resulting from infections with 16 antibiotic resistance (AMR)– bacterium combinations occurred in the European Union (EU) and European Economic Area (EEA) in 2015 [2]. By applying the same approach, ca 7,160 infections, 276 associated deaths and 7,400 DALYs were estimated for Switzerland in 2015 [3]. A comparison with individual EU and EEA countries revealed that the 2015 estimate for Switzerland (87.8 DALYs per 100,000 population) was higher than those in neighbouring Austria (77.2) or Germany (64.3) but considerably lower than adjacent Italy (448.4) or France (220.7). Compared with other countries with similar economic performance indicators such as Luxembourg (70.9 DALYs per 100,000 population), Denmark (52.3) or Norway (33.1), the estimate for Switzerland was also rather high, whereas in a Europe-wide comparison (EU/EAA median 170 DALYs per 100,000 population) it was rather low [2,3].

Published studies [2,3] have focused on (supra) national estimates in one or two time points. The main aim of the current investigation was to update the estimate of the burden of disease due to infections with antibiotic-resistant bacteria in 2019 and analyse the epidemiological trend since 2010. Due to well-documented differences in resistance patterns depending on the hospital types (i.e. university vs non-university hospitals) and linguistic regions in Switzerland [4-6] analyses were stratified by these factors. An additional objective was to qualitatively explore whether measures to curb AMR in Switzerland [7] might have some- what affected DALYs.

Methods

Data retrieval and estimation of infections

The COVID-19 pandemic may have increased or decreased the burden of antimicrobial resistance [8]. To avoid interference, this study was restricted to the years before the pandemic (2010–2019).

The methodology from Cassini et al. [2] was adopted and the same 16 AMR–bacterium combinations were included (Table). Data from blood and cerebrospinal fluid (invasive isolates, hereinafter referred to as BSIs) were obtained from the Swiss Centre for Antibiotic Resistance (ANRESIS) national database. Data were deduplicated by keeping only the first isolate of a given microorganism per patient per year. Aggregations were performed by the resistance–bacterium combination, age group (categorical variable, i.e. 0–1, 2–4, 5–9, 10–14, …, 80–84, ≥ 85 years) and sex (binary variable, i.e. male/female). Unknown age and sex data were redistributed by imputation. As the hospitalisation date was not available for most infections, no distinction was made between community- and hospital-acquired infections.

Table 1. Bacteria and antibiotic resistance categories included in the study[a], Switzerland, 2010–2019

Bacteria	Antibiotic resistance[b]	Acronym
Acinetobacter spp.	Colistin-resistant	ColRACI
	Carbapenem-resistant (excluding isolates also resistant to colistin)	CRACI
	Aminoglycoside- and fluoroquinolone-resistant[c] (excluding isolates also resistant to colistin and/or carbapenem)	MDRACI
Enterococcus faecalis and *E. faecium*	Vancomycin-resistant	VRE
Escherichia coli	Colistin-resistant	ColREC
	Carbapenem-resistant (excluding isolates also resistant to colistin)	CREC
	Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/ or carbapenem)	3GCREC
Klebsiella pneumoniae	Colistin-resistant	ColRKP
	Carbapenem-resistant (excluding isolates also resistant to colistin)	CRKP
	Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/ or carbapenem)	3GCRKP
Pseudomonas aeruginosa	Colistin-resistant	ColRPA
	Carbapenem-resistant (excluding isolates also resistant to colistin)	CRPA
	Resistance to three or more antibiotic groups[c] (excluding isolates also resistant to colistin and/or carbapenem)	MDRPA
Staphylococcus aureus	Meticillin-resistant	MRSA
Streptococcus pneumoniae	Penicillin-resistant (excluding isolates also resistant to macrolides)	PRSP
	Penicillin- and macrolide-resistant (excluding isolates only resistant to penicillin)	PMRSP

EARS-Net: European Antimicrobial Resistance Surveillance Network.
[a] Adapted from Cassini et al. [2].
[b] An isolate was considered resistant to an antimicrobial group when tested and interpreted as resistant (R) in accordance with the clinical breakpoint criteria used by the local laboratory.
[c] Resistances used as a marker of multidrug resistance.
For more information on the antibiotics included in each antibiotic group, please refer to the EARS-Net protocol [37].

BSIs are the most completely reported infections in Switzerland, while other infections are less fully reported. Ratios of BSIs to non-BSIs (conversion factors) for each AMR–bacterium combination derived from the European Centre for Disease Prevention and Control (ECDC) point prevalence survey (PPS) 2016– 2017 [9] were therefore used to estimate the number of urinary tract infections, respiratory tract infections, surgical site infections, and other infections. In the PPS 2016–2017, infection site incidence for each resistance–bacterium combination was calculated by applying the Rhame and Sudderth formula to the prevalence data [10]. Uncertainty around the conversion factors was assessed using bootstrap resampling. The number of estimated non-BSIs (urinary tract infections, etc.) was then added to the number of BSIs to obtain the total number of infections.

The percentage of secondary BSIs from the PPS 2016– 2017 was deducted from each of the non-BSIs in the Swiss dataset as described in [2]. To automatise different data processing steps, parametrised workflows were built using the KNIME Analytics Platform version 4.3.1.

Data analysis

For the classification of data according to the linguistic region, the French and the Italian speaking parts are grouped as 'Latin part'. The German-speaking part is referred to as 'German part' for simplicity. Demographic data were obtained from the Swiss Federal Statistical Office [11].

For the main analysis (hereinafter referred to as 'first analysis') coverage correction factors for different hospital types (university vs non-university) and for different linguistic regions were calculated using the number of hospitalisation days [12] of the comprised hospitals (see Supplementary Table S1 for different coverage rates). Numbers of infections found at each stratification level were added after applying the coverage correction factors to get the total number of infections for the whole country. These findings were then compared with two additional models ('second' and 'third analysis'). In both models, coverage correction factors were calculated yearly for the whole country without any further stratification. In the second analysis data from all hospitals included in ANRESIS were used, while in the third analysis the dataset was restricted to hospitals, that have been reporting to ANRESIS since 2010.

In contrast to Cassini et al. [2], the term 'associated infections' is used in this study instead of 'attributable infections' to express that estimations are based on a scenario in which all drug-resistant infections were replaced by no infection, rather than on a scenario in which all drug-resistant infections were replaced by susceptible ones. This terminology is in accordance with a recent study from Murray et al. [13].

DALYs and associated deaths were estimated according to Cassini et al. [2] using the ECDC BCoDE toolkit Version 2.0.0 [14] based on 10,000 Monte Carlo simulations, without time discounting. Uncertainties of conversion factors were included in the models as PERT distributions and disease model parameters were given with 95% uncertainty intervals (UIs). Medians of the distributions were used as point estimates. When aggregating output values, two different proceedings were applied to calculate the corresponding UIs. In one approach a 100% positive correlation between sampled values was assumed and UIs were summed; in another approach total independence was assumed and UIs were approximated by the square root of the sum of squares. Hereinafter only results from the first more conservative proceeding are presented (see Supplementary Figure S7 for two examples using the second approach).

The R software environment (version 4.0.4) was used to execute the BCoDE toolkit and for analyses and visualisations, which were performed with the BCoDE output parameters [15].

Measures to curb antibacterial resistance

During the study period, several measures were implemented in Switzerland to curb AMR. Most of them were bundled in the Swiss Strategy on Antibiotic Resistance (StAR), which was implemented as of 2016 [7]. A qualitative comparison of these measures with annual AMR burden estimates was discussed in terms of the effectiveness of such interventions. A selection of important measures is schematically represented in Figure 1.

Results

First analysis – estimation of the burden of infections with antibiotic-resistant bacteria stratified by linguistic region and hospital type

A total of 5,610 BSIs were counted for the study period (before applying country coverage factors). The patient's age was available for all isolates, and information about the sex for 5,608 (99.96%).

Distribution of the burden by year across the study period

It was estimated that 3,110 (95% UI: 2,516–3,844) infections due to antibiotic-resistant bacteria from different locations occurred in 2010 increasing to 6,342 (95% UI: 5,316–7,538) in 2019 (+ 104%; see stacked bar charts of different antibiotic-resistant bacteria in Supplementary Figure S1 and absolute numbers in 2010 and 2019 in Supplementary Table S3). These estimates accounted for 3,995 DALYs (95% UI: 3,327–4,805) in 2010 increasing to 6,805 DALYs (95% UI: 5,820–7,949) in 2019 (+ 70%; see Figure 2A and Supplementary Table S3). Deaths associated with infections due to antibiotic-resistant bacteria increased from 136 (95% UI: 114–161) in 2010 to 286 (95% UI: 243–335) in 2019, corresponding to + 111% (when calculating from the initially non-rounded estimates). This increase is illustrated in Supplementary Figure S2 (see stacked segments in the bar charts corresponding to different antibiotic-resistant bacteria) and absolute values for each year are presented in Supplementary Table S3. These estimates correspond to 40 infections per 100,000 population (95% UI: 32–49) in 2010 and 74 infections per 100,000 population (95% UI: 62–88) in 2019 respectively, 51 DALYs per 100,000 population (95% UI: 42–61) in 2010 and 79 DALYs per 100,000 population (95% UI: 68–92) in 2019 respectively and 1.72 deaths per 100,000 population (95% UI: 1.44–2.05) in 2010 and 3.32 deaths per 100,000 population (95% UI: 2.82–3.89) in 2019 respectively.

Throughout the whole study period, most DALYs were associated with third-generation cephalosporin-resistant *Escherichia coli* (1,461 DALYs (95% UI: 1,294–1,634) in 2010 and 3,511 DALYs (95% UI: 3,187–3,851) in 2019) (Figure 2A and Supplementary Table S3), which contributed to 37% of the total DALYs in 2010 (Figure 2B). After a relatively steep increase until 2013, this value stabilised at around 50% during subsequent years (52% in 2019), resulting in a less pronounced overall increase in DALYs in the later years of the study (Figure 2A). The second biggest contributor to the burden was meticillin-resistant Staphylococcus aureus (MRSA) with 1,022 DALYs (95% UI: 898–1,169) in 2010 and 656 DALYs (95% UI: 581–742) in 2019, corresponding to 26% in 2010 and 10% in 2019. As the burden from MRSA continuously decreased during this period, it became surpassed in 2012 by carbapenem-resistant *Pseudomonas aeruginosa* with 510 DALYs (95% UI: 333–739) in 2010 and 1,012 DALYs (95% UI: 735–1,348) in 2019, corresponding to 13% in 2010 and 15% in 2019. Other carbapenem-resistant bacteria remained at a low level throughout the whole study period (e.g. carbapenem-resistant *E. coli* with 53 DALYs (95% UI: 32–76) in 2010 and 51 DALYs (95% UI: 34–69) in 2019, corresponding to 1 % in 2010 and 1 % in 2019). Similarly, all

colistin-resistant bacteria remained at a low level or were even absent (see Figure 2A and Figure 2B for their representation in stacked bar charts, Supplementary Table S3 for absolute numbers and https://www.anresis.ch/wp-content/ uploads/2022/03/2022_02_bubble_plot_ allstrat_ agg.html to get a dynamic picture of how numbers of infections, DALYs and deaths from different antibiotic-resistant bacteria evolve over time).

Distribution of the burden by age and sex

Males accounted for 62% of the estimated total number of DALYs (2010–2019 pooled data) and the burden in DALYs per 100,000 population was higher compared with females in every age group, with 25–29 and 35–39-year-olds being exceptions (Figure 3A and 3B). In both males and females, the highest values were found in age groups between 65 and 84 years old. In the distribution of the burden by age and sex, a second peak, which was more pronounced in males was observed in neonates and infants up to 1 year old. DALYs per 100,000 population (using age group specific denominators) in up to 4-year-old children were decreasing during the study period from 134 (95% UI: 95–191) in 2010 to 83 (95% UI: 55–125) in 2019 (− 38%, Figure 3C). In contrast, values concerning the elderly population were increasing during that period. For example, for those ≥ 75 years old DALYs per 100,000 population increased from 79 (95% UI: 53–115) to 170 (95% UI: 108–254) (+ 117%; when calculating from the initially non-rounded estimates). Age-specific distributions stratified by linguistic region and hospital type are described in Supplementary Figure S4.

Distribution of the burden by linguistic regions and hospital type

DALYs which were standardised per 100,000 population were higher in the Latin part of Switzerland (98 DALYs per 100,000 population; 95% UI: 83–115) compared with the German part (57 DALYs per 100,000 population; 95% UI: 49–66). Values were increasing in both linguistic regions (Figure 4), however, a higher relative increase (+ 85%) was observed in the German part (Latin part: + 22%). The highest increase was observed in non-university hospitals of the German part (+ 111%) whereas in other settings more moderate increases were observed (university hospitals, German part: + 82%; non-university hospitals, Latin part: + 60%; university hospitals, Latin part: + 15%; Supplementary Figure S5).

Infections with antibiotic-resistant bacteria in university hospitals accounted for 41% of DALYs (23,242; 95% UI: 19,673–27,408) over the whole study period, infections in non-university hospitals for 59% of DALYs (33,413; 95% UI: 28,691–38,956). These numbers correspond to 165 DALYs per 100,000 hospitalisation days (95% UI: 140–194) for university hospitals and 62 DALYs per 100,000 hospitalisation days (95% UI: 53–72) for non-university hospitals (denominator data can be found in Supplementary Table S1).

Different distributions of antibiotic-resistant bacteria were found depending on the linguistic region and the hospital type (Supplementary Figure S6). Notably, a higher proportion of DALYs was associated with carbapenem-resistant *P. aeruginosa* in university hospitals (German and

Latin parts, both 18%) compared with non-university hospitals (German part 10%, Latin part 12%). In contrast, proportions of DALYs which were associated with third-generation cephalosporin-resistant *E. coli* were lower in university hospitals (German part 42%, Latin part 37%) compared with non-university hospitals (German part 60%, Latin part 50%).

Comparison of different estimation approaches

In the second analysis without stratifications by linguistic region and hospital type, it was found that DALYs increased by + 36% (Figure 5). A more pronounced increase (+ 74%) between 2010 and 2019 was observed in the third analysis which was restricted to hospitals, that have been reporting to ANRESIS since 2010.

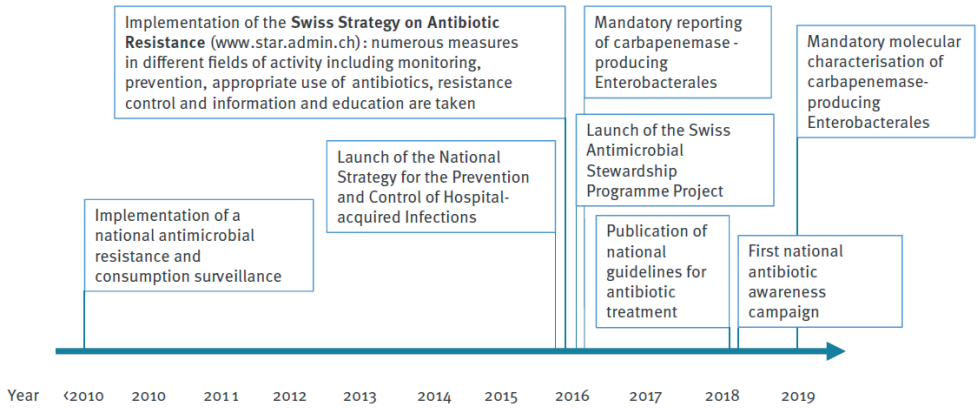

Figure 1. Some measures to prevent the development of resistant bacteria and limit their transmission and spread in Switzerland, prior and during the 2010–2019 study period

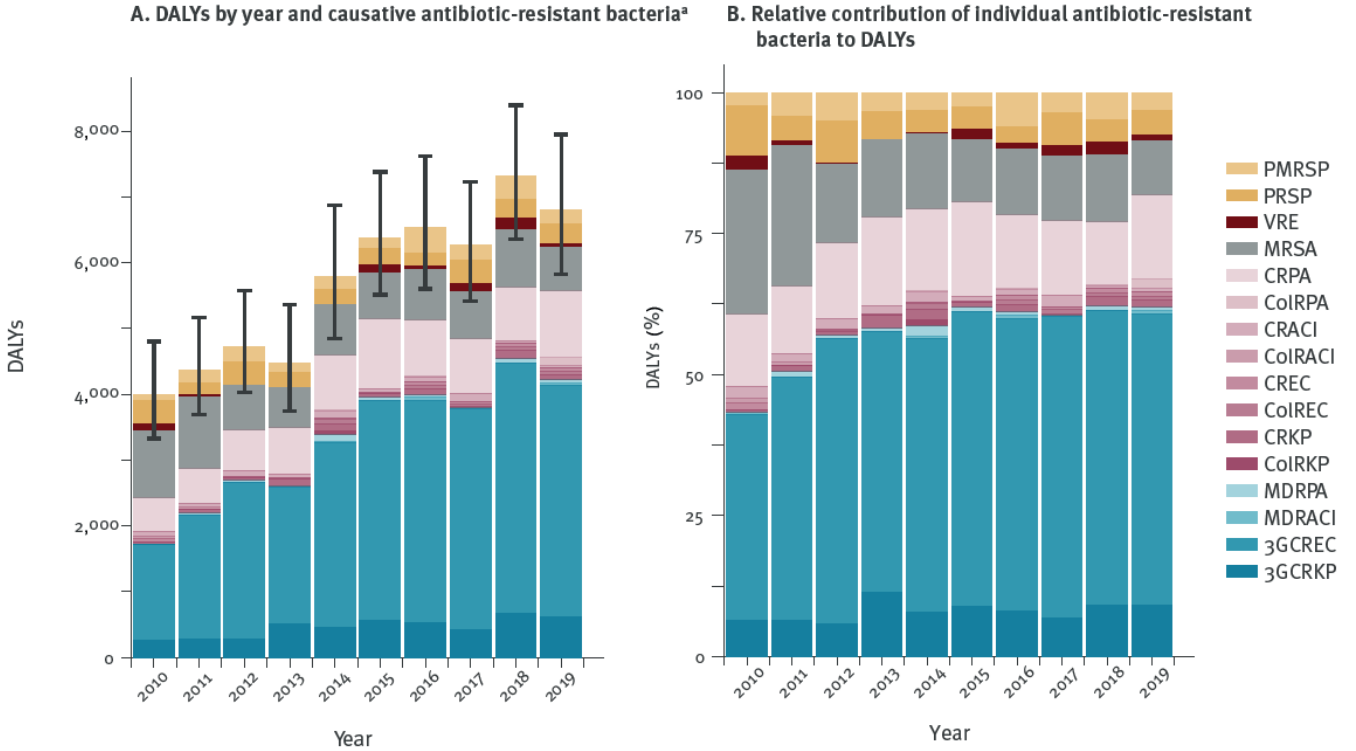

Figure 2. (A) Disability-adjusted life-years (DALYs) caused by infections with antibiotic-resistant bacteriaa and (B) relative contributions of individual antibiotic-resistant bacteria to the DALYs, Switzerland, 2010–2019

ColRACI: colistin-resistant *Acinetobacter* spp.; ColREC: colistin-resistant Escherichia coli; ColRKP: colistin-resistant *Klebsiella pneumoniae*; ColRPA: colistin-resistant *Pseudomonas aeruginosa*; CRACI: carbapenem-resistant *Acinetobacter* spp.; CREC: carbapenem-resistant E. coli; CRKP: carbapenem-resistant *K pneumoniae*; CRPA: carbapenem-resistant *P. aeruginosa*; MDRACI: multidrug-resistant *Acinetobacter* spp.; MDRPA: multidrug-resistant *P. aeruginosa*; MRSA: meticillin-resistant *Staphylococcus aureus*; PMRSP: penicillin-resistant and macrolide-resistant *S pneumoniae*; PRSP: penicillin-resistant *Streptococcus pneumoniae*; VRE: vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*; 3GCREC: third-generation cephalosporin-resistant *E. coli*; 3GCRKP: third-generation cephalosporin-resistant *K pneumoniae.*

[a] Absolute values and 95% uncertainty intervals (black bars) of the yearly totals are shown on panel A.

Data which had been stratified according to the linguistic region and the hospital type were aggregated.

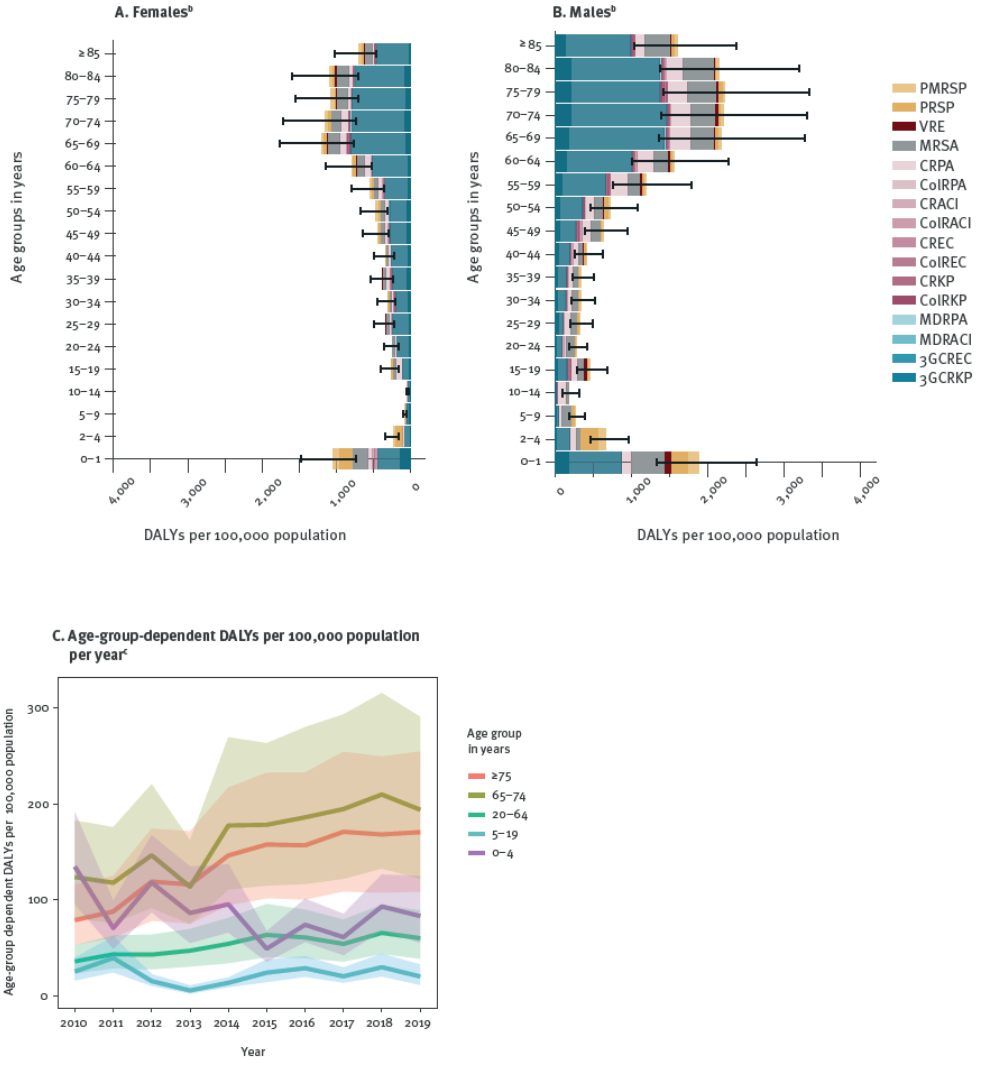

Figure 3. Age-group-dependent model estimates of DALYs[a] per 100,000 population for the whole study period by (A) female[b] and (B) male[b] sex, and (C) for each year of the study[c], Switzerland, 2010–2019

ColRACI: colistin-resistant *Acinetobacter* spp.; ColREC: colistin-resistant *Escherichia coli*; ColRKP: colistin-resistant *Klebsiella pneumoniae*; ColRPA: colistin-resistant *Pseudomonas aeruginosa*; CRACI: carbapenem-resistant *Acinetobacter* spp.; CREC: carbapenem-resistant *E. coli;* CRKP: carbapenem-resistant *K pneumoniae*; CRPA: carbapenem-resistant *P. aeruginosa*; DALYs: disability-adjusted life-years; MDRACI: multidrug-resistant *Acinetobacter* spp.; MDRPA: multidrug-resistant *P. aeruginosa*; MRSA: meticillin-resistant *Staphylococcus aureus*; PMRSP: penicillin-resistant and macrolide-resistant *S pneumoniae*; PRSP: penicillin-resistant *Streptococcus pneumoniae*; VRE: vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*; 3GCREC: third-generation cephalosporin-resistant *E. coli*; 3GCRKP: third-generation cephalosporin-resistant *K pneumoniae*.

[a] DALYs are caused by infections with antibiotic-resistant bacteria.

[b] Data from 2010 to 2019 were aggregated for these representations.

[c] Age-group-dependent DALYs per 100,000 population per year are shown in panel C. Sexes and original age groups were pooled in this representation for an improved visualisation. 95% uncertainty intervals are depicted by semi-transparent ribbons.

Discussion

The availability and quality of BSI data collected since more than a decade by the ANRESIS surveillance system allowed to estimate the burden of infections with 16 AMR–bacterium combinations in Switzerland over an extended period (2010–2019) according to Cassini et al. [2]. Moreover, it was possible to investigate the burden of AMR by hospital type and regional characteristics based on linguistic regions.

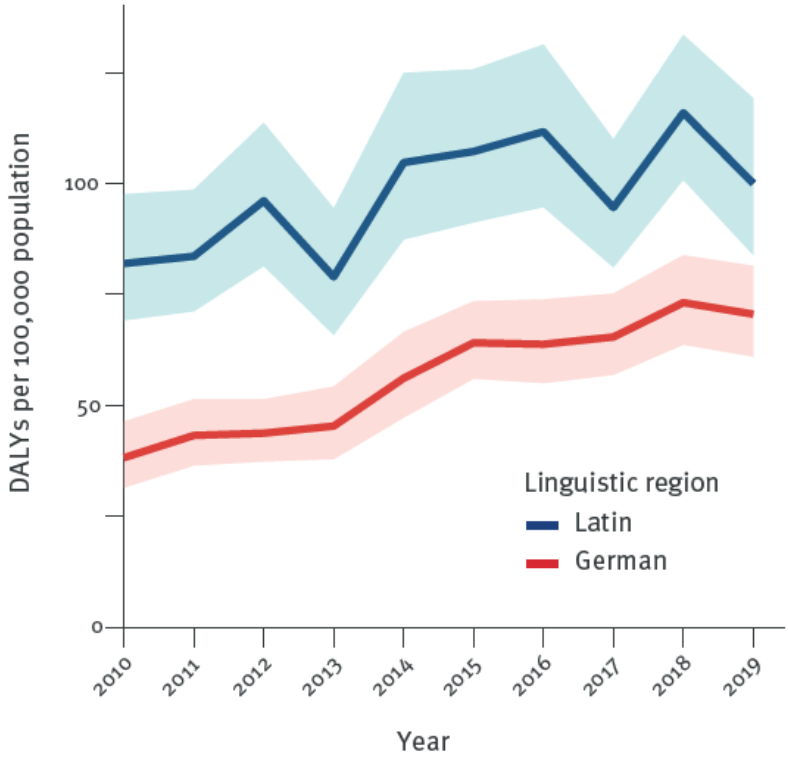

Figure 4. Model estimates of the burden of infections with antibiotic-resistant bacteria of public health importance in DALYs per 100,000 population by linguistic region, Switzerland, 2010–2019
DALYs: Disability-adjusted life-years Disability-adjusted life-years.
95% uncertainty intervals are depicted by semi-transparent ribbons.

The first analysis has shown that the number of infections has more than doubled between 2010 and 2019 leading to a corresponding increase in the number of deaths (+ 111%). The latter observation is comparable with findings from the EU and EEA, where the overall number of deaths increased by a factor of 2.46 however, during a shorter and shifted period (2007–2015) [2]. Interestingly, these high increases in the number of infections and deaths are only partially reflected in the increase of DALYs (+ 70%). This might be due to age group specific long-term trends as shown in Figure 3C. Increases in numbers of infections and deaths were mainly observed in the ≥ 65-year-olds, while decreases were observed in children under 4

years of age during the study period. Thus, given how DALYs are computed (in particular, the years of life lost (YLL) component), this increase in infections and deaths would only marginally increase the number of DALYs.

Several measures (Figure 1), which were implemented by the Swiss authorities, professional societies, healthcare professionals and academia during the last years [7] may have contributed to some stabilisation of the situation after 2015. Besides the implementation of a national surveillance of antimicrobial resistances and consumption as basis for all measures, active intervention strategies were enforced in parallel in different settings. Some interventions which were implemented in the inpatient setting are the introduction of guidelines for the prevention, control and tackling of outbreaks of multidrug-resistant pathogens [16] and for antibiotics use [17], patient screening and isolation of carriers of multidrug-resistant organisms [16,18] as well as the mandatory reporting of carbapenemase-producing Enterobacterales. These measures may have had a strong effect on the number of deaths by keeping infections with high mortality (such as those with microorganisms resistant to carbapenem) at bay, and they may further explain decreasing MRSA rates which have been observed between 2008 and 2021 [19,20] and decreasing DALYs attributed to MRSA infections.

It is important to note that correlating the measures with the available data is difficult, as several measures were bundled and implemented differently in individual cantons due to Switzerland's federal system.

Unfortunately, so far, interventions in the outpatient sector like the implementation of national guidelines for the appropriate use of antibiotics or public campaigns [7] were only partially able to prevent the increase in DALYs from third-generation cephalosporin-resistant *E. coli*, an important pathogen in the outpatient sector [21]. A similar situation was described by Cassini et al. for the EU and EEA, where a strong increase in DALYs associated with these pathogens was observed between 2007 and 2015, contributing the highest proportion of DALYs [2]. Interestingly, the increase in Switzerland was most prominent in people ≥ 65 years old, a finding which merits closer analysis.

In line with previous studies [22,23], it is not surprising that the burden was estimated to be higher in males compared with females. Explanations for sex-dependent resistance patterns are diverse and complex and include both biological and socio-cultural aspects [23,24]. Remarkably, the burden was higher in females than in males in age classes of 25–29 and 35–39 years old, mainly due to infections with third-generation cephalosporin-resistant Enterobacterales. This observation may be explained by increased incidences of urinary tract infections in younger women or infections during pregnancies and childbirths in these cohorts [25].

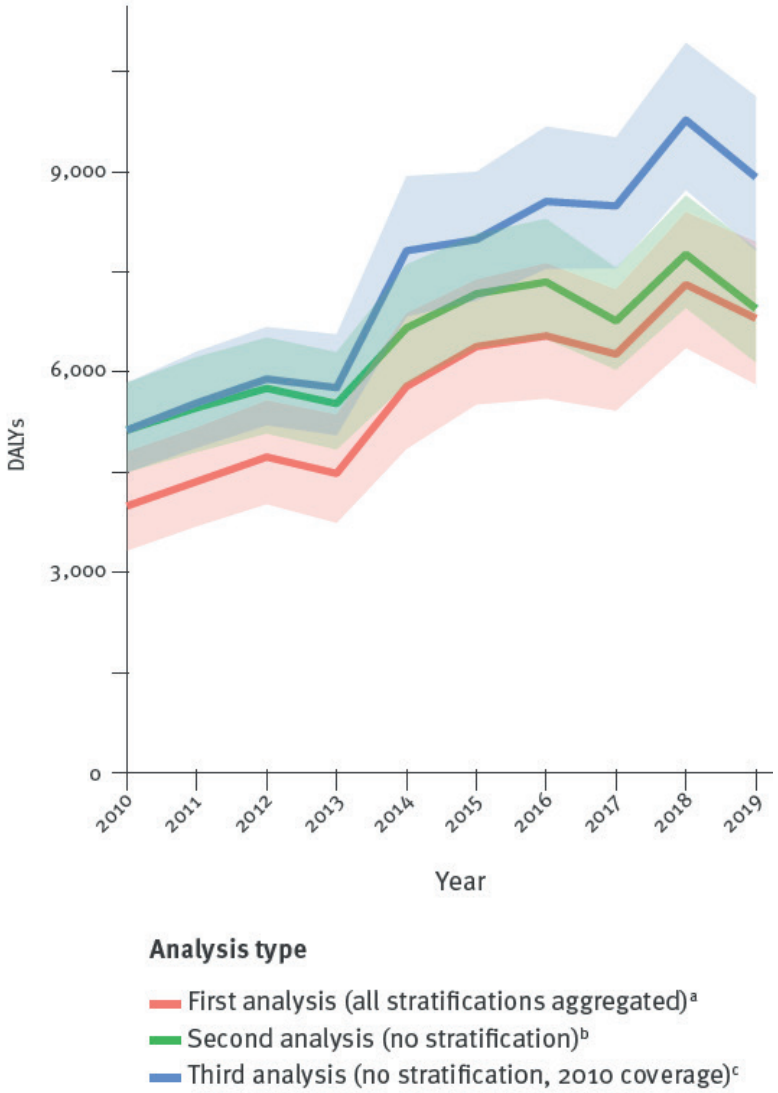

Figure 5. Estimation by three different methodological approaches of DALYs caused by infections with antibiotic-resistant bacteria in Switzerland, 2010–2019

DALYs: Disability-adjusted life-years Disability-adjusted life-years.

[a] In the first analysis, the coverages and outputs for each linguistic region and hospital type combination were estimated yearly and all values were then aggregated.

[b] In the second analysis, the coverage was calculated yearly but no stratification was performed.

[c] The third analysis included only hospitals which were covered by ANRESIS from the first year of the study (2010) and no stratification was performed.

95% uncertainty intervals are depicted by semi-transparent ribbons.

DALYs per 100,000 population were higher in the Latin part of Switzerland, which borders France and Italy compared with the German part bordering Germany. As burden estimates for Italy and France are higher than those for Germany [2] this finding may be explained by the cross-border movement of individuals, including patients and medical staff between neighbouring countries. This effect may be particularly relevant in the Latin part as numbers of cross-border commuters are considerably higher in this area than in the larger German part [26]. Centrally located in continental Europe, Switzerland is a highly connected country and similar incidence rates and even genetic characteristics of antibiotic-resistant bacteria in neighbouring countries and the bordering regions of Switzerland have been reported previously [5,6]. Another relevant factor may be the region-specific levels of antibiotic consumption. While in 2019 total antibiotic consumption in hospital care was relatively similar in different linguistic regions, considerably higher numbers were observed in the Latin part compared with the German part in the outpatient setting [19]. Filippini et al. hypothesised that these differences may also be explained by cultural variations [27], i.e. that public perception and 'medical attitudes' may be influenced by those in neighbouring countries.

It was not unexpected that numbers of DALYs which were standardised by the hospitalisation days were significantly higher for university-hospitals as these hospitals traditionally accommodate more complex cases. Remarkably, the increase in estimated DALYs was more pronounced in non-university hospitals of the German part than in any other setting. This observation may be driven by large high-end cantonal hospitals, mainly located in the German part, which are increasingly treating complex cases, as suggested by an increasing number of intensive care unit (ICU) patients in non-university hospitals (ANRESIS internal data).

Comparisons of different analysis types (Figure 5) show an increase in the number of DALYs for all three approaches. However, the model configuration (i.e. the selection of hospitals and the stratification) has a remarkable effect on both the slope and the level of DALYs time series. The approach using yearly calculated hospital coverage correction factors but without stratifications according to the hospital type and the linguistic regions probably leads to an overestimation of the burden in the early years of the study as proportionally more data from larger university hospitals were available at this time (see Supplementary Table S1 for coverage rates and Supplementary Table S2 for medians and means of hospitalisation days per hospital type). Similarly, de Kraker et al. reported that tertiary care hospitals which may harbour more resistant strains more likely participate in surveillance programmes than smaller hospitals [28] – a statement, which may be particularly relevant at an early stage of the implementation of a surveillance programme. Such a bias may be levelled out in this study in the later years when the surveillance coverage improved and increasingly more non-university hospitals were providing data. Thus, the less pronounced increase, which arises from the unstratified approach has probably no epidemiological causation and may lead to an over-optimistic prognosis for the years to come. In the third analysis, where the extrapolation was restricted to hospitals, that have been reporting to ANRESIS since 2010 the aforementioned effect may be observed throughout the whole study period i.e. the inclusion

of larger hospitals with more severe cases may have led to a constant overestimation of the burden. Thus, by stratifying by the hospital type and the linguistic region an overestimation bias may be reduced throughout the whole study period. This bias may become particularly relevant when the burdens of different countries differing in coverage rates are compared – especially countries with national surveillance systems at an early implementation stage, which mainly include higher level-of-care hospitals.

Of note, in the preceding study [3] estimating the 2015 AMR burden for Switzerland no stratification was used. If these estimates are compared with the equivalent estimates (i.e. the 'no stratification' approach) of the current study, values are relatively close to each other (7,400 DALYs in the preceding study vs ca 7,200 DALYs in the current study). A small residual difference remains, due to the different point prevalence studies which were used [9,29] and due to the variation from the Monte Carlo simulations.

To our knowledge only one similar study exists estimating the AMR burden for Switzerland. Mestrovic et al. [30] used the approach of Murray et al. [13] to estimate the associated and the attributable deaths for the whole World Health Organization (WHO) European region and for each individual country. For Switzerland they estimated 149 attributable (i.e. comparing with a scenario where infections with resistant pathogens are replaced with susceptible ones) and 738 associated (i.e. comparing with a scenario where drug-resistant infections would not occur at all) deaths for 2019 using the 11 antibiotic-resistant bacteria which were considered in both studies. The latter value is higher compared with the estimate of 278 associated deaths for the same 11 antibiotic-resistant bacteria obtained in this study in 2019. However, a direct comparison is difficult because the counterfactual scenarios are not exactly the same and the model architectures of the two approaches are completely different.

As the method of Cassini et al. [2] was applied, most of the limitations which are described in detail in their study (p 64 and appendix p 204) are also valid for this research. From our point of view the potentially largest uncertainties in the here presented estimations may result from the extrapolation steps. Namely, the application of factors used for converting the number of BSIs to other types of infection bares uncertainties, as the daily prevalences from the PPS [9] used in this study are depending on the day of the measurement and data originate from a different geographical area (EU/EEA countries). In addition, PPS incidences were estimated by the Rhame–Sudderth formula. Not all data which were necessary for these calculations (specifically the length of stay for all patients) could be acquired from the PPS itself i.e. data from a survey of the previous year had to be used. A future improvement and potentially less bias-prone approach would be to use a method that is not dependent on any assumptions about the underlying parameter distributions [31,32]. Such an approach (i.e. a Grenander estimator) has already been used in a sensitivity analysis of the 2016–2017 PPS [9]. Additional uncertainties in DALYs' estimates result from the application of disease models (outcome trees) which are based on published literature.

Another limitation was that no data were available on age-dependent hospitalisation days per hospital type. It was therefore not possible to calculate age-specific incidence rates. Furthermore, attributing epidemiological trends to control measures presented a challenge. Switzerland has a federal structure and putting in place many measures proposed nationally is the responsibility of the cantonal authorities. As a result, implementation over the country is often a gradual, with timing of effects if any, difficult to pinpoint.

One important strength of this work lies in the quality and quantity of surveillance data from Swiss hospitals providing different levels of care over a period of 10 years. In particular, during the last years of the study, the number of BSI infections are highly reliable as data of all isolates from university hospitals and around 85% from non-university hospitals were collected. As a result, it was possible to robustly stratify by hospital type and linguistic region.

Finally, this study clearly demonstrates the value of analysing routinely collected data, from the individual patient to the national level. The ability to determine and follow sources and trends of antimicrobial resistance can provide crucial decision support to the development of treatment regimens as well as the design of local and national interventions. Thus, through this type of analysis the Swiss surveillance system may also inspire other countries that have more recently embarked on developing their surveillance systems.

There are numerous publications proposing improvements in AMR-bacteria burden estimations [28,33-35]. Some measures which can be considered as particularly beneficial within the context of this study include (i) a more complete sampling from other locations than blood (e.g. urinary tract or respiratory tract) and the direct inclusion of these data into the models, (ii) extending the estimations to pathogens such as *Neisseria gonorrhoeae* and others from the priority classes 2 and 3 of the WHO global priority list [36], (iii) a more distinct separation of hospital and community-acquired infections and an increased exploitation of the latter data, as well as (iv) the improvement of the models by integrating clinical data and the linkage of these data with corresponding outcomes (as proposed by Pezzani et al. [34]).

Conclusion

This work shows that the burden of infections with antibiotic-resistant bacteria was steadily increasing over the last decade in Switzerland. This increase mainly originates from the ≥ 65-year-olds and is predominately attributed to third-generation cephalosporin-resistant *E. coli*, an important pathogen in the outpatient sector. A bundle of measures which were implemented into the Swiss healthcare system over the last years [7] may have kept typical highly resistant inpatient pathogens such as MRSA or carbapenem and colistin-resistant microorganisms at bay and thus, helped to maintain the overall burden at a moderate level.

As coverage rates and estimated outcomes in Switzerland differ considerably depending on the linguistic region and the hospital type, a stratification by these factors improved the overall burden estimation. Particularly in countries with low surveillance coverages, a potential overestimation of the burden might be reduced by using a stratified approach.

Ethical statement

This study was based on national surveillance data submitted to the Swiss Centre for Antibiotic Resistance ANRESIS. Because of the anonymous nature of the data, neither ethical approval nor written informed consent from patients was required.

Data availability

All data can be made available upon request to the corresponding author.

Supplementary information

Supplement: https://www.eurosurveillance.org/deliver/fulltext/eurosurveillance/28/20/22-00532_GASSER_Supplement.pdf?itemId=%2Fcontent%2Fsuppdata%2F10.2807%2F1560-7917.ES.2023.28.20.2200532-1&mimeType=pdf

Competing Interests

None declared.

Authors' contributions

Study conception: MGa, AOK. Data processing, modelling and statistical analyses: MGa. Data interpretation: MGa, AC, DLFW, MGe, SAN, WZ, AOK. Drafting the manuscript: MGa, AC, DLFW, MGe, SAN, WZ, AOK. Approving the final version: MGa, AC, DLFW, MGe, SAN, WZ, AOK.

Funding

This work is financially supported by the Swiss Federal Office of Public Health and the Institute for Infectious Diseases of the University of Bern, Switzerland.

Acknowledgments

We thank Tommi Karki (ECDC) for his expertise regarding point prevalence studies (PPS) and data manipulations in R, as well as for providing PPS data and we thank Chantal Studer (ANRESIS) for her assistance in the data processing.

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CHAPTER 9

General discussion

9

In this PhD thesis, we have developed tools, resources and results of the burden of IDs in EU/EEA countries, while translating complex epidemiological results into options for decision-making, thus empowering the role science plays on public health policies (1). The objectives were 1. to promote evidence-based methods in epidemiology, 2. to facilitate planning and prioritization related to public health decision making, 3. to identify gaps in surveillance data availability and quality, and 4. to provide a comprehensive framework for communicating complex information to decision-makers. These objectives are fulfilled within the research presented in this thesis and summarised below.

In **Chapter 2** we have presented a standardised and accessible approach to the estimation of DALYs for IDs, the BCoDE toolkit software application. The objectives were to enable scientists across the EU/EEA countries, and beyond, to access what is normally a computationally intensive task. The friendliness of the BCoDE toolkit is two-fold: a flexible and easy to use interface coupled with disease models that already include baseline information. Data sources were assessed for data availability and quality to tailor the models to the EU/EEA context, as well as to different populations. The methodological choices mentioned in the Introduction (**Chapter 1.4**) were validated and justified in **Chapter 2**.

The toolkit was used and tested during the estimation of the burden of IDs in **Chapters 3, 4 and 5**. A combination of solutions were explored to estimate the incidence, the starting point being the EU/EEA official surveillance system, TESSy. Estimation of the incidence and mortality inevitably varied for each disease and context, with ad-hoc solutions explored together with ECDC and country experts. The disease models were reviewed and improved, and the results were put into perspective to explore the impact on public health. Options for policy-making and examples of interventions were proposed.

Finally, in **Chapter 6** we provide a few examples of how the studies included in this thesis, or the methodology it developed, have helped shape specific public health policies from the European Commission (responsible for proposing legislation for all EU/EEA countries), an EU Member State (Slovenia) and beyond (Switzerland).

9.1 Empowering the estimation of DALYs for infectious diseases: the BCoDE toolkit

The balance between providing users with sufficient information to enable rapid estimation of DALYs with the flexibility to adapt the models to other contexts was a challenging one to strike. The balance is fundamentally one between the quality of the scientific data sustaining the modelling, the flexibility and adaptability of the tool, and the modelling and statistical features of the computational tool. In this chapter we illustrate the solutions developed to fulfil the objectives of the thesis (estimation of the burden of the diseases and syndromes under surveillance in EU/EEA countries and, therefore, availability of scientifically robust outcome trees) in combination with a software that is flexible and user friendly, while maintaining rigorous modelling and statistical approaches. The result is the BCoDE toolkit which can

be downloaded from https://www.ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys#sthash.9GmX1e3Q.dpuf.

These three features underlying the development of the BCoDE toolkit will be compared to other DALY calculators, such as the one provided by the Global Health Cost-Effectiveness Analysis (GH CEA) Registry (2) (http://ghcearegistry.org/orchard/daly-calculator) which main goal is to provide tools for analysing the economic benefits of interventions using DALYs, the DALY Calculator developed by the Center for Burden and Risk Assessment (CBRA) (3) (http://daly.cbra.be/) and the DisMod-MR developed by the IHME for the GBD studies and freely available on GitHub (https://github.com/ihmeuw/dismod_mr) (4).

9.1.1 The evidence behind the BCoDE toolkit: disease models

Undertaking the estimation of DALYs for any disease is a time consuming and computationally intensive task. Challenges include the collection and analysis of basic epidemiological information to determine the incidence, short- and long-term complications, and mortality. Most diseases will also require the understanding and modelling of pathophysiological pathway and transmission patterns such as, for example, the role of asymptomatic carriers, age-specific trends, risk of developing sequelae related to a specific symptomatology and the competing aetiology of complications in multimorbid patients. Most burden of ID studies focused mainly on the acute phase of a disease, instead of researching and proposing the mounting evidence of their long-term consequences.

For these purposes, we decided to develop outcome trees to represent the disease progression pathway of the IDs under study. Each box represents a disease outcome with its related duration and disability weight, while arrows represent the probability of moving from one outcome to another. Degrees of severity are represented by separate health states within health outcomes.

The BCoDE toolkit includes models for 32 diseases, 6 healthcare-associated syndromes and 16 AMR microorganism-antimicrobial resistance combinations available today in the BCoDE toolkit. The 16 outcome trees related to AMR were subsequently adapted to 5 types of infections (bloodstream infections [BSIs], urinary tract infections [UTIs], respiratory tract infections, surgical site infections [SSIs], and other infections), added to 5 baseline infections with antimicrobial-susceptible microorganisms, totalling 85 disease models for the burden of AMR. The BCoDE toolkit includes, therefore, models for 123 IDs or syndromes; these increase to 131 models when counting neonatal- or sex-specific outcome trees (see below).

Estimates of the data points included in outcome trees were derived from reviews of the literature for each disease or syndrome included. For most outcome trees evidence was found to be limited and meta-analysis were generally not possible. Therefore, critical appraisal of the evidence by disease-specific experts was necessary, together with integration of information stemming from other epidemiological sources. The role of expert review varied according to the evidence found in the scientific literature. Disease models for AMR were

based on a systematic review of the literature sifting through more than 360 publications. However, evidence for each microorganism-antimicrobial resistance combination (16 in the AMR burden study) within each of the five infection sites was often limited. A long process of expert appraisal was necessary to build Table 1 of page 176 of the Appendix to the publication (duration and case fatality of AMR) (5). Expert groups and meetings were organised to critically appraise of the evidence generated through systematic reviews of the literature (6). In other instances, the systematic review generated separate publications (7).

Other DALY calculators, such as the one developed by CBRA (only includes two examples "Taenia solium cysticercosis in Cameroon" and "Congenital toxoplasmosis and DALYs in the Netherlands"), do not have disease models integrated in the toolkit or lack long-term sequelae (e.g., GH CEA). Moreover, the CRBA DALY calculator allows the simultaneous assessment of up to eight disease categories or outcomes, which is limiting for complex models.

The descriptive epidemiological meta-regression tool developed by the IHME, DisMod-MR, is not a DALY calculator, but aims at estimating the prevalence and incidence of disease sequelae and duration (as well as prevalence and incidence of disease, see **Chapter 9.2**). DisMod-MR is based on meta-regression built on a Bayesian compartmental model framework (differential equations iteratively modulate the relationships between compartments of SIR models).

An example in the BCoDE toolkit of integrating evidence from the literature and reported data is the approach used to model fatalities due to campylobacteriosis. The overall case fatality related to campylobacteriosis was found to be 0.001–0.05% in the scientific literature. However, given the sensitive nature of DALYs to age-specific epidemiology and following disease expert review, it was important that this was reflected appropriately across the 19 age groups of the outcome trees. As a solution, the number of deaths was distributed according to the age-specific deaths due to campylobacteriosis reported to TESSy.

Another example of age-specific modelling are the ID infecting newborns. For those under ECDC surveillance, the outcome trees were created separately, such as congenital toxoplasmosis, gonorrhoea, rubella, syphilis, and perinatal listeriosis and chlamydia.

Finally, for some diseases it is necessary to consider sex-specific risks because of the differing manifestations of the acute disease or of the short- and long-term complications. Women might experience pelvic inflammatory disease following infection with gonorrhoea or chlamydia, for example, and indeed, female- and male-specific outcome trees were developed.

Comorbidity is another challenge when modelling health outcomes. The methodology to estimate the disability weights of comorbid states was chosen early in the development of the toolkit (8). However, the evidence on the risk of developing comorbid states and the consequences of these states, varied across diseases. For example, the concomitant display of physical impairment, renal failure and post-traumatic stress disorder (PTSD) following a BSI is demonstrated and quantified by the scientific literature (6). On the other hand, the

realm of complications during the acute phase of pertussis is well known but not so much the extent of their interactions. Hence, it was decided to aggregate all cases of acute pertussis with secondary infections (e.g., such as otitis media and pneumonia) and neurological complications, (e.g., seizures and encephalopathy) in a specific health state, separate from the uncomplicated acute cases of pertussis.

An important value of the BCoDE toolkit is transparency; results of literature reviews and integration from other data sources are documented and reported on a data synthesis sheet available for each outcome tree. Decisions are explained and summarised in tables, which also help the users adapt or update the data. Other examples of DALY calculators, such as the one available from GH CEA Registry, do not inform users of the data used to calculate a DALY.

9.1.2 A flexible and user-friendly tool set for knowledge translation

The BCoDE toolkit includes an interactive tutorial to help understand and navigate the toolkit. Moreover, developers focused on a user-friendly interface to improve access to all public health specialists, including those less verse on modelling and statistical methodologies. The menus and interfaces are intuitive and were developed according to contemporary easiness of use and communication standards such as left-hand general menus, pop-up windows, information when hovering over items and drop-down menus. The user can easily navigate the visualisation of each disease, consult the science behind the default outcome tree and change its parameters. Export and import to excel files are possible to save the models, import large datasets and export results in tables and graphs.

Disease models and population are the first choices a user needs to make. By default, the toolkit includes modelling features (e.g., number of iterations, time discounting rates), basic population data for EU/EEA countries and for all disease models. The model parameters can be edited – including re-distribution of probabilities across ages or sex. This entails a higher degree of responsibility from the user, who will have to validate their choices. The choices that a user needs to make are also those related to the modelling options, although default values are available (3% discounting rate and no age weighting). In fact, users can choose if and which time discounting to apply, which uncertainty method (normally based on the availability of the evidence). This approach nudges users towards a proactive and critical thinking way of using the tool, instead of passively accepting the input and outputs of the tool.

Another tool which is freely available on GitHub is DisMod-MR, but requires an in-depth programmer, modelling and statistical knowledge. A user-friendly experience is limited on tools such as GH CEA or CBRA as they are based on R statistical programming environment: again, users require programming knowledge of R to understand, change of develop disease models. Disability weights of the BCoDE toolkit were derived from the latest study done in four European countries (9) and assigned to health states through disease expert reviews. On the other hand, tools such as the GH CEA DALY calculator include older disability weights, or do not propose any at all (CRBA tool).

The BCoDE toolkit was developed to be flexible, although developers of the BCoDE toolkit decided to add a few restrictions, such as the absence of age weighting. The BCoDE toolkit has the purpose of estimating the health impact of IDs, and not the economic value of these. For the latter, several adjustments need to be made, as we will see further in this thesis. Finally, the ethical arguments against the application of age weighting (10) ensued that the developers decided not to include this option in the BCoDE toolkit. Other restricted approach is the DALY formula and the statistical approach based on Monte Carlo simulations.

Developers have extensively worked with public health specialists and decision-makers to warrant that the output tables and graphs were translated into options for interventions aiming at identifying and reducing the burden of IDs. The results available in the toolkit allow for identification of general overviews of the burden ("Aggregate results" tab), as well as the possibility of zooming-in specific age-, sex- and disease-specific results ("Detailed results tab"). The latter, for example, includes the possibility of visualising the impact of YLDs compared to YLLs, or of sequelae compared to the acute phase of the disease. Moreover, results are presented through several metrics, ranging from incidence, mortality and DALYs, to provide all epidemiological information for the different audiences. Innovative approaches such as bubble and pie charts attempt new ways to look at results striving for better understanding from non-epidemiologists. In practice, this allows for immediate consideration of key populations to target for example (11), or in different areas such as food safety (12), as we will see in **Chapter 9.3**. Within this context, the BCoDE toolkit plays its role in providing tools for knowledge translation and bridging the gap between epidemiologists and public health decision makers.

9.1.3 A free tool with advanced modelling and statistical properties

The BCoDE toolkit is based on Microsoft Windows® 32-bit desktop application written in C++. These development tools were chosen for simplicity (anticipating further improvements and capabilities), performance in presenting user-friendly frameworks and graphs, and customisation of parameters from users. A single calculation engine ensures high performance, limited maintenance and low risk of calculation crashing.

As discussed earlier, sources of information populating the disease outcome tress stem from various scientific publications, surveillance systems and expert knowledge. These carry inherent uncertainties related to underestimation and population heterogeneity. Therefore, epidemiological data are normally reported with probability distributions. Users can choose between 5 kinds of modelling uncertainty, Uniform, Pert, Beta, Gamma, LogNormal by choosing the preferred option from a drop-down menu at the top of each input table or inserting it in the incidence input data. To process the models and associated uncertainties, and to generate results, the calculation engine uses Monte Carlo simulations (13). Results in the BCoDE toolkit are presented through medians, averages and 95% uncertainty intervals.

The modelling of diseases needs adapting to reflect their pathophysiology. For example, evidence on the risk of developing complications of IDs, especially long-term ones, can reflect

annual or lifetime risks. Therefore, some transition probabilities are lifetime (LTP, indicating that it applies once to all cases exiting the health outcome) and others are annual (ATP, which apply cyclically to all cases in the health outcome for the duration of the latter).

9.2 Methods, results and lessons learned estimating DALYs for infectious diseases

The Introduction provided an overview of the methodology for calculating DALYs and the choices that need to be made according to the objectives and ethical considerations to convey burden of disease results. **Chapters 3, 4 and 5** provided practical examples and solutions to tackle the application and adaptation of the DALY calculation to IDs.

The following chapter explores the methods and two areas for careful consideration stemming from these experiences: providing solutions to the estimation of the incidence of disease as main input data and using the burden of disease results to put in perspective the impact of IDs on human health.

9.2.1 Overview of the methodological choices

An excellent overview of the methodological choices to undertake a burden of disease study calculating DALYs is provided by von der Lippe and colleagues (14) of the COST Action Burden of Disease network (15). The 11 methodological steps are described as being part of either the calculation of YLLs, YLDs or DALYs in general.

Within the estimation of YLLs, a first challenge is estimating the source of **mortality data** (Step 1) and **redistributing ill-defined deaths** (Step 2). Von der Lippe and colleagues suggest exploring and apply data stemming from vital registration systems, which have cause of death statistics coded using the WHO International Statistical Classification of Diseases and Related Health Problems (ICD) (16). However, for our studies, direct information from ICD causes of death was deemed insufficient for reflecting the role played by communicable diseases in the precipitation of morbidity to the death of an individual. In fact, IDs are not always immediate causes of death, being often an intermediate or precipitating factor. Given the limitations of the ICD system and the heterogeneity across and within countries in reporting multiple causes of death, we decided to implement a different approach based on scientific published literature, as explained in **Chapter 9.1.2**. In this endeavour, we strived to estimate case fatality proportions that were geographically representative and age-/sex-specific.

Finally, as part of the calculation of YLLs, the choice of the appropriate **life table** (Step 3) is crucial given that the burden of most IDs is related to YLLs. After epidemiological and ethical discussions with disease experts, we concluded that 1. European countries have generally a high life expectancy; 2. we agreed on the assumption that existing differences in life expectancy between males and females and across countries did not reflect the healthy life span that all European citizens have the right to aspire to; and 3. cross-country comparisons were and important objective. Therefore, our studies all applied the GBD standard reference life table (17).

As already described and justified in the Introduction (**Chapter 1**), the main methodological approach based on an incidence- and pathogen-based approach was decided since the inception of the our studies. The **definition of diseases** (Step 4, part of YLD and YLL) to be analysed was based on the Commission Implementing Decision (EU) 2018/945 (18) which lists the IDs for mandatory surveillance in EU/EEA countries. Moreover, IDs were further selected based on experts of the ECDC Advisory Forum scoring of selection criteria (data availability, incidence, outbreak potential and whether the disease is preventable with widely used vaccines, see **Chapter 3**). The central roles of **counting disease frequency**, **application of severity distributions** and **correcting for multimorbidity** (Steps 5, 6 and 7 part of YLD) warrant separate subchapters, which we chose to disentangle by describing the methods to develop disease outcome trees (see 9.1.2) and estimating disease incidence (see 9.2.2).

As previously mentioned, **disability weights** (Step 8) were derived from a comprehensive study done in four European countries (9) to best reflect values of the European population. These were subsequently integrated with similar studies in non-European countries for defining those to be used for the GBD (19). Descriptions of health states to be administered to pools of judges can be either disease specific or generic to a health state. Disease specific descriptions, however, generate significant biases related to message-framing effects (20, 21). Therefore, methods to estimate the disability weights were not based on disease specific descriptions and required the appropriate assignment to health outcomes or severities. This was done in concertation with disease experts who had access to lay descriptions of each disability weight, without the actual final number, when considering the best fit for the outcome under consideration.

General methodological choices related to calculating DALYs include **age weighting and time discounting** (Step 9), which was discussed in **Chapter 9.1.2**, and how to **deal with uncertainty in estimates** (Step 10, see **Chapter 9.1.3**).

Choice of the standard population (Step 11) for presentation of results according to rates is the final methodological step as described by von der Lippe and colleagues. Crude DALY results are seldom useful, particularly for an international project aiming at comparing the burden of several diseases across countries, such as the studies presented in this thesis. A first step is to age-standardise rates (ASR), which was done for the burden of AMR for the purpose of comparing countries (**Chapter 5**) based on the Eurostat revised standard population (22). Another interesting use of population rates is distinguishing between the age-group and the age-group specific burden of disease. In the former, the denominator for the burden of each age-group is the total population, whereas in the latter it's the same age-group population. The former will provide an idea of the burden of disease per age-group with a societal perspective (i.e., in general, which age groups are most affected by a disease) and the latter will tell which are the age groups at risk for that disease. As expected, results of the general burden of ID study (**Chapter 3**) found that DALYs per 100,000 age-group specific population were higher in infants and elderly over 80 years old, which represent high risk groups for infections.

9.2.2 Challenging the availability and quality of surveillance data

As part of the primary objectives to identify gaps in European surveillance data availability and quality, the starting data source for epidemiological data were official surveillance reporting systems such as TESSy. To meet this objective, the founding principle to estimate the age-group and sex incident number of cases was to analyse these data sources under the lens of the morbidity surveillance pyramid (23). As defined by Gibbons et al. "surveillance systems fail to capture cases at two distinct levels of the surveillance pyramid: from the community since not all cases seek healthcare (under-ascertainment), and at the healthcare-level, representing a failure to adequately report symptomatic cases that have sought medical advice (underreporting)." The combination of underreporting and under-ascertainment adds to the underestimation of the incidence of diseases. The aim of this dimension of our studies was to determine the underestimation of diseases under compulsory surveillance.

TESSy provides EU/EEA Member States (MS) with a single collection system for the collection, validation, cleaning, analysis and dissemination of data. It's a flexible metadata-driven system including an output visualisation tool via a dedicated dashboard (ECDC Surveillance atlas of infectious diseases). Countries are committed to report epidemiological surveillance of certain communicable diseases by Commission Implementing Decision (EU) 2018/945 (18). TESSy represents, therefore, the main surveillance system of the EU/EEA countries and was the main object of analysis in terms of epidemiological data availability and quality for IDs.

For every study included in **Chapters 3, 4** and **5** (in particular **Chapter 3**), we undertook a scoping exercise on the most solid data sources. This was done in a stepwise approach for each disease or ID syndrome included in the studies: 1. Mapping of countries reporting any data to TESSy for the years in study; 2. Characterisation of reported data such as case definition, case-base versus aggregate data, compulsory or voluntary reporting, comprehensive or sentinel (including if aiming at a national or different type of coverage), active or passive surveillance; 3. Reviewing and comparing reported incidence rates across countries and years. The latter step relied on expert assessments to critically discuss if outliers and trends were related to changes in the case definition, surveillance system (reporting practices, healthcare providers' awareness, healthcare system characteristics) or the epidemiology (e.g., outbreaks and disease exposure).

In parallel, a review of the literature for each disease provided evidence on the underestimation (or combination of under-ascertainment and underreporting) in EU/EEA MS. The scientific publications were assessed and scored for quality and geographical representativeness, as well as population representativeness, i.e., if focusing on specific ages.

The estimation of the burden of AMR and of HAIs followed a similar approach, although it involved modelling different approaches to surveillance: a sentinel system based on participating laboratories reporting the cases of BSIs to the European Antimicrobial Resistance Surveillance Network (EARS-Net) and a point prevalence survey (PPS) of healthcare-associated infections (HAIs) done recurrently every 4-5 years.

This methodological approach adopted for estimating the incidence and, therefore, the main input data for the DALY estimation modelling, contributed to a better understanding of the surveillance system. For example, disease experts were able to identify countries that were reporting data in an incomplete or unsatisfactory manner and react with the experts responsible in the country. Experts in the public health institutes had the opportunity to review their surveillance completeness and quality, and react with corrective measures or plan improvements in the longer term. Finally, through the thorough appreciation of its surveillance basis, our studies ultimately gave value to TESSy and other epidemiological surveillance across European countries.

Other research efforts aiming at estimating global DALYs such as the IHME have chosen a different approach. These decisions were probably driven both by the aspiration to explore and exploit all accessible epidemiological data, and the lack of good quality surveillance systems in most countries in the world. For example, for the global burden of AMR (GRAM) study (24), researchers have compiled datasets directly from hospitals and laboratories, pharmaceutical companies, clinical trials, large multi-sites and small studies published in the scientific literature, as well as global, national and regional surveillance networks. The comprehensiveness and completeness of the data collection undertaken for the GRAM study is reflected in the processing of 471 million individual records or isolates covering 7585 study-location-years to be used as input data to the estimation process. The data are integrated and modelled according to the meta-analytic methods used in, for example, DisMod-MR. This approach allows for systematic integration of differing data sources and imputation of missing data. However, its intent is not to inform on the completeness and quality of surveillance systems and, if not properly calibrated through appropriate Bayesian methods, is at risk of being extremely skewed towards unrepresentative data. Finally, it is more difficult (and at times impossible) to ensure transparency of the relative roles and weights of each data source in the final estimation of the input data.

9.2.3 Results from the studies: putting them into perspective

The aspirations for the BCoDE project were launched in 2007 with the publication of an editorial on Eurosurveillance by ECDC's Director Zsuzsanna Jakab (25). Founded in 2005, at the time of the Director's editorial, ECDC was under construction and mainly focusing on public health emergencies such as responding to a H5N1 outbreak in Turkey (26). Evidence on the impact of current infectious threats were based on data stemming from cases reported to network surveillance systems managed by large academic consortia and financed through ad-hoc grants from the European Commission. In time, surveillance coordination was taken over by ECDC, funnelled through TESSy and with the aim to harmonise its quality and understanding. The 2007-2013 ECDC programme identified a number of infectious threats, ranging from those due to foodborne pathogens, AMR and HAIs, influenza, HIV and sexual-transmitted infections, imported tropical diseases, tuberculosis, and vaccine-preventable childhood diseases in some areas of the EU.

However, the relative impact of these IDs was unclear. The first matter of principle was to choose the relevant perspective. Given ECDC mandate to protect the health of European citizens from diseases due to infections, it was decided that the burden of IDs would be measured and expressed through health metrics. Hence, DALYs were deemed to be most appropriate.

Once the perspective was clear, the results of the studies allowed for a new viewpoint on the ranking of the impact of IDs on the population. This is evident by comparing the rankings based on average notification rates and on DALYs, such as shown in Figure 8 of **Chapter 3** and Figure 5 of **Chapter 4**. Almost all diseases change position, some even dramatically. When combining results from all three studies, with the double of DALYs compared to all other IDs presented in **Chapter 3**, it seems that HAIs currently pose the biggest infectious threat to the European population. AMR follows closely, although given that 75% of its burden is healthcare-associated, the overlap makes it inappropriate to fully compare the burden of AMR and of HAI side by side. The burden AMR remains significantly high, its DALYs accounting for the cumulated DALYs due to influenza, HIV/AIDS and TB.

Comparisons of the data produced within the studies presented in this thesis can be compared to those of the GBD by downloading the 2011 GBD data for the European Union from the IHME GHDx website (27) and the GRAM study (24, 28) given that the GBD does not provide DALY estimates for HAIs. The first notable difference is related to the overall burden of IDs: the GBD estimated 4.7 times higher burden of IDs (not counting AMR from either studies) with a total of 1285 DALYs per 100,000 population, whereas our study estimated 273. Looking more specifically at diseases, we could compare results for a limited number of IDs (in order of lowest to highest number of DALYs from the GBD: diphtheria, rabies, measles, tetanus, pertussis, gonorrhoea, chlamydia, syphilis, acute HBV, TB and HIV/AIDS). It's also possible to compare the burden of enteric diseases by adding the burden of those from the studies presented in this thesis: again, the GBD found a higher number of DALYs by a factor of 4. Likewise, comparing the burden of enteric diseases shows a 6 times higher number of DALYs calculated in the GBD study.

When comparing ranking of results, the GBD study, similarly to our studies, found that TB and HIV/AIDS were diseases with the highest burden, significantly higher than the other diseases. TB and HIV are followed by HBV infections in both studies, although the GBD only estimated DALYs for acute HBV and found 1.64 DALYs per 100,000, more than 80 times compared to the the studies published in this thesis. The remaining diseases accounted for low number of DALYs in both studies. Therefore, a small number of cases can significantly change the results. Nevertheless, notable ranking differences were found for syphilis (higher ranking in the GBD study) and measles (higher ranking in our study study).

A similar comparison was done between the global and European GRAM study (24, 28) and the AMR results presented in **Chapter 5**. All studies have shown highest burden due to antibiotic-resistant infections with *E. coli* and *S. aureus*, which are infections transmitted in

community and healthcare settings, are classified as priority pathogens (29) and are part of the SDG indicators for which countries should set targets of reduction (30). The studies also consistently found that carbapenem-resistant infections with *K. pneumoniae* (and in some areas to *P. aeruginosa* and to *Acinetobacter* spp.) were a rising threat to healthcare provision.

The global and European GRAM studies attempted a comparison between their estimates of number of deaths and the one published in our publication (**Chapter 5**). As correctly underlined by the authors, these comparisons are extremely difficult to make because of the different methodologies: the GRAM studies are based on modelling of data stemming from ICD codes and cause of death notifications, whereas our study was based on critical appraisals of systematic reviews of the scientific literature. Moreover, the geographical scope was different (WHO Europe Region versus EU countries) and the inclusion criteria for the antibiotic-microorganism combination. Finally, the authors of the GRAM study introduce the distinction between *attributable* deaths (counterfactual of infections with resistant pathogens that are replaced with susceptible ones) and *associated* deaths (alternative scenario is that drug-resistant infections would not occur at all). Our study, on the other hand, focused solely on attributable deaths, although the methods to estimate these would better fit in the GRAM definition of *associated*. The GRAM authors do not provide a comparison between their estimation of associated deaths for the 11 overlapping antibiotic-microorganism combinations and countries; they estimated 23,100 deaths attributable and compared to our estimation of around 30,000 deaths. To make an appropriate comparison, we estimated the attributable (according to the GRAM definition) number of deaths in 2015 in EU/EEA countries and found little over 11,000 deaths, approximately half of the GRAM study. This finding is consistent with the higher estimated DALYs and deaths found by GBD studies.

Estimating the burden of AMR is particularly complex; to start, AMR is not a disease, rather a condition determining treatment failure. Infections with drug-resistant microorganisms often occur and have a health impact in otherwise multimorbid patients or people undergoing invasive procedures and that are already fragile. Hence, estimating the relative causality of AMR on disability and death is challenging and attribution is often debateable.

9.3 Translating findings in opportunities for public health

Evidence for prioritising interventions aiming at preventing and controlling IDs is often limited by the availability of data, as seen in the subchapter 9.2.2, and our understanding of the impact of the disease on the population. The combination of these needs was the basis for launching the BCoDE project (25). However, the role of ECDC focuses on risk assessment, rather than risk management (i.e., what are the problems, then provide options for solving them for the European Commission and EU Member States to consider). Within the context of this mission, the ECDC 2007-2013 Strategic multi-annual programme highlighted the role of estimating the impact of IDs and of its economic impact (26).

The plan mentioned the significant impact of foodborne infections on consumers and the agricultural industry. Aiming at providing a better understanding of their relative impact and identify preventive interventions, the European Commission organised several expert workshops and stakeholder meetings to shape legislation around infection control in the poultry industry. The author was invited in 2014 to provide an overview of the relative impact of foodborne diseases, which was published as presented in **Chapter 7**. Based on other European agency's scientific opinion (31) and ECDC's study, the EU regulated and reported on hygiene for poultry slaughterhouses focusing on *Campylobacter* control (32-34).

In terms of using DALYs for economic studies, most have targeted HIV and malaria in African countries (35). An interesting exception is the Organisation for Economic Co-operation and Development (OECD) report published in late 2018, based on a collaboration with ECDC, *Stemming the Superbug Tide: Just A Few Dollars More* (36). The report models several practical interventions to curb AMR, estimating its cost-effectiveness and number of DALYs averted. This work was adapted to health policy audiences and fitted into briefing note to inform the 2019 EU Health Ministerial Meeting on AMR (37).

As discussed in **Chapter 9.2**, the qualities of the approach described in this thesis are its flexibility when estimating the incidence of diseases (which depends on the availability and quality of surveillance data), coupled with a rigorous methodological approach to estimate DALYs. The latter allows for comparing the results of the impact of IDs and, ultimately, "*package*" them for health policy decision-making.

We use the word packaging because it should be clear to epidemiologists that results from these complex studies need to be critically assessed and interpreted before communicated to decision-makers. For example, results from the study described in **Chapter 3** indicate that most vaccine-preventable diseases, such as measles, represent a very low burden. This could convey the wrong message and suggest that investments and efforts to improve the vaccination coverage for measles are not needed (the paradox of prevention: "All successful prevention undermines the reasons for its own existence"). Therefore, as discussed in the publication, complementing the results with scenarios, for example, is crucial to fine tune the public health message. In this specific case, we decided to show how the 2010 measles outbreak in a country with lower vaccination coverage (Bulgaria) generated a number of DALYs comparable to those generated by HIV/AIDS.

Another "packaging" approach is providing evidence on the burden of ID per population group. All results presented in **Chapters 3, 4** and **5** show the burden in DALYs either per 100,000 general population or per 100,000 age group-specific population (e.g., Figures 5 and 6 of **Chapter 3**). The former provides a societal snapshot of which population group accounts for the highest number of DALYs, whereas the latter provides an estimation of which age group is at higher risk for the ID. The resulting epidemiological information can inform on where transmission occurs more often, and which age group will suffer the most.

This can be further fine-tuned by overturning the visualisation and explore the burden of IDs per age categories (e.g., Figure 7 of **Chapter 3**). This allowed to show that most DALYs under 15 years old were due to vaccine-preventable diseases, and that respiratory diseases (some preventable by regular vaccinations such as influenza and pneumococcal disease) were the main cause of disease and premature mortality in the elderly over 65 years old.

A burden of disease study is the most quantitative risk ranking approach on a scale starting from qualitative studies [O'Brien, 2016]. However, there are other epidemiological, societal and economic aspects that should be considered before making conclusions on a more comprehensive view of the impact of diseases. Moreover, the perspective and perception of health policy decisions makers and the public will dictate the resources and attention invested to tackle an infectious disease issue. Hence, communicating effectively all aspects related to infectious threats critical to disentangle scientific evidence and societal values when exploring possible solutions.

With this goal in mind, we produced Figure 3 of **Chapter 3** and Figures 1 of **Chapter 4** and **5** mapping the burden expressed in bubble charts in relation to mortality and incidence. We attempted to map disease risk according to how much they occur and kill; certain diseases may receive more attention because causing relatively higher number of fatalities, although resulting in lower overall burden and incidence. We see, therefore, that Legionnaires' disease has a relatively low burden (diameter of the bubble), low incidence but a notable mortality. This is probably due to higher age groups being more at risk of infection and developing a severe disease. On the other hand, chlamydia is often under the public health radar despite its high incidence, but triggering almost no deaths. Similarly, in Figure 4 of **Chapter 3** a high DALY per case, representing severe disease, plotted against total DALYs will highlight diseases, provides information on highly lethal diseases such as rabies and variant Creutzfeldt–Jakob disease. The Figure reminds public health experts of the threats due to diseases with epidemic potential, as was recently experienced in European countries managing outbreaks of diphtheria (38).

It's relatively intuitive that benchmarking countries or other geographical regions is a driver for accountability and change. Producing high quality burden estimates at the national level might not always be possible due to limited data availability, although the GBD circumvents these limitations via proxies-based indicators (which can also be non-health related). Our studies proposed aggregate results in **Chapters 3** and **4**, and underlined the limitations in surveillance systems for most IDs in Europe. On the other hand, years of improvements in the clinical and microbiological surveillance of AMR, enable to show the heterogeneity of its burden across countries (Figure 3, **Chapter 5**). This increases the information to decision-makers, the media and the general population, and increases the chance that corrective actions are discussed and put in place.

Country estimations of the burden of AMR were presented early in 2017 to a few countries, such as in Italy. The fact that about a third of the total EU/EEA number of deaths occurred

in Italy was a definitive nudge for the country to develop and publish its first national action plan (NAP) against AMR (39). Given the increase of the burden of infections due to resistant bacteria typically transmitted in tertiary healthcare facilities, much of the Italian NAP outlines at length the necessary measures such as strengthening IPC and antimicrobial stewardship in hospitals. A very similar approach occurred in Greece, resulting in the revision and publication of the second NAP, also focusing on tackling AMR threats in hospitals (40).

Even at the continental level, estimates inspire action: the European Commission's overview of the AMR threat, mainly based on the results presented in **Chapter 5** and the twinning report from the OECD detailing the economic burden of AMR (36) is outlined (41) and translated as part of EU Regulations (42).

A notable experience in using the burden of disease described in this thesis approach to inform public health policy occurred in Slovenia in 2019. In 2014 the National Institute of Public Health (NIJZ) of Slovenia observed increasing incidence of tick-borne encephalitis (TBE), mainly in adults over 50 years old. Colleagues at the NIJZ decided to partner with ECDC and estimate the burden of TBE across a few years, to document trends and propose reimbursement in priority age groups (TBE vaccination was out of the pocket in Slovenia). Using our approach, we were able to demonstrate that the burden in Slovenia was significantly higher than the EU average and that it occurred mainly in children aged 5-14 years old, see **Chapter 6**. Consequently, in 2016 the Slovenian National Immunisation Technical Advisory Group (NITAG) issued evidence-based recommendations to the Ministry of Health, which were put into effect in 2019 (11).

A very recent example of national health policy implications stemming from a study based on the methodology described in this thesis is the estimation of the burden of AMR in Switzerland mandated by the Federal Office of Public Health (FOPH) to the University of Bern, which also has the responsibility for AMR surveillance (Swiss Centre for Antibiotic Resistance, ANRESIS. The estimates in **Chapter 8** show that, albeit a 1.7 times increase in the burden of AMR between 2010 and 2019, this has not been as dramatic as seen in other European countries (see **Chapter 5**). Moreover, the increase was mainly due to growing burden due to infections with third generation cephalosporin-resistant *E. coli*, a community-associated infection. Trends of infections due to carbapenem-resistant microorganisms have remained relatively stable, a notable difference with some neighbouring countries such as Italy. Also, good news is the reduction of the burden related to infections with meticillin-resistant *S. aureus* (MRSA), in countertrend with what was observed in most EU/EEA countries.

A first conclusion drawn by the FOPH and Swissnoso, the national organisation tasked with setting IPC standards in healthcare facilities (43), was that the many IPC and antimicrobial stewardship interventions implemented in the country are having an impact. Switzerland was the first country to develop national minimal standards for IPC (44), based on the WHO IPC core components (45) and IPC minimum requirements (46). Publications such as the one

presented in **Chapter 8** contribute to the recent push in translating the minimal standards into indicators to monitor and evaluate, as well as embedding the standards in the performance contracts between the cantons and the healthcare facilities.

In conclusion, this PhD thesis proposes a comprehensive framework for calculating DALYs for infectious diseases and provides estimates of the burden in EU/EEA countries. The thesis describes how the BCoDE toolkit and the BCoDE results were developed and adapted to facilitate planning and prioritization related to public health decision making, while communicating complex epidemiological information. The framework described in this PhD thesis includes the methodological steps to calculate YLLs, YLDs and the uncertainties related to each step to provide the most meaningful approach for infectious diseases. The steps necessarily proceed through assessing the availability and quality of surveillance data, and identifying the related gaps. All results were compared to the published scientific literature and, for the first time, DALYs were calculated for AMR and HAIs. Overall, the PhD thesis fulfils its objectives by empowering the role of science in public health policies, facilitating and promoting evidence-based decision-making.

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9

APPENDICES

A

Brief summaries in English, Dutch, Italian and French

In this thesis we describe tools, resources and methodological options for estimating the burden of infectious diseases (IDs) in the European Union (EU)/European Economic Area (EEA) expressed in disability-adjusted life years (DALYs). The objectives were to promote evidence-based methods in epidemiology, facilitate planning and prioritization of public health decision making, identify gaps in surveillance data availability and quality, and provide a comprehensive framework for communicating complex information to decision-makers.

The thesis presents the methodological challenges and solutions for calculating DALYs for the main community-acquired infections, antimicrobial resistance (AMR), and healthcare-associated infections (HAIs), while taking into consideration different approaches to efficiently use data sources depending on their availability and quality. The results were put into perspective and compared with data from other studies estimating DALYs for IDs.

Our studies found that:

- Influenza, tuberculosis and HIV/AIDS have the highest burden measured in DALYs among the most common community-acquired infections. Vaccine-preventable diseases have lower burden, although in countries where coverage is low the burden can be comparable to the top three diseases.
- The burden of AMR was comparable to the cumulative burden of influenza, tuberculosis and HIV/AIDS. It is mainly healthcare-associated (which has increased significantly in the past decades), hence, antibiotic stewardship and enforced IPC in hospitals are the most effective interventions.
- The burden of HAIs was twice of the other IDs under surveillance in EU/EEA countries, making HAIs the major ID problem in the region.
- The burden of IDs varies greatly between countries and interventions to reduce the burden need to be adapted or tailored.

The methods developed in this thesis were used to provide data to decision-makers and promote evidence-based change. Examples included in the thesis was the shift towards universal vaccination against tick-borne encephalitis in children in Slovenia, EU/EEA legislation for campylobacter control in the poultry industry and the validation of strategies to combat AMR in Swiss hospitals.

In dit proefschrift beschrijven we instrumenten, bronnen en methodologische opties voor het schatten van de ziektelast van infecties (ID's) in de Europese Unie (EU)/Europese Economische Ruimte (EER), uitgedrukt in voor invaliditeit gecorrigeerde levensjaren (DALY's). De doelstellingen waren het bevorderen van wetenschappelijk onderbouwde methoden voor epidemiologische vraagstukken, het onderbouwen van besluitvorming op het gebied van de volksgezondheid, het identificeren van hiaten in de beschikbaarheid en kwaliteit van surveillance gegevens, en het bieden van een alomvattend kader voor het communiceren van complexe informatie aan besluitvormers.

Het proefschrift beschrijft de methodologische uitdagingen en oplossingen voor het berekenen van DALY's voor de belangrijkste infecties die buiten (CAIs) of binnen (HAIs) het ziekenhuis worden opgelopen, en de mogelijk geassocieerde antimicrobiële resistentie (AMR), waarbij verschillende benaderingen worden gebruikt om de verschillende gegevensbronnen efficiënt te gebruiken, afhankelijk van hun beschikbaarheid en kwaliteit. De resultaten werden in perspectief geplaatst en vergeleken met gegevens uit andere onderzoeken waarin DALY's voor ID's werden geschat.

Uit onze studies bleek dat:

- Gemeten in DALY's, influenza, tuberculose en hiv/aids de hoogste ziektelast hebben van de meest vóórkomende infecties, die buiten het ziekenhuis opgelopen worden. Ziektes die door vaccinatie kunnen worden vóórkomen, een lagere ziektelast hebben, alhoewel in landen met een lage vaccinatie dekking de ziektelast vergelijkbaar kan zijn met de last van de top drie ziektes.
- De ziektelast van infecties met AMR vergelijkbaar was met de cumulatieve last van griep, tuberculose en hiv/aids. Deze ziektelast is voornamelijk zorggerelateerd (en is de afgelopen decennia aanzienlijk toegenomen), daarom zijn sterk antibiotica beleid en betere infectiepreventie maatregelen in ziekenhuizen de meest effectieve interventies.
- De ziektelast van HAI's twee keer zo groot was als die van de andere ID's die in de EU/EER-landen onder toezicht staan, waardoor HAI's het grootste ID-probleem in de regio zijn.
- De ziektelast van ID's sterk tussen landen en interventies varieerde, wat aangeeft dat interventies aangepast of op maat gemaakt moeten worden.

De methoden die in dit proefschrift zijn ontwikkeld, werden gebruikt om gegevens te verstrekken aan besluitvormers en om wetenschappelijk onderbouwde verandering te bevorderen. Voorbeelden die in het proefschrift zijn opgenomen, waren de verschuiving naar universele vaccinatie tegen tekenencefalitis bij kinderen in Slovenië, EU/EER-wetgeving voor de bestrijding van campylobacter in de pluimvee-industrie en de validatie van strategieën ter bestrijding van AMR in Zwitserse ziekenhuizen.

In questa tesi descriviamo strumenti, risorse e opzioni metodologiche per stimare l'impatto delle malattie infettive nei paesi dell'Unione Europea (UE)/Area Economica Europea (AEE) espresso in anni di vita vissuti con disabilità (DALYs). Gli obiettivi erano di promuovere metodi epidemiologici basati sull'evidenza, facilitare la pianificazione e la prioritizzazione delle decisioni di sanità pubblica, individuare lacune nella disponibilità e qualità dei dati di sorveglianza e fornire un quadro completo per comunicare informazioni complesse ai decisori.

La tesi presenta le sfide metodologiche e le soluzioni per calcolare i DALYs per le principali infezioni acquisite in comunità, la resistenza agli antimicrobici e le infezioni correlate all'assistenza sanitaria (ICA), considerando diverse approcci per utilizzare in modo efficiente le fonti di dati a seconda della loro disponibilità e qualità. I risultati sono stati messi in prospettiva e confrontati con dati provenienti da altri studi che stimavano i DALYs per malattie infettive.

Le nostre ricerche hanno riscontrato che:

- L'influenza, la tubercolosi e l'HIV/AIDS hanno il carico più elevato misurato in DALYs tra le comuni infezioni acquisite in comunità. Le malattie prevenibili mediante vaccinazione hanno un carico più basso, sebbene in paesi dove la copertura è bassa il carico possa essere paragonabile alle malattie con impatto più alto.
- L'impatto dell'antibiotico-resistenza era paragonabile al carico cumulativo di influenza, tubercolosi e HIV/AIDS. L'impatto è principalmente correlato all'assistenza sanitaria (che è aumentata significativamente negli ultimi decenni), quindi la gestione responsabile degli antibiotici e l'implementazione del controllo delle infezioni nelle strutture ospedaliere sono le misure più efficaci.
- Il carico delle ICA era il doppio delle altre malattie infettive sotto sorveglianza nei paesi dell'UE/AEE, rendendo le ICA il principale problema delle infettivo in questa regione.
- Il carico delle malattie infettive varia notevolmente tra i paesi e le misure per ridurre il carico devono essere adattate o personalizzate.

I metodi sviluppati in questa tesi sono stati utilizzati per fornire dati ai decisori e promuovere cambiamenti basati sull'evidenza scientifica. Esempi inclusi nella tesi includono il passaggio verso la vaccinazione universale contro l'encefalite da zecche nei bambini in Slovenia, la legislazione UE/AEE per il controllo del campylobacteriosi nell'industria avicola e la convalida delle strategie per combattere l'antibiotico-resistenza negli ospedali svizzeri.

Dans cette thèse, nous décrivons les outils, les ressources et les options méthodologiques pour estimer la charge des maladies infectieuses dans l'Union européenne (UE)/Espace économique européen (EEE), exprimée en années de vie ajustées en fonction de l'incapacité (DALYs). Les objectifs étaient de promouvoir des méthodes épidémiologiques basées sur l'évidence scientifique, de faciliter la planification et la priorisation des décisions en matière de santé publique, d'identifier les lacunes dans la disponibilité et la qualité des données de surveillance, et de fournir un cadre complet pour communiquer des informations complexes aux décideurs.

La thèse présente les défis méthodologiques et les solutions pour calculer les DALYs pour les principales infections acquises en communauté, la résistance aux antimicrobiens (RAM) et les infections associées aux soins (IAS), tout en tenant compte des différentes approches pour utiliser efficacement les sources de données en fonction de leur disponibilité et de leur qualité. Les résultats ont été mis en perspective et comparés aux données d'autres études estimant les DALYs pour les IDs.

Nos études ont montré que :

- La grippe, la tuberculose et le VIH/SIDA ont la charge la plus élevée mesurée en DALYs parmi les infections plus courantes acquises en communauté. Les maladies évitables par la vaccination ont une charge moins élevée, bien que dans les pays où la couverture est faible, la charge puisse être comparable aux trois maladies avec charge élevée.
- L'impact des infections avec organismes antibiorésistants était comparable à la charge cumulée de la grippe, de la tuberculose et du VIH/SIDA. L'impact des RAM est principalement associé aux soins (et a considérablement augmenté ces dernières années), donc la gestion responsable des antibiotiques et la mise en œuvre du contrôle des infections dans les hôpitaux sont les interventions les plus efficaces.
- La charge des IAS était deux fois plus élevée que celle des autres maladies infectieuses sous surveillance dans les pays de l'UE/EEE, ce qui en fait le principal problème infectieux dans la région.
- L'impact des maladies infectieuses varie considérablement entre les pays et les interventions pour réduire la charge doivent être adaptées.

Les méthodes développées dans cette thèse ont été utilisées pour fournir des données aux décideurs et promouvoir un changement fondé sur l'évidence scientifique. Les exemples inclus dans la thèse incluent le passage à la vaccination universelle contre l'encéphalite à tiques chez les enfants en Slovénie, la législation de l'UE/EEE pour le contrôle du Campylobacter dans l'industrie avicole et la validation des stratégies de lutte contre la RAM dans les hôpitaux suisses.

Acknowledgments

As some might be aware, the author of this thesis is not (and has never been) an academic researcher. I've always worked in regional, national or international public health organisations (except a few years as a private consultant in London) and the publications included in this book were inspired by public health needs, hypothesis and queries that I encountered from 2015 to 2022. The only reason I managed to pull through a few scientific publications (hopefully of good quality) is because during my journey I had the immense fortune to rub shoulders with a large number of outstanding professionals. My first thanks go, therefore, to all the co-authors, editors, handlers, reviewers and people acknowledged whom I've met throughout this journey, without whom these publications would not have been possible. Moreover, I've met so many other colleagues (too many to name them all) whom I met at conferences and work trips and who were generous enough to exchange thoughts and suggestions, all of which have greatly improved the quality of the articles in this thesis; to all of them, thank you.

I had fantastic PhD supervisors that guided me in translating these public health needs into solid research outputs, and a heartfelt thank you goes to Professors Mirjam Kretzschmar and Eric Fèvre. I also thank the reading committee who invested their valuable time to read this thesis and suggest improvements; I am lucky to have a PhD discussion panel of exceptional researchers, many of whom I met and collaborated with previously, others with whom I had interesting online and face to face discussions.

In one's professional life one might come across a few remarkable colleagues who become mentors, often in spite of themselves and their willingness to be an example. In the Italian medical community, these people are sometimes referred to as "maestri" and I've had the great fortune to meet quite a few maestri to whom I co-dedicate this thesis.

Chronologically across my professional path, I would like to start with Professor Erino Angelo Rendina, full professor and Director of thoracic surgery at the Sant'Andrea Hospital, Sapienza University in Rome. Erino is known for being tough but just towards his students and I will always thank him for showing me that teaching and researching can be inspiring and loving, as much as caring for our patients. He showed us the value of teamwork, multidisciplinarity being not a threat, but the only way to produce quality research and care. A characteristic I tried to apply as much as possible while working on the papers presented in this thesis: I never hesitated to ask and involve epidemiologists, statisticians, modellers, economists, sociologists, microbiologists, public health and policy experts, to name a few. Since day one, Erino also instilled in me the importance of details and analysis as the only way to do something that is robust and lasting. I hope I managed to apply these qualities in the work presented in this thesis. Finally, the well-being of the people surrounding him (he saw us as people before seeing us as junior doctors), was so important to him that when I announced I was going to change career paths he hugged me and wished me good luck, dispelling my sense of guilt to a maestro who dedicated time and knowledge, treating us as peer clinicians.

Professor Gaetano Maria Fara, Professor Emeritus of hygiene and preventive medicine, Sapienza University Rome accepted to take over a young doctor who was coming straight from clinical medicine and had no experience in public health. The potential he saw in me was a mystery, but I immediately was fascinated by his passion, immense culture and good nature. He taught me to look beyond, to be curious and never take oneself too seriously. Thanks to Professor Fara I always ask "why", who is to benefit, how many lives will we touch, will we make a difference. It's with this curiosity and humility, for example, that in 2015 I started exploring the idea to attempt the estimation of the burden of HAIs and AMR, something seemingly impossible. Each time I encountered a hurdle, I learned to study the matter, involve and question better experts than me and together ultimately attempt different routes. I have to thank Professor Fara for always being there to listen, suggest solutions or people who can provide them. And above all, I thank him for the huge freedom he gave me, allowing me to expose myself to experiences across Europe.

Back in late 2014 Doctor Dominique Monnet, head of AMR and HAI at ECDC became supervisor of a young(ish) public health expert who had seen his project suppressed (the BCoDE) and was therefore slightly bitter towards management. Dominique being a hugely respected and respectful professional, we sat down and explored possible projects together. To my surprise, he offered to support the deceased project (on top of others we shaped together), to take it to the next level and that decision resulted in the publications of this thesis. Hence, he is probably the colleague most responsible for this achievement. Not only did I stumble across a great boss, but throughout the years I discovered a dedicated professional partner, always ready to dedicate extra time to review, teach and improve my understanding of AMR and HAIs. It's uncommon to be able to work with a colleague who has such a deep knowledge of the technical and scientific intricacies of infectious diseases, coupled with such sensitivity towards the public health importance of a given problem, as well as clear skills in translating and communicating to decision-makers. Once again, a maestro with a knack for details: Dominique, although I might have joked about being obsessive, I thank you from the deep of my heart for your guidance and time. I also discovered a great person with whom I travelled across European countries, both convinced that we could change policies from the bottom, starting from local realities. We spent many days and many nights (often in hotel lobbies until 2-3 in the morning) visiting hospitals, GPs and pharmacies, solving practical and operational problems, analysing and shaping our messages to authorities, involving and bonding with colleagues who were kind and dedicated enough to follow us. In the midst of this controlled chaos, Dominique also dedicated time to read my articles with such attention and concentration that he would inevitably improve the output.

I would also like to thank a few colleagues who have definitely shaped my professional experience and decisions. Doctor Robert Hollamby (at the time CEO of Total Healthcare Solutions, British private consultancy), thank you for teaching me the respect for deadlines and hard work. Professor Donato Greco, grazie per avermi mostrato interesse e rispetto nonostante la mia giovane età; il Tuo entusiasmo infettivo è travolgente per tutti quelli che hanno la fortuna di conoscerTi. Grazie anche per avermi mostrato quanto possa essere semplice quello che

facciamo, finché lo ancoriamo nella realtà. Professor Johan Giesecke (Professor Emeritus at Karolinska University and previously Chief Scientist at ECDC) for his support and guidance when I needed it most. Professor Stephan Harbarth (Head of IPC at University of Geneva Hospitals) for being the academic editor of my first important manuscript, for his availability to discuss any matter, his incredible scientific knowledge, his sense of humour and being such a great shoulder during my new Swiss experience. Professor Benedetta Allegranzi (Head of the IPC Hub and Taskforce at WHO, Geneva) is one of the best researchers and public health officials I've ever met; her dedication, her energy, integrity and belief in the common good have been a true inspiration. It's an honour to consider her a close colleague and to be involved in some projects she leads. Finally, I would like to thank my current boss Doctor Karim Boubaker (Chief medical officer of Vaud Canton) for allowing me to learn and prove my qualities at the local level, for his trust and the freedom he allows me to operate in, for sharing his massive knowledge on operational public health and guiding me through a new adventure. This recent experience is made even more valuable by the colleagues and teams I lead, à vous tous des Maladies transmissibles du Canton de Vaud: un grand merci!

Achieving a PhD is not only a matter of having access to the right experts for the specific research projects, it's also important to be surrounded by colleagues who in time one can confidently call friends. My dear lunch, weekend and at times holiday buddies, with whom I've debated on so many issues under so many different perspectives, that make being a public health professional such a fascinating job. Sebastian Garcia Saiso, Jerome Pfaffmann, Michele Cecchini, Marlieke de Kraker, Edoardo Colzani, Julien Beauté, Ettore Severi, Jonathan Suk, Diamantis Plachouras, Hakim Khenniche and so many others. A special mention, if I may, for Edoardo Colzani whom I met by chance at a local football game. We started chatting about his PhD at Karolinska, continued discussing when he joined ECDC, we have shared authorship, good times, debated, argued, raised our voices and made peace a few minutes later. Only a solid relationship allows for such intellectual honesty, I've taken advantage of this whenever I could, throwing the wildest ideas to Edo, knowing that he would be sincere and ultimately the exchange would lead to better solutions.

In my experience, achieving the research for a PhD needs a supportive and particularly understanding group of close friends and family. Maria che spero decida che le nostre strade si possano riincontrare. Pops e Moms, Oli e Newsha (e ovviamente Matteo e Leo), Carlo, Monika, Federica e Andrea: mi avete sopportato e supportato durante tutti questi anni, anche quando avevo voglia di mollare. Mi avete visto scrivere, assentarmi, mi avete ascoltato e consigliato nelle situazioni più assurde, in barca a vela, nei bar dei porti durante cene che dovevano essere vacanze estive. Un grazie di cuore.

Infine le mie bambine Allegra e Lavinia, grazie per aver accettato con comprensione le mie serate e fine settimana al computer invece che fuori a giocare con voi. Questo dottorato è dedicato a voi e all'amore della mia vita, la vostra mamma. Fla, sei stata la mia prima tifosa, la mia confidente e amica, mi hai accompaganto durante tutto questo percorso, hai accettato e facilitato questo mio impegno. Il nostro amore ne é uscito ancora più forte.

About the author

Alessandro Cassini was born on a Saturday in 1976 in Etterbeek, Belgium. The family kept wandering around until a teenage Alessandro decided to settle down in Rome, finish school and attend the local public medical school, Sapienza University. After dwindling with thoughts of becoming a psychiatrist, then a thoracic surgeon, he finally decided to settle for a fascinating specialisation that would allow him to focus his professional life on areas ranging from sociology, epidemiology, behavioural science, medicine, economics…

Alessandro graduated in public health and preventive medicine, and completed his studies with a MSc in Health policy, planning and financing from LSE & LSHTM. After a few years in the private sector in London (because he had met Flaminia and she worked there), they decided to move to Stockholm at ECDC. During his 10 years at ECDC he was responsible for estimating and expressing the health burden of infectious diseases, developing risk ranking methodologies, and exploring knowledge translation solutions between scientific research and decision-makers. He has also been responsible for country visits evaluating the response to the increasing AMR threat and for managing the EUCAST project. During these years, Alessandro took advantage of unpaid leave to participate in several missions with NGOs such as MSF and CUAMM.

In 2019, the family moved to Geneva where Alessandro joined the WHO to work on infection prevention and control, to coordinate activities related to the epidemiology of sepsis, and to work on strategies to control and respond to AMR. In 2022 he joined the Swiss healthcare system as the Deputy Chief medical officer of Vaud as well as the Lausanne University Hospital. He has been deployed several times as a field epidemiologist as part of response teams during many outbreaks including Ebola and COVID-19.

Burden of infectious diseases in Europe: methodological challenges and opportunities for public health policy