The disease burden of hepatitis B, influenza, measles and salmonellosis in Germany: first results of the Burden of Communicable Diseases in Europe Study†

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SUMMARY

Setting priorities in the field of infectious diseases requires evidence-based and robust baseline estimates of disease burden. Therefore, the European Centre for Disease Prevention and Control initiated the Burden of Communicable Diseases in Europe (BCoDE) project. The project uses an incidence- and pathogen-based approach to measure the impact of both acute illness and sequelae of infectious diseases expressed in disability-adjusted life years (DALYs). This study presents first estimates of disease burden for four pathogens in Germany. The number of reported incident cases adjusted for underestimation served as model input. For the study period 2005–2007, the average disease burden was estimated at 33 116 DALYs/year for influenza virus, 19 115 DALYs/year for *Salmonella* spp., 8708 DALYs/year for hepatitis B virus and 740 DALYs/year for measles virus. This methodology highlights the importance of sequelae, particularly for hepatitis B and salmonellosis, because if omitted, the burden would have been underestimated by 98% and 56%, respectively.

Key words: Disability-adjusted life years, hepatitis B, influenza, measles (rubeola), *Salmonella*.

INTRODUCTION

European countries face increasing demands and costs in the healthcare sector [1] resulting in the urgent need to establish evidence-based methods for the prioritization of diseases in, for example, resource allocation for research and in planning of intervention measures [2–5]. Currently, a large share of financial resources in high-income, post-industrial countries is allocated to the control of chronic diseases that cause extensive burden and incur substantial treatment expenses [1]. In this context it may not be sufficiently appreciated to what extent infectious disease (ID) control may have an impact on the control of chronic diseases. While the associations between

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certain pathogens, such as human papilloma virus and cervical cancer in women, *Helicobacter pylori* and gastric ulcer, and hepatitis B virus (HBV) and liver cirrhosis, are widely known, the associations of other pathogens and chronic diseases may be less well recognized [6–9]. Approaches for prioritization, in particular when IDs are included, need to take into account the potential of IDs to cause chronic diseases in order to achieve robust and reliable estimates [10].

Several methods for prioritization have been developed but these approaches are limited in their ability to compare between IDs and non-communicable diseases or other health impairments. Therefore, the burden of disease methodology, as it was introduced in the Global Burden of Disease and injury study (GBD) in the late 1980s, is a promising approach because it allows both setting priorities for infectious conditions and comparing the disease burden of non-communicable diseases and IDs [11]. The burden of disease (BoD) approach, as used in the GBD and the Burden of Communicable Diseases in Europe (BCoDE) studies, utilizes the disability-adjusted life year (DALY) as a summary measure for the impact of disease and injury conditions on population health by combining effects of mortality and morbidity in a single measurement unit that quantifies years of healthy life lost [12].

Addressing known limitations of this approach [13] the BCoDE project, initiated by the European Centre for Disease Prevention and Control (ECDC), uses an incidence- and pathogen-based approach, which takes into account all (future) sequelae following an infection. The BCoDE project aims to generate comprehensive, evidence-based and comparable estimates of the disease burden due to IDs for European Union Member States measured by DALYs [14].

Currently, Germany has no national burden of ID estimates available that use the DALY or other summary measures of population health. Therefore, the main objective of this study is to generate a first set of disease burden estimates for a selected set of IDs.

Four pathogens with different characteristics were selected for analysis. This study presents the BoD due to HBV, influenza virus, measles virus and non-typhoidal *Salmonella* spp. for the period between 2005 and 2007 in Germany.

METHODS

The pathogens were selected for their different transmission routes, variable availability of vaccine, different notification paths, and strong heterogeneous nature in terms of time scale and details of disease progression (Table 1). Including these four pathogens allowed testing of the applicability of the methods in Germany for a wide range of settings and parameters.

Estimates were generated using the incidence-based DALY approach [12], which in addition was changed from the disease to the pathogen perspective relating short- and long-term sequelae to the initial infection with a specific pathogen [15–18].

For every studied pathogen an outcome tree was designed that represents the natural history of disease starting with the initial infection [14–16]. These outcome trees provide a qualitative representation of disease progression by ordering all relevant disease-related health outcomes along a timeline. Transitional probabilities describing the flow between consecutive health outcomes were extracted from the literature and validated by disease specialists from the ECDC and RIVM (for more details on outcome trees, disability weights, durations, and transition probabilities see supplementary online material). Using the pathogen-based approach all disease burden resulting from sequelae somewhere in the future after the initial infection are ascribed to the year of infection [16]. The components of the DALY, namely years of life lost due to premature death (YLL) and years lived with disability (YLD) were calculated separately for all health outcomes included in the outcome tree.

According to the outcome tree, YLD were calculated for each health outcome (l) by multiplying the number of incident cases (n) with the disability weight (w) for a specific health outcome (l), and the duration of the disabling condition (t) [see equation (1)]. All input parameters in both YLD and YLL formulae were chosen to be age (a) and sex (s) dependent when such information was available, where a stands for age at infection and $\tilde{a}$ for age at onset of a condition or death [15, 16].

$$\mathrm{YLD} = \sum_l n_l^{a,s} * t_l^{\tilde{a},s} * w_l^{\tilde{a},s}. \tag{1}$$

To estimate the YLL for those health outcomes (l) that can lead to death, the number of fatal cases (d) for a specific health outcome (i) for an infection acquired at age (a) is multiplied by the remaining life expectancy (e) at age $\tilde{a}$ [see equation (2)].

$$\mathrm{YLL} = \sum_l d_l^{a,s} * e_l^{\tilde{a},s}. \tag{2}$$

Table 1. *Characteristics of the pathogens chosen for the analyses*

	Hepatitis B virus	Influenza A virus	Measles virus	*Salmonella* spp.
Agent	Virus	Virus	Virus	Bacterium
Transmission	Person-to-person (sexual contacts and at birth)/contaminated blood or other bodily fluids	Person-to-person/air, touch	Person-to-person/air	Food and water, animal contacts, person-to-person (faecal route)
Vaccine available	Yes	Yes	Yes	No
Vaccination programme in Germany	*Since 1982*: recommended vaccination for high-risk populations (e.g. medical personnel) *Since 1995*: recommended vaccination of newborns including booster vaccination	Recommended vaccination for high-risk populations and persons aged >60 years	Recommended two-dose vaccination of newborns (starting in former East Germany in 1970, and since 1973 in former West Germany)	Not available
Reporting (reference category)	Mandatory notification of clinical, laboratory-confirmed cases	Mandatory notification of clinical-laboratory and clinical-epidemiologically confirmed cases	Mandatory notification of clinically, clinical-epidemiologically, and clinical-laboratory confirmed cases	Mandatory notification of clinical-epidemiologically and clinical-laboratory confirmed cases
Disease course	Acute illness with probability of chronification with severe life-threatening sequelae occurring after a long chronic phase	Acute short course, mostly self-limiting, low-probability of long-term sequelae (mostly observed in older and immunocompromised)	Acute short course, mostly self-limiting, low probability of long-term sequelae, but when occurring these sequelae are very severe and life-threatening	Acute short course, mostly self-limiting within days or weeks, low probability of developing non-fatal and self-limiting sequelae but with duration of symptoms from a few weeks to a few years
Disease occurrence in Germany	Low-endemicity with a strong influx of migrant cases	Yearly seasonal epidemics, affecting a large number of the population	Outbreak related, mostly occurring in localized under-vaccinated settings	Second most commonly notified bacterial infection in Germany with most cases occurring in the summer months and occasional outbreaks

For the baseline estimates, life expectancy (LE) was chosen according to the standards provided by the WHO [19, 20]. Female and male LE values at birth were set to 82·5 and 80 years, respectively [12]. Sensitivity analyses were undertaken using national German LE in 2005–2007 [21]. No age weighting or time discounting were applied.

Data

Basic model input

For all pathogens, the annual average number of newly infected acute cases (incidence) reported to the Robert Koch Institute, from 2005 to 2007, and split by sex and 5-year age groups, was used to calculate DALYs [22]. The rationale for choosing this time-frame is explained elsewhere [16]. These raw incidence data were corrected by pathogen-specific multiplication factors (MFs) to account for underestimation of notified cases [15, 23].

Multiplication factors

Ideally, MFs should be age- and sex-dependent. However, as information on MFs is scarce and frequently non-existent with regard to age groups and sexes, a single range of disease-specific MFs was applied for both sexes and all age groups. The MFs were based on available information from published literature and were confirmed in discussions within the BCoDE Consortium and with disease-specific experts from the ECDC and RIVM. In cases where information from published studies was insufficient expert consensus was used. MFs were chosen either to correct in one step (underestimation), or in two steps (under-reporting and under-ascertainment) [15, 23].

The number of reported acute HBV infections was corrected in two steps. In expert discussions it was decided to use a MF of 2 for under-ascertainment which is based on the assumption that Europe is a low-incidence region for HBV infections [24] but that symptoms are severe enough to prompt health-seeking behaviour in ~50% of cases. Since no consensus could be arrived at to select a single MF for under-reporting and studies suggested a variety of correction factors, and with no consent by disease specialists for one or the other study a MF was created by modelling the minimum and maximum MF as a uniform distribution between 1·2 and 3·0 [25, 26]. These estimates were selected from studies considered most relevant to reflect the high reporting rate of HBV in Germany. The combined MF was used to estimate the annual number of symptomatic acute HBV infections. For HBV we additionally estimated the number of asymptomatic infections using information on age-dependent percentages of infections being asymptomatic [26].

Due to lack of studies regarding the underestimation of influenza the number of mandatory reported cases were corrected based on a default population-based symptomatic attack rate of 1–2% for the German population [27]. This was the best available method for the correction of influenza data since the literature (which largely focuses on pandemic influenza and influenza-like illnesses) did not provide appropriate MFs for seasonal influenza in Germany.

To correct the notification data for measles a MF (one step) defined by a PERT distribution (minimum 1·5, maximum 2·5, most likely 2·5) was applied [28, 29]. Measles is a severe disease which would increase the chance of a case being ascertained and it is also highly recognizable as well as being notifiable in Germany, leading to a higher probability of being correctly diagnosed and reported. These values were selected from the literature by expert consensus as they were considered to best represent the combined level of low under-reporting and low under-ascertainment in Germany.

Salmonellosis notification data were corrected using a MF (one step) with a most likely value of 8·7 (modelled as PERT distribution with a minimum 2·1 and maximum 26·8). These estimates were derived from 1000 simulations drawn from the model described by Havelaar et al. [30].

Model

All models were built in Microsoft Excel with the add-in software @Risk (Palisade Corp., USA). Uncertainty in MFs and transition probabilities were modelled and quantified [95% uncertainty intervals (UI)] by performing Monte Carlo simulations (10 000 iterations). Results are presented at the population level and case level, in both aggregated (i.e. DALY) and disaggregated (i.e. YLL, YLD) forms.

RESULTS

Disease burden due to HBV

An average of 1137 acute HBV infections per year has been reported in Germany, of which 68·2% were males [22]. Corrected for underestimation, the number of acute cases was estimated at 4775 cases/year

Table 2. *Results overview of disease burden for the selected pathogens expressed in average YLD, YLL, DALYs (values in parentheses are the 95% uncertainty intervals, using standard life expectancy)*

	Hepatitis B virus	Influenza virus	Measles virus	*Salmonella* spp.
Total per year				
YLD	3910 (3431–4389)	16040 (14260–17882)	66 (53–79)	11697 (9655–13928)
YLL	4797 (3774–5888)	17077 (15244–18965)	674 (348–998)	7418 (4227–11635)
DALYs	8708 (7335–10163)	33116 (29504–36849)	740 (413–1066)	19115 (14803–24328)
Acute illness per year				
YLD	170 (151–189)	12363 (11029–13739)	17 (17–18)	1065 (898–1237)
YLL	0	17077 (15244–18965)	671 (345–996)	7418 (4227–11635)
DALYs	170 (151–189)	29439 (26283–32708)	688 (363–1013)	8482 (5239–12752)
Sequelae per year				
YLD	3740 (3272–4270)	3677 (3224–4144)	49 (36–62)	10632 (8731–12715)
YLL	4797 (3774–5888)	0	3 (3–3)	0
DALYs	8537 (7171–9986)	3679 (3224–4144)	52 (39–65)	10632 (8731–12715)
DALYs/100000				
Total	10·57 (8·9–12·33)	40·2 (35·8–44·7)	0·90 (0·5–1·29)	23·19 (17·96–29·52)
Acute illness	0·21 (0·18–0·23)	35·7 (31·9–39·7)	0·83 (0·44–1·23)	10·29 (6·36–15·47)
Sequelae	10·34 (8·7–12·12)	4·5 (3·9–5)	0·06 (0·05–0·08)	12·9 (10·59–15·43)
DALYs per case				
Total	1·84 (1·54–2·51)	0·03 (0·03–0·03)	0·26 (0·14–0·38)	0·03 (0·03–0·04)
Acute illness per case	0·04 (0·04–0·04)	0·02 (0·02–0·02)	0·24 (0·13–0·36)	0·01 (0·01–0·02)
Sequelae	1·97 (1·51–2·11)	0·01 (0·01–0·01)	0·02 (0·01–0·02)	0·02 (0·02–0·02)

DALYs, Disability-adjusted life years; YLD, years lived with disability; YLL, years of life lost due to premature death. DALY results presented have been rounded to significant numbers and thus the summary rows do not always add up to exactly 100%.

(95% UI 4239–5309), and after correction for asymptomatic cases, the number of infected cases was estimated at 16170 cases/year (95% UI 14438–17909) in 2005–2007. According to the model, on average 36 cases (95% UI 26–47) would develop fulminant liver failure in the year of infection. An average of 800 cases/year would be expected to develop chronic hepatitis B (95% UI 707–894) in the future. Further, 228 cases (95% UI 194–263) of compensated liver cirrhosis, 114 cases (95% UI 94–136) of decompensated cirrhosis and 121 cases (95% UI 84–161) of hepatocellular carcinoma were estimated to occur later in life.

The corrected incident cases resulted in an average loss of 8708 DALYs/year (95% UI 7335–10163), representing 10·6 DALYs/100000 population (95% UI 8·9–12·3) and 1·8 DALYs/symptomatic case (95% UI 1·5–2·2) (Table S9).

According to the natural history of HBV infection (Fig. S1), 170 DALYs/year (95% UI 151–189) were due to acute symptomatic infection, which represents 2% of the overall burden. Thus, 98% of the burden was related to the chronic disease course and sequelae which occur in later stages of infection or after a long phase of chronic infection (Fig. 1).

The disease burden due to chronic hepatitis B infection and hepatocellular carcinoma was estimated at 2763 DALYs/year (95% UI 2428–3097) and 2795 DALYs/year (95% UI 1833–3810), respectively.

The results highlight these health outcomes as the most burdensome (with 31·7% and 32·1% of the overall HBV DALYs). Fulminant liver failure contributed 145 DALYs/year (95% UI 98–202). Compensated liver cirrhosis and decompensated liver cirrhosis are further sequelae mostly occurring after a long chronic period. The disease burden due to these sequelae was estimated at 651 DALYs/year (95% UI 551–754) and 2182 DALYs/year (95% UI 1791–2594), respectively (Fig. 2).

The highest DALYs for HBV can be found for females in the 15–19 years age group (1430 DALYs/year, 95% UI 817–2123) and for males in the 0–1 year age group (1017 DALYs/year, 95% UI 586–1487) (Fig. 3). Men aged 15–19 years also presented high DALYs/year with 975 DALYs (95% UI 557–1451). Overall, 44·9% of the disease burden caused by HBV was due to YLD and 55·1% due to YLL.

The majority of disease burden was identified in the 0–49 years age range, accounting for 96·3% of the
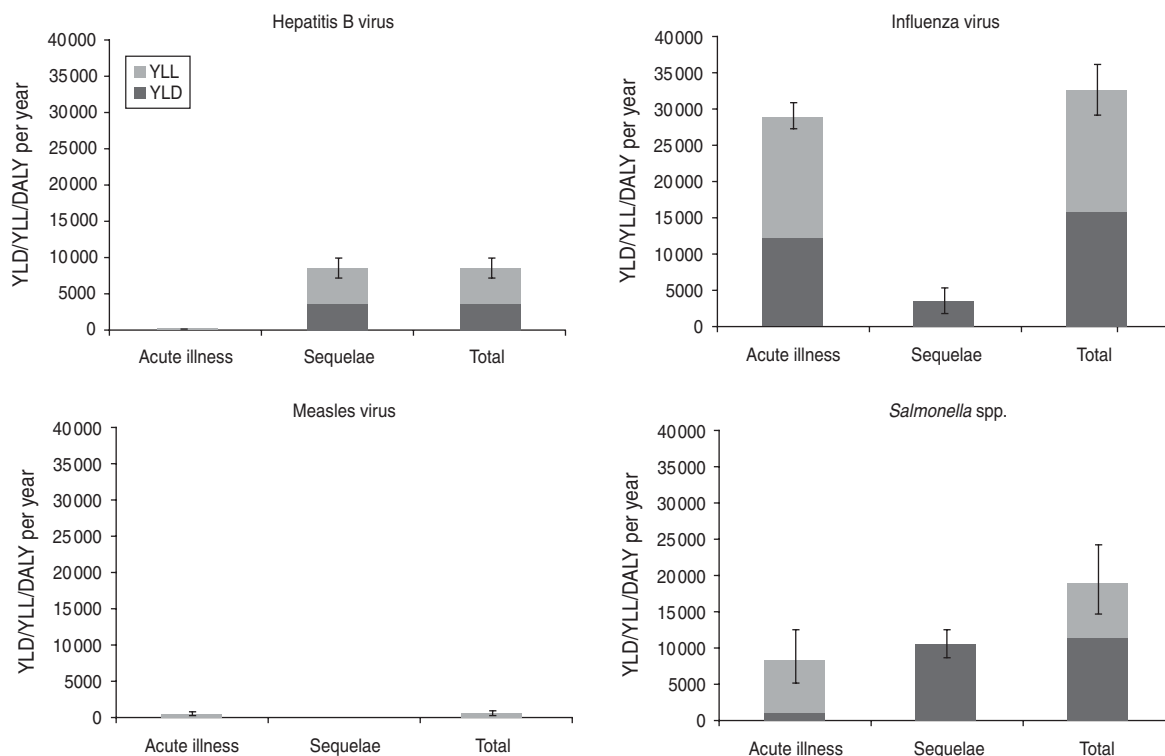
Fig. 1. Disability-adjusted life years (DALYs) per year split by years lived with disability (YLD)/years of life lost due to premature death (YLL) and acute illness/sequelae for the selected pathogens in Germany, using standard life expectancy (error bars indicate 95% uncertainty intervals).
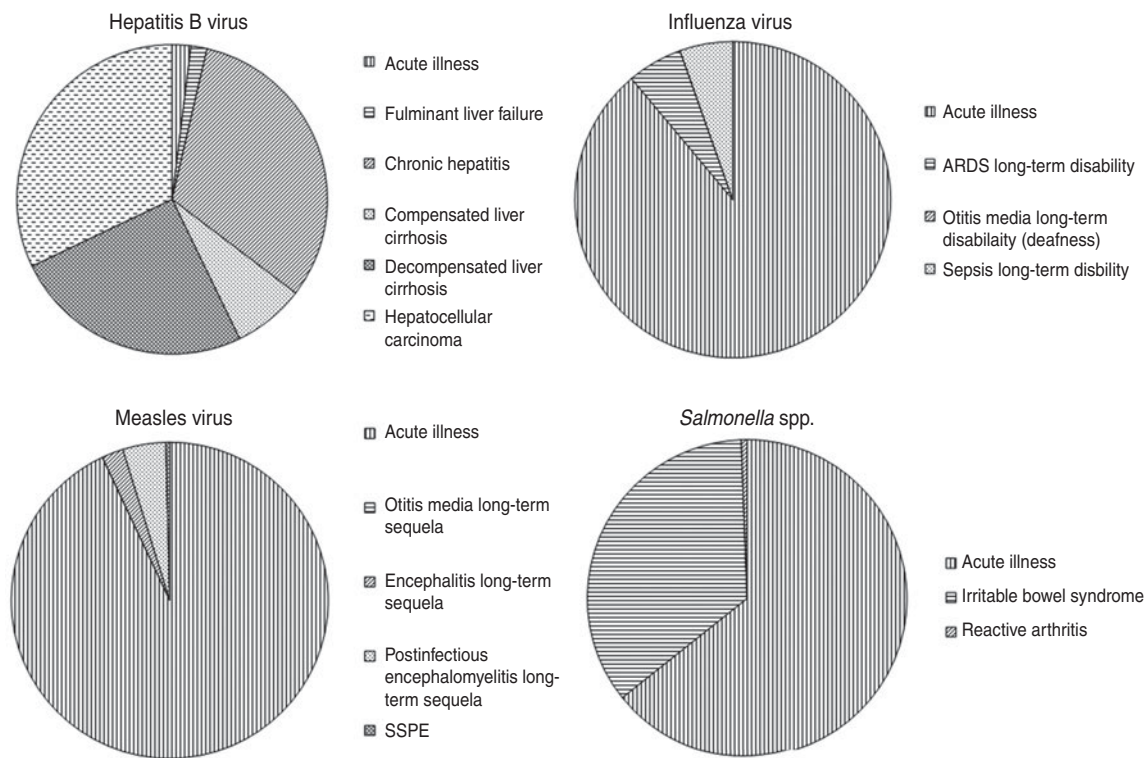

Fig. 2. Share of acute illness and single sequelae on average disability-adjusted life years. ARDS, Acute respiratory distress syndrome; SSPE, subacute sclerosing panencephalitis.
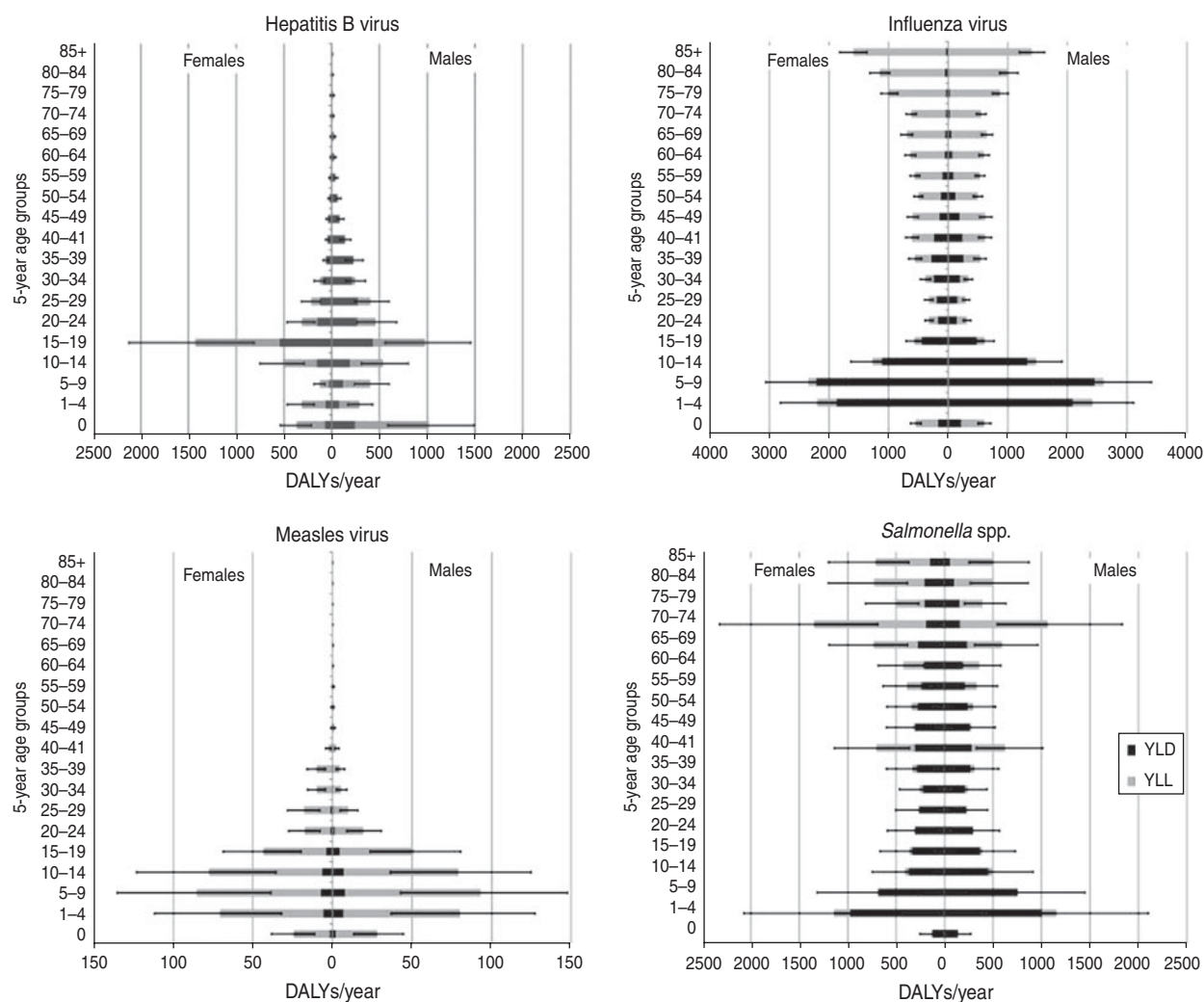
Fig. 3. Average disability-adjusted life years (DALYs), years lived with disability (YLD) and years of life lost due to premature death (YLL) per year by sex and age group (error bars indicate 95% uncertainty intervals).

total disease burden. In persons up to 19 years the disease burden was dominated by YLL because (according to our model) people in these age groups have a high cumulative probability of developing severe long-term sequelae and of consequent mortality (Fig. 3).

The estimated DALY rates/100 000 population were higher for males, with 12·4 DALYs/100 000 (95% UI 9·9–15·2) compared to 8·8 DALYs/100 000 (95% UI 6·7–11·1) for females. The highest rates for both sexes were identified in the 0–1 year age group, with 288·1 DALYs/100 000 (95% UI 165·9–421·1) and 110·8 DALYs/100 000 (95% UI 64·7–161·6) for men and women, respectively (Table S9).

Disease burden due to influenza virus

An overall average of 11 772 cases of acute influenza infections per year was reported between 2005 and

2007, of which 51·8% were males [22]. Corrected for underestimation an average number of 1 236 269 influenza cases (95% UI 1120752–1354268) was estimated. Based on the underlying outcome tree, an average of 160 cases (95% UI 143–178) of acute respiratory distress syndrome (ARDS) (long term), 0·5 cases (95% UI 0·4–0·5) of deafness (long-term sequelae due to otitis media) and 98 (95% UI 88–109) cases of long-term disability due to sepsis would be expected to develop.

The corrected incident cases resulted in an average loss of 33 116 DALYs/year (95% UI 29504–36485), representing 40·2 DALYs/100 000 population (95% UI 35·8–44·7) and 0·03 DALYs/symptomatic case (Table S10). The highest DALYs/year for influenza were found for both sexes in the younger age groups, between 1 and 14 years and in older age groups, ⩾85 years (Fig. 3). Overall 48·4% of the disease

burden caused by influenza was due to YLD and 51·6% due to effects of YLL.

In the younger age groups up to 14 years for men and 19 years for women the disease burden was dominated by YLD due to the lower probability of dying from influenza. With increasing age, in particular starting with the 35–39 years age group, the proportion of YLL increased.

The overall DALY rates/100 000 population were slightly higher for males with 41·3 DALYs/100 000 (95% UI 34·7–47·6) compared to 39·3 DALYs/100 000 (95% UI 33·5–45·1) for females. The highest rates for men were in the oldest age group with 368·6 DALYs/100 000 (95% UI 312·7–424·9) while for women it was in the youngest age group with 172·1 DALYs/100 000 (95% UI 142·8–200·9) (Table S10).

According to the natural history of influenza infection, 29 439 DALYs/year (95% UI 26283–32708) were due to the acute symptomatic infections accounting for 88·9% of the overall burden. Future sequelae contributed 3677 DALYs/year (95% UI 3224–4144) to the overall burden (Fig. 1). The long-term consequences of ARDS and disability due to sepsis resulted in the highest sequelae DALYs with 1878 DALYs/year (95% UI 1647–2117) and 1794 DALYs/year (95% UI 1573–2021), respectively (Fig. 2).

Disease burden due to measles virus

An overall average of 1217 cases of acute measles infections per year was reported between 2005 and 2007, of which 51·4% were males [22]. Corrected for underestimation an average of 2840 cases/year (95% UI 2738–2925) were estimated. Modelling the long-term sequelae on average would result in one case of encephalitis (long term), one of post-infectious encephalomyelitis (long term) and less than one case of deafness and subacute sclerosing panencephalitis.

The estimated cases resulted in an average loss of 740 DALYs/year (95% UI 413–1066) representing 0·9 DALY/100 000 population (95% UI 0·5–1·3) and 0·3 DALY/symptomatic case (95% UI 0·1–0·4) (Table S11).

The highest DALYs for measles can be found for both sexes in the 5–9 years age group with 93·2 DALYs/year (95% UI 43–148) for men and 86 DALYs/year (95% UI 39–136) for women. The disease burden due to measles is highly concentrated in the younger age groups between 0 and 19 years with 85·7% of the disease burden located in this age

range. The overall disease burden is dominated by effects of premature mortality with 90·8% of DALYs being due to YLL (Fig. 3).

The DALY rates/100 000 population, were slightly higher for men with 0·9 DALY/100 000 (95% UI 0·4–1·5) than for women with 0·8 DALY/100 000 (95% UI 0·4–1·3). The highest rates for both sexes were identified in the youngest age group between 0 and 1 year with 8 DALYs/100 000 (95% UI 3·8–12·6) and 7·3 DALYs/100 000 (95% UI 3·4–11·5) for men and women, respectively (Table S11).

Following the natural history of measles infection (Fig. S3), 688 DALYs/year (95% UI 363–1013) were lost due to the acute symptomatic infections accounting for 93% of the overall burden. Future sequelae contributed 52 DALYs/year (95% UI 39–65) to the overall burden (Fig. 1). The long-term consequences encephalitis and post-infectious encephalomyelitis resulted in 16 DALYs/year (95% UI 16–17) and 33 DALYs/year (95% UI 20–45), respectively (Fig. 2).

Disease burden due to *Salmonella* spp. (excluding *S.* Typhi and *S.* Paratyphi)

An average of 52 322 acute salmonellosis cases per year was reported between 2005 and 2007, of which 51·2% were females. After correction for underestimation we estimated an average 565 981 symptomatic salmonellosis cases [i.e. acute gastroenteritis (GE)] per year (95% UI 477435–657638), 49 804 irritable bowel syndrome (IBS) cases per year (95% UI 40917–59657), and 2939 reactive arthritis (ReA) cases per year (95% UI 1731–4352).

The estimated burden due to infections with *Salmonella* spp. was on average 19 115 DALYs/year (95% UI 14803–24328) representing 23·2 DALYs/100 000 population (95% UI 18–29·5) and 0·03 DALY/symptomatic case (95% UI 0·03–0·04) (Table S12). About 8482 DALYs (44·4% of the total burden) can be attributed to GE. Long-term sequelae account for 55·6% of the overall BoD (Fig. 1). IBS with 10 459 DALYs/year (95% UI 8593–12528) and ReA with 173 DALYs/year (95% UI 102–257) together contribute strongly to the overall BoD (Fig. 2).

The highest burden per year for *Salmonella* occurred in the 1–4 and 70–74 years age groups for both sexes. In the 1–4 years age group the burden was 1158 DALYs/year (95% UI 457–2103), a peak value for the male population. The disease burden for females was highest in the 70–74 years age group with 1349 DALYs/year (95% UI 696–2325) (Fig. 3).

The shares of YLD on the overall DALYs estimated for the male population were highest for men aged 0–64 years, and range between 53·1% (60–64 years age group) and 100% (0, 5–9, 20–24, 25–29 years age groups). Except for the 40–44 years age group (YLD 45·3%) the DALYs in this age range were mostly due to morbidity effects. After the 65–69 years age group, YLL values were constantly higher than YLD values. Similar patterns were observed for the female population, athough the share of YLL in the 80–84 and ⩾85 years female age groups was 9·5% and 9·1% higher, respectively, compared to males.

The DALY rate/100 000 was higher for females with 24·1 DALYs/100 000 population (95% UI 16·9–34) compared to 22·2 DALYs/100 000 (95% UI 15·5–31·1) for males. However, DALYs and especially YLL in the >80 years age groups were clearly higher for the male population (Table S12).

Sensitivity analysis

In the sensitivity analysis the standard LE was replaced by the LE of the German population for the study period, which for males and females was 77·5 and 80·2 years, respectively [21]. Even though LE at birth for Germany was lower compared to the standards provided by the WHO the remaining LE in the older age groups was constantly higher.

The estimate for HBV showed a slight decrease by 96·3 DALYs (−1·1%). The largest changes were observed for influenza, with an 8% (2638 DALYs/year) increase for total BoD and increasing DALY rates from 40·2 to 43·4 DALYs/100 000. Where YLD decreased slightly, most of the change was due to the mortality component with an increase of 2646 YLL/year. In contrast the BoD estimates for measles remained stable with only a marginal increase by 2·8 DALYs/year (+0·4%) from 737 to 740 DALYs/year. Using country-specific LE, the BoD estimates of *Salmonella* increased by 1153 DALYs (+5·7%) with DALY rates increasing from 23·2 to 24·6 DALYs/100 000 population. The largest changes were estimated for the mortality component where YLL/year increased from 7417 to 8570 (+13·5%) and higher increases were observed for males with 16·2% compared to 11·1% for females (for more details see Tables S13–16)

DISCUSSION

The results from this study provide the first national DALY estimates for a selected set of infectious pathogens in Germany. Using an outcome measure such as the DALY allows integration of the effects of mortality and morbidity into a single measure and thus – especially for diseases for which death is not the primary consequence – offers a distinct view on their impact on population health.

In particular, our analysis of *Salmonella* spp. infections highlighted the need to include morbidity, because YLD contributed 62% to the overall BoD. For HBV and influenza virus the importance of morbidity was also high with 45% and 48%, respectively. For measles virus, although large numbers were affected, most of the disease burden was related to YLL (91%) as duration and severity of the acute disease are low resulting in a small number of YLD. Even though sequelae of measles are rare, these sequelae are life-threatening and the largest contributors of premature death (YLL). Although the number of DALYs due to measles virus in Germany is low (compared to the other pathogens), it cannot be concluded that these infections are of little priority, rather it shows that a good vaccination programme is important in maintaining the burden at a low level.

In addition to the impact of non-fatal health outcomes, the study also highlights the impact of future sequelae resulting from an initial infection. Ignoring future sequelae would lead to a notable underestimation of disease burden for *Salmonella* spp. by 55·6%, and 98% for HBV. For the remaining two diseases, which generate most of the burden during the acute disease, 11% (influenza virus) and 7% (measles virus) of the overall BoD, are due to sequelae and would be missed if only acute disease consequences were considered.

In contrast to the disease-specific approach in which disease burden is mapped over certain disease endpoints (which may have different aetiologies; e.g. liver cirrhosis as a separate health outcome independent from, e.g. previously acquired HBV infection), the pathogen-specific approach considers all relevant health outcomes and health states so that the disease burden can be attributed to a pathogen rather than a disease endpoint [13]. This allows a more comprehensive assessment of burden for IDs compared with the disease-endpoint approach [11, 19]. Furthermore, the approach allows for direct comparison between the impact of acute infections and sequelae on population health.

It should be noted that using our approach, all future (short- and long-term) consequences are projected to the year(s) selected for the analysis, which is assumed to be the year of infection. Thus, the

measured disease burden is a sum of the current and future burden. With information regarding the duration of each health outcome given in the outcome tree, it is possible to incorporate the time dimension and describe how the burden of a certain pathogen may develop in future, allowing the identification of temporal trends. Various developments (e.g. demographic change, introduction of vaccination) can also be included in such projections of disease burden [31].

The input data for the models, as described in the Methods section and in the online supplementary material, consist of information needed to construct the outcome tree. For these parameters the body of evidence varies between pathogens, which may selectively affect the quality of the outcome trees. Our outcome trees represent the best available evidence (in the published literature) and were developed in a consensus approach including consultation with various disease experts inside and outside the BCoDE Consortium. We aimed to include as detailed information as possible, in particular for those parameters which tend to differ by age and sex. This level of detail was not available for a number of basic input parameters, which may have resulted in under- or overestimation of disease burden.

In our models we took into account uncertainty in MFs and transitional probabilities by using iterative processes and present the propagated uncertainty in 95% uncertainty intervals. However, parameters relating to the outcome trees were not strongly responsible for the resulting uncertainty around the DALY estimates. Most uncertainty was related to the estimated numbers of incident cases and thus, to the MFs applied in the analysis. There is no doubt that underestimation is present in all surveillance data [32]; however, the exact extent of under-reporting and under-ascertainment is usually not known in much detail. The MFs applied here are based on reviews of the published literature and show that further efforts to quantify the magnitude of underestimation are needed to overcome these large uncertainties (e.g. salmonellosis MF ranges from 2·1 to 26·8). Here, studies aiming at the reconstruction of the surveillance pyramid are of great importance to gain more detailed insights into the different levels of underestimation [33].

In addition to correction for underestimation, great care was taken to account for asymptomatic cases (where asymptomatic cases are assumed to contribute to disease burden). For instance, for HBV we estimated 11 395 asymptomatic cases not captured by any medical service. Ignoring these cases would result in an enormous underestimation of disease burden by 80·1%, resulting in only 1718 DALYs/year compared to the baseline estimates of 8708 DALYs/year. However, our model is limited to the use of incidence data for calculations and thus does not adequately consider prevalent HBV infections acquired outside Germany or prior to the year of analysis. This will result in underestimation of HBV burden in Germany.

The parameters used in the models are based on simplified generalizations for the disease courses, that in reality might be very heterogeneous. Parameters representing a lack of perfect knowledge (MFs and transition probabilities) were explicitly modelled by using probability distributions in Monte Carlo simulations. For disability weights and durations where variability represents the inherent heterogeneity, e.g. the differences in disease severity levels in infected persons, we decided to use average values as simplifications in the model [16].

Furthermore, country-specific data suitable for use in outcome trees/natural history models is rarely available. The parameter values used in the outcome tree models were therefore intended to represent an average European setting allowing their use in several countries. However, differences in disease-specific courses, that might be relevant for several pathogens/diseases because of, e.g. variations in healthcare service provision or vaccination policies, and many other country-specific differences may lead to over- or underestimation of disease burden.

The performed sensitivity analyses, indicate that for a country such as Germany with a high LE the replacement of the standard LE has only a slight impact on disease burden. Using a national LE has an impact on diseases where a significant part of disease burden, particularly associated with premature mortality, is located in the older age groups.

In the current methodology, a steady-state for the future development of diseases is assumed, which might not hold for some of the pathogens/diseases [14]. Therefore, in future work we aim to introduce ID-specific dynamics, demographic developments and further adjustments to our models to allow flexible modelling of different scenarios.

Furthermore, as a result of the absence of comparable DALY estimates in Germany, we can only make comparisons between IDs. Therefore a national BoD study is needed to carry out a comprehensive assessment of the health status of the German population. At this time, comparison between IDs can already

provide useful information to complement existing data on IDs and priority-setting approaches in Germany [10].

CONCLUSION

Our analyses indicate that including ID-specific characteristics in BoD analyses, as done in the BCoDE project probably yields more comprehensive estimates of the BoD due to IDs. Applying this methodology to other IDs may in some cases lead to unexpected results, which may require the re-examination of disease prioritization in existing disease control programmes. Even within one particular disease programme, revised BoD estimates may suggest different control strategies that focus more on primary prevention of the infection than on secondary prevention of the long-term sequelae resulting from these infections.

APPENDIX. BCoDE CONSORTIUM

Members of the BCoDE Consortium (in alphabetical order for institutions). Arie Havelaar, Mirjam Kretzschmar, Alies van Lier, Scott McDonald [*National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands*]; John Brooke, Juanita Haagsma (*Erasmus University Medical Center, Rotterdam, The Netherlands*); Marie-Josee Mangen, Ardine de Wit (*University Medical Centre Utrecht, Utrecht, The Netherlands*); Alexander Kraemer, Paulo Pinheiro, Dietrich Plaß (*Bielefeld University, Bielefeld, Germany*); Eric Fèvre, Cheryl Gibbons (*University of Edinburgh, Edinburgh, UK*); Elisabetta Franco, Silvia Longhi, Walter Ricciardi, Chiara de Waure (*Catholic University of the Sacred Heart, Rome, Italy*); Beate Jahn, Nikolai Mühlberger, Uwe Siebert (*UMIT – University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria*); Taavi Lai, Ardo Matsi, Kristi Rueuetel (*National Institute for Health Development, Tallinn, Estonia*); Alessandro Cassini, Edoardo Colzani, Piotr Kramarz (*European Centre for Disease Prevention and Control, Stockholm, Sweden*).

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268813003312.

DECLARATION OF INTEREST

Alessandro Cassini and Piotr Kramarz (co-authors) are employed by the European Centre for Disease Prevention and Control, which has funded this research.

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