Microbial Risk Analysis 2–3 (2016) 48–52

Contents lists available at ScienceDirect

Microbial Risk Analysis

journal homepage: www.elsevier.com/locate/mran

The burden of *Campylobacter*-associated disease in six European countries

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ARTICLE INFO

Article history:
Received 6 January 2016
Revised 4 April 2016
Accepted 12 April 2016
Available online 3 May 2016

Keywords:
Infectious diseases
Value of life
Burden of disease
Disability-adjusted life years
Campylobacter spp

ABSTRACT

Background: Foodborne pathogens cause significant morbidity and mortality worldwide. Economic evaluations of interventions for *Campylobacter* are scarce. The aim of this study was to estimate the burden of disease associated with thermophilic *Campylobacter* spp. in Denmark, the Netherlands, Norway, Poland, Spain and the United Kingdom, to be used in an economic evaluation of interventions to reduce human campylobacteriosis.

Methods: Burden of disease expressed as Disability-Adjusted-Life-Years (DALYs) was estimated using a disease model developed within the Burden of Communicable Diseases in Europe (BCoDE) project. The model links acute disease and future sequelae to the initial infection by conditional probabilities. Average numbers of country-specific symptomatic incident cases were estimated using reported cases for 2010 and adjusted for underestimation using multiplication factors (MF) based on a Swedish returning traveler study. We applied time discounting and present both discounted and undiscounted DALY estimates.

Results: Of the countries studied, the Scandinavian countries had the lowest estimated disease burden/100,000 inhabitants for *Campylobacter* (< 10 DALY/100,000). Spain and Poland had the highest disease burden for *Campylobacter* (>100 DALY/100,000). Disease burden due to acute infections (i.e., gastroenteritits) accounted for < 25% of the total disease burden associated with *Campylobacter* infections in humans. Time-discounting and assumed life-expectancy had an impact on the DALY calculations.

Conclusion: Differences in reporting systems and practices necessitate country-specific MFs, with model results most sensitive to their uncertainty. Large differences in disease burden estimates were found between the six countries. Not considering sequelae strongly underestimated disease burden. The current country-specific disease burden can be used in future economic evaluation of interventions to reduce human campylobacteriosis.

1. Introduction

Foodborne pathogens cause significant morbidity and mortality worldwide. Economic evaluation of interventions to control pathogens such as thermophilic *Campylobacter* spp. is scarce. But before new and effective interventions can be introduced, decision-makers often require additional information on the health benefits in humans associated with the alternative resource allocation decision. Cost-effectiveness analysis can provide such information (e.g., Havelaar et al., 2007, Mangen et al., 2007). The quantification of the disease burden associated with *Campylobacter*-associated infections in humans is a first step in such an economic evaluation. There exist several methods to quantify disease burden (Gold et al., 2002). A commonly used summary metric is the disability-adjusted life year (DALY) that indicates the impact of disease and injury conditions on population health by combining effects of mortality and morbidity into a single number (Murray and Lopez, 1996).

The DALY methodology has been widely used in both national and global disease burden estimations (e.g., Murray and Lopez, 1996, Lopez et al., 2006, Lai et al., 2009, Stouthard et al., 2000, de Hollander et al., 2006, Murray et al., 2012, Plass et al., 2014). In Europe, the Burden of Communicable Disease in Europe (BCoDE) project, initiated by the European Centre for Disease Prevention and Control (ECDC), used an incidence- and pathogen-based DALY approach to generate comprehensive, evidence-based and comparable estimates of the disease burden due to infectious diseases for

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http://dx.doi.org/10.1016/j.mran.2016.04.001
2352-3522/

Table 1
Laboratory-confirmed reported cases to national authorities for 2010 and applied MFs.

Country (inhabitants)	Reported cases for 2010[a] (coverage[b])	Multiplication factors (MFs) used distribution and mean
Denmark (5.6 million)	4037 (100%)	Lognormal(1.27; 0.55)[c]; Mean: 4.12
The Netherlands (16.6 million)	4322 (51%)	Lognormal(2.92; 0.56)[c]; Mean: 21.78
Norway (4.9 million)	2682 (100%)	Pert(1; 1.79 ;6)[c,d]; Mean: 2.36
Poland (38.2 million)	375 (100%)	Lognormal(8.17; 0.54)[c]; Mean: 4100
Spain (46.1 million)	6340 (25%)	Lognormal(5.47; 0.54)[c]; Mean: 274.45;
United Kingdom (61.3 million)	70,298 (100%)	Lognormal(1.34; 0.55)[c]; Mean: 4.42;

[a] Cases were stratified by gender and age (i.e.: 0; 1–4; 5–9; 10–14; 15–19; 20–24; 25–29; 30–34; 35–39; 40–44; 45–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75–80; 80–84 and ≥85 years). Source: (European Centre for Disease Prevention and Control (ECDC) 2013).
[b] Source: (European Centre for Disease Prevention and Control (ECDC) 2010).
[c] Distribution and mean were derived from detailed results of 1000 runs from the model of Havelaar et al., (2013).
[d] The minimum MF as obtained from the 1000 runs was below 1. We therefore opt for a pert-distribution defining the minimum to be equal to 1 (i.e., no underestimation of reported cases) and taking the 97.5% percentile as maximum.

Glossary

DALY	Disability Adjusted Life Years
GBD	Global burden of disease
GBS	Guillain-Barré Syndrome
GE	Gastro-enteritis
IBS	Irritable bowel syndrome
MF	Multiplication factors
ReA	Reactive arthritis
YLL	Years of Life Lost due to premature death
YLD	Years of Life lived with a Disability

European Union Member States (Mangen et al., 2013, Kretzschmar et al., 2012). Using the same approach as applied in the BCoDE-project, the aim of the current study was to estimate the burden of disease associated with *Campylobacter* spp. in six European countries, namely Denmark, the Netherlands, Norway, Poland, Spain and the United Kingdom, to be used as input in an economic evaluation of interventions to reduce human campylobacteriosis (van Wagenberg and van Horne, 2016).

2. Methods

The DALY is a standard summary metric of population health obtained by adding years of life lived with a disability (YLD), and years of life lost due to premature death (YLL) (Gold et al., 2002, Murray and Lopez, 1996). In short, YLD is calculated as the product of the duration of the illness (t) and the disability weights (w) of a specific health outcome, accumulated over the number of incident cases (n) of all health outcomes (l):

$$YLD = \sum_{l} n_l^{a,s} * t_l^{\tilde{a},s} * w_l,$$

where t and n for health outcome l may be age-dependent (a) and/or sex-dependent (s), where a stands for age at infection and $\tilde{a}$ for age at disease onset and death.

And YLL for a specific health outcome are calculated by summation of the number of all fatal cases (d) due to the health outcome (l) at age (a), each case multiplied by the remaining individual life expectancy (e) at the age of death $\tilde{a}$. d for health outcome l may be age-dependent (a) and-or sex-dependent (s). e is by definition age- and sex-dependent. Thus

$$YLL = \sum_{l} d_l^{a,s} * e_l^{\tilde{a},s}.$$

The DALY is then calculated as the sum of the YLL and YLD (for full details see Mangen et al., (2013)).

In order to attribute all health outcomes of an infection to the initial infectious event, and thus provide thorough and reliable estimates of the benefits of intervention, an outcome tree representing the natural history of the infection and its short- and long-term sequelae is required. *Campylobacter* spp. was assumed to result in gastroenteritis, mostly self-limiting and seldom fatal, while reactive arthritis (ReA), Guillain–Barré Syndrome (GBS) and irritable bowel syndrome (IBS) were assumed to be potential sequelae of a *Campylobacter* infection (Havelaar et al., 2007, Havelaar et al., 2000, Havelaar et al., 2012, Mangen et al., 2005).

DALYs were calculated for each country separately using the disease natural history model for *Campylobacter* spp. presented in Mangen et al. (Mangen et al., 2013). The model was extended to allow for time discounting of the disease burden, a necessity when conducting an economic evaluation. The model was implemented in @Risk, an add-in to Excel, and was run with 50,000 iterations. The country-specific numbers of cases reported to ECDC for the year 2010 (European Centre for Disease Prevention and Control (ECDC) 2013) were adjusted for underestimation by a multiplication factor (MF) based on a returning Swedish travellers study (Havelaar et al., 2013) (see Table 1). These MFs corrected for underestimation (under-ascertainment and under-reporting) (Gibbons et al., 2014) and where necessary for coverage of the sentinel surveillance system (European Centre for Disease Prevention and Control (ECDC) 2010). Incident cases of fatal GE, ReA, GBS and IBS cases were estimated following the outcome tree and using the disease progression parameters as presented in Mangen et al., (2013). Disability weights and duration of illnesses, as presented in Mangen et al., (2013), were used for estimating YLD. The Coale and Demeny West Level 26 and 25 life tables were used in the baseline model, and country-specific life expectancies for 2010 (World Health Organisation (WHO) 2012) and the new Global Burden of Disease (GBD) 2010 reference life table (World Health Organisation (WHO) 2013) were used in scenario analyses. Time-discounting was applied using discount rates of 0% (i.e., no discounting), 3%, 6% and country-specific rates for the year 2010 (i.e., 4.2% for Denmark, 5% for the Netherlands, 4% for Norway, 7% for Poland, 5% for Spain and 5.5% for the United Kingdom) (van Wagenberg and van Horne, 2016).

Data were presented both in aggregated form (DALYs per year) and in disaggregated form (YLD per year and YLL per year), from a societal perspective (DALY/YLL /YLD per year per country) and from an individual perspective (DALY per year per symptomatic campylobacteriosis case). To allow comparison between countries, DALY estimates per year per country were also presented as DALY per 100,000 inhabitants per year per country. We report the mean and the 2.5th- and 97.5th-percentiles of the uncertainty distributions of output variables.

Table 2
Undiscounted disease burden associated with campylobacteriosis in 2010 in six European countries using the Coale and Demeny West Level 26 and 25 life tables.

	Denmark	The Netherlands	Norway	Poland	Spain	United Kingdom
Symptomatic campylobacteriosis cases						
Average	17,700	96,000	6300	1550,000	1760,000	328,900
(95 C.I.)	(13,100–27,300)	(75,100–126,700)	(5500–7200)	(1160,000–2135,000)	(1190,000–2800,000)	(246,700–489,000)
Fatal GE-associated campylobacteriosis cases per year						
Average	5.0	27	1.8	441	502	94
(95 C.I.)	(2.5–8.7)	(14–43)	(1.0–2.6)	(221–709)	(236–904)	(47–158)
DALY per year						
Average	476	2582	170	41.605	47.308	8836
(95 C.I.)	(340–743)	(1952–3480)	(141–203)	(30,253–58,295)	(31,199–76,346)	(6422–13,263)
YLD per year						
Average	412	2234	148	36,006	40,950	7643
(95 C.I.)	(296–641)	(1697–3006)	(123–174)	(26,293–50,404)	(27,088–65,997)	(5585–11,452)
YLL per year						
Average	64	348	23	5600	6358	1192
(95 C.I.)	(35–109)	(197–532)	(13–33)	(3097–8779)	(3281–11,161)	(653–1956)
DALY / symptomatic case						
Average	0.027	0.027	0.027	0.027	0.027	0.027
(95 C.I.)	(0.024–0.030)	(0.024–0.030)	(0.024–0.030)	(0.024–0.030)	(0.024–0.030)	(0.024–0.030)
Symptomatic campylobacteriosis cases / 100,000 inhabitants						
Average	320	580	130	4100	3800	540
(95 C.I.)	(240–490)	(450–760)	(110–150)	(3000–5600)	(2600–6100)	(400–800)
DALY per year/100,000 inhabitants						
Average	8.6	15.5	3.5	109	103	14.4
(95 C.I.)	(6.1–13.4)	(11.7–20.9)	(2.9–4.1)	(79–153)	(68–166)	(10.5–21.6)

Table 3
Relative change of disease burden estimations for the different scenario analyses. Baseline was equal to 100%.

	Denmark	The Netherlands	Norway	Poland	Spain	United Kingdom
a) Using different discount rates (Baseline = no time–discounting was set at 100%)						
Baseline*	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
3% discounting	89%	89%	89%	89%	89%	89%
6% discounting	82%	82%	82%	82%	82%	82%
Country-specific discount rate	86%	84%	86%	80%	84%	83%
b) Using different life expectancies (Baseline = Coale and Demeny West Level 26 and 25 life tables was set at 100%)						
Baseline*	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Country-specific life table	104%	103%	103%	100%	104%	103%
New GBD 2010 reference life table	104%	104%	104%	104%	104%	104%

* In the baseline model no time discounting was applied and the Coale and Demeny West Level 26 and 25 life tables were used.

3. Results

In Table 2 and in Supplemental Tables A.1–A.6, incidence data and undiscounted disease burden estimates from both a societal perspective and an individual perspective using the Coale and Demeny West Level 26 and 25 life tables are presented. The Scandinavian countries had the lowest disease burden per 100,000 inhabitants (<10 DALY/100,000), Spain and Poland had the highest disease burden (>100 DALY/100,000).

The relative reduction of the estimated disease burden when using different time-discounting rates was summarized in Table 3a and in the Supplemental Tables A.7–A.12. The estimated disease burden when using country-specific life expectancy rather than Coale and Demeny West Level 26 and 25 life tables increased by 0% (i.e., Poland) up to 4% (i.e., Denmark and Spain), see Table 3b and Supplemental Tables A.7–A.12. By using the 2010 GBD life expectancies rather than Coale and Demeny West Level 26 and 25 life tables the disease burden estimates increased by 4% (see Table 3.b).

As the same outcome tree and the same conditional probabilities were used for all countries, the proportions of undiscounted average burden of campylobacteriosis due to acute illness (i.e., gastroenteritis) and sequelae (i.e., reactive arthritis, Guillain–Barre syndrome and irritable bowel symptoms) were the same in all six countries. About 87% of the estimated disease burden was due to morbidity (i.e., YLD) and only 13% was due to premature mortality (i.e., YLL). Gastroenteritis, including fatal cases, accounted for 18% of the total disease burden and sequelae for 82%. IBS, GBS and ReA accounted for 84%, 14% and 2% of the disease burden of campylobacteriosis-associated sequelae, respectively (for more details see Supplemental Tables A.1–A.6).

4. Discussion

In the current study we found large differences in the burden of disease estimates for campylobacteriosis. The Scandinavian countries had in 2010 the lowest estimated disease burden/100,000 inhabitants for *Campylobacter* infections (<10 DALY/100,000). Spain and Poland had the highest disease burden for *Campylobacter* infections (>100 DALY/100,000) of the six countries under study. This was directly related to differences in incidence. As shown here, the proposed incidence- and pathogen-based approach allowed for a comprehensive estimation of the total burden of disease caused by

infection with a pathogen, and allowed comparison between countries. For *Campylobacter* infections the burden associated with sequelae was higher than that caused by acute illness. Not considering these sequelae could therefore lead to considerable underestimation of the total burden.

Our approach has several limitations. Although estimates of MFs should be disease, country, age- and sex-specific (Gibbons et al., 2014), relevant data were mostly missing or inconsistent, resulting in MF estimates that were disease- and country-specific only. Consequently, the same MF was used for all age- and sex-classes. A potential drawback of using notified data corrected with MFs for estimating numbers of symptomatic incident cases was that those age- and sex-classes with relatively more (or fewer) notified severe cases were over-represented (or under-represented). For health outcomes with short-term and self-limiting illnesses the numbers of incident cases are of major importance, and over-representation (or under-representation) within specific age- and sex-classes is negligible. However, for infections with long-term sequelae an incorrect stratification of estimated incident cases over age- and sex-classes has an impact on the total disease burden estimates. Over-representing (or under-representing) older age-classes, and under-representing (or over-representing) younger age-classes might result in an underestimation (or overestimation) of the total disease burden.

Estimates for MFs would be ideally based on community-cohort studies, but even then uncertainties around the MF estimates are often huge, resulting in large uncertainty around the disease burden estimates. There were only very few community-cohort studies available in Europe allowing to estimate MFs for *Campylobacter* spp. (e.g., de Wit et al., 2001a,b Wheeler et al., 1999), and only limited to single countries. Haagsma et al., (2013), Havelaar et al., (2013) and Ekdahl and Giesecke, (2004) were the only studies we were aware of that looked at underestimations for *Campylobacter* spp. in Europe and studied underestimation in more than one country. However, only in Havelaar et al., (2013) all six countries under study were covered. Therefore we chose to base our MFs on the Havelaar et al. study.

In our baseline we used the Coale and Demeny West Level 26 and 25 life tables, but country-specific life tables and the new GBD 2010 reference life table were used in scenario analysis. Using different life tables impacted the DALY calculations, though the changes were small compared to the impact of discounting.

In the current study we used the same transition probabilities for health outcomes in the outcome tree for all six countries. Various factors such as different habits with respect to food and food preparation, different *Campylobacter* strains with different potential to cause GBS, and different healthcare systems might call for more country-specific transition probabilities. These were, however, not available. In particular the estimated number of fatal and GBS cases might be sensitive to the transition probabilities.

Contrary to Havelaar et al., (2012) and Mangen et al., (2005), we did not consider inflammatory bowel disease as a potential sequela as so far only a statistical association has been shown, but not a causal relationship.

This study showed that the disease burden of campylobacteriosis in the six countries is high. The here presented DALY estimates are suitable to be used in future economic evaluations of potential interventions aiming at reducing *Campylobacter* infections in humans.

Conflict of interest

Mangen declares fees paid by Wageningen UR to UMCU to estimate the disease burden for the here presented countries. No other conflict of interest.

Financial disclosure

Mangen declares fees paid by Wageningen UR to UMCU to estimate the disease burden for the here presented countries.

Contributors

All authors contributed to the work presented in this paper. MJJM and AHH developed the model. MJJM, AHH and JAH collected the data. MJJM performed the analysis. MJJM, AHH, JAH and MEK interpreted and discussed the results. MJJM drafted the manuscript and all other co-authors critically revised the manuscript. All authors have approved the final article.

Role of the funding source

Apart from defining the six countries and providing country-specific interest rates had the Sponsor no role in the design, analysis, interpretation of the data, or the writing of the manuscript.

Acknowledgments

The BCoDE-project was funded through the Specific agreement No 1 to Framework Partnership Agreement GRANT/2008/003. This study built on the methodology and disease models outlined by the BCoDE-project. The authors acknowledge the Burden of Communicable Disease in Europe (BCoDE) Consortium for the disease progression model.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mran.2016.04.001.

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