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

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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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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.