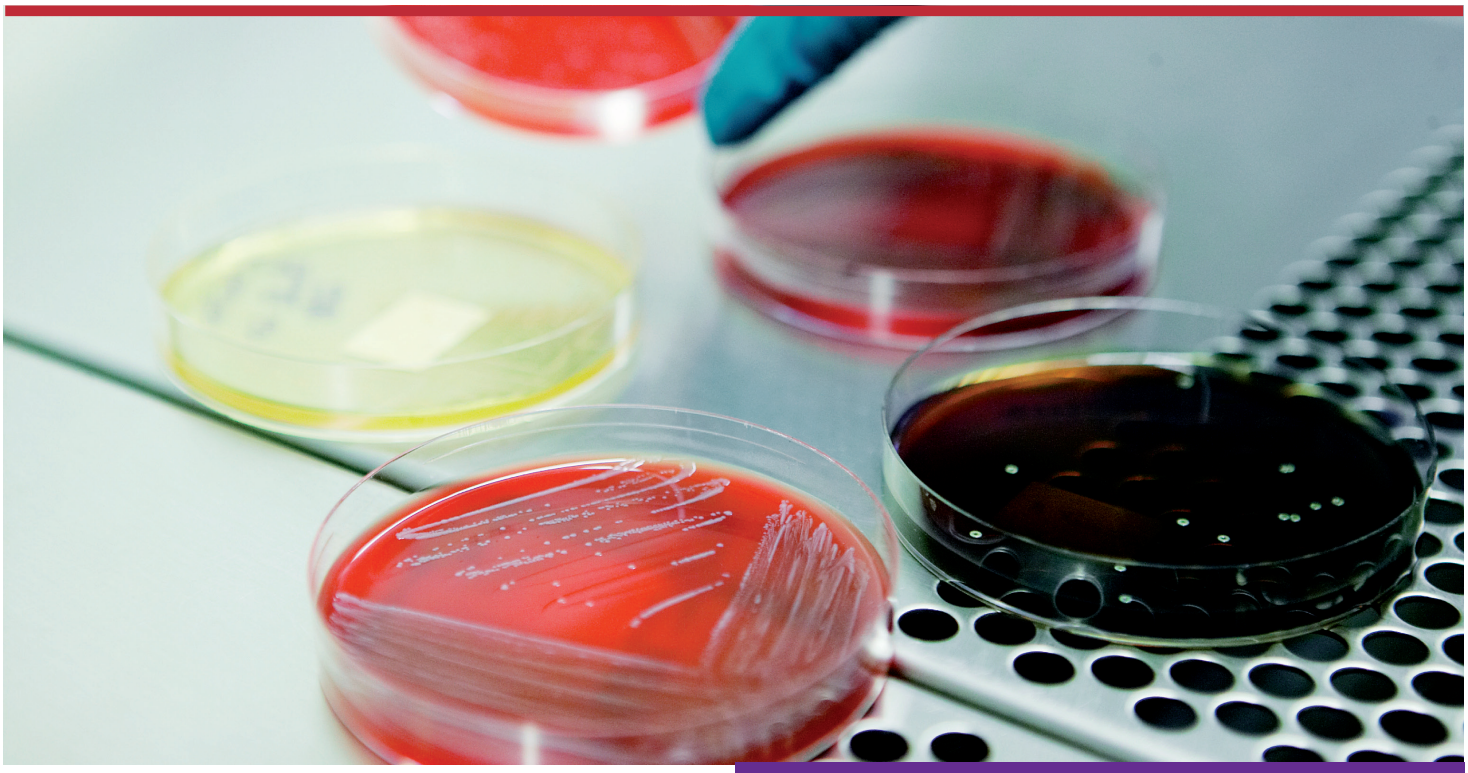
Burden of Disease of Foodborne Pathogens in Denmark

Technical Report



DTU Food
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Sara M. Pires

National Food Institute
Division of Epidemiology and Microbial Genomics

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Summary

In Denmark as in most countries throughout the world, the true impact of foodborne diseases is still unknown. To identify and prioritize food safety interventions to reduce the burden of foodborne diseases, it is necessary to: 1) estimate the total burden of foodborne diseases in the population, 2) compare and rank these diseases in terms of their public health impact, and 3) identify which foods are the more important contributors to this burden.

Public health surveillance is able to capture cases of disease caused by several foodborne pathogens, but the number of such cases is known to be grossly underreported. Additionally, even though the most common clinical presentation of foodborne bacterial infections takes the form of gastrointestinal symptoms, such infections can also lead to chronic, life-threatening symptoms including neurological, immunological disorders and death. These long term effects and sequelae may be difficult to account for and to link to earlier occurring foodborne infections, but have an important impact on the overall disease burden.

Salmonella, *Campylobacter* and verocytotoxin-producing *Escherichia coli* (VTEC) are amongst the pathogens with high public health relevance in Denmark. This report describes the first national estimates of the burden of diseases associated with these pathogens, as well as the relative contribution of different foods for this burden.

To estimate the total incidence of disease by selected pathogens in Denmark, we have estimated multiplication factors that correct the reported number of cases for underdiagnosis and underreporting. Underdiagnosis and underreporting of enteric disease are due to a failure in one of multiple steps that must take place before a case is identified and reported: the ill person must seek medical care, the physician must request and submit a stool specimen to a clinical laboratory to be tested; the causative pathogen be isolated and identified at the laboratory; and the results reported to public health surveillance. We estimated multipliers by re-constructing the surveillance pyramid, using a probabilistic model to account for uncertainty. These multipliers were applied to surveillance data from 2012, segregated into six age categories and gender, to account for differences in the incidence of disease in different age and gender groups.

To estimate the public health impact of these diseases, integrating incidence estimates with information on mortality and severity of each disease, we have derived burden of disease estimates using the so-called *disability adjusted life years* (DALYs). DALYs represent the years of life lost due to decreased quality of life and/or premature death as a consequence of a given disease or condition. DALYs aggregate mortality, expressed in years of life lost (YLL), and morbidity and disability, expressed in years lived with disability (YLD), into one combined figure. DALYs were calculated for all health outcomes that could potentially be associated with infections with the three pathogens.

The estimated total DALYs for each pathogen were then combined with source attribution estimates from pathogen-specific studies to further estimate the relative contribution of different foods for the overall burden of disease. DALY estimates were derived for each pathogen-food combination, and combined by food (i.e. summed over pathogens) to estimate the overall burden attributable to a specific source in the population.

The estimated degree of underdiagnosis and underreporting in the population in 2012 varied between pathogens. We estimated that for each reported *Salmonella* infection, around seven (95% Confidence Interval, CI: 4.2-15.6) people were in fact infected and ill. This estimate was higher for *Campylobacter* (12 infections;

95% CI: 6.6- 20.8) and even higher for VTEC, for which we estimated that only 1 in 31 cases were captured by public health surveillance (95% CI: 7.2- 83.7). In total, we estimated that 9,249 cases of salmonellosis, 41,120 cases of campylobacteriosis, and 4,158 cases of VTEC infections occurred in Denmark in 2012, resulting in a total of 1,622 hospitalized cases. The incidence of *Salmonella* and VTEC infections was higher in children under five years of age, but similar for both sexes; in contrast campylobacteriosis appeared to be more frequent in male adults.

The overall burden of disease was estimated to be higher for *Campylobacter* (total DALYs: 1,593). A total of 389 DALYs were estimated for *Salmonella*, and 113 for VTEC. Among the different health outcomes associated with the different pathogens, irritable bowel syndrome (IBS) contributed most to the total burden of both salmonellosis and campylobacteriosis. For VTEC, end-stage renal disease was responsible for the majority of the disease burden. The burden of campylobacteriosis was higher in males, whereas females bore a slightly higher fraction of the burden estimated for *Salmonella* and VTEC.

Attributing the total DALYs associated with diseases to different foods was only possible for *Salmonella* and *Campylobacter*, because food attribution estimates for VTEC do not exist in Denmark. Results showed that the majority of the (domestic) disease burden was caused by broilers, followed by cattle reservoir (incl. beef) and imported meats. For these three sources, *Campylobacter* was responsible for the largest proportion of total DALYs. A substantial proportion of the total DALYs was estimated to be associated with international travel (45% for *Salmonella* and 38% for *Campylobacter*).

Our results show that, among the three studied foodborne pathogens, *Campylobacter* is the one causing the higher burden of disease in Denmark. Our findings are in agreement with those of other countries, particularly the Netherlands, and emphasize the importance of intervention strategies in the food chain targeted at reducing this burden in the population. Attribution of the estimated burden of disease to different food sources showed that broilers are the most important source of *Campylobacter* infections, suggesting that controls efforts in this and other top food-animal sources should be continued and potentially increased. It is, however, still unknown how large a proportion of the burden is coming directly from the consumption of chicken meat, and how much is from e.g. environmental contamination originating from the broiler reservoir.

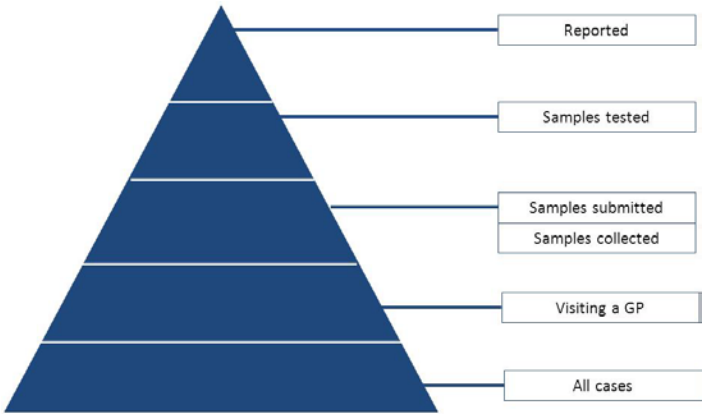
The presented burden of disease estimates rely on a number of assumptions and on data collected from a variety of studies because of still existing knowledge gaps. As an example, the association between some of the health outcomes currently considered and these foodborne infections, such as IBS and Inflammatory Bowel Disease (IBD), has been disputed. We are currently conducting further epidemiological studies to address these gaps, and will use upcoming evidence to revise our current estimates in the future. At this point, the estimates represent the best available evidence of the burden of these foodborne diseases in Denmark.

Because burden of disease studies quantify the health impact of diseases in a population by integrating information on the incidence, mortality and disability caused by all potential harmful health effects of these diseases, they allow for objective and complete comparisons between different diseases. However, these studies may provide the scientific evidence necessary to allow policy makers to rank different foodborne diseases at the population and individual level and thus prioritise interventions to reduce their public health, as well as economic burden. We will expand our efforts to estimate the burden of other foodborne diseases in Denmark, thereby providing a more complete picture of the public health burden. The next step will be to integrate these estimates with economic analyses and calculate the total costs of foodborne illnesses in Denmark.

Sammendrag (in Danish)

I Danmark, ligesom i de fleste andre lande, er det sande omfang af fødevarebårne sygdomme stadig ikke kendt. For at kunne identificere og prioritere indsatsen til forbedring af fødevaresikkerheden med henblik på at reducere sygdomsbyrden i samfundet er det nødvendigt at 1) estimere den totale sygdomsbyrde som følge af fødevarebåren sygdom; 2) sammenligne og rangere sygdommene efter deres betydning i befolkningen; og 3) identificere hvilke fødevarer, der er de vigtigste kilder til sygdomsbyrden.

Den laboratoriebaserede overvågning registrerer sygdomstilfælde der forårsages af en række fødevarebårne mikroorganismer, men disse tilfælde dækker over underrapportering i forskelligt omfang. Dertil kommer, at selv om fødevarebårne infektioner overvejende optræder som mave-tarm infektioner, kan nogle af dem være forbundet med kroniske og nogle gange livstruende følgesygdomme i nerve- eller immunsystem. Sammenhængen mellem disse langtidseffekter og den fødevarebårne infektion, de er udløst af, er ofte vanskelige at dokumentere, men langtidseffekterne er vigtige at have med, da de har stor betydning for den samlede sygdomsbyrde.



Overvågningspyramiden. Toppen repræsenterer registrerede tilfælde, medens bunden repræsenterer det sande antal infektioner

Salmonella, Campylobacter og verotoksinproducerende *Escherichia coli* (VTEC) er blandt de fødevarebårne patogener, der har størst sundhedsmæssig betydning i Danmark. Denne rapport estimerer for første gang den fødevarebårne sygdomsbyrde som følge af disse infektioner, og kombinerer sygdomsbyrden med estimater for det relative bidrag af forskellige fødevarekategorier. For at kunne beregne den totale sygdomsforekomst som følge af infektion med de tre ovennævnte patogener, har vi estimeret multiplikationsfaktorer, der angiver hvor meget det rapporterede antal tilfælde skal ganges med for at korrigere for underdiagnosticering og underrapportering. Underdiagnosticering og underrapportering af mave-tarm infektioner skyldes, at processen bremses i et af følgende led, der normalt skal gennemløbes før et tilfælde bliver diagnosticeret og rapporteret: den syge person skal søge læge; lægen skal få udtaget og indsende, en prøve til mikrobiologisk undersøgelse på et laboratorium; den sygdomsfremkaldende mikroorganisme skal påvises og identificeres af laboratoriet; og endelig skal resultatet lægges ind i det offentlige rapporteringssystem. Vi har estimeret multipli-

kationsfaktorerne på grundlag af alle led i denne såkaldte overvågningspyramide, og vi har anvendt sandsynlighedsmodeller for at tage højde for usikkerheder. Til beregning af den sande sygdomsforekomst anvendte vi overvågningsdata fra 2012. Data blev opdelt i 6 alderskategorier samt køn, for at kunne tage højde for eventuelle alders- og kønsforskelle i sygdomsforekomsten.

For at beregne sygdomsbyrden i enheden DALYs (disability adjusted life years, sygdomsjusterede leveår) har vi kombineret den estimerede forekomst med oplysninger om dødelighed og sværhedsgrad for hver enkelt sygdom. DALY er et mål for antal leveår, der er mistet som følge af nedsat livskvalitet og/eller for tidlig død som følge af en bestemt sygdom, enten på individniveau eller på populationsniveau. DALY samler derved mortalitet udtrykt som YLL (years of life lost, antal mistede leveår), og sygelighed/invaliditet udtrykt som YLD (years lived with disability, leveår med nedsat livskvalitet) i ét integreret mål. Da infektion med samme sygdoms-fremkaldende mikroorganisme kan have flere forskellige udfald (fx diarré, ledbetændelse, nervebetændelse og død) beregnes der DALYs for alle sygdomsudfald, som potentielt kan kædes sammen med den pågældende mikroorganisme.

Det estimerede antal DALYs for hvert patogen er derefter kombineret med smittekildeestimater fra andre undersøgelser for at anslå bidraget fra forskellige fødevarer til den samlede sygdomsbyrde. DALY estimaterne er beregnet for hver kombination af fødevare og bakterie og derefter summeret for at kunne beregne den samlede sygdomsbyrde pr. fødevarekilde.

Den estimerede grad af underdiagnosticering og underrapportering i 2012 var forskellig for de 3 bakterier. Vi estimerede, at for hvert rapporteret salmonellatilfælde var der i virkeligheden omkring 7 (95% CI: 4,2-15,6), der var syge. Estimatet var højere for *Campylobacter* (12; 95% CI: 6,6-20,8) og i særlig grad for VTEC, hvor vi fandt at kun 1 ud af 31 (95% CI: 7,2-83,7) tilfælde blev rapporteret i statistikken. I alt estimerede vi, at der i 2012 var 9.249 tilfælde af *Salmonella*, 41.120 tilfælde af *Campylobacter* og 4.158 tilfælde af VTEC, og at de samlet resulterede i 1.622 indlæggelser på hospitaler. Forekomsten af *Salmonella* og VTEC infektioner var højest i aldersgruppen under 5 år, men uden forskel mellem drenge og piger. Til sammenligning sås campylobacterinfektioner hyppigst hos voksne mænd.

Den samlede sygdomsbyrde var højest for *Campylobacter* (1.593 DALY), efterfulgt af *Salmonella* med 389 DALY og 113 DALY for VTEC. Blandt de forskellige følgesygdomme bidrog irritabel tyktarm mest til den totale sygdomsbyrde for såvel salmonella- som campylobacterinfektioner. For VTEC var det nyresvigt, som bidrog mest til den samlede sygdomsbyrde. For *Campylobacter* var sygdomsbyrden højest hos mænd, medens den for både *Salmonella* og VTEC var en smule højere hos kvinder.

Beregning af fordelingen af DALYs på smittekilder var kun muligt for *Salmonella* og *Campylobacter*, fordi der ikke findes et smittekilderegnskab for VTEC i Danmark. Resultaterne viser, at hovedparten af sygdomsbyrden for infektioner erhvervet i Danmark skyldes slagtekyllingereservoiret, efterfulgt af kvægreservoiret (inkl. oksekød) og importeret kød. For disse tre kilder var *Campylobacter* ansvarlig for den største andel af

sygdomsbyrden. En væsentlig andel af det samlede antal DALY var rejseassocieret (45% for *Salmonella* og 38% for *Campylobacter*).

	Salmonella			**Campylobacter**			**VTEC**		
Rapporteret antal tilfælde	1,198			3,728			191		
	Mean	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
Total antal*	12,159	12,131	[10,239; 14,278]	51,821	51678	[43,415; 61,016]	5,920	5873	[4,099; 7,997]
Dødsfald	8	7	[3; 13]	21	21	[12; 30]	0	0	[0; 2]
DALY Total	389	379	[286; 547]	1,593	1,586	[1,372; 1,857]	113	104	[11; 265]
DALY/tilfælde	0.032			0.031			0.019		
DALY /100,000	6.94			28.4			2.02		
YLD	294	292	[274; 350]	1342	1339	[1,199; 1,499]	94	87	[10; 222]
YLL	95	85	[12; 246]	252	241	[94; 470]	19	0	[0; 118]

Beregnede sygdomsbyrder for Salmonella, Campylobacter og VTEC i Danmark i 2012

	Salmonella	***Campylobacter***	**Total**
Total DALYs	379 [286; 547]	1586 [1372; 1857]	1965
Svin	34.9 [28.9; 41.2]	0.00	34.9
Kvæg	27 [23.9; 30.2]	165.4 [99.6; 230.2]	192.4
Konsumægsprod. høns	5 [1.5; 9.0]	0.00	5
Slagtekyllinger	0.00	391.5 [320.6; 458.4]	391.5
Ænders	3.3 [1.1; 5.9]	32.3 [15.7; 51.6]	35.7
Kalkuner	0.00	0.00	0
Importeret kød	23 [10.7; 36.9]	144.7 [115.5; 173.5]	167.7
Ukendt	113.5 [102.9 ; 117.3]	215.8 [137.6; 289.9]	329.3
Total indenlandsk BoD	206.7[169.1; 240.6]	949.7 [689.0; 1203.5]	1156.3
Rejser	170.5 [167.9; 173.0]	583.3 [576.0; 590.5]	753.8

Samlet beregnet sygdomsbyrde for Salmonella og Campylobacter fordelt efter smittekilde samt udlandsrejse (median og 95% konfidensinterval). Smittekilderegnskabsmetoden kan ikke skelne mellem smitteveje indenfor det samme animalske reservoir dvs. "kvæg" inkluderer fx både fødevarer (oksekød og mejeriprodukter), direkte kontakt med kvæg og miljøsmitte fra kvægreservoiret. ***Note****: Median estimaterne resulterer fra simulering, og summerer ikke altid til det totale antal DALY.*

Vores resultater viser dermed, at af de tre patogener, der indgår i undersøgelsen, er det *Campylobacter* der bidrager mest til sygdomsbyrden. Dette er i overensstemmelse med resultater fra andre lande, især Holland, og understreger betydningen af målrettet kontrol mod kilder til campylobacterinfektioner. Inddragelse af resultater fra smittekilderegnskaber viste desuden, at slagtekyllinger er den væsentligste kilde til denne sygdomsbyrde, og at der kan være en gevinst ved at fokusere indsatsen her men også inddrage andre

væsentlige kilder. Det er desuden fortsat uklart, hvor meget af smitten fra slagtekyllinger der kommer direkte fra indtag af kyllingekød og hvor meget der skyldes fx miljøsmitte, men som stammer fra kyllingereservoiret.

Beregning af sygdomsbyrden giver kvantitative mål for, hvor meget fødevarebårne sygdomme betyder for folkesundheden ved at integrere oplysninger om antal tilfælde, dødelighed samt følgesygdomme og giver dermed et objektivt grundlag for sammenligning af forskellige sygdomme. Ikke desto mindre hviler beregningerne på en række antagelser og input fra lignende studier fra andre lande, fordi der på nogle områder stadig mangler viden og data. Eksempelvis diskuteres det stadig, hvor kraftig relationen er mellem tarminfektion med fødevarebårne bakterier og sygdomsudfaldene irritabel tyktarm (IBS) og inflammatorisk tarmlidelse (IBD), da disse også kan have andre årsager. Vi foretager derfor yderligere epidemiologiske undersøgelser for at øge vores viden, og vil derefter opdatere vore sygdomsestimater. På trods heraf repræsenterer de nuværende beregninger et forbedret grundlag for de beslutninger, som både myndigheder og politikere skal træffe med henblik på at forbedre fødevaresikkerheden i Danmark.

DTU Fødevareinstituttet vil også søge at forsætte arbejdet med at beregne sygdomsbyrden for andre fødevarebårne sygdomme, og dermed bidrage til et mere komplet billede af fødevarebårne sygdommes betydning for folkesundheden. Næste trin vil være at integrere estimater for sygdomsbyrden med økonomiske analyser og dermed beregne de totale omkostninger ved fødevarebårne sygdomme i Danmark.

1. Introduction

Foodborne diseases cause a substantial public health, social and economic impact worldwide. They can be caused by a variety of microbial or chemical hazards, or by risk factors that are to a large extent associated with life-style (e.g. dietary patterns, cooking habits).

In Denmark as in most countries throughout the world, the true impact of foodborne diseases is still unknown. Because microbial foodborne agents typically cause acute disease, public health surveillance is able to capture cases of infection by several foodborne pathogens occurring in the population, and data on the incidence of diseases provides evidence on the relative occurrence of different pathogens. In other words, surveillance data allows us to compare foodborne diseases in terms of incidence in the population.

However, this evidence does not provide a true picture of the impact of different foodborne diseases. On one hand, cases of foodborne gastroenteritis are known to be largely underreported. The degree of underreporting varies between countries and between pathogens, but, because it is also associated with patient-behavior, is expected to be large even in countries with efficient surveillance systems like Denmark (Havelaar et al., 2012; Muller et al., 2009). On the other hand, even though the most common clinical presentation of foodborne diseases takes the form of gastrointestinal symptoms, such diseases can also lead to chronic, life-threatening symptoms including neurological, gynecological or immunological disorders as well as multi-organ failure, cancer and death. These long term effects and sequelae are difficult to account for and link to earlier foodborne infections.

Burden of disease studies quantify the health impact of diseases in a population by integrating the effect of mortality, morbidity and disability. Burden of disease metrics therefore allow for comparisons between distinct diseases and risk factors and take into account all potential health outcomes of a given disease. They provide the scientific evidence to allow policy makers to quantitatively rank different foodborne diseases at the population and individual level and thus prioritize interventions to reduce their public health and economic burden.

1.1. *FoodBurden*: the Danish Initiative to estimate the Burden of Foodborne Diseases

The initiative to estimate the burden of foodborne diseases in Denmark (*FoodBurden*) was launched in February 2013. The purpose is to build on ongoing international efforts and develop BoD projects that are focused on the country's priorities and resources.

The overall goals of *FoodBurden* are:

- To provide science-based evidence of the impact of food-associated diseases, including microbial and chemical foodborne diseases, and diet-related diseases.
- To provide options for intervention in the food chain to reduce the burden of food-associated diseases at Danish and international level.

To accomplish these goals, the following objectives were defined:

1. To estimate the true burden of foodborne microbial, chemical and nutritional diseases in Denmark (and other countries).
2. To estimate the most important animal, food and environmental sources of this burden.
3. To identify effective intervention strategies to reduce this burden.

FoodBurden involves multiple divisions of DTU Food and runs in close collaboration with the Statens Serum Institute (SSI) (see Figure 1).

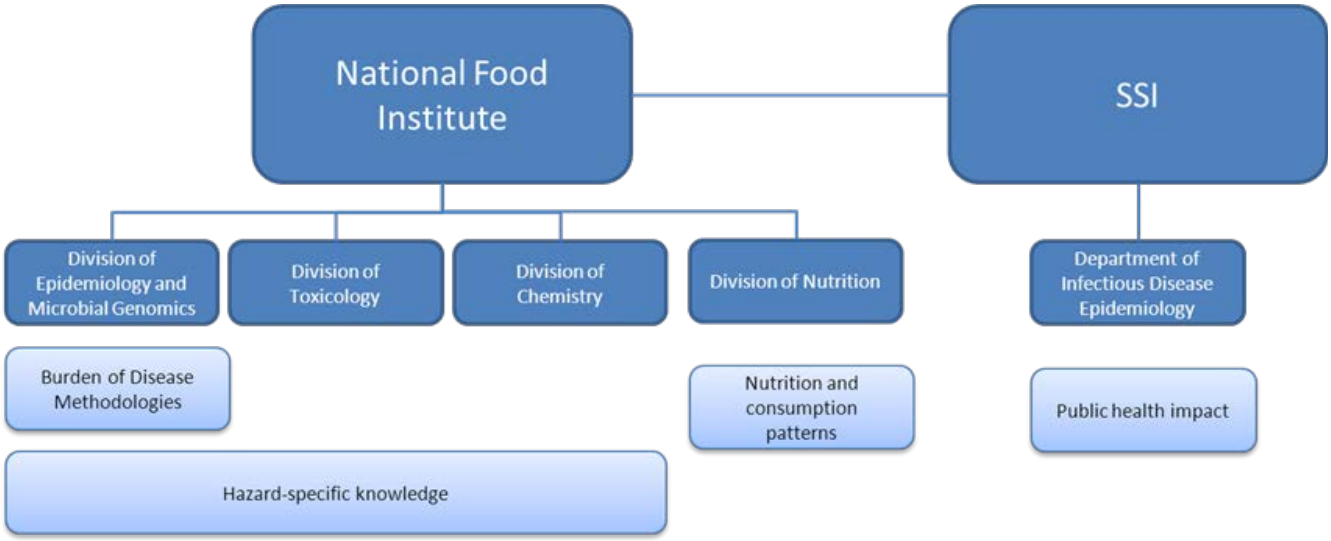


Figure 1: The *FoodBurden* Task Force: partners and roles.

At the launch of the project, three projects involving different partners were started:

I. Burden of disease of foodborne pathogens (VTEC) (Div. G; SSI).

II. Burden of disease associated with the formation of harmful components during heat-treatment of meats Div. G, Div. T, Div. K., Div. E).

III. Burden of disease associated with exposure to acrylamide through foods (PhD project; Div. T, Div. G, Div. E).

This report describes the strategy, methodology and preliminary results of project I.

1.2. Burden of disease of foodborne pathogens

The main purpose of this project is to estimate the burden of foodborne disease associated with foodborne pathogens in Denmark. The specific objectives are:

1. To estimate the true incidence of foodborne pathogens in Denmark, by accounting for underdiagnosis and underreporting in the population.

2. To identify all potential health outcomes associated with infection by each foodborne pathogen, and estimate the probability of their occurrence given infection.
3. To developed (or modify previously developed) health-outcome trees using the information gathered in objective 2.
4. To estimate the BoD by each pathogen on the basis of the data and estimates collected in objectives 1 to 3.
5. To compare and rank diseases on the basis of their public health impact in Denmark (measured using BoD metrics).

As a starting point, three foodborne pathogens were selected to develop the methodology and estimate the burden of disease. Subsequently, these will be used to develop a framework for estimating the BoD of other foodborne pathogens (in following projects).

The general approach defined for the project was:

1. Select pathogens for a pilot study.
2. Define data requirements and collect available data.
3. Estimate the incidence of disease by these pathogens.
4. Develop health-outcome trees for these pathogens.
5. Estimate DALYs on the basis of this incidence.

2. Methods

The pathogens selected for the project were *Salmonella spp*., *Campylobacter spp.*, and verocytotoxigenic *E. coli* (VTEC). These agents were prioritized due to their public health significance (thus far assessed in terms of incidence in the population), because they are estimated to be largely foodborne, and because data were to a large extent available in Denmark.

Collected data are from 2012 and represent the entire Danish population (with age and gender stratification).

2.1. Incidence of disease by foodborne pathogens

2.1.1. Public health surveillance data

In Denmark, human cases due to foodborne zoonotic pathogens are reported to Statens Serum Institut (SSI) through different channels, depending on the disease. *Salmonella*, *Campylobacter*, VTEC (and *Yersinia enterocolitica* and *Listeria monocytogenes*) are notifiable through the laboratory surveillance system.

Physicians send specimens from suspected cases to one of the clinical microbiology laboratories, depending on the county of residence of the requesting physician. The laboratories must report positive results to SSI within

one week, and results are recorded in the Register of Enteric Pathogens and the Microbiological Database (MiBa) maintained by SSI. Positive cases are reported as episodes, i.e. each patient-infectious agent combination is only recorded once in any six-month period.

2.1.2. Underdiagnosis and underreporting

Even though cases of disease by these pathogens are notifiable, a passive surveillance system inevitably underestimates the real number of ill people. This underestimation is a consequence of underdiagnosis and underreporting of enteric disease, which are due to a failure in one of multiple steps that must take place before a case is identified and reported: the ill person must seek medical care, the physician must request and submit a stool specimen to a clinical laboratory to be tested; the causative pathogen must be isolated and identified at the laboratory; and the results must be reported to public health surveillance system (Figure 2).

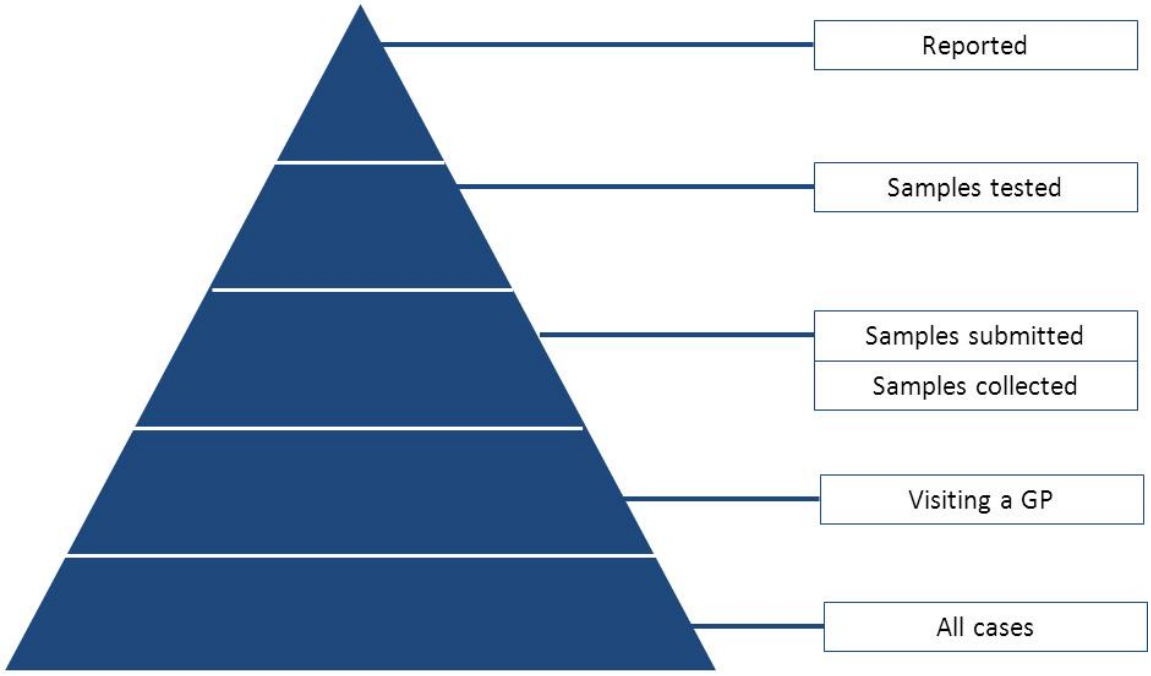


Figure 2. The foodborne diseases surveillance pyramid. The tip of the pyramid represents pathogen-specific cases reported to public health surveillance, whereas the base represents all cases by that pathogen occurring in the country in a given year.

Underdiagnosis corresponds to the failure of the health care system to capture cases in the community that do not seek medical care, whereas underreporting is due to the failure in diagnosis, classification or notification of cases that have sought care (Haagsma et al., 2012). The degree of underdiagnosis and underreporting varies by pathogen and country due to differences in health care and laboratory practices.

2.1.3. Estimating the incidence of foodborne pathogens

To estimate the total incidence of disease by selected pathogens in Denmark, we have estimated multiplication factors that correct the reported number of cases for underdiagnosis and underreporting by re-constructing the surveillance pyramid as described by Haagsma et al. (2012). The model consists of a set of non-pathogen specific and pathogen-specific parameters defined by probability distributions (Tables 1 and 2). These parameters were informed by data collected through a population-based telephone survey conducted in 2009 (Müller et al., 2011), by evidence from National Health Registries, or by literature review. In the telephone survey, of 1,853 people interviewed, 206 met the case definition (diarrhea) and provided information for the analysis. Of these, 158 reported having non-bloody diarrhea, and 5 having bloody-diarrhea in the 28 days before the interview. Participants that reported symptoms were also asked about duration of disease, care seeking behavior, stool sample collection, and absence from work or normal activities.

All parameters were described as probability distributions, defined on the basis of the data available. The parameters informed by data from the telephone survey were in general defined as beta distributions (on the basis of the number of positive responses for that variable and the total number of interviewed persons within that category), whereas parameters informed by literature or expert elicitations were defined as Beta-Pert or Triangular distributions (defined by a minimum, most likely and maximum value for the parameter). Estimated multipliers were applied to surveillance data from 2012 (available at SSI). Data were segregated in six age categories and by gender to account for differences in the incidence of disease in different age and gender groups.

Probability of seeking care

Assuming that non-bloody diarrhea-cases with short duration (i.e. 1 to 2 days) are likely to correspond to viral infections and are less likely to seek care, whereas cases with longer duration (3 or more days) would most likely correspond to bacterial infections and would have a higher probability of consulting a GP, we have stratified the Danish data and analyzed it separately to calculate two different under-diagnosis multipliers: one for viral foodborne infections, and one for bacterial foodborne infections. As a consequence, the data available to estimate underdiagnosis of bacterial diseases was reduced, as only 38 of the respondents reported having diarrhea with a duration of $\geq$3 days. This assumption was not made for bloody-diarrhea cases.

Probability of submitting a stool sample for analysis

For both non-bloody diarrhea and bloody-diarrhea cases, this parameter was estimated on the basis of the proportion of cases interviewed in the population survey that reported having a stool sample taken and submitted. For hospitalized cases, we have assumed that this proportion would be higher.

Probability of reporting a positive laboratory result

The probability of a positive laboratory test being reported to national public health surveillance was defined on the basis of the proportion of cases that have been reported in MiBa in the period from 2009-2013 and on the National Registry for Foodborne Pathogens (Steen Ethelberg, Personal Communication). This proportion applies for all reported cases, regardless of the severity.

Table 1. General enteric disease parameters used to estimate the true incidence of foodborne disease.

Notation	Description	Distribution	Data source
	Probability of seeking medical care		
P_{CSnb}	Non-bloody diarrhea	Beta(14;26)*	Muller et al. (2009)
P_{CSb}	Bloody diarrhea	Beta(4;3)**	Muller et al. (2009)
	Probability of submitting a stool sample for analysis		
P_{SSnb}	Non-bloody diarrhea	Beta(7;16)	Muller et al. (2009)
P_{SSb}	Bloody diarrhea	Beta(2;3)	Muller et al. (2009)
P_{SSh}	Hospitalized patients	Pert(0.3;0.7;0.9)	Assumption[†]
	Probability of reporting a positive laboratory result		
P_{RRnb}	Non-bloody diarrhea	Beta(9;1)	MiBa[1]
P_{RRb}	Bloody diarrhea	Beta(9;1)	MiBa[1]
P_{RRh}	Hospitalized patients	Beta(9;1)	MiBa[1]

*Data from cases that reported having diarrhea for 3 or more days.

**Data from patients that reported having bloody diarrhea, regardless of the duration.

[†]The probability of sample submission was assumed to be higher than for non-bloody and bloody-diarrhea; no data available.

[1]MiBa: The Danish Microbiological Data Base

Probability of testing for a pathogen in a stool sample

The probability that a laboratory will test for a specific pathogen varies. This probability is higher for Salmonella and Campylobacter, which are the most common foodborne pathogens and which are included in the standard testing protocol of a gastroenteritis patient, but is lower for VTEC because there is historically less awareness, laboratory testing methods have changed overtime, and the pathogen has been included later in laboratories' routine procedures and at different times throughout the countries.

Sensitivity of laboratory analysis

The sensitivity of a laboratory test, which translates the ability of the test to identify correctly affected individuals, varies between laboratory methods and thus between pathogens. The sensitivity is defined as a probability and was modelled as a pathogen-specific parameter.

Proportion of bloody diarrhea in cases and proportion of hospitalized cases

The probabilities of a patient having bloody diarrhea and of being hospitalized are related to the severity of disease and vary between pathogens. A literature review suggests that the proportion of cases with bloody diarrhea is substantially higher for VTEC (Haagsma et al., 2012), whereas the proportion of hospitalized cases follows the same ranking but with more similar values between VTEC and Salmonella (Helms et al., 2006; Flemming Scheutz, Personal Communication).

Table 2. Pathogen-specific parameters used to estimate the true incidence of foodborne disease.

Notation	Description	Salmonella	Campylobacter	VTEC	Data source
P_{TP}	Probability of testing for pathogen in sample	Beta(9.9;0.1)	Beta(9.9;0.1)	Beta(4;6)	S. Ethelberg, PC*
Sen	Sensitivity of laboratory analysis	Triang(0.85;0.88;0.91)	Triang(0.7;0.76;0.82)	Beta (7; 3)	Haagsma et al., 2012
P_{bd}	Proportion of bloody diarrhea in cases	Beta(2.34;3.81)	Beta (4.74;21.3)	Beta (2.79;0.73)	Haagsma et al., 2012
P_h	Proportion of hospitalized cases	Beta(5,811;22,085)	Beta(2,221;15,771)	Beta (165;424)	Espenhaim, 2012

*PC: Personal communication

Model for re-constructing the surveillance pyramid

To estimate the overall multiplying factor to correct reported cases to the true infections with each pathogen occurring in a year in the population, we have combined the defined parameters in different steps. All modelling steps were performed in @risk 6.0 (Palisade Corporation, 2014).

Table 3. Variables and calculation steps to re-construct the foodborne diseases' surveillance pyramid.

Notation	Description	Calculation
N	Number of reported cases	Data
N_h	Number of hospitalized cases	N* P_h
N_{CS}	Number of cases that seek care (non-hospitalized)	N- N_h
P_{CS}	Probability of seeking medical care	((1- P_{bd})* P_{CSnb}) + (P_{bd})* P_{CSnb})
P_{SS}	Probability of submitting a stool sample for analysis	((1- P_{bd})* P_{SSnb}) + (P_{bd})* P_{SSb})
P_{RRnb}	Probability of reporting a positive laboratory result	((1- P_{bd})* P_{RRnb}) + (P_{bd})* P_{RRb})
T_{nh}	Total number of non-hospitalized cases	N_{CS}*1/(P_{CS}*P_{SS}*P_{RRnb}* P_{TP}* *Sen*)
T_h	Total number of hospitalized cases	N_h*1/(P_{SSh} *P_{RRnb}* P_{TP}* *Sen*)
T	Total number of cases	T_{nh+} T_h
M	Multiplier	T/n

2.2. Disability adjusted life years (DALYs)

The most common metric used to estimate the burden of diseases is *disability adjusted life years* (DALYs). The concept of the DALY was introduced in 1993 by the World Bank, and after its application in the Global Burden of Disease and Injury (GBD) study in 1996 it has gained wide adherence (Anon., 1993; Murray et al., 1996). DALYs are conceptually simple: they represent the years of life lost due to decreased quality of life and/or premature death as a consequence of a given disease or condition, at the individual or population level. DALYs

aggregate mortality, expressed in years of life lost (YLL), and morbidity and disability, expressed in years lived with disability (YLD) into a single figure, and is calculated as:

DALY = YLL + YLD.

YLL represents the time lost due to premature mortality and is calculated with the following formula:

$YLL = \Sigma d_i * e$

where *d* is the number of fatal cases due to health outcome *i* in a certain period and *e* is the residual expected individual life span at the age of death.

YLD represents the healthy time lost while living with a disease or disability and is calculated as:

$YLD = \Sigma (n_i * t_i * dw_i)$

where *n* is the number of cases with health outcome *i*, *t* the duration of the health outcome (the average number of days of illness or injury consequences) and *dw* the disability weight assigned to health outcome *i*. See figure x for a theoretical example of DALYs.

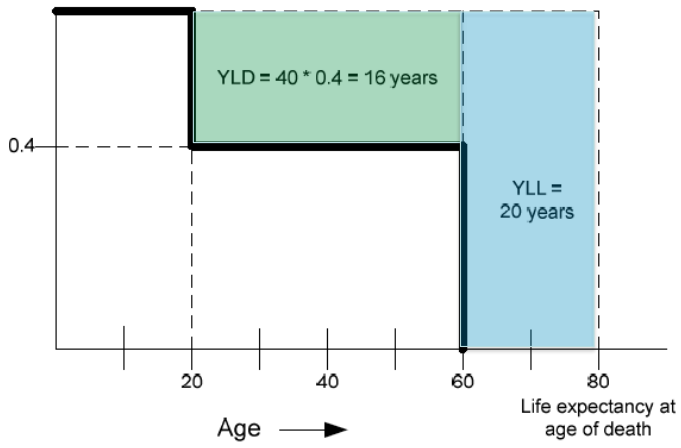


Figure 3: Theoretical example of DALYs. If this graph is to represent the life of an individual, it shows that this person is born with a perfect state of health, and that 20 years later a given event (e.g. a food-associated disease) leads to a decrease of his/her quality of life of around 60%. The person lives in this new health state for other 40 years, at which point dies prematurely. We calculate the burden associated of this disease for this individual (total DALYs) by summing the years of life lost due to living with disability (YLD) with the years of life lost due to premature death, when compared with the life expectancy in the population (YLL).

DALYs are calculated for all health outcomes that can potentially be associated with an infection by a foodborne pathogen. Therefore, this calculation requires that all health outcomes are identified, and that the

probability of their occurrence is estimated. Health outcomes include acute symptoms and long-term sequelae/chronic disease.

2.2.1. Health-outcomes of foodborne infections

Estimating the disease burden associated with the selected pathogens required that all potential health outcomes followed infection were identified. The disease outcomes of foodborne infections and the probabilities of transferring to these outcomes following infection can be described in an outcome tree. Figures 4 to 6 represent the outcome trees for *Salmonella*, *Campylobacter*, and VTEC. The outcome trees currently used were developed on the basis of a literature review of other BOD studies and of studies associating specific outcomes with foodborne infections (see e.g. Havelaar et al., 2012). An ongoing large-scale cohort study designed to estimate the probability of different health outcomes given infection with these pathogens will allow for the revision and improvement of these health outcomes in the near future (see chapter 4.5. Future studies).

Once all health outcomes had been identified, the probabilities of their occurrence given infection were collected through a literature review. Table 4 presents collected input for these parameters. Whenever possible, the uncertainty associated with these input data were considered by including them in the model as probability distributions.

Table 4. Description of health outcomes' input and data sources.

	Input			
Health outcome	**Salmonella**	**Campylobacter**	**VTEC**	**Reference**
Diarrhea	Total incidence	Total incidence	Total incidence	See 2.1.3
Reactive arthritis (ReA)	Calculated based on the probability of having ReA for a patient GE patient visiting a GP (Salmonella: RiskPert(0.023;0.08;0.15); Campylobacter: RiskBeta(46;565)), the probability of seeking care for a patient with ReA (RiskBeta(10;37)), and the probability of hospitalization for ReA patients who visit a GP (RiskBeta(2;45))		NA	Havelaar et al. (2012) (based on Raybourne et al. (2003))
Irritable bowel syndrome (IBS)	Pert(7.2; 8.8; 10.4)		NA	Haagsma 2010
Inflammatory bowel disease (IBD)	Calculated based on the age specific risk of IBD and the excess risk IBD.		NA	Havelaar et al. (2012) (based on Helms et al. (2006) and Statistics Netherlands)

Gulliaine Barré Syndrom (GBS)	NA	Beta(60;29,942)	NA	Havelaar et al. (2000)
Hemolytic uremic syndrome (HUS)	NA	NA	Incidence*	Surveillance
End-stage renal disease	NA	NA	Beta(24; 712)	Havelaar et al. (2004)
Mortality	Diarrhea: Based on excess mortality risk for laboratory-confirmed cases (Salmonella:1.3; Campylobacter:0.9 (Helms et al., 2003)). This multiplier was applied to age-specific mortality risk by all causes (Statistics Netherlands' data used as surrogate)		Mortality	Surveillance
		GBS: RiskPert(0.01;0.02;0.05)		Havelaar et al. (2000)

*Reported incidence of HUS was used, assuming that all cases of VTEC associated HUS are diagnosed and reported. However, it is likely that some HUS diagnosed cases are not linked to VTEC infections, which means that this incidence may be an underestimate. More data is needed to correct this data input.

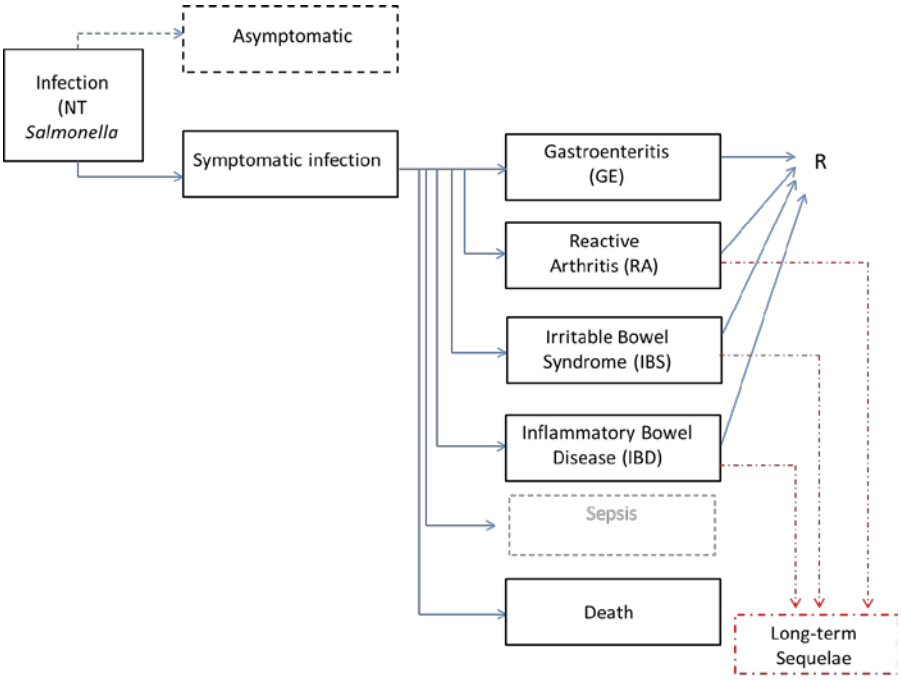


Figure 4. Outcome tree for non-typhoidal *Salmonella*. Outcomes in grey are currently not considered in the model.

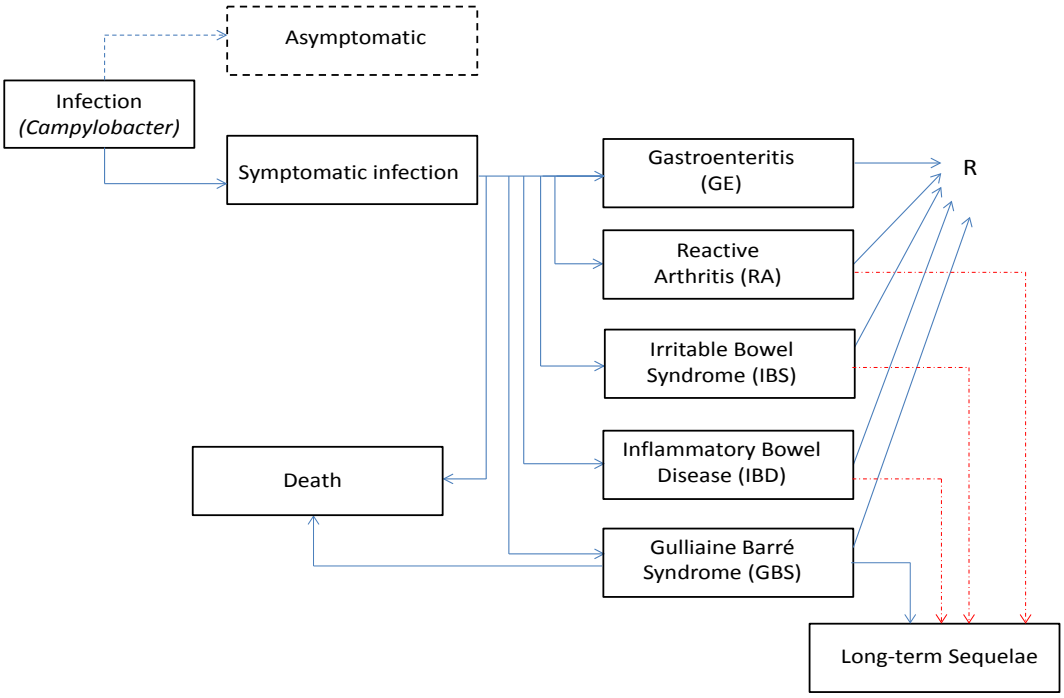


Figure 5. Outcome tree for *Campylobacter*.

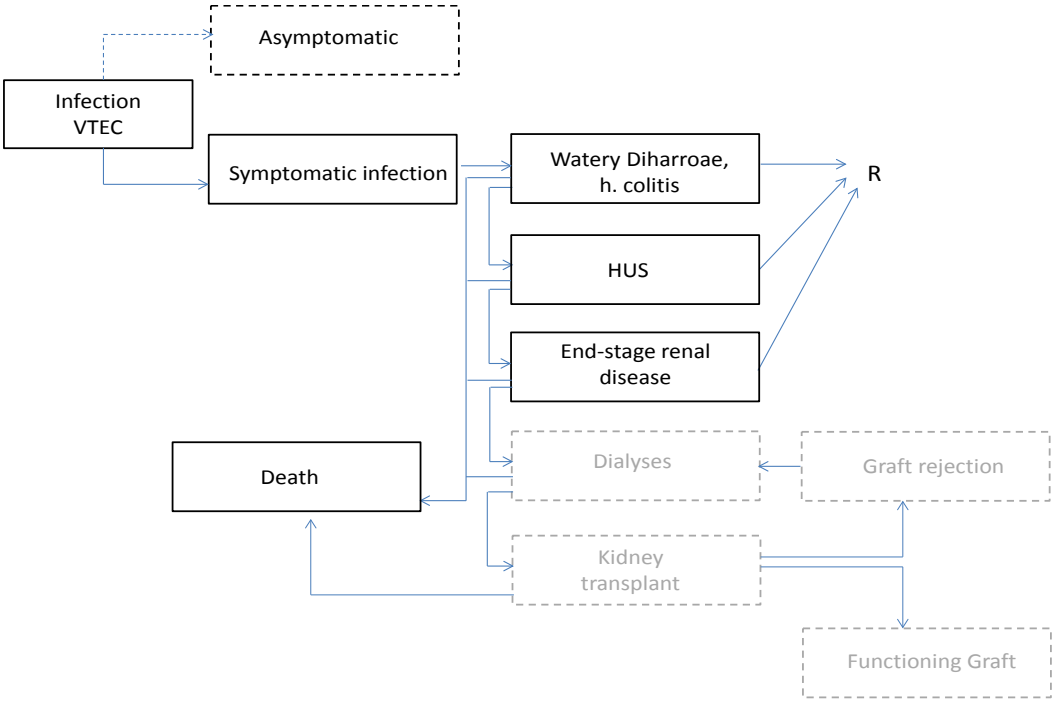


Figure 6. Outcome tree for: *VTEC*. Outcomes in grey are currently not considered in the model.

2.2.2. Disability weights and duration

The disability weight (DW) reflects the impact of a health condition in terms of health-related quality of life, and has a value ranging from 1, indicating worst imaginable health state, through 0, indicating full health. It is thus a value that is assigned to living with disability; this value is commonly based on preferences obtained from a panel of judges (Salomont et al., 2013). Preferences are defined as quantitative expressions or valuations for certain health states, which reflect the relative desirability of the health states.

We have adopted the DWs from the GBD2010 study (Salomont et al., 2013) (Table 5). When the DW for a specific health outcome was not available, we have used a proxy DW, from an outcome which has similar health effects. When DWs for specific health outcomes differentiated between multiple degrees of severity, we have calculated an overall DW on the basis of the proportion of cases that presented these degrees in Denmark (estimated based on BoI estimates).

Data on the duration of each health outcome were collected through a literature review (see Table 5 for references).

Table 5. Duration and disability weights of health ouctomes.

Health outcome	**Duration (years)**	**DW**				**Source**
Diarrhea Salmonella and Campylobacter	<5: 0.008 (0.003;0.019)	Mild: 0.061 (0.036-0.093)	Moderate: 0.202 (0.133-0.299)	Severe: 0.281 (0.184-0.399)	OVERALL: 0.0817*	Salmont et al. (2013)
	>5: 0.008 (0.003;0.019)					
Diarrhea VTEC	0.019 (0.014;0.027)	Mild: 0.061 (0.036-0.093)	Moderate: 0.202 (0.133-0.299)	Severe: 0.281 (0.184-0.399)	OVERALL: 0.0817*	Majowicz et al. (2014); Salmont et al. (2013)
Sepsis/invasive	0.08 (0.02;0.15)	0.21 (0.139-0.298)				Salmont et al. (2013)
Reactive arthritis	0.608219178	Not visiting GP**: 0.127	Visiting GP**: 0.21	Hospitalized**: 0.37		Mesle et al (1998); Salmont et al. (2013)
Irritable bowel syndrome (IBS)	5	0.042				Haagsma 2010
Inflammatory bowel disease (IBD)	Life-long	0.26				Mangen et al (2004,2005)
Gulliaine Barré Syndrom (GBS)	Life-long	Mild	Moderate	Severe	0.0817 (0.05; 0.123)	Havelaar et al. (2000)
Hemolytic uremic syndrome (HUS)	0.077 (0.038;0.115)	0.21				Kirk et al. (in preparation)
End-stage renal disease	Life-long	0.573 (0.397-0.749)				Havelaar et al. (2004)

* Calculated on the basis of the proportion of DK Salmonella cases that were classified as mild (87%) (assumed to be the same as the proportion of cases not consulting a GP); moderate (10%) (cases consulting a GP); and severe (3%) (hospitalizations).

**Assumed to represent degrees of severity: not visiting a GP – mild; visiting a GP: moderate; hospitalized: severe.

2.2.3. Life expectancy

Life expectancy at a specific age can be derived from country-specific life tables (if available), or standard life tables with fixed life-expectancy. As an example, the GBD2010 study uses a standard chosen to match the highest national life expectancy observed (Japan, specifically 82.5 years for females and 80.0 for males). We have chosen to use the Danish life expectancy estimates as estimated for 2012: men: 78.0 years; women: 81.9 years (Statistics Denmark, accessed June 16th, 2014).

2.2.4. Age weighting and time discounting

Age weighting is applied to reflect that individuals have different roles and changing levels of dependency and productivity with age (van Lier and Havelaar, 2007). Its application means that the time valued at different ages is valued unequally. Specifically, youngest and oldest age are given less weight. Age weighting is highly debatable, and we have decided not to apply it in this project.

Applying time discounting means that future life years are assigned less value than those lived today. Its application is based on the economic concept that immediate profits are preferred over benefits later in time. For the time being, we have decided not to apply discounting in this project. Different scenarios (discounted and non-discounted disease burden estimations) will be ran at a later stage and compared.

2.2.5. The DALY model

To calculate the total DALYs associated with selected foodborne pathogens in Denmark, we have estimated the incidence of all considered health outcomes in the country, and combined this with all variables described above. Total years of life lost to disability (YLD), to mortality (YLL), and overall DALYs for each sequeale of each disease were calculated by applying a stochastic model using the DALY Calculator interface developed in R (http://users.ugent.be/~bdvleess/DALYcalculator/).

2.2.6. Sensitivity analyses

Because the association between some of the currently considered health outcomes and foodborne infections has been disputed (Jess et al., 2011), we have compared the final total burden of disease estimated for selected pathogens when considering and not considering these in the DALY model. Specifically, we have estimated the total burden of salmonellosis and campylobacterioisis excluding the health outcomes IBS and IBD. The purpose was to assess the impact of these health outcomes on the total burden of disease.

2.3. Attributing disease burden to transmission routes and food-producing animals

To attribute the disease burden of different foodborne pathogens to the responsible food-animal routes, we combined estimated total DALYs per pathogen with source attribution estimates from pathogen-specific studies. We chose to attribute disease at the reservoir level, i.e. sources correspond to the animal reservoirs that represent the origin of the pathogens. Because the used source attribution approach does not distinguish between foodborne transmission and other routes of transmission to humans (such as environmental, animal contact or person-to-person), sources are described as food-animal reservoirs, and other potential sources (not considered in the model) are grouped into the category “unknown source”. “Unknown” can include for

instance pet animals, wild animals or environmental sources. A more complete overview of source attribution concepts and methods can be found in Pires et al. (2009). We also attributed total DALYs to international travelling, thereby distinguishing between domestically-acquired and travel-related cases.

This exercise was only possible for *Salmonella* and *Campylobacter*, because there are no food attribution estimates for VTEC (in Denmark or elsewhere). We attributed the total burden of *Salmonella* and *Campylobacter* to the responsible food-animal reservoirs, international travelling and unknown using *Salmonella* source attribution estimates from the (routine) *Salmonella* source account for 2012 (Anon, 2013), and *Campylobacter* source attribution estimates published by Boysen et al. (2013) (Table 16). Because the *Campylobacter* source attribution proportions only applied to domestically acquired cases, we have normalized these estimates to account for the proportion of travel-related campylobacteriosis using estimates published by Ethelberg *et al*. (2010) and surveillance data. Appendix 1 gives a detailed description of this normalization. All attributable-proportion estimates were defined using a probability distribution (Beta-Pert distribution, with the most likely value defined as the median estimate, and 95% credibility intervals defining the minimum and maximum value).

After attributing the total foodborne DALYs of a given pathogen to specific food sources, estimates of DALYs attributed to sources can then be combined by source (i.e. summed over pathogens) to estimate the overall burden attributable to a specific source in the population (see Figure 7 for a theoretical explanation of the burden of disease-attribution process).

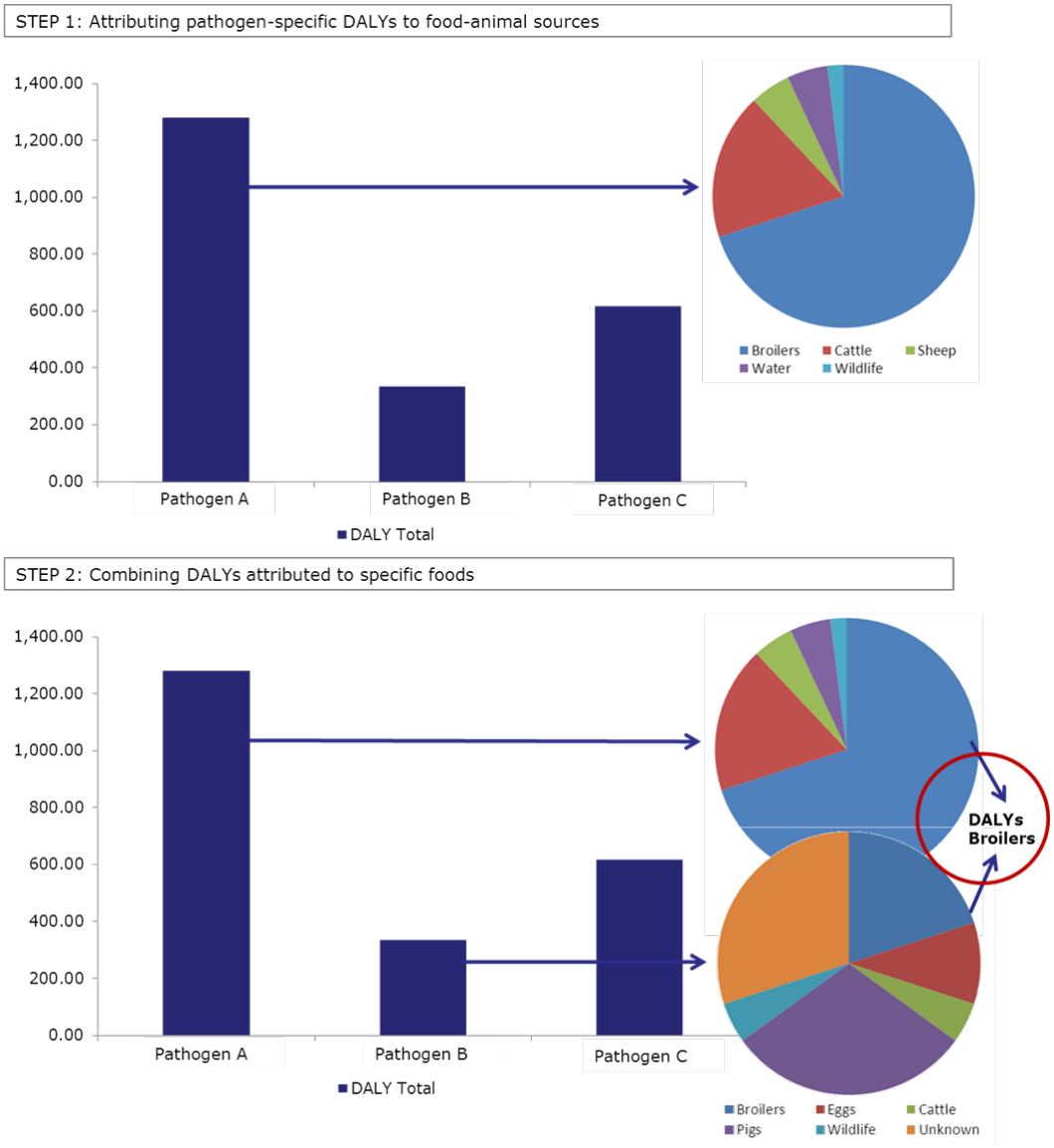


Figure 7. Theoretical example of attributing DALYs to sources.

3. Results

3.1. Incidence of disease by foodborne pathogens

The total estimated multiplier to correct reported cases to the real number of cases occurring in the population in 2012 varied between pathogens (Tables 6 to 8). This multiplier was lower for *Salmonella* (7.2), and higher for VTEC (31.2); for *Campylobacter*, we estimated that for each case captured by public health surveillance, around 12 people were ill in the country. Corrections for underreporting and underdiagnosis suggested that a total of 9,249 cases of salmonellosis, 41,120 cases of campylobacteriosis, and 4,158 cases of VTEC occurred in

Denmark in 2012, resulting in around 473, 1,012 and 137 hospitalizations, respectively. Tables 6 to 8 present the reported, estimated (total) incidence and estimated hospitalizations per 100,000 inhabitants due to *Salmonella*, *Campylobacter* and VTEC infections in Denmark, 2012.

Table 6. Estimated incidence and hospitalizations due to *Salmonella* infections in Denmark, 2012 (cases per 100,000 inhabitants).

	Reported / 100,000		**Multiplier**	**Estimated total incidence/100,000 (Median [95% CI])**		**Estimated hospitalizations/100,000 (Median [95% CI])**	
	Male	**Female**		**Male**	**Female**	**Male**	**Female**
Total population	22.1	21.6	7.2 [4.2;15.6]	171.3 [82.0; 398.1]	167.9 [80.5; 14.2]	8.7 [6.5; 14.4]	8.6 [6.4; 14.2]
Age group							
0-4	63.5	57.1		492.9 [235.9; 1145.8]	443.3 [212.1; 1031.1]	24.9 [18.7; 41.7]	22.3 [17.1; 37.4]
5-14	17.1	19.1		132.3 [63.5; 307.9]	148.2 [71.2; 344.7]	6.8 [5.0; 11.2]	7.7 [5.5; 12.6]
15-44	18	20.1		139.9 [67.0; 325.3]	156.4 [75.0; 363.6]	7.2 [5.3; 11.8]	8.0 [5.9; 13.2]
45-64	19.2	20.8		149.1 [71.3; 346.6]	161.1 [77.1; 374.6]	7.6 [5.6; 12.5]	8.2 [6.2; 13.5]
65+	25.4	17.3		197.6 [94.7 ;459.1]	134.5 [64.4; 312.9]	10.0 [7.5 ; 16.6]	6.9 [5.1; 11.3]

Table 7. Estimated incidence and hospitalizations due to *Campylobacter* infections in Denmark, 2012 (cases per 100,000 inhabitants).

	Reported / 100,000		**Multiplier**	**Estimated total incidence/100,000 (Median [95% CI])**		**Estimated hospitalizations (Median [95% CI])**	
	Male	**Female**		**Male**	**Female**	**Male**	**Female**
Total population	71	63	12.0 [6.6;20.8]	717.4 [426.1; 1703.9]	694.6 [377.5; 390.5]	8.7 [6.5; 14.4]	8.6 [6.4; 14.2]
Age group							
0-4	92.7	65		1026.9 [558.3; 2232.5]	719.8 [391.4; 1031.1]	24.9 [18.7; 41.7]	22.3 [17.1; 37.4]
5-14	50.3	29.6		12.9 [302.6; 1210.4]	327.5 [178.1; 344.7]	6.8 [5.0; 11.2]	7.7 [5.5; 12.6]
15-44	83.5	83.7		925.1 [502.7;	927.1 [503.9; 363.6]	7.2 [5.3; 11.8]	8.0 [5.9; 13.2]

			2010.6]			
45-64	67.1	63.5	742.9 [403.8; 1614.6]	703.1 [382.1; 374.6]	7.6 [5.6; 12.5]	8.2 [6.12; 13.5]
65+	54.2	40.3	600.3 [326.4; 1304.8]	446.8 [242.8; 312.9]	10.0 [7.5; 16.6]	6.9 [5.1; 11.3]

Table 8. Estimated incidence and hospitalizations due to VTEC infections in Denmark, 2012 (cases per 100,000 inhabitants).

	Reported/ 100,000		**Multiplier**	**Estimated total incidence/100,000 (Median [95% CI])**		**Estimated hospitalizations/100,000 (Median [95% CI])**	
	Male	**Female**		**Male**	**Female**	**Male**	**Female**
Total population	3.9	3.1	31.18 [7.2; 83.7]	60.6 [17.8; 302.8]	73.8 [21.6; 369.1]	5.5 [2.3; 16.7]	6.7 [2.8; 20.4]
Age group							
0-4	16.2	19		345.4 [101.5; 1725.9]	326.4 [95.9 ;1632.8]	31.1 [13.1; 95.2]	29.6 [12.5; 90.0]
5-14	5	4.6		84.4 [24.7; 421.7]	100.1 [29.3; 500.9]	7.6 [3.2; 23.2]	8.9 [3.7; 27.7]
15-44	2.8	2.2		40.9 [12.0; 204.3]	54.5 [16.0; 272.6]	3.7 [1.6; 11.2]	4.9 [2.1; 15.0]
45-64	2.1	2		38.3 [11.2; 191.2]	41.0 [12.1; 204.9]	3.5 [1.5; 10.5]	3.7 [1.6; 11.2]
65+	4.4	1.1		25.5 [7.5; 127.0]	69.9 [20.4; 349.0]	2.2 [0.9; 7.1]	6.4 [2.7; 19.3]

3.2. Burden of disease of foodborne pathogens

The overall burden of disease was estimated to be higher for *Campylobacter* (total DALYs: 1,593). A total of 389 DALYs were estimated for *Salmonella*, and of 113 for VTEC (Figure 8, Table 9).

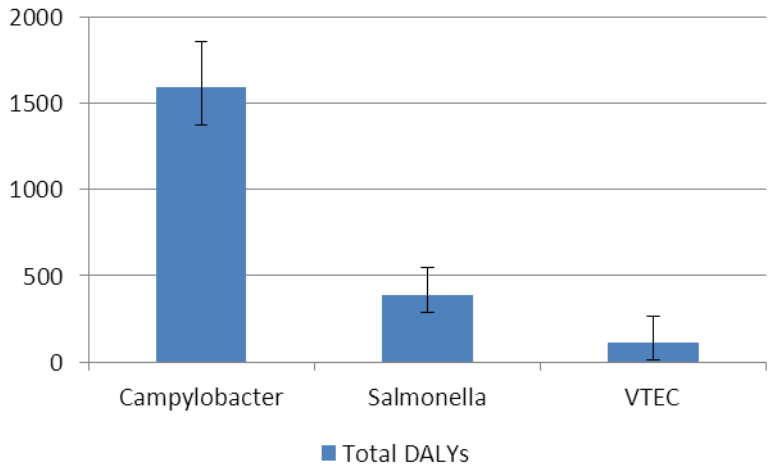


Figure 8. Total burden of disease associated with Campylobacter, Salmonella and VTEC in Denmark, 2012 (median and 95% CI).

Table 9. Estimated total DALYs, YLL and YLL for Salmonella, Campylobacter and VTEC in Denmark, 2012.

	Salmonella			**Campylobacter**			**VTEC**		
Reported cases	1,198			3,728			191		
	Mean	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**	**Mean**	**Median**	**95% CI**
Total cases*	12,159	12,131	[10,239; 14,278]	51,821	51678	[43,415; 61,016]	5,920	5873	[4,099; 7,997]
Deaths	8	7	[3; 13]	21	21	[12; 30]	0	0	[0; 2]
DALY Total	389	379	[286; 547]	1,593	1,586	[1,372; 1,857]	113	104	[11; 265]
DALY/case	0.032			0.031			0.019		
DALY /100,000	6.94			28.4			2.02		
YLD	294	292	[274; 350]	1342	1339	[1,199; 1,499]	94	87	[10; 222]
YLL	95	85	[12; 246]	252	241	[94; 470]	19	0	[0; 118]

*NOTE: the DALY calculator uses the estimated total incidence of disease as a basic input for the model, which is defined as probability distribution with most likely value the median, and minimum and maximum value the 95% percentiles. Even through these estimates were based on the BoI estimates described on chapter 3.1., the use of a probability distribution in another stochastic model leads to different results on the total cases of each pathogen.

Table 10. Estimated total DALYs, YLL and YLL associated with different health outcomes of *Salmonella* infection Denmark, 2012 (median and 95% CI).

	Diarrhea			**ReA***			**IBS****			**IBD*****		
	Median	**2.5%**	**97.5%**	**Median**	**2.5%**	**97.5%**	**Median**	**2.5%**	**97.5%**	**Median**	**2.5%**	**97.5%**
DALY	91	21	257	59	100	0	163	151	176	41	2	95
YLD	8	6	13	0	0	0	163	151	176	41	2	95
YLL	82	12	248	450	406	0	0	0	0	0	0	0
Cases	10784	8875	12910	0	0	0	778	719	837	4	1	8
Deaths	7	3	13	0	0	0	0	0	0	0	0	0

*ReA: Reactive arthritis; **IBS: Irritable Bowel Syndrome; ***IBD: Irritable Bowel Disease

Table 11. Estimated total DALYs, YLL and YLL associated with different health outcomes of *Campylobacter* infection Denmark, 2012.

	Diarrhea			**ReA***			**IBS***			**IBD*****			**GBD†**		
	Median	**2.5%**	**7.5%**	**Median**	**2.5%**	**7.5%**	**Median**	**2.5%**	**7.5%**	**Median**	**2.5%**	**7.5%**	**Median**	**2.5%**	**7.5%**
DALY	262	123	474	41	165	246	731	697	766	163	82	262	131	44	281
YLD	35	22	55	0	0	0	731	697	766	163	82	262	118	41	233
YLL	226	88	437	4	779	727	0	0	0	0	0	0	0	0	82
Cases	46102	37898	55515	0	0	0	3480	3318	3646	14	7	22	8	3	15
Deaths	21	12	30	0	0	0	0	0	0	0	0	0	0	0	1

*ReA: Reactive arthritis; **IBS: Irritable Bowel Syndrome; ***IBD: Irritable Bowel Disease; †GBS: Guillian-Barré Syndrome

Table 12. Estimated total DALYs, YLL and YLL associated with different health outcomes of VTEC infection Denmark, 2012.

	Diarrhea			**HUS***			**ESRD****		
	Median	**2.5%**	**7.5%**	**Median**	**2.5%**	**7.5%**	**Median**	**2.5%**	**7.5%**
DALY	11	6	128	1	1	2	76	0	212
YLD	9	5	15	1	1	2	76	0	212
YLL	0	0	120	0	0	0	0	0	0
Cases	5787	4001	7895	85	67	103	3	0	6
Deaths	0	0	2	0	0	0	0	0	0

*HUS: Hemolytic Uremic Syndrome; **ESRD: End-stage renal disease.

Results of the total DALYs caused by each different health outcome associated with the different pathogens show that irritable bowel syndrome (IBS) was the biggest contributor for the total burden of salmonellosis and campylobacteriosis. For VTEC, end-stage renal disease was responsible for the majority of the burden caused by the disease. Figure 9 shows the relative contribution of different health outcomes to the burden of each disease.

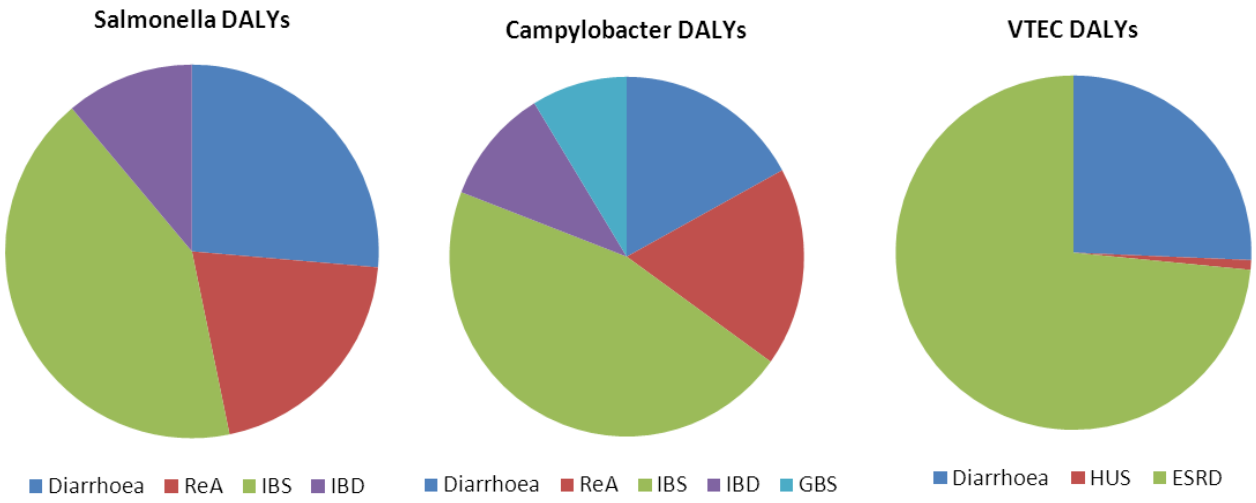


Figure 9. Relative contribution of DALYs caused by different health outcomes to total burden of salmonellosis, campylobacteriosis and VTEC infections in Denmark, 2012.

The total burden estimates by age and gender group per 100,000 inhabitants show that the burden of disease is substantially higher for young children (<5 years of age) for all pathogens (Figures 10 to 12). The total DALYs for salmonellosis are slightly higher for females than males in all age groups except in children under 5 years of age, the burden of campylobacteriosis is consistently higher in males, especially in the older age group (people with 65 years of age or more), and the burden of VTEC infections higher for women in all age groups. Tables 13 to 15 show the detailed estimates of burden, cases and deaths for all groups.

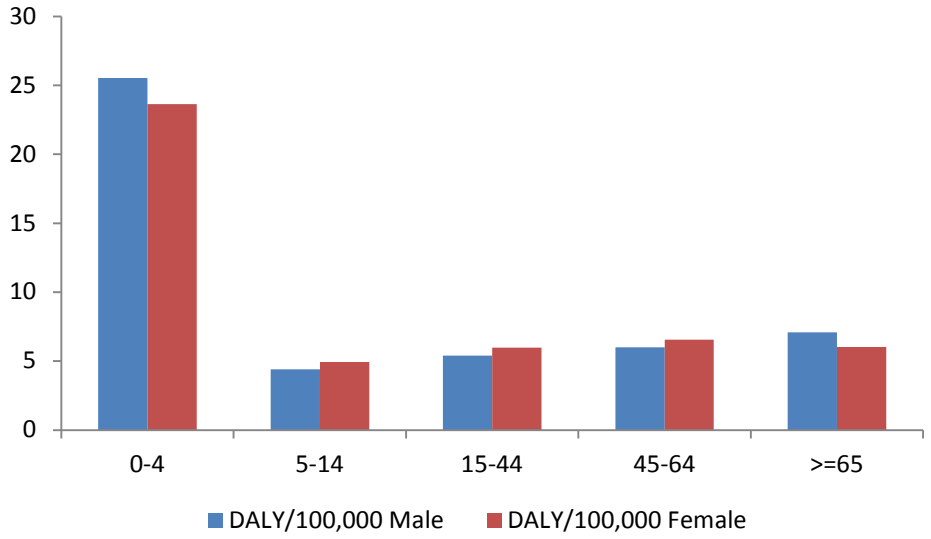


Figure 10. Distribution of total burden of disease of *Salmonella* infections in age and gender groups in Denmark, 2012 (total DALYs/100,000 inhabitants).

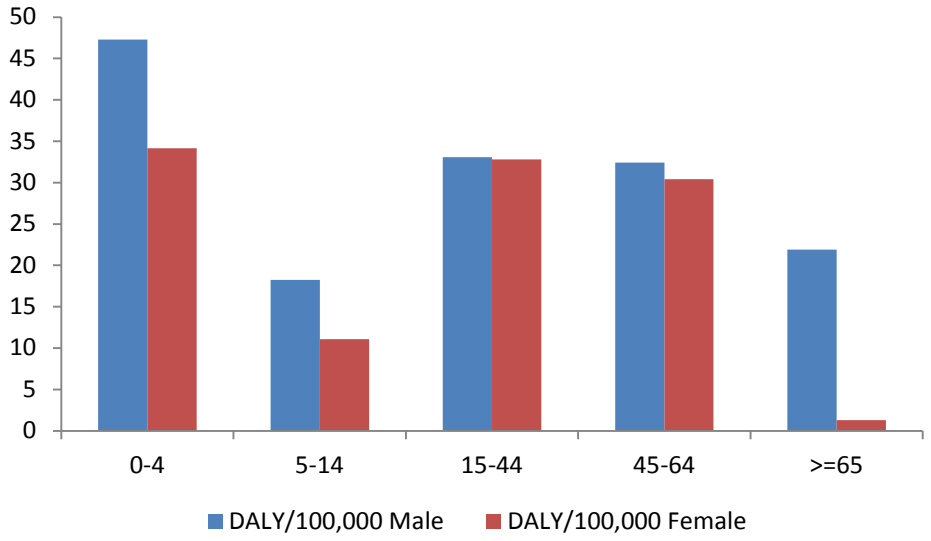


Figure 11. Distribution of total burden of disease of *Campylobacter* infections in age and gender groups in Denmark, 2012 (total DALYs/100,000 inhabitants).

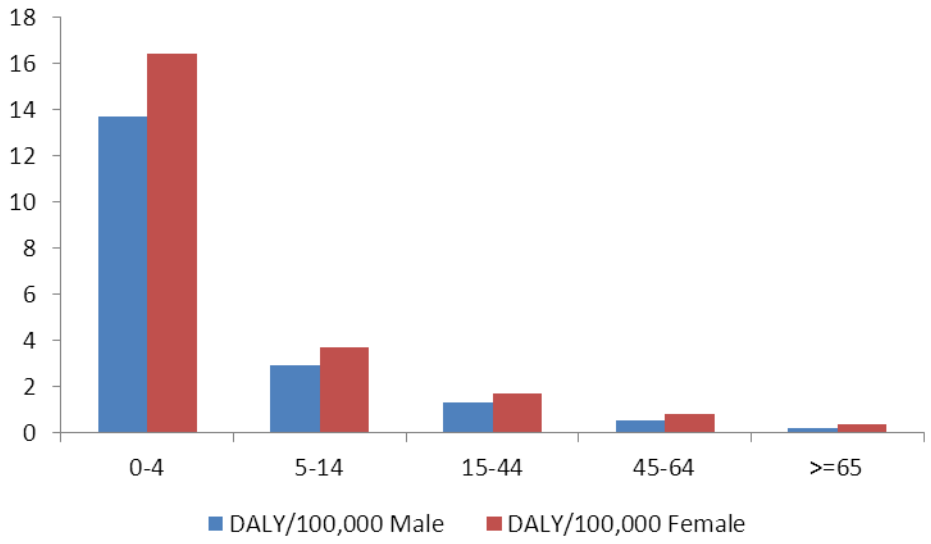


Figure 12. Distribution of total burden of disease of VTEC infections in age and gender groups in Denmark, 2012 (total DALYs/100,000 inhabitants).

Table 13. Estimated total DALYs, YLLs, YLLs, total cases and deaths associated with *Salmonella* infections in Denmark, 2012 by age and gender groups (mean).

	DALY		**YLD**		**YLL**		**Cases**		**Deaths**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
0-4	41	36	22	19	18	17	1016	866	0	0
5-14	15	16	14	15	1	1	577	616	0	0
15-44	58	63	54	59	4	4	1928	2103	0	0
45-64	45	49	33	35	12	14	1434	1543	1	1
65+	32	33	24	20	9	14	1144	942	2	3

Table 14. Estimated total DALYs, YLLs, YLLs, total cases and deaths associated with *Campylobacter* infections in Denmark, 2012 by age and gender groups (mean).

	DALY		**YLD**		**YLL**		**Cases**		**Deaths**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
0-4	76	52	49	33	27	19	2066	1372	0	0
5-14	62	36	61	35	2	1	2370	1330	0	0
15-44	356	345	336	326	19	19	12458	12198	0	0
45-64	243	227	192	175	51	52	6967	6573	2	2
65+	99	7	71	64	29	33	3398	3059	8	8

Table 15. Estimated total DALYs, YLLs, YLLs, total cases and deaths associated with VTEC infections in Denmark, 2012 by age and gender groups (mean).

	DALY		YLD		YLL		Cases		Deaths	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
0-4	22	25	17	21	5	4	870	784	0	0
5-14	10	12	8	10	2	2	449	511	0	0
15-44	14	18	12	15	2	3	692	903	0	0
45-64	4	6	4	5	1	1	450	482	0	0
>=65	1	2	1	2	0	0	182	598	0	0

The sensitivity analysis conducted to assess the weight of the burden of disease due to IBD and IBS on the total burden of salmonellosis and campylobacteriosis shows that, if these health outcomes were not considered in the models for these pathogens, the total estimated DALYs would decrease substantially (Table 16). Specifically, total DALYs decreased by an order of 2.8 for Salmonella and of 2.3 for Campylobacter. The estimated YLDs dereased nearly by 7 and 3 times for these pathogens, respectively, and the YLL remained unchanged because neither of the health outcomes is associated with increased risk of mortality.

Table 16. Total estimated DALYs, YLD and YLL for Salmonella when considering and not considering IBS and IBD as health outcomes of infection (mean and 95% CI).

	Salmonella				Campylobacter			
	With IBS and IBD		**Without IBS and IBD**		**With IBS and IBD**		**Without IBS and IBD**	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
DALY	389	[286; 547]	138	[55; 292]	1593	[1372; 1857]	695	[497; 937]
YLD	294	[24; 350]	44	[35; 54]	1342	[1,119; 1,499]	444	[341; 569]
YLL	95	[12; 246]	95	[12; 246]	252	[93; 470]	252	[93; 470]
YLD/DALY	77%		39%		84%		65%	
YLL/DALY	23%		61%		16%		35%	

3.3. Attributing the burden of disease to food sources.

The proportion of *Salmonella* and *Campylobacter* infections attributed to the different animal-food sources and travel is presented in Table 17.

Table 17. Proportion of disease by *Salmonella* and *Campylobacter* attributable to food-producing animals, imported meat, and travel (%) (median and 95% CI).

	Salmonella	***Campylobacter****
Pigs	9.2 (7-11.6)	0
Cattle	7.1 (6-8.3)	10 (4-16)
Laying hens (table eggs)	1.3 (0.08-2.9)	0
Broilers	0	25 (18-31)
Duck	0.8 (0.08-0.2)	2 (1-4)
Turkey	0	4 (1-9)
Imported meat	5.8 (1.8-11.6)	9 (1-12)
Travel	45 (44-46)	37 (36-38)
Unknown	30.8 (24-31)	14 (1-20)

*Normalized results of the Hald-adapted microbial subtyping model were used for comparability purposes (include proportion attributed to "unknown"). Original results can be found in the publication (Boysen et al., 2013).

Table 18 shows the total DALYs attributed to specific food-animal sources, international travel and unknown sources for *Salmonella* and *Campylobacter*. The largest proportion of the total domestic burden was attributed to broilers (392 DALYs) and the cattle reservoir (192). A very large proportion of the burden of disease was acquired when travelling internationally.

Table 18. Overall disease burden by *Salmonella* and *Campylobacter* by food-animal source in Denmark and acquired abroad, 2012 (median and 95% CI).

	Salmonella	***Campylobacter***	**Total**
Total DALYs	379 [286; 547]	1586 [1372; 1857]	1965
Pigs	34.9 [28.9; 41.2]	0.00	34.9
Cattle	27 [23.9; 30.2]	165.4 [99.6; 230.2]	192.4
Laying hens (table eggs)	5 [1.5; 9.0]	0.00	5
Broilers	0.00	391.5 [320.6; 458.4]	391.5
Duck	3.3 [1.1; 5.9]	32.3 [15.7; 51.6]	35.7
Turkey	0.00	0.00	0
Imported meats	23 [10.7; 36.9]	144.7 [115.5; 173.5]	167.7
Unknown	113.5 [102.9 ; 117.3]	215.8 [137.6; 289.9]	329.3
Total domestic BoD	206.7[169.1; 240.6]	949.7 [689.0; 1203.5]	1156.3
Travel	170.5 [167.9; 173.0]	583.3 [576.0; 590.5]	753.8

NOTE: Median attribution estimates result from simulation and may not sum up to the total attributed DALYs.

A visual representation of results shows that the total domestic burden of disease attributed to broilers was due to *Campylobacter* infections, as was the majority of the DALYs associated with the cattle reservoir and imported meat (Figure 13). In contrast, *Salmonella* infections were estimated to be responsible for the total burden attributed to pigs and laying hens.

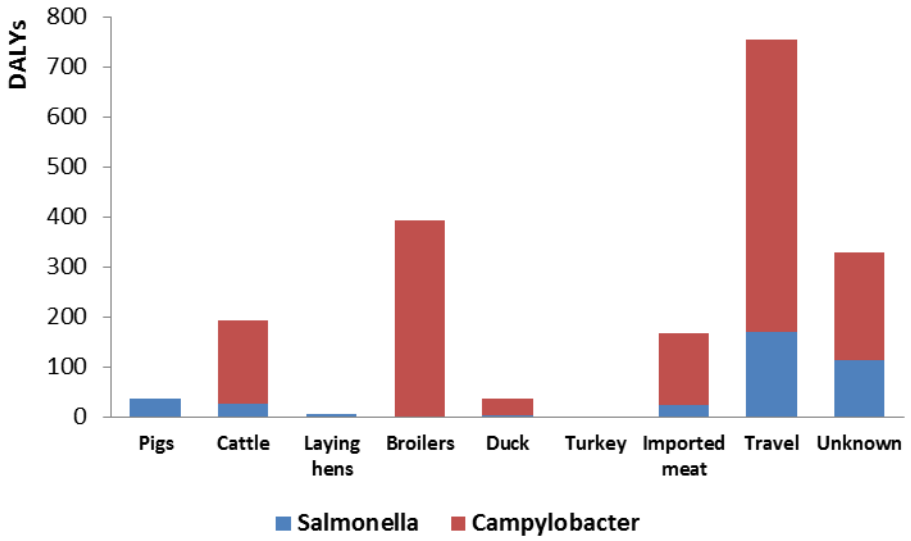


Figure 13. Total burden of disease by *Salmonella* and *Campylobacter* attributed to food-producing animals, imported meat and international travel in Denmark, 2012 (median DALYs).

4. Discussion

These are the first estimates of the burden of foodborne diseases in Denmark. Even though we have thus far calculated burden for only three bacterial pathogens, results allows us to rank these, and the developed methods can be applied to other hazards in the future.

4.1. True incidence of foodborne pathogens

Our results suggest that campylobacteriosis was the most frequent infection by pathogens commonly transmitted through foods in Denmark in 2012, with an estimated incidence of 734 cases per 100,000 inhabitants, followed by *Salmonella* (165 per 100,000) and VTEC (74 per 100,000). This ranking goes in line with the ranking of reported incidence, but estimates demonstrate a large and variable degree of underreporting for the three pathogens. Notably, the pathogen with the largest degree of underreporting and underdiagnosis (i.e. with the largest difference between reported and estimated total cases) was VTEC, for which a multiplier of around 31 was estimated (compared with 7.2 for *Salmonella* and 12 for *Campylobacter*). This finding is not surprising, since, even though the symptoms of mild, uncomplicated disease by all these three pathogens may be similar, doctors and laboratories are more likely to request isolation of *Salmonella* and *Campylobacter*, and VTEC cases often go undiagnosed in the country. This picture is already changing in some counties in Denmark (Espenhaim, 2012), and is likely to change nation-wide once more awareness on the likelihood of a gastroenteritis case being caused by diarrheagenic *E. coli* is raised. Nonetheless, the VTEC multiplier could further increase, if we were to consider underdiagnosis and underreporting of VTEC-associated HUS cases.

Thus far, we have assumed that all VTEC-HUS cases are diagnosed and reported. However, it is likely that some HUS diagnosed cases are not linked to VTEC infections, which means that the currently used incidence may be underestimated. More data are needed to correct for this.

Several previous studies conducted in different countries have estimated multipliers to correct for underreporting and underdiagnosis of these three pathogens. Estimates varied substantially (for example from 5 in the UK to 51 in Greece for *Salmonella*), as did the methods applied. When we compare our estimates with results from studies conducted in countries that can be considered comparable to Denmark (e.g. northern European countries), Danish estimates are slightly higher than the those published for UK for all pathogens, and generally similar to estimates from The Netherlands (varied differences between pathogens) (Table 19). These differences can be explained by differences in the surveillance of different pathogens in the countries (for example surveillance in the Netherlands does not cover the entire population), and on the methods used to correct for underreporting, which varied substantially in all studies.

Table 19. Overview of multiplication factors estimated to correct for underreporting of *Salmonella*, *Campylobacter* and VTEC infections in different countries worldwide.

Country	**Study**	**Multiplication factor**		
		Salmonella	***Campylobacter***	**VTEC**
DK	Havelaar, 2012	4.4	4.1	NA
Greece	Gkogka, 2011	51.45 (3.2-99.7)	NA	NA
UK	IID2, 2012	4.7 (1.2-18.2)	9.3 (6-14.4))	7.4 (0.5-104.4)
DK	Haagsma, 2010	24.7 (5.2-64.7)	22.9 (8.2-50)	NA
Japan	Kubota, 2011	74 (35.8-140.7)	379.6 (184.7-716.9)	NA
Australia	Hall, 2008	13.06 (6.37-67.83)	14.15 (6.8-73.32)	14.35 (7.38-64.34)
Canada	Thomas, 2013	12.7	27.2	20.1
USA	Scallan, 2011	29.3	30.3	26.1
Netherlands	Bouwknegt, PC	17.6	12.3	24.8
DK	**FoodBurden**	**7.2**	**12.0**	**31.2**

4.2. Burden of disease of foodborne pathogens

The ranking of foodborne diseases using burden of disease estimates was the same as the ranking of disease incidences, but the difference in the impact of diseases is larger when comparing DALYs (as opposed to number of cases). The fact that the ranking is the same was to be expected, since all three diseases have similar mild symptoms, and *Salmonella* and *Campylobacter* have similar sequelae. The exception is that *Campylobacter* causes Guillian-Barré syndrome, a long-term and potentially severe disease that partly explains the additional DALYs attributed to campylobacteriosis. VTEC infections are less frequent and, even though sequelae may be severe, account for a lower number of DALYs. Still, the total VTEC burden may be an underestimate because we have considered no underreporting of VTEC-associated HUS cases (see 4.1).

The currently used health-outcomes of the three foodborne infections have been identified through literature reviews. However, recent scientific evidence has raised questions about the association between infection with foodborne pathogens and some of the health outcomes currently considered in our outcome trees. In particularly, the association between *Salmonella* and *Campylobacter* infection and IBD has been disputed (Jess et al. 2011). This study suggested that the estimated increased risk of IBD after infection with *Salmonella* or *Campylobacter* may be due to detection bias related to repeated stool testing in patients with unclear gastrointestinal symptoms rather than aetiology, suggesting that risk estimates derived for this and other health outcomes may be overestimated. The sensitivity analysis conducted to assess the weight of the burden due to IBS and IBD on the total estimated burden of salmonellosis and campylobacteriosis revealed that, if IBD and IBS were not considered as health outcomes of infection, the total burden of salmonellosis and campylobacteriosis would decrease to around one third and a half, respectively. Because none of these outcomes is associated with increased risk of death, the estimated years of life lost due to mortality would remain the same, but the total years lived with disability estimated for these pathogens would decrease to a seventh for salmonellosis, and one third for campylobacteriosis. These results highlight the large contribution of these health outcomes for the currently estimated public health impact of these diseases, and emphasize the importance of further studies investigating the link between foodborne infections and the probability of different health outcomes. Conversely, other health outcomes, thus far not associated with these foodborne infections, may exist. This may particularly be the case for VTEC infections, which could lead e.g. to IBS or neurological sequelae, as suggested by some studies (Keithlin et al., 2014). To address these data needs, we are currently conducting a large-scale epidemiological study that will provide stronger evidence to improve our health-outcome trees (see "4.5. Future studies").

Our burden of disease' estimates are in agreement with the latest Dutch DALY estimates (corresponding to 2009, Havelaar et al., 2012) (Table 20). Specifically, *Salmonella*-estimated DALYs were very similar (6.95 DALYs/100,000 inhabitants in Denmark, and 7.7/100,000 in the Netherlands), higher in Denmark for Campylobacter (28.4/100,000, compared to 20 in the Netherlands), and also higher for VTEC in Denmark (2.2/100,000, compared to 0.7/100,000). It is important to note that Dutch estimates for VTEC only include VTEC 0157, and therefore differences were to be expected.

Table 20. Comparison of burden of disease estimates for Denmark (2012) and the Netherlands (2009), total DALYs/100,000 inhabitants.

	Salmonella	**Campylobacter**	**VTEC**
DK	6.95	28.4	2.02
NL	7.7	19.8	0.7*

*Estimates only include VTEC O157.

We have also used the BcODE tool kit developed by ECDC[1] and compared its output with DALY calculator results (detailed results not shown). Results were not identical, but were coherent. Overall, the two modelling

[1] http://www.ecdc.europa.eu/en/healthtopics/burden_of_communicable_diseases/project/pages/project.aspx

approaches were in agreement with regards to the relative importance of studied diseases, but BcODE estimated a much higher burden of disease for VTEC and, to a lower extent, *Campylobacter* (Table 21). Differences are explained by distinct model specifications. Specifically, the models included different health outcomes (for example BcODE includes IBS as a health outcome of VTEC, for which many DALYs are estimated, whereas this sequelae is currently not included in our model). Additionally, the models present large differences in mortality estimates due to differences in data sources used. It is however important to note that the BcODE's health outcome trees and models are still being revised, and the version now in used is still not publically available.

Table 21. Comparison of burden of disease's estimates as obtained by the DALY model and BcODE (total DALYs).

	DALY model	**BcODE**
Salmonella	389	334
Campylobacter	1,593	1,281
VTEC	113	618

4.3. Age and gender distribution of the burden of foodborne diseases

Our estimates show that the incidence of disease and hospitalizations of all studied pathogens is substantially higher for children under five years of age. Gender differences were less marked, but could be identified in the burden of campylobacteriosis, which appears to be more frequent and consequently have a higher impact in males, and VTEC infections, for which we estimated a higher burden for females. The public health impact of diarrheal diseases, including diseases caused by pathogens commonly transmitted through foods, has been found to be higher for children of young age in other studies (Salomon et al., 2012; Havelaar et al., 2012). Because disease may be more severe in children due to higher vulnerability or lower immune status, this evidence highlights the importance of control strategies to reduce the burden of foodborne diseases in the population.

4.4. Attributing the burden of disease to sources

We have distributed the total estimated burden of disease by *Salmonella* and *Campylobacter* to specific food-animal sources and travel on the basis of previously conducted studies. VTEC was excluded from this exercise because no source attribution study focusing on VTEC infections has been published so far, neither in Denmark nor in other countries. An exception is a comparative risk assessment study conducted in the UK (Kosmider et al., 2010), but the results could not be used for our purpose (the model could not attribute disease to any of the included sources.

Zoonotic pathogens, including the pathogens commonly transmitted through foods considered in this study, have animals as reservoirs. However, these pathogens may have many different reservoirs, including not only production animals, but also wildlife and pets. Additionally, pathogens commonly transmitted through foods

can also be transmitted from their reservoirs to humans via other routes (environmental, contact with live animals, and person-to-person). The extent to which different pathogens are foodborne varies from pathogen to pathogen and potentially country or region to region, and determining the overall burden that is attributed to foods can be an important step to be able to produce evidence to inform risk management decisions. Specifically, food safety interventions implemented at the end of the food production chain would necessarily have to be based on the relative contribution of foods to the overall burden of disease. On the contrary, intervention strategies focused on the origin of the problem (i.e. on the reservoirs of the pathogen) are expected to reduce the burden of disease in the population regardless of the transmission route from animals to humans. Consequently, estimating the proportion of the burden that is foodborne is not relevant to inform these strategies. Denmark has had a tradition of implementing control programmes at the reservoir level (Wegener et al., 2003; 2009). Several of the designed interventions, specifically for *Salmonella* control, have been based on or been evaluated on the basis of source attribution estimations conducted routinely (Anon., 2013).

To attribute the burden of disease to specific food-producing animals, we have used results of source attribution studies conducted in Denmark, both of which used Danish surveillance data. *Salmonella* estimates originating from the routinely applied microbial subtyping source attribution model, are robust and correspond to the same time period as the presented burden estimates. As for the *Campylobacter* estimates, these originate from a one-time conducted research study, and are based on data from a different time period (2007/2008). *Campylobacter* source attribution is thus far not conducted routinely in Denmark, and more recent estimates are not available at this point.

The *Salmonella* and *Campylobacter* source attribution models based on subtyping attribute disease at the reservoir level, meaning that they estimate the proportion of cases that originates from the animal reservoir of the pathogen (e.g. pigs, cattle), not considering if transmission was foodborne or through any other route. Still, models do estimate the proportion of cases that was acquired abroad, and these are subtracted from the total cases in the country to estimate the number of domestically acquired cases by each pathogen.

Our results suggest that the majority of the domestic burden for these two diseases was caused by broilers, followed by cattle and imported meat. For these three sources, *Campylobacter* was responsible for the largest proportion of total DALYs. A substantial proportion of the total DALYs was estimated to be associated with international travel. Even though travelling is not a transmission route *per se*, it is important that it is considered in attribution studies because it should be excluded from the domestically-acquired burden, which can be influenced (optimally reduced) by the implementation of intervention strategies at the national level.

4.4. Applicability of modelling approach to other pathogens and perspectives

Focusing on three foodborne pathogens with relevant public health significance in Denmark, we have developed a methodology that allows us to estimate the burden of disease caused by different agents and sources. The methodology encompasses burden of illness, burden of disease and source attribution studies, and is able to integrate results of each in a relatively simple and systematic way. Given data availability, it can

easily be extended to other pathogens, which will allow for a more complete and broader comparison between diseases and thus increase the utility of our results.

4.5. Future studies

We are currently conducting a large registry-based cohort study that will allow us to a) identify all potential health outcomes associated with different foodborne infections, b) estimate the probability of occurrence of these health outcomes in the Danish population, and subsequently c) revise the health-outcome trees currently used in our burden of disease models. As examples, the output of this study would allow for the clarification of currently considered outcomes (e.g. by studying the association between IBD and salmonellosis and campylobacteriosis), and could also allow for the identification of outcomes thus far not recognized, particularly for VTEC infections. This study will be crucial to improve and increase available evidence on the link between foodborne infections and sequelae, and will allow for the application of the *FoodBurden* model to other pathogens, as well as the revision of current estimates. The above presented results should therefore not be considered final.

Another potential study that would allow for the improvement of the current estimates would be focused on providing evidence to correct the reported incidence for underdiagnosis and underreporting. The current model used to estimate the true incidence of disease of foodborne pathogens relies on data from a telephone survey conducted in 2009 that aimed to determine the incidence of acute gastrointestinal illness in Denmark (Müller et al., 2011). While its methods are sound and appropriate, the study was able to collect data from a relatively low number of gastrointestinal patients, and thus data to inform some of our model parameters were sparse. This leads to an increased uncertainty of our estimates, which may or may not be reflected on our statistical confidence intervals. An update of this study would be very useful for the overall *FoodBurden* project.

5. Acknowledgements

We would like to acknowledge the collaboration and input from partners from the Statens Serum Institute, particularly Steen Ethelberg (Department of Infectious Disease Epidemiology) and Flemming Scheutz (WHO Collaborating Centre for Reference and Research on Escherichia and Klebsiella), and from Martjin Bouwknegt from the National Institute for Public Health and the Environment (RIVM), the Netherlands (Centre for Zoonoses & Environmental Microbiology).

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Appendix 1. Integration of available *Campylobacter* source attribution estimates with travel data

Campylobacter source attribution estimates were retrieved from Boysen et al. (2013). This study applied a microbial subtyping model based on Hald et al. (2004) and estimated the proportion of *Campylobacter* cases attributable to six food sources and *unknown* (Table A1). These estimates only applied to domestically acquired cases and cases with unknown travel history (i.e. *Campylobacter* cases that have reported having travelled abroad in the week before onset of symptoms were excluded from the model). The proportion of cases reported with unknown travelling information that could potentially have been acquired abroad was estimated on the basis of the cases with travel information that had reported to have travelled (see Boysen et al. (2013) for more details on this approach).

To account for the full proportion of travel-related campylobacteriosis, we have normalized these proportions using estimates published by Ethelberg *et al*. (2010) and surveillance data (available at www.ssi.dk, accessed on September 10th, 1024). Ethelberg et al. (2010) interviewed 208 patients with a *Campylobacter* infection reported in 2008 (around 6% of all reported cases) and asked about travelling behavior on the seven days before onset of symptoms. Of these patients, 33.4% reported to have travelled abroad. Between 2010 and 2012, among *Campylobacter* cases captured by public health surveillance that reported travel history before onset and disease, between 38 and 58% reported to have travelled abroad (www.ssi.dk). These proportions were used to inform a probability distribution that defines the proportion of *Campylobacter* cases attributable to travel (a beta-Pert with a minimum of 30%, most likely of 33% and maximum of 45%).

Table A1 shows the detailed attributable proportions as estimated by Boysen eta l. (2013) and normalized to account for international travel

Table A1. Proportion of campylobacteriosis attributable to food sources and unknown as estimated by Boysen et al. (2013) and normalized to account for international travel (mean and 95% Credibility Interval).

Source	Attributable proportion, Boysen et al. (2013) (mean % and 95 CI)	Normalized attributable proportion (mean % and 95 CI)
Pigs	0	0
Cattle	16 [7; 25]	10 [4-16]
Laying hens	0	0
Broilers	38 [28; 47]	25 [18-30]
Duck	3 [1; 6]	1.9 [0.7-4]
Turkey	6 [1; 13]	4 [0.6-8]
Imported meat	14 [1; 18]	9 [7-1]
Travel	3 [2; 4] *	37 [36-27]
Unknown	21 [1; 31]	14 [7-20]

*Proportion of cases with unknown travel history that are estimated to be travel-related

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