Public Health England

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To compare the methodologies used to estimate foodborne disease in the UK to those used in other countries

Final report

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Contents

Glossary

CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
Cr	Credible intervals
EHEC	Enterohaemorrhagic *Escherichia coli*
FSA	Food Standards Agency
GI	Gastrointestinal disease
GP	General Practice
GSURV	National surveillance database for general outbreaks of IID
HUS	Haemolytic Uraemic Syndrome
IID	Infectious Intestinal Disease
IID1	The First Study of Infectious Intestinal Disease in the Community
IID2	The Second Study of Infectious Intestinal Disease in the Community
NHS	National Health Service
OECD	Organisation for Economic Cooperation and Development
STEC	Shiga toxin producing *Escherichia coli*
VTEC	Verocytotoxin producing *Escherichia coli* (now known as STEC)
UK	United Kingdom
WHO	World Health Organisation

Executive Summary

Background

Foodborne disease presents a continuous threat to public health, with a significant economic impact on communities in the UK and worldwide. Estimating the true incidence of foodborne infectious intestinal disease (IID) has proven challenging. Established surveillance systems are vulnerable to under-diagnosis of infections causing mild illness, as cases may not present to healthcare. Under-reporting of infections occur when specimens are not submitted for testing, or test results are not reported. In terms of trade and global health, it is important to understand and compare incidence of foodborne IID in different countries.

Several countries have conducted population-based studies to better estimate the true burden of foodborne IID within the community. Methodologies have been developed and adapted that attempt to estimate pathogen-specific incidence of foodborne IID within countries, using data from multiple sources. The aim of this study was to conduct a systematic review and, where appropriate, meta-analyses to compare the methodologies and estimates of foodborne IID in different countries, and to assess whether these estimates could be compared with the UK.

Methods

Literature searches were performed in three databases (Ovid Medline, Scopus and Web of Science) and grey literature, spanning the years 1990 to 2018. For study eligibility, the indicator was the burden and estimation of foodborne IID in each country, and the outcome was the incidence and prevalence of IID measured using population level surveys. The studies were reviewed independently by two reviewers to ensure that they conformed to the inclusion and exclusion criteria. Data were extracted and grouped into three subgroups based on study design (cross-sectional, cohort and surveillance pyramid). Meta-analyses was conducted on cross-sectional and surveillance pyramid studies.

Results

In total, 33 studies met the eligibility criteria and were included in this review; 19 were retrospective, cross-sectional surveys, six cohort studies, five surveillance pyramid studies and three studies could not be grouped into the three categories. All selected articles were published between 1994 and 2017.

Most of the studies (52%) included had conducted cross-sectional surveys and were undertaken in 14 different countries (UK, Germany, Poland, Denmark, Italy, Sweden, Ireland, Australia, Norway, Canada, France, New Zealand, US and The Netherlands). These studies involved self-reported symptoms, where a representative sample of the population were contacted and asked about their

symptoms in the recent past. Case definitions were often based on syndromic symptoms, such as diarrhoea and vomiting, therefore providing an overall estimate unassigned to a specific pathogen. All 19 cross-sectional surveys were included in a meta-analysis. The pooled rate of IID was estimated at 0.88 episodes per person year (CI 95% 0.72-1.05), with considerable heterogeneity (I^2 98.7%, p<0.001).

Prospective cohort studies involved a methodology where a sample population is recruited and study participants are required to report on a weekly basis on whether they had experienced symptoms of diarrhoea and vomiting. In most cases (5/6 studies) those reporting symptoms submit stool samples for microbiological examination. However, a major drawback is that participation rates can be low and losses to follow up may be high, in addition these studies are complex and expensive to conduct.

The surveillance pyramid model estimates the number of cases, hospitalisations and deaths due to foodborne pathogens. This approach involves estimating the number of cases missed through underdiagnosis and underreporting. Multipliers are used to extrapolate from laboratory confirmed illnesses to estimate the overall number of cases in the community.

Five studies were identified that used a surveillance pyramid methodology, accounting for the under-ascertainment of infections captured by surveillance systems. All five studies provided an overall estimated number of domestically acquired foodborne illnesses by population and by pathogen. Norovirus accounted for the highest proportion of foodborne IID in the US, Australia, Canada and New Zealand. *Campylobacter* spp. accounted for the highest proportion of bacterial foodborne IID in Australia, New Zealand and the UK. The pooled estimate was highest for *Campylobacter* spp. at 5.93 infections per 1000-person year (1^2 66.0%, p value 0.019).

Conclusion

A variety of study designs been used to summarise the incidence of foodborne IID in different countries. This systematic review describes the methodologies used to estimate the true burden of foodborne IID. Our meta-analyses attempt to compare overall and pathogen-specific estimates between countries. However, we have presented several limitations within study designs that currently create challenges in accomplishing accurate and meaningful comparisons between countries.

Comparisons between countries using the cross-sectional study design can be difficult due to differences in cases definitions, study designs, recall periods and study populations. The high heterogeneity (I^2 98.7%, p<0.001) suggests that differences between studies exist that cannot be explained by chance alone.

Prospective cohort studies were the most accurate way of estimating the burden of illness as specimens from symptomatic individuals can be tested to enable pathogen

specific estimates to be calculated. The IID1 and IID2 studies in the UK were the only prospective cohort studies using the same methodology repeated at different points in time in the same country. They were the only two studies where the pathogen specific estimates could be compared over time. Data for the surveillance pyramid method relies on the quality and representativeness of the surveillance system within the country to calculate the overall burden of foodborne IID. The parameters used to reconstruct the pyramid should be fully considered as incidence rates vary between countries.

1. Introduction

Gastrointestinal (GI) infections, caused by organisms such as bacteria, viruses or protozoa [1], are common; leading to diarrhoea and vomiting as well as other more serious health problems, such as haemolytic uraemic syndrome (HUS) [2], Guillain-Barré syndrome [3] irritable bowel syndrome [3, 4] and reactive arthritis [5], and can result in interference with normal day-to-day activities. Published estimates suggest that around one in four people in the UK suffers an episode of infectious intestinal disease (IID) per year and foodborne disease (which is the proportion of IID attributable to food) in England and Wales results in costs of around £9.1 billion per year to the NHS, the economy and individuals [6, 7].

Many cases of foodborne disease go undetected or unreported, as not everyone who is ill will seek medical attention (under diagnosed), and even when they do not everyone will have a sample taken for analysis. Even at the healthcare level, cases will be missed with failure to report symptomatic cases that have sought medical advice (under reporting). In the UK, it is estimated that for every one case of IID that is reported to national surveillance, there are 147 cases in the community [6]. Several countries produce estimates of cases to adjust for this underreporting. The methodology used to estimate foodborne disease varies across different countries, in part due to differences in health care and surveillance systems, which means the data available on which to produce estimates are not always consistent.

The aim of this review is to compare the different methods used by countries to produce estimates of foodborne disease and to assess whether the different estimates are the result of methodological approaches.

The objectives are to:

1) Ascertain whether reported differences in foodborne disease rates are genuine or artefacts of different estimation methodologies.

2) Explore whether the methods used to estimate foodborne diseases in the UK could be improved by learning from estimation approaches used by other countries.

2. Methods

2.1 Review and scope

To answer these questions, we conducted a systematic review and meta-analysis to report and compare the estimates of foodborne IID caused by gastrointestinal pathogens. The review was carried out between January and July 2019, guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8] .

2.2 Study eligibility

Studies were eligible for inclusion based on the review PIO question (Population, Indicator, Outcome). The following definition of foodborne IID was used for eligibility purposes: “An episode of gastrointestinal illness/systemic infection, resulting from the ingestion of contaminated food or drinking water.”

The indicator was the burden and estimation of foodborne IID in each country. The outcome of interest was the incidence and prevalence of IID measured using population level surveys and reporting of the methodology used to measure IID at a population level.

2.3 Search strategy and selection criteria

Electronic searching of three databases was performed: Medline, Web of Science and Scopus. (Appendix 1). Multiple databases were searched to ensure relevant articles were not missed, as different databases index articles from different journals, and articles may also be indexed differently within those databases. The results were restricted to publications that collected data after 1990 to ensure results were as relevant as possible to present day, as food consumption and populations change over time. The review is restricted to studies using incidence or prevalence as a burden of disease measure.

The lists of studies from the database searches were reviewed for inclusion to identify relevant articles that were not captured via electronic searching. Finally, grey literature was searched by entering the terms “gastrointestinal infection”, “gastroenteritis”, “burden of foodborne disease”, “estimating foodborne disease” into Google search engine and Google Scholar search application. The first 100 results from each search were screened for inclusion.

Citations were collected and managed and de duplicated in Endnote and screened in Rayyan. The papers were screened by two reviewers (BV and AS) to ensure consistency in the application of the inclusion and exclusion criteria. Discrepancies were discussed and resolved through a consensus process. Once the search results were obtained, the selection of studies for inclusion was made using a two-stage process. This process was applied throughout the screening process.

During the first stage, search results were screened based on title and abstract based on all the pathogens included in the search terms. In the second stage, the remaining studies were screened again to include studies that focused on specific pathogens, due to the large amount of studies resulting after the title and abstract screen (n=483). The following pathogens were included; non-typhoidal *Salmonella*, *Campylobacter* spp*.,* Shiga toxin-producing *Escherichia coli* (STEC), *Giardia* spp*., Listeria monocytogenes, Cryptosporidium* spp., *Clostridium perfringens* and norovirus. These pathogens were listed because they represent the main gastrointestinal pathogens known to cause the greatest burden of foodborne IID in the UK[6, 9]. In addition, studies were restricted to developed countries because foodborne disease data are largely missing in developing countries and outbreaks often go underreported [10]. To systematically apply this, countries that are members of the Organisation for Economic Cooperation and Development (OECD) were included. Full details of the inclusion and exclusion criteria are reported in Table 1. Once the two-stage process was complete, a full text review was performed independently by the two reviewers.

Table 1: Inclusion and exclusion criteria

Category	Inclusion	Exclusion
Study design	• Observational studies (cohort; case-control; cross-sectional; ecological) • Studies providing estimated incidence or prevalence of any IID	• Intervention/experimental studies (randomised controlled trials) • Outbreak reports • Surveillance reports • Review studies • Case reports
Study population	• Human subjects • Representative sample of the total country population • Studies from countries that are members of the Organisation for Economic Cooperation and Development (OECD), reporting data after 1990	• Non-human subjects • Unrepresentative population sample (studies focusing on a sub population i.e. elderly, children, specific ethnic group, healthcare setting) • Studies analysing travel-related cases only
Language	• Studies written in or translated to English language	• Non-English language papers
Study period	• Studies reporting on data collected between January 1990 and December 2018	• Studies reporting on data collected before January 1990
Disease	• *Campylobacter* spp. • *Clostridium perfringens* • *Cryptosporidium* spp. • *Giardia* spp.	• All other pathogens • Non-pathogenic causes of intestinal disease

Category	Inclusion	Exclusion
	• *Listeria monocytogenes* • Norovirus/Norwalk-like virus • *Salmonella* spp. (excluding serotypes Typhi and Paratyphi) • Shiga toxin/Verocytotoxin-producing *Escherichia coli*	

2.4 Data processing

Studies were categorised into three subgroups based on study design (cross-sectional, cohort and surveillance pyramid studies), described in Section 5. Data were extracted and populated into a standardised template (Appendix 2, 3 and 4) in Microsoft Excel by two reviewers (BV and AS). The template, accounting for the three different study designs, included captured information on study populations, estimation methodologies, and outcomes (incidence/prevalence of disease).

Study estimates were first converted to a common scale so that estimates could be compared, and pooled; for instance, converting rates per person year to per 1000 years or vice versa, by multiplying rates/confidence intervals/standard errors as required.

Where confidence intervals (CIs) were not reported, an appropriate level of uncertainty was calculated on the basis of the original binomial data (retrospective studies) or appropriate Poisson distribution of cases (prospective studies). The resulting 95% CI was rescaled to match the given rate if only the CI was missing: for instance, with a binomial proportion $p=r/n$ obtained from a given number of cases r and denominator n, the ratio of the reported result, p_{rep} to the raw proportion, p_{rep}/p was used to rescale the calculated CIs. In the majority of cases this was a minor adjustment, likely due to factors such as applying sample weights to produce the reported estimates, differences in numbers sampled with the sample used in the analysis (due to incomplete data/non-response) and other factors.

If a central estimate was also not provided, then both this and the CI were calculated on the basis of the given binomial data. In either case, results obtained from raw data were scaled to produce a rate/proportion on the correct scale. For instance, retrospective studies consist of binomial data for the proportion with GI in the last 28 days; the estimate and CI were then rescaled to an annual rate via $p*(365.25/28)$, where p is the proportion with GI in the last 28 days.

For studies that scaled up laboratory cases to produce overall burden (*adjusted cases studies*), the given rates and CI were converted to a common scale (incidence per 1000 person years). In the case that CIs were missing, the procedure followed that above but with an additional step to incorporate the uncertainty of the scaling process. This depends on the combination of various distributions incorporating uncertainty at each step (proportion foodborne, proportion reported to laboratory etc.) that would be difficult to derive directly. Therefore, this quantity was estimated based on the following principle.

The total variance of the log estimated rates from “adjusted case” studies is given by:

$$V = V_s + V_m$$

where V_s is the variance due to statistical uncertainty of the observed number of cases and V_m is the uncertainty attributable to the scaling method employed. For studies with reported rates and CIs, the overall variance was obtained from the log of

the given CIs and the statistical uncertainty calculated from the number of observed cases, assuming these have a Poisson distribution. The difference between these was then obtained to provide an estimate of V_m, which was averaged across studies for each pathogen.

For adjusted cases studies that did not report CIs, we calculated the statistical uncertainty V_s from the data and added the estimated V_m to produce the overall variance V, and hence obtain appropriate (if approximate) CIs for these studies. Again, these calculations assume a Poisson distribution for numbers of cases, with the underlying variances assumed additive on the log scale, prior to converting back to estimates and confidence intervals. Although these methods are approximations, failing to account for the likely uncertainty of the scaling process otherwise would have severely underestimated the uncertainty of these studies.

As most adjusted cases aimed to produce national estimates of burden, the resulting estimates of total GI cases were scaled by the relevant country population size to produce rates per 1000 person years.

2.5 Meta-analysis

Having derived estimates and confidence intervals for each study (where required) and converted to a common scale, the estimates were then pooled using fixed and random effects meta-analysis. The fixed effect model assumes that each study estimates the same quantity and differences between study estimates is solely attributable to sampling variation. The pooled estimate is a weighted average of the study estimates, with each weighted according to the inverse of its variance.

The random effects (DerSimonian and Laird) model assumes that rather than the quantity of interest being fixed, it has a distribution, and each study estimate is a realisation of this distribution. In other words, studies estimate something similar, but not identical. Studies are thus weighted by the inverse of the study variance plus the variance of the random effect (the variance of the quantity being estimated), i.e:

$$w_i = \frac{1}{v_i + \tau^2}$$

Where v_i is the within-study variance and τ^2 the random effects variance. This tends to weight studies more evenly, especially when the random effects variance τ^2 is comparatively high. This approach also produces a *p*-value for heterogeneity; i.e., a statistical test for whether the quantity being estimated is fixed, or studies are estimating a distribution of effects. Heterogeneity may also be quantified by the proportion of the total variance of the pooled estimate that is attributable to between-study variance (the other source of variance being the sampling variability of the studies). This is expressed as a percentage, referred to as I^2, with zero corresponding to no detectable heterogeneity, values of 30-60% being moderate heterogeneity, and above 70-80% being “high” – although there are no fixed rules on this. However, where I^2 reaches 90% or more it becomes questionable as to whether

the quantities being estimated by each study can still be considered in any way “similar” and produced by the same underlying process.

All data processing (post-extraction) was conducted using Stata 15.1. Meta-analysis was carried out using **metan** command, with subgroup estimates produced as required. The results were visualised as forest plots, showing the estimates and confidence intervals for each study and the pooled estimates represented by diamonds. The resulting plots include fixed and random effects estimates, *p*-values for heterogeneity and I^2. Effect estimates and inverse-variance study weights are shown on the plot, with boxes indicating the relative weight of each study.

3. Results

3.1 General characteristics of the selected studies

Figure 1 shows the flow diagram of the search of existing studies measuring the burden of foodborne disease studies and the main reasons for exclusion. Thirty-three studies met the eligibility criteria and were included in the review. Table 2 shows the 33 studies that have been included for the review. Of the 33 studies; 19 were retrospective, cross-sectional surveys, 6 cohort studies, 5 surveillance pyramid studies and three studies could not be grouped into the three categories. All selected articles were published between 1994 and 2017.

Figure 1: Flow diagram of assessment of studies included in the systematic review and meta-analysis

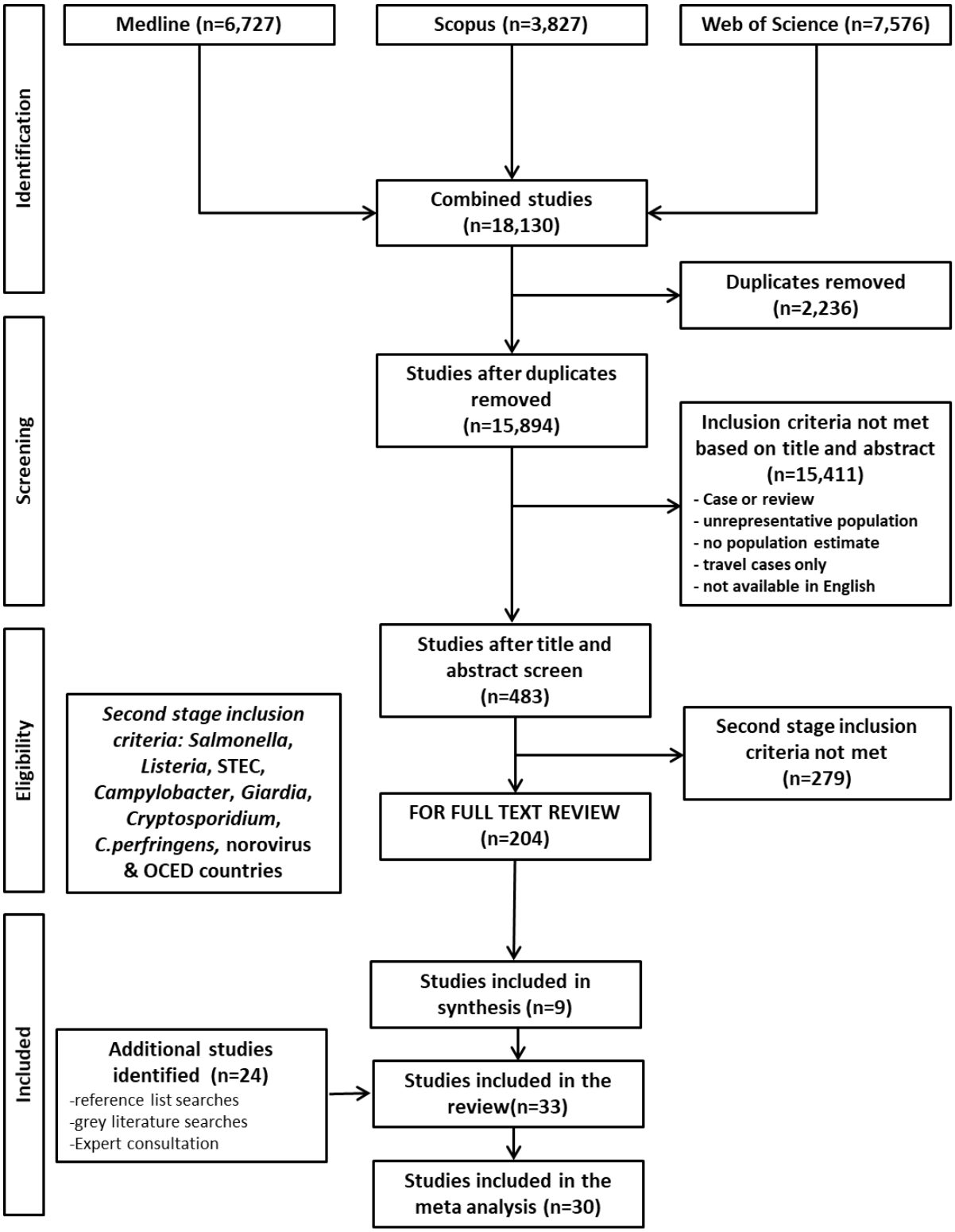


Table 2: List of included studies

Author (reference)	Year	Title	Country	Type of study
Adak et al. [1]	2002	Trends in indigenous foodborne disease and deaths, England and Wales: 1992 to 2000	UK	Surveillance pyramid approach
Adlam et al.[11]	2009	Acute gastrointestinal illness in New Zealand: a community study	New Zealand	Retrospective Telephone survey
Baumann-Popczyk et al.[12]	2012	Incidence of self-reported acute gastrointestinal infections in the community in Poland	Poland	Retrospective Telephone survey
Cressey et al. [13]	2012	Estimated incidence of foodborne illness in New Zealand: Application of overseas models and multipliers.	New Zealand	Surveillance pyramid approach
De Wit et al. [14]	2001	Sensor, a population based cohort study on gastroenteritis in The Netherlands, incidence and etiology	The Netherlands	Cohort study

Author (reference)	Year	Title	Country	Type of study
De Wit et al. [15]	2001	Gastroenteritis in Sentinel General Practice, the Netherlands	The Netherlands	Cohort study
Doorduyn et al. [16]	2012	The burden of infectious intestinal disease (IID) in the community: a survey of self-reported IID in The Netherlands	The Netherlands	Retrospective Paper/internet survey
Edelstein et al.[17]	2016	Quantifying the incidence and cost of acute gastrointestinal illness in Sweden, 2013–2014	Sweden	Cohort study
Feldman et al. [18]	1994	The frequency of culturing stools from adults with diarrhoea in Great Britain	UK	Retrospective Face to face survey
Hall et al. [19]	2005	Estimating Foodborne gastroenteritis, Australia	Australia	Retrospective Telephone survey
Hansdotter et al[20]	2015	The incidence of acute gastrointestinal illness in Sweden.	Sweden	Retrospective Paper/internet survey
Havelaar et al. [21]	2012	Disease burden of foodborne pathogens in the Netherlands, 2009	The Netherlands	Other

Author (reference)	Year	Title	Country	Type of study
Herikstad et al. [22]	2002	A population-based estimate of the substantial burden of diarrhoeal disease in the United States; FoodNet, 1996–7.	US	Retrospective Telephone survey
Hoogenboom-Verdegaal et al. [23]	1994	Community based study of the incidence of gastrointestinal diseases in The Netherlands.	The Netherlands	Cohort study
Imhoff et al.	2004	Burden of self-reported acute diarrheal illness in FoodNet surveillance areas, 1998-1999	US	Retrospective Telephone survey
Jones et al. [24]	2007	A population-based estimate of the substantial burden of diarrhoeal disease in the United States; Food Net, 1996–2003.	US	Retrospective Telephone survey
Kirk et al. [25]	2014	Foodborne illness, Australia, circa 2000 and circa 2010	Australia	Surveillance pyramid approach
Kumagi et al. [26]	2014	Estimating the burden of foodborne diseases in Japan.	Japan	Other

Author (reference)	Year	Title	Country	Type of study
Kuusi et al.[27]	2003	Incidence of gastroenteritis in Norway-a population based survey	Norway	Retrospective Telephone survey
Majowicz et al.[28]	2004	Magnitude and distribution of acute, self-reported gastrointestinal illness in a Canadian community	Canada	Retrospective Telephone survey
Muller et al.[29]	2012	Burden of acute gastrointestinal illness in Denmark 2009: a population based telephone survey	Denmark	Retrospective Telephone survey
O'Brien et al.[9]	2016	Modelling study to estimate the health burden of foodborne disease: cases, general practice consultations and hospitalisations in the UK, 2009	UK	Other
Scallan et al. [30]	2011	Foodborne illness acquired in the United States, Major Pathogens	US	Surveillance pyramid approach
Scallan et al. [31]	2004	Acute gastroenteritis in Northern Ireland and the	Ireland	Retrospective Telephone survey

Author (reference)	Year	Title	Country	Type of study
		Republic of Ireland: a telephone survey.		
Scavia et al.[32]	2012	The burden of self-reported acute gastrointestinal illness in Italy: a retrospective survey, 2008-2009	Italy	Retrospective Telephone survey
Tam et al. [33]	2012	Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice.	UK	Cohort study
Thomas et al. [34]	2013	Estimates of the burden of foodborne illness in Canada for 30 specified pathogens and unspecified agents, circa 2006.	Canada	Surveillance pyramid approach
Thomas et al.[35]	2006	Population distribution and burden of acute gastrointestinal illness	Canada	Retrospective Telephone survey
Thomas et al.[36]	2017	The Incidence of Acute Gastrointestinal Illness in Canada, Foodbook Survey 2014-2015	Canada	Retrospective Telephone survey

Author (reference)	Year	Title	Country	Type of study
Van Cauteren et al.[37]	2012	Burden of acute gastroenteritis and healthcare seeking behaviour in France: a population based study	France	Retrospective Telephone survey
Vivani et al[38]	2016	Estimating the incidence of acute infectious intestinal disease in the community in the UK: a retrospective survey	UK	Retrospective Telephone survey
Wheeler et al. [39]	1999	Study of infectious intestinal disease in England: rates in the community presenting to general practice, and reported to national surveillance	UK	Cohort study
Wilking et al[40]	2013	Acute gastrointestinal illness in adults in Germany: a population based telephone survey	Germany	Retrospective Telephone survey

3.2 Cross-sectional retrospective surveys

We identified 19 retrospective cross-sectional, population surveys conducted in 14 different countries (Table 3). These are surveys of self-reported IID, where a representative sample of the population are contacted and asked about their symptoms in the recent past. The case definitions for these studies are based on syndromic symptoms such as diarrhoea and vomiting, therefore only provide overall, rather than pathogen specific, IID estimates. These population level based surveys were conducted in the UK, Germany, Poland, Denmark, Italy, Sweden, Ireland, Australia, Norway, Canada, France, New Zealand, US and The Netherlands. Surveys were conducted between 1994 to 2017. Almost all studies conducted their surveys over approximately a 12-month study period apart from; Hansdotter *et al,* (Sweden, 1 month) Feldman *at al.* (UK, 4 months) and Vivani *et al* (UK, 18 months). Fifteen of the studies contacted their study participants via telephone, three studies administered paper/internet surveys and one study conducted face to face interviews. Incidence rates from these studies ranged from 0.31 episodes per person-year (Handsdotter *et al*. -Sweden) to 1.40 episodes per person-year (Muller *et al*. and Herikstad *et al*).

Case definitions varied between studies (Table 3). Eight of 19 studies used the case definition proposed by Majowicz *et al* at the third Annual Meeting of the International Collaboration on Enteric Disease 'Burden of Illness' Studies: a case of IID is defined as a person with ≥ 3 loose stools, or any vomiting, in 24 hours, in the four weeks prior to completion of the questionnaire, but excluding those with cancer of the bowel, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibrosis, coeliac disease or another chronic illness with symptoms of diarrhoea or vomiting and those who report their symptoms were due to drugs, alcohol or pregnancy [41]. The incidence rate for the studies using this case definition ranged from 0.33 episodes per person-year (France) to 1.40 episodes per person-year (Denmark). Wilking *et al.* deviated from the case definition to make it more specific by adding three episodes of vomiting in one day. Despite the more specific definition, Germany's IID rate (of 0.95) was comparable to that of The Netherlands (0.96 episodes per person year) and Poland (0.90 episodes per person year). France reported the lowest IID rate amongst the studies using the 'Burden of Illness' definition. The authors hypothesised the low incidence could be down to the more restrictive exclusion criteria as the number of non-cases (46%) was higher compared to studies; proportion of non-cases ranged from 16-37%. The exclusion criteria for the French study was the same as the other studies using the international case definition with the exception of the addition of overeating and menstruation.

The New Zealand study used three different case definitions, one of which was the international case definition. However, 16.5% of their cases were unable to provide information on the number of loose stools in a 24-hour period. The weighted estimate excluding the cases that were unable to provide information on the number

of stools was 4.2% (95% CI 3.5-5.0) and the weighted estimate including the cases was 5.6% (95% CI 4.8-6.5). In contrast, the two Canadian studies [28, 35] used a broad case definition and did not exclude individuals who reported other causes of vomiting and diarrhoea due to causes such as excess alcohol. Vivani *et al*. (UK) used a more sensitive case definition by not specifically defining 'diarrhoea' – the only study not to do so, which meant the definition of diarrhoea was open to interpretation by the study participant [38].

All but three studies used only a 28-day recall period; the UK also used a 7-day recall period, Italy used a 30-day recall period and Sweden used a 365-day recall period. Vivani *et al*. estimated the rate for two different recall periods with the 7-day (1.53 episodes per person year) recall three times higher than the 28-day (0.53 episodes per person year) recall group. The authors hypothesised that one of the reasons could be down to respondents forgetting their illness with time, this was supported by the observation that more respondents reported visiting a GP in the 28-day recall group compared to the 7-day recall group [38]. This observation suggests that people were better at remembering an illness that happened a couple of weeks (prior to their interview) if it was severe and in particular required medical attention. Another possible reason could be that participants in the 7-day recall group were at home recovering therefore inflating the estimate [33].

Hansdotter *et al*. used the longest recall period at 365 days. A longer recall period could result in underestimation of IID as participants may forget the episodes of IID that have occurred earlier in the year. This is reflected in the rate for Sweden, reporting the lowest rate of IID at 0.31 episodes per person year. The authors stated this recall period was used to align with the recall period used in other studies conducted in Sweden. The Swedish study was also one of two studies to have a short survey period, the survey was conducted in a month. Feldman *et al.* was the other relatively short study, conducting over a 4-month period. All other studies were conducted within or over a year.

From 1996 to 2003, the United States Foodborne Disease Active Surveillance Network (FoodNet) conducted four 12 month cycles of populations based telephone surveys to determine the prevalence of self-reported diarrhoeal illness. Herikstad *et al*. (cycle one) and Imhoff *et al.* (cycle two) are two of the studies that are part of the four survey cycles analysed by Jones *et al.* with two other unpublished population based surveys performed during 2000-2003. The methods of the four surveys were consistent with both the same case definition (Table 3) and recall periods in each survey. Overall, rates of IID remained stable over the four cycles.

Nineteen studies were included in the meta-analysis (Figure 2). The pooled rate of IID estimated by cross-sectional studies was 0.88 episode per person year (CI 95% 0.72-1.05), with considerable heterogeneity (I^2 98.7%, $p<0.001$). Wilking *et al* contributed the most weight (18.3%) to the meta-analysis.

Table 3: Cross-sectional retrospective studies providing estimates of the rate of IID

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
Adlam *et al.*	New Zealand	Feb 2006-Jan 2007	Telephone	*Household*-Random digit dialling of fixed landlines *Individual*-Last birthday method	Any diarrhoea, vomiting or both experienced in the previous 4 weeks.	Non-infectious causes such as chronic illness, medication, medical treatment and pregnancy	28 day	1.11 (1.00-1.23)
Baumann-Popczyk *et al.*	Poland	Dec 2008 -Nov 2009	Telephone	*Household*-Random digit dialling of fixed landlines *Individual*-Next birthday method	Case definition based on 'Burden of Illness' studies. Three or more loose stools, or any vomiting for a period of 24 house during the 4 weeks prior to interview.	Bowel cancer, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibrosis, celiac disease, or other chronic illness with symptoms of	28 day	0.90 (0.80-1.00)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
						diarrhoea or vomiting, in addition to any symptoms that were related to pregnancy and drug or alcohol abuse.		
Doorduyn *et al.*	The Netherlands	Feb 2009-Feb 2010	Questionnaire by post	Selected at random from a population registry	Case definition based on 'Burden of Illness' studies. Three or more loose stools, or any vomiting for a period of 24 hours during the 4 weeks prior to interview.	Cancer of the bowel, irritable bowel syndrome, Crohn's disease, ulcerative colitis, celiac disease or another chronic illness with symptoms of diarrhoea or vomiting or report their	28 day	0.96 (0.81-1.11)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
						symptoms were due to drugs, alcohol, or pregnancy.		
Feldman *et al.*	UK	Oct 1992-Jan 1993	Face to face interviews	Randomly selected private households	Three or more loose stools in a 24-hour period	-	28 day	0.95 (0.88-1.02)
Hall *et al*.	Australia	Sep 2001-Aug 2002	Telephone	*Household*-Random digit dialling of fixed landlines *Individual*-Next birthday method	A case was defined as three or more stools or two or more episodes of vomiting or if respiratory symptoms were present, four or more loose stools or three or more episodes of vomiting in a 24-hour period.	Non-infectious cause for diarrhoea or vomiting	28 day	0.92 (0.77-1.06)
Hansdotter *et al.*	Sweden	May 2009	Questionnaire by post	Selected at random from	A case was defined as a	Six months of participant who	365 day	0.31 (0.28-0.34)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
				a population registry	person with three or more loose stools or at least three of the following symptoms: vomiting; stomach cramps; nausea; fever.	reported stomach, intestine or belly surgery; recurrent problems with diarrhoea or chronic gastrointestinal disease such as Crohn's disease, 10 days of the participant having been abroad.		
Herikstad *et al.*	US	Jul 1996-Jun 1997	Telephone	FoodNet sites Random digit dialling	Three or more loose stools or bowel movements in any 24-hour period.	Persons with chronic illness in which diarrhoea was a major symptom e.g. colitis, irritable bowel	28 day	1.35 (1.22-1.42)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
						syndrome, or who had surgery to remove part of their stomach or intestine		
Imhoff *et al.*	US	Jul 1998-Jun 1999	Telephone	FoodNet sites Random digit dialling	Three or more loose stools or bowel movements in any 24-hour period.	Persons with chronic diarrhoea or had part of their stomach surgically removed, reported vomiting with no diarrhoea, persons with a chronic diarrheal illness e.g. Crohn's disease or irritable bowel syndrome).	28 day	1.3 (1.22-1.36)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
Jones et al.	US	1996-2003	Telephone	FoodNet sites Random digit dialling	Three or more loose stools or bowel movements in any 24-hour period.	Persons with chronic illness in which diarrhoea was a major symptom e.g. colitis, irritable bowel syndrome, or who had surgery to remove part of their stomach or intestine	28 day	0.67 (0.63-0.70)
Kussi *et al.*	Norway	Jun 1999-Jun 2000	Questionnaire by post	Selected at random from a population registry	A case was defined as a person with three or more loose stools, or any vomiting for a period of 24, or at least of the following symptoms:	Chronic diarrhoeal illness	28 day	1.2 (1.07-1.34)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
					vomiting, nausea, abdominal cramps or fever 38c.			
Majowicz *et al.*	Canada	Feb 2001-Feb 2002	Telephone	Household-Randomly selected telephone numbers Individual-Next birthday method	Any vomiting or diarrhoea in the 28 days prior to the interview. defined as loose stool or stool with abnormal liquidity	Crohn's disease, irritable bowel syndrome, lactose intolerance and pregnancy	28 day	1.30 (1.10-1.40)
Muller *et al.*	Denmark	Jan-Dec 2009	Telephone	Selected at random from a population registry	Case definition based on 'Burden of Illness' studies. Three or more loose stools, or any vomiting for a period of 24 house during the 4 weeks prior to interview.	Bowel cancer, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibrosis, celiac disease, or other chronic	28 day	1.4 (1.2-1.6)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
						illness with symptoms of diarrhoea or vomiting, in addition to any symptoms that were related to pregnancy and drug or alcohol abuse.		
Scallan *et al.*	Ireland	Dec 2000-Nov 2001	Telephone	Household-Random digit dialling of fixed landlines Individual-Next birthday method	A case was defined as diarrhoea three or more times in a 24-hour period, or bloody diarrhoea, or vomiting together with at least one other symptom (diarrhoea, abdominal	Non-infectious causes of diarrhoea or vomiting such as Crohn's disease, ulcerative colitis, excess alcohol, pregnancy, menstruation or medication	28 day	0.60 (0.55-0.66)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
					pain/cramps, fever)	known to cause vomiting		
Scavia *et al.*	Italy	Jul 2008-Jun 2009	Telephone	Household-Landlines randomly chosen from a registry Individual-Next birthday method	Case definition based on 'Burden of Illness' studies. Three or more loose stools, or any vomiting for a period of 24 house during the 4 weeks prior to interview.	Bowel cancer, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibrosis, celiac disease, or other chronic illness with symptoms of diarrhoea or vomiting, in addition to any symptoms that were related to pregnancy and drug or alcohol abuse.	30 day	1.08 (0.90-1.14)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
Thomas *et al.*	Canada	Jun 2002-Jun 2003	Telephone	Household-Randomly selected telephone numbers Individual-Next birthday method	Any diarrhoea or vomiting, where diarrhoea was defined as any loose stool or stool with abnormal liquidity	Pregnancy, medication use, food allergy and/or medical condition previously diagnosed by a doctor (e.g. colitis, diverticulitis, Crohn's disease, irritable bowel syndrome)	28 day	1.3 (1.10-1.40)
Thomas *et al.*	Canada	Apr 2014-Apr 2015	Telephone	Household-Randomly selected telephone numbers (70% listed, 10% random digit dialling) and cell	Case definition based on 'Burden of Illness' studies. Three or more loose stools, or any vomiting for a period of 24 house during the 4 weeks prior to interview.	Diarrhoea or vomiting due to pregnancy, medical treatment (e.g. chemotherapy), or medical conditions (e.g. Crohn's	28 day	0.57 (0.41-0.78)

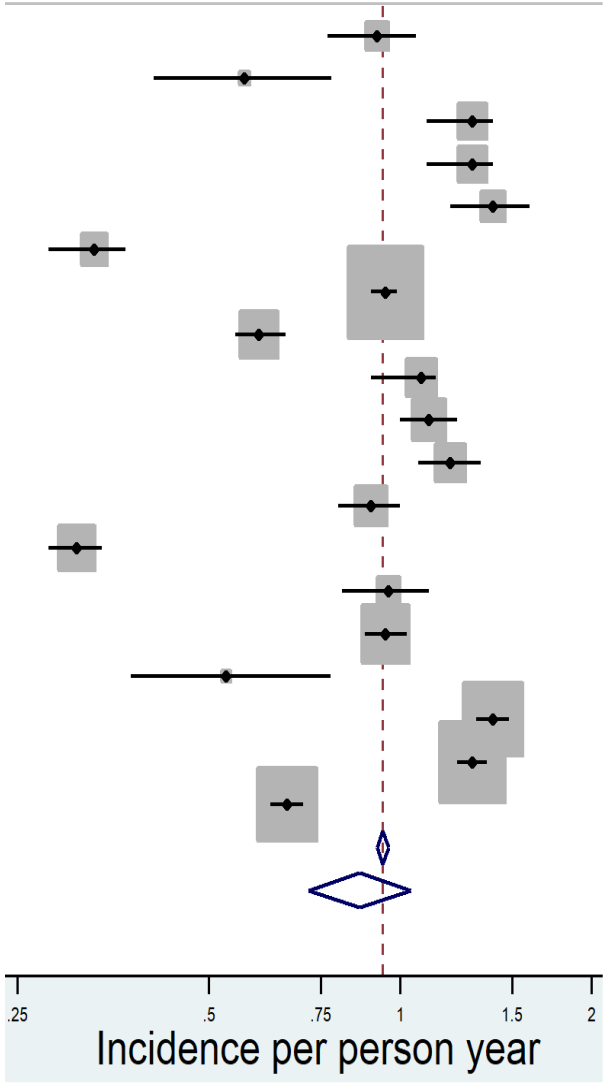
Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
				phones (20%) Individual- 50% next birthday (children), 50% last birthday (adult)		disease, colitis, irritable bowel syndrome, and alcoholism.		
Van Cauteren *et al.*	France	May 2009-Apr 2010	Telephone	Household- Randomly selected telephone numbers Individual- Next birthday method	Case definition based on 'Burden of Illness' studies. Three or more loose stools, or any vomiting for a period of 24 house during the 4 weeks prior to interview.	Non-infectious causes such as chronic gastrointestinal disorders overeating, excess alcohol consumption, pregnancy, menstruation or medication.	28 day	0.33 (0.28-0.37)
Vivani *et al.*	UK	Feb 2008-Aug 2009	Telephone	Household- Random	Loose stools or clinically significant	Non-infectious causes of	7 day 28 day	0.53 (0.38-0.78)

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
				digit dialling of fixed landlines Individual - randomly selected participants	vomiting lasting less than 2 weeks, in the absence of a known infectious cause.	diarrhoea or vomiting, including Crohn's disease, ulcerative colitis, cystic fibrosis, coeliac disease, surgical obstruction, excess alcohol, morning sickness and regurgitation in infants. Excluded individuals who reported travel outside of the UK 10 days prior to onset		

Author	Country	Study period	Participant contact	Sampling method	Case definition	Exclusion criteria	Recall period	Incidence (episodes per person year (CI 95%)
Wilking *et al.*	Germany	Jul 2008-Jun 2009	Telephone	Household - Random digit dialling of fixed landlines Individual- most recent birthday method	Case definition based on 'Burden of Illness' studies. Diarrhoea was defined as three or more 3 loose stools in a 24h period. Vomiting was defined as having at least 3 episodes on one day.	Chronis gastrointestinal disease such as Crohn's disease, ulcerative colitis, stomach cancer and intestinal tumours, irritable bowel or coeliac disease.	28 day	0.95 (0.90-0.99)

Figure 2: Meta-analysis of cross sectional retrospective studies

Country	Paper ID	Author	Year	Study period	Rate	LCI	UCI	Weight
Australia	8	Hall et al	2005	Sep 2001 -Aug 2002	0.92	0.77	1.06	1.6%
Canada	12	Thomas et al	2017	Apr 2014-Apr 2015	0.57	0.41	0.78	0.4%
Canada (British Columbia)	11	Thomas et al	2006	Jun 2002-Jun 2003	1.30	1.10	1.40	2.9%
Canada (Ontario)	10	Majowicz et al	2004	Feb 2001-Feb 2002	1.30	1.10	1.40	2.9%
Denmark	4	Muller et al	2012	Jan-Dec 2009	1.40	1.20	1.60	2.0%
France	13	Van Cauteren et al	2012	May 2009-Apr 2010	0.33	0.28	0.37	2.1%
Germany	2	Wilking et al	2013	Jul 2008-Jun 2009	0.95	0.90	0.99	18.3%
Ireland	7	Scallan et al	2004	Dec 2000-Nov 2001	0.60	0.55	0.66	5.0%
Italy	5	Scavia et al	2012	Jul 2008-Jun 2009	1.08	0.90	1.14	3.0%
New Zealand	14	Adlam et al	2011	Feb 2006 - Jan 2007	1.11	1.00	1.23	3.9%
Norway	9	Kussi et al	2003	Jun 1999-Jun 2000	1.20	1.07	1.34	3.2%
Poland	3	Baumann-Popczyk et al	2012	Dec 2008-Nov 2009	0.90	0.80	1.00	3.3%
Sweden	6	Handsdotter et al	2015	May-09	0.31	0.28	0.34	4.4%
The Netherlands	19	Doorduyn et al	2012	Feb 2009-Feb 2010	0.96	0.81	1.11	1.7%
UK	17	Feldman et al	1994	Oct 1992-Jan 1993	0.95	0.88	1.02	7.2%
UK	1	Vivani et al	2016	Feb 2008-Aug 2009	0.53	0.38	0.78	0.3%
US	15	Herkistad et al	2002	Jul 1996 -Jun 1997	1.40	1.32	1.49	11.7%
US	16	Imhoff et al	2007	Jul 1998-Jun 1999	1.30	1.23	1.37	14.1%
US	20	Jones et al	2007	1996-2003	0.67	0.63	0.70	12.0%
				I-V overall (I-squared = 98.7%, p<0.001)	**0.94**	**0.92**	**0.96**	**100.0%**
				D+L overall	**0.86**	**0.72**	**1.04**	



I-V weight = inverse variance weight, diamond = pooled estimate; I-V=fixed effect, D+L= DerSimonian and Laird random effects estimate. P-values are given to 3 decimal places.

3.3 Prospective cohort studies

There were six studies that used a prospective cohort design conducted in three countries; UK, Sweden and The Netherlands (Table 3). The studies were conducted between 1994 and 2012. These studies have similar methodologies where a sample population is recruited and study participants report on a weekly basis on whether they had experienced symptoms of diarrhoea and vomiting. All studies except Edelstein *et al.* asked participants reporting symptoms to submit stool samples for microbiological examination. Three studies (Edelstein *et al.,* Hoogenboom *et al.* and De Wit *et al.*) did not calculate a measure of frequency by pathogen; The IID1 and IID2 studies presented pathogen specific rates by person-year and calculated rate ratios comparing rates in the community to the rates presenting to the GP and rates reported to national surveillance, therefore studying the population at three levels in the surveillance pyramid. In the final study (Sensor study), a nested case control study was conducted and results of the microbiological findings of cases and controls were presented as standardised percentages but without rates per population. In addition, the standardised percentages can only be interpreted as an indication and not as definite numbers due to the small numbers in the age, gender and cohort used to standardise the percentages [14] (Appendix 4). Pathogen specific estimates cannot therefore directly be compared within or between countries.

Table 4: Community and GP incidence of IID reported in prospective cohort studies

Study	Study period	Case definition	Community incidence number of cases of IID per 1000 person years	General Practice incidence number of cases of IID per 1000 person years
IID1 (UK)[39]	1993 - 1996	Loose stools or clinically significant vomiting lasting less than two weeks, in the absence of known infectious cause, preceded by a symptom free period of three weeks. Vomiting was considered if it occurred more than once in a 24-hour period and if it incapacitates the case or was accompanied by other symptoms such as cramps or fever. Exclusions: people with non-infectious causes of diarrhoea - such as Crohn's disease, ulcerative colitis, cystic fibrosis, and coeliac disease - and non-infectious causes of vomiting such as surgical obstruction, alcohol intoxication, morning sickness, infant regurgitation.	194	33
IID2 (UK)[33]	Aug 2008 - Aug 2009	Loose stools or clinically significant vomiting lasting less than two weeks, in the absence of known infectious cause, preceded by a symptom free period of three weeks. Vomiting was considered if it occurred more than once in a 24-hour period and if it incapacitates the case or was accompanied by other symptoms such as cramps or fever.	274	17.7

Study	Study period	Case definition	Community incidence number of cases of IID per 1000 person years	General Practice incidence number of cases of IID per 1000 person years
		Exclusions: people with non-infectious causes of diarrhoea - such as Crohn's disease, ulcerative colitis, cystic fibrosis, and coeliac disease - and non-infectious causes of vomiting such as surgical obstruction, alcohol intoxication, morning sickness, infant regurgitation.		
Sensor study (Netherlands)[14]	Dec 1998 - Dec 1999	Three or more loose stools in 24 hours; or diarrhoea with two additional gastrointestinal symptoms (vomiting, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool); or vomiting with two additional gastrointestinal symptoms (diarrhoea, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool) preceded by a symptom-free period of two weeks.	283	-
De Wit *et al.* (Netherlands)[15]	1996 - 1999	Three or more loose stools in 24 hours; or diarrhoea with two additional gastrointestinal symptoms (vomiting, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool); or vomiting with two additional gastrointestinal symptoms (diarrhoea, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool) preceded by a symptom-free period of two weeks.	-	7.97

Study	Study period	Case definition	Community incidence number of cases of IID per 1000 person years	General Practice incidence number of cases of IID per 1000 person years
Edelstein *et al.* (Sweden)[17]	Nov 2013 - Nov 2014	Three or more loose stools in 24 hours; or diarrhoea with two additional gastrointestinal symptoms (vomiting, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool); or vomiting with two additional gastrointestinal symptoms (diarrhoea, nausea, fever, abdominal cramps, abdominal pain, blood in stool, mucus in stool) preceded by a symptom-free period of two weeks.	360	-
Hoogenboom *et al.* (Netherlands)[23]	**Mar 1991 – Jul 1991**	**Two or more stools daily or vomiting and at least two additional symptoms of either nausea, abdominal pain, cramps, blood or mucus in stools within the period of one week.**	**630**	**-**

Although these studies shared similar methods, their case definitions differed (Table 4).

The community rate from IID increased by 40% from IID1 and IID2 and the GP consultation rate decreased by 46%. This could be explained by a major change in primary care utilisation since the 1990s and the introduction of telephone information and advice services such as NHS Direct and internet resources. Researchers reported that the use of NHS Direct was low among respondents during the IID2 study and could not account for the decline in GP consultations. However it was suggested that self-management and perhaps a decrease in the severity of illness from certain pathogens may be responsible [6]. For future IID studies, the community aspect maybe a more significant design element of the study than the GP element, as observations from the IID2 study suggest that changes in healthcare usage have led to fewer cases presenting to the GP, indicating that the community element of the study may provide more weight to the overall estimation of IID.

Three separate studies were conducted in The Netherlands; Hoogenboom *et al*. reported the highest incidence at 630 cases per 1000 person years in 1991, whereas in a subsequent 1999 study it was estimated at 283 cases per 1000 person years. However, these measures were not comparable over time as the earlier study estimated community based incidence of IID in The Netherlands, with a different definition of diarrhoea (two or more stools daily, Table 4) compared to the later community based Sensor study (three of more stools daily, Table 4) which used the same definition as a GP survey by De Wit *et al*.

Edelstein *et al*. used the same case definition as the Sensor study. Unlike the IID and Sensor studies, stool samples were not collected from participants and therefore pathogen-specific estimates were not available. Hoogenboom *et al.* collected stool specimens from participants meeting the case definition but they did not report on the results of the laboratory examinations in the published article. Therefore, pathogen specific estimates could not be directly compared between countries.

Prospective studies in comparison to retrospective studies reported much lower incidence rates. This is reflected in studies from The Netherlands where the prospective Sensor study conducted in 1999 reported 283 cases per 1000 person-years[14] three times lower compared to the retrospective study conducted in 2009 with 964 episodes per 1000 person years [16]. Even when identical case definitions were used, estimates between retrospective and prospective study designs differed, the IID2 prospective study estimated a rate of 274 cases per 1000 person years [6] compared to the retrospective element at 533 episodes per 1000 person-years [38], the latter twice as high than the prospective element [39].

3.4 Surveillance pyramid studies

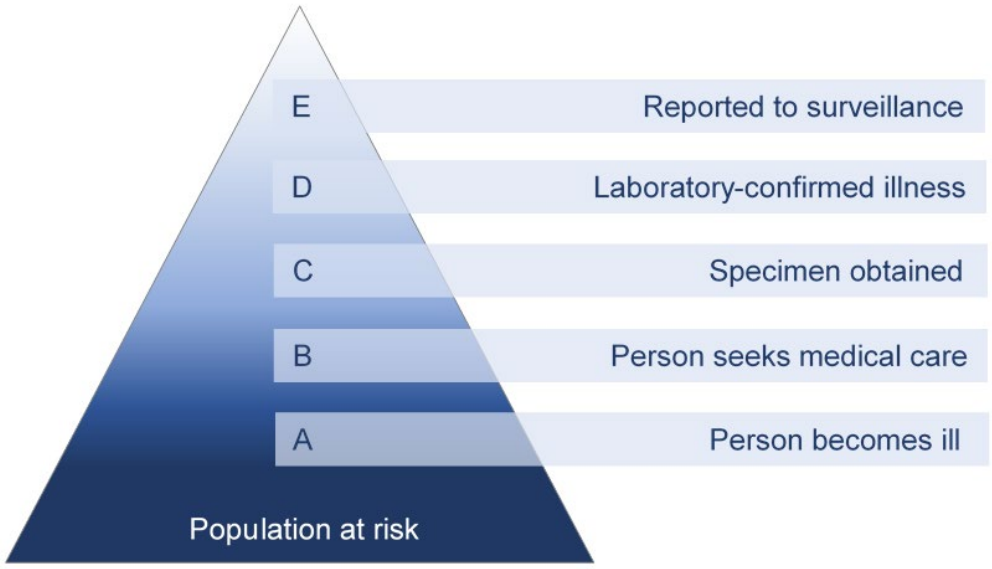
Five studies were identified that attempted to estimate the incidence of IID by pathogen using surveillance data and population surveys. All five studies were conducted in countries with established laboratory based surveillance systems (United States, Canada, Australia, New Zealand, and the United Kingdom). Study periods spanned the years 1995 – 2010, with four of the five studies conducted in the latter ten-year period. All five studies attempted to estimate the annual number of episodes (cases) of domestically acquired foodborne illness in each country, caused by the eight pathogens targeted in this review.

Four studies were based on the *surveillance pyramid* approach outlined by Scallan *et al* (US) [30]. This approach was derived by the Foodborne Disease Active Surveillance Network (FoodNet) Working Group to take account of the cascade of events that must occur before an episode of foodborne illness is reported to a laboratory-based surveillance system (Figure 3) [42]:

A. A person becomes ill with a foodborne disease
B. The person seeks medical care (for example, by visiting a healthcare facility)
C. A specimen is obtained from the ill person
D. The specimen is referred to a microbiology laboratory for testing, and the causative agent is identified
E. The laboratory test result is reported to the relevant health department and the confirmed infection is recorded in the surveillance system.

A break in the cascade of events leads to under-ascertainment of the true burden of foodborne illness, in the form of under-reporting and under-diagnosis. If ill individuals do not seek care, or specimens are not sent for testing, this gives rise to under-diagnosis of episodes of foodborne illness. Failure to test a specimen or refer the result to the surveillance system results in under-reporting of the episode.

Figure 3: The prevalence of illness pyramid. Adapted from Foodborne Diseases Active Surveillance (FoodNet)



The surveillance pyramid approach integrates a multiple array of data sources and factors affecting the estimation of the true burden of IID by pathogen (Tables 5 - 8). The method is based on two model structures, where reported case numbers for a pathogen were either “scaled up” to the total population to account for illnesses that were not reported to public health authorities, or “scaled down” from the population at risk to estimate the total number of illnesses attributable to a pathogen [30]. The Adak *et al* (UK) study was based on a similar approach previously outlined by Mead *et al.* [43].

National surveillance data was used to obtain the number of laboratory-confirmed illnesses caused by each pathogen (scaling up). However, when this data was unobtainable (for example, confirmed cases of norovirus), an estimated rate of acute gastrointestinal illness (AGI) per person per year was applied to the population (scaling down).

A multiplier for proportion of illnesses that could be attributed to each pathogen was also applied, using data from outbreak surveillance, population-based cohort studies or expert elicitation, to estimate the total number of pathogen-specific illnesses. To adjust for under-diagnosis (failure to complete steps B – D of the pyramid), pathogen-specific multipliers were applied to account for care seeking and sample submission. Differences in diagnosis for severe and mild illnesses were also considered, under the notion that severe cases were more likely to seek medical care and have a specimen submitted for testing. Two studies (US and Canada) also implemented data from national laboratory surveys on laboratory testing and test sensitivity as additional factors contributing to under-diagnosis [30, 34]. This data referred to the coverage of sample testing (either routine or requested), and the probability of a true positive (disease) being identified as positive by a given test.

To adjust for underreporting (failure to complete step E of the pyramid), another multiplier was applied to account for the proportion of cases not reported to public health authorities in the surveillance system.

Lastly, pathogen-specific multipliers accounting for the number of illnesses acquired through travel and food were applied, using data from outbreak surveillance, case-control studies and evidence-based research.

Studies typically used a Monte Carlo simulation approach to account for the inherent uncertainty of each step in the scaling process: for each proportion/multiplier, a distribution can be assigned representing the uncertainty of this quantity. The simulation approach then propagates the uncertainty of each step, such that this is accounted for in the final estimate of food-borne illness. The PERT distribution was used for many quantities, which has an intuitive interpretation, being defined by specified minimum, maximum and most likely values.

All five studies provided an overall estimated number of domestically acquired foodborne illnesses by population (Table 8) and an estimated proportion of domestically acquired foodborne illness attributed to each of the eight pathogens targeted in this review (Table 9).

Norovirus accounted for the highest proportion of foodborne IID in the US, Australia, Canada and New Zealand. For bacterial pathogens, *Campylobacter* spp. accounted for the highest proportion of bacterial foodborne illness in Australia, New Zealand and the UK whereas *C. perfringens* accounted for the highest proportion of bacterial foodborne illness in Canada and *Salmonella* spp. was highest in the US (Table 9).

The forest plot presents a meta-analysis of the incidence rates of the eight pathogens captured by the five surveillance pyramid studies (Figure 4). The pooled estimate was highest for *Campylobacter* spp. at 5.93 infections per 1000 person years (1^2 66.0%, p value 0.019) and lowest for *Listeria monocytogenes* at <1 infections per 1000 person years (1^2 78.5%, p value 0.001).

Table 5: Data sources used to estimate the total number of laboratory confirmed illnesses, by pathogen and country population

	Australia	Canada	New Zealand	UK	USA
STEC O157/non-O157	STEC surveillance study[44]	Surveillance (NESP)	Surveillance (Episurv)	Surveillance (LabBase); case-control study[45]	Surveillance (FoodNet)
Clostridium perfringens	Surveillance (NNDSS)	UK IID2 study[6, 33]; Scallan *et al* (2011)[30]	Surveillance (Episurv); Scallan *et al* (2011)	Surveillance (LabBase); UK IID1 study[46]	FDOSS outbreak surveillance
Campylobacter spp.	Surveillance (NNDSS); Study[47]	Surveillance (CNDSS)	Surveillance (Episurv)	Surveillance (LabBase); UK IID1 study; *Campylobacter* sentinel surveillance scheme[48]	Surveillance (FoodNet)
Listeria monocytogenes	Surveillance (NNDSS)	Provincial reportable disease data	Surveillance (Episurv)	Enhanced surveillance data[49]	Surveillance (FoodNet)
Cryptosporidium spp.	Surveillance (NNDSS); Study[47]	Surveillance (CNDSS; C-EnterNet; provincial	Surveillance (Episurv)	Surveillance (LabBase); UK IID1 study	Surveillance (FoodNet)

	Australia	Canada	New Zealand	UK	USA
		reportable disease data)			
Giardia spp.	Surveillance (NNDSS)	Surveillance (CNDSS)	Surveillance (Episurv)	Surveillance (LabBase); UK IID1 study	NNDSS passive surveillance
Salmonella spp., non-typhoidal	Surveillance (NNDSS); Study[47]	Surveillance (CNDSS)	Surveillance (Episurv)	Surveillance (LabBase); UK IID1 study	Surveillance (FoodNet)
Norovirus	Outbreak surveillance (OzFoodNet Outbreak Register); WQS; NGSII	UK IID2 Study; Scallan *et al* (2011)	UK IID2 Study; Scallan *et al* (2011)	Surveillance (LabBase); UK IID1 study	Population surveys (Netherlands[14]; UK IID2[6, 33]; Australia[50])

Abbreviations:

STEC – Shiga toxin-producing *E. coli*. IID – infectious intestinal disease.

Data sources:

NNDSS – National Notifiable Diseases Surveillance System. OzFoodNet – outbreak surveillance; CNDSS - Canadian Notifiable Disease Surveillance System; NESP – National Enteric Surveillance Program; C-EnterNet - Canada enteric disease surveillance system based on sentinel sites; Episurv - notifiable disease surveillance data; LabBase - national database for laboratory confirmed infections; Water Quality Study – randomised controlled trial of household water treatment to prevent gastroenteritis, 1997-1999; NGSII – National Gastroenteritis Survey II, cross-sectional telephone survey, 2008-2009; provincial data (Canada) on listeriosis and travel-related cryptosporidiosis from British Columbia reportable disease system, 2008- 2010.

Table 6: Data sources used to adjust estimates of IID by the proportion of infections acquired domestically

	Australia	Canada	New Zealand	UK	USA
STEC O157/non-O157	Surveillance (NNDSS)	Surveillance (C-EnterNet; provincial reportable disease data)	NZ surveillance summary reports	Surveillance (LabBase)	Surveillance (FoodNet)
Clostridium perfringens	Surveillance (NNDSS) – assumed to be 100%	Scallan *et al* (2011)[30] – assumed to be 100%	Scallan *et al* (2011)[30]	Surveillance (LabBase)	FDOSS outbreak surveillance
Campylobacter spp.	Surveillance (NNDSS); Study[47]	Surveillance (C-EnterNet; provincial reportable disease data)	NZ surveillance summary reports	*Campylobacter* sentinel surveillance scheme [48]	Surveillance (FoodNet)
Listeria monocytogenes	Surveillance (NNDSS) – assumed to be 100%	Surveillance (Enhanced National Listeriosis Surveillance Initiative; C-EnterNet; provincial reportable disease data)	NZ surveillance summary reports	Enhanced surveillance data[49]	Surveillance (FoodNet)
Cryptosporidium spp.	Surveillance (NNDSS)	Surveillance (C-EnterNet; provincial	NZ surveillance summary reports	Surveillance (LabBase)	Surveillance (FoodNet)

	Australia	Canada	New Zealand	UK	USA
		reportable disease data)			
Giardia spp.	Notifiable disease data, Victoria state[51]	Surveillance (C-EnterNet)	NZ surveillance summary reports	Surveillance (LabBase)	Case-control study[52]
Salmonella spp., non-typhoidal	Surveillance (NNDSS)	Surveillance (C-EnterNet; provincial reportable disease data)	NZ surveillance summary reports	Surveillance (LabBase)	Surveillance (FoodNet)
Norovirus	WQS	Scallan *et al* (2011)[30] - assumed to be low	Scallan *et al* (2011)[30]	Surveillance (LabBase)	Population surveys (Netherlands[14]; UK IID2[6, 33]; Australia[50] – assumed to be low

Proportion of domestically acquired infections calculated as 1 - proportion of travel-related infections, where known.

Abbreviations: STEC – Shiga toxin-producing *E. coli*.

Data sources: NNDSS – National Notifiable Diseases Surveillance System; C-EnterNet - Canada enteric disease surveillance system based on sentinel sites; LabBase - national database for laboratory confirmed infections; Water Quality Study – randomised controlled trial of household water treatment to prevent gastroenteritis, 1997-1999; provincial data (Canada) on listeriosis and travel-related cryptosporidiosis from British Columbia reportable disease system, 2008- 2010; FoodNet – Foodborne Diseases Active Surveillance System; FDOSS – Foodborne Disease Outbreak Surveillance System.

Table 7: Data sources used to adjust estimates of IID by the proportion of infections attributed to foodborne transmission

	Australia	Canada	New Zealand	UK	USA
STEC O157/non-O157	Expert consultation	Expert elicitation survey[53]	Expert consultation (Cressey & Lake *et al*, 2005) [54]	Surveillance (GSURV)	FDOSS outbreak surveillance data
Clostridium perfringens	Expert consultation	Scallan *et al* (2011)[30]	Scallan *et al* (2011)	Surveillance (GSURV)	FDOSS outbreak surveillance data
Campylobacter spp.	Expert consultation	Expert elicitation survey	Expert consultation (Cressey & Lake et al, 2005)	Surveillance (GSURV)	FoodNet case-control study[55]
Listeria monocytogenes	Expert consultation	Expert elicitation survey	Expert consultation (Cressey & Lake et al, 2005)	Mead *et al* (1999)[43]	Multiple studies (evidence based)[56-60]
Cryptosporidium spp.	Expert consultation	Expert elicitation survey	Scallan *et al* (2011)	Surveillance (GSURV)	Canadian surveillance study[61]
Giardia spp.	Expert consultation	Scallan *et al* (2011)	Scallan *et al* (2011)	Mead *et al* (1999)	FDOSS outbreak surveillance data

	Australia	Canada	New Zealand	UK	USA
Salmonella spp., non-typhoidal	Expert consultation	Expert elicitation survey	Expert consultation (Cressey & Lake et al, 2005)	Surveillance (GSURV)	NNDSS passive surveillance; FDOSS outbreak data
Norovirus	Expert consultation	Expert elicitation survey	Expert consultation (Cressey & Lake et al, 2005)	Surveillance (GSURV)	FDOSS outbreak surveillance data

Abbreviations: STEC – Shiga toxin-producing *E. coli*.

Data sources: GSURV - National surveillance database for general outbreaks of IID; FoodNet – Foodborne Diseases Active Surveillance System; FDOSS – Foodborne Disease Outbreak Surveillance System; NNDSS – National Notifiable Diseases Surveillance System.

Table 8: Calculations of domestically acquired foodborne illnesses and incidence rate from surveillance pyramid studies

	First author	Country	Pathogens reviewed	Estimated number of domestically acquired foodborne illnesses	Estimated incidence rate per 1000 person years
(a)	Scallan *et al*. [30]	USA	31 pathogens	9,388,075	31.4
(b)	Scallan *et al*. [30]	USA	*Campylobacter* spp. *Clostridium perfringens* *Cryptosporidium* spp. STEC O157/STEC non-O157 *Listeria monocytogenes* *Salmonella* spp., non-typhoidal *Giardia intestinalis* Norovirus	8,612,226	28.8
(c)	Kirk *et al*. [25]	Australia	18 pathogens and unidentified pathogens	4,115,140	192.4
(d)	Kirk *et al*. [25]	Australia	*Campylobacter* spp. *Clostridium perfringens* *Cryptosporidium* spp. STEC *Listeria monocytogenes* *Salmonella* spp., non-typhoidal *Giardia lamblia* Norovirus	518,600	24.2
(e)	Thomas *et al*. [34]	Canada	30 pathogens	1,630,636	50.2

	First author	Country	Pathogens reviewed	Estimated number of domestically acquired foodborne illnesses	Estimated incidence rate per 1000 person years
(f)	Thomas *et al*. [34]	Canada	*Campylobacter* spp. *Clostridium perfringens* *Cryptosporidium* spp. VTEC O157/VTEC non-O157 *Listeria monocytogenes* *Salmonella* spp., non-typhoidal *Giardia* spp. Norovirus	1,501,181	46.2
(g)	Cressey *et al*. [13]	New Zealand	24 pathogens	557,542	32.4
(h)	Cressey *et al*. [13]	New Zealand	*Campylobacter* spp. *Clostridium perfringens* *Cryptosporidium* spp. STEC O157/STEC non-O157 *Listeria monocytogenes* *Salmonella* spp., non-typhoidal *Giardia intestinalis* Norovirus	508,657	29.5
(i)	Adak *et al*. [1]	UK	25 pathogens	2,365,909	45.7
(j)	Adak *et al*. [1]	UK	*Campylobacter* spp. *Clostridium perfringens* *Cryptosporidium parvum* VTEC O157/VTEC non-O157	512,483	9.9

	First author	Country	Pathogens reviewed	Estimated number of domestically acquired foodborne illnesses	Estimated incidence rate per 1000 person years
			Listeria monocytogenes *Salmonella* spp., non-typhoidal *Giardia duodenalis* Norwalk-like virus		

Key:

(a)(c)(e)(g)(i): total estimated domestically acquired foodborne illnesses and estimated incidence rate per 1000 person years of all pathogens reviewed in each respective paper.

(b)(d)(f)(h)(j): total estimated domestically acquired foodborne illnesses and estimated incidence rate per 1000 person years of the eight pathogens targeted in this systematic review.

Abbreviations:

STEC – Shiga toxin-producing *E. coli*; VTEC – Verocytotoxin-producing *E. coli*. STEC and VTEC are synonymous for the same organism.

Table 9: Estimated proportion of domestically acquired foodborne IID caused by eight pathogens†, by country

Organism	Australia	Canada	New Zealand	UK	US
Clostridium perfringens	0.4%	10.9%	11.7%	2.6%	10.3%
Campylobacter spp.	4.3%	8.9%	34.1%	11.9%	9.0%
Cryptosporidium spp.	>0.1%	0.1%	1.2%	0.1%	0.6%
Giardia spp.^	0.1%	0.5%	0.7%	0.1%	0.8%
Listeria monocytogenes	>0.1%	>0.1%	>0.1%	>0.1%	>0.1%
Norovirus	6.7%	64.3%	39.2%	2.9%*	58.2%
Salmonella spp., non-typhoidal	1.0%	5.4%	4.1%	4.0%	10.9%
STEC, O157 serotype	-	0.8%	0.2%	>0.1%	0.7%
STEC, non-O157 serotypes	-	1.3%	>0.1%	>0.1%	1.2%
STEC (any serotype)	0.1%	-	-	-	-

Abbreviations: STEC – Shiga toxin-producing *E. coli*.

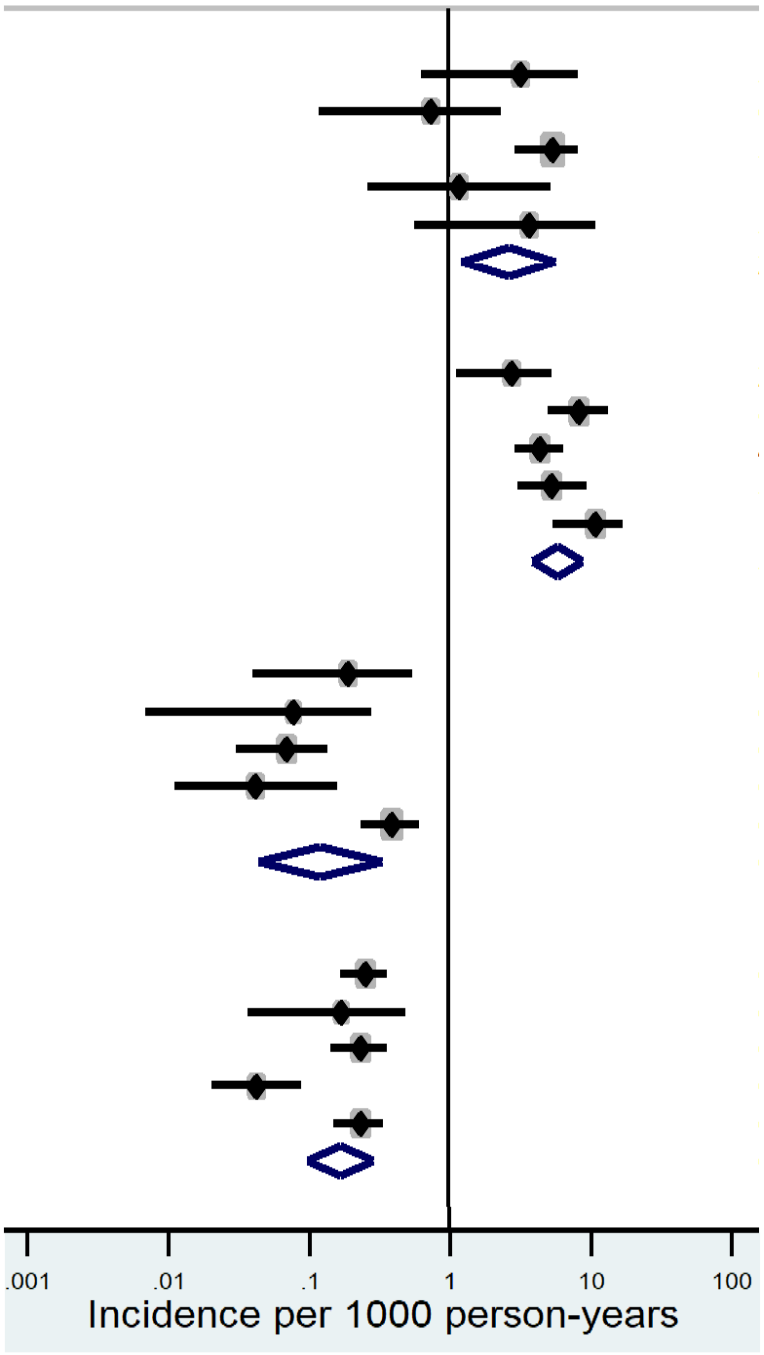
^*G. intestinalis, G. lamblia* and *G. duodenalis* are synonymous for the same organism.

*Norwalk-like virus.

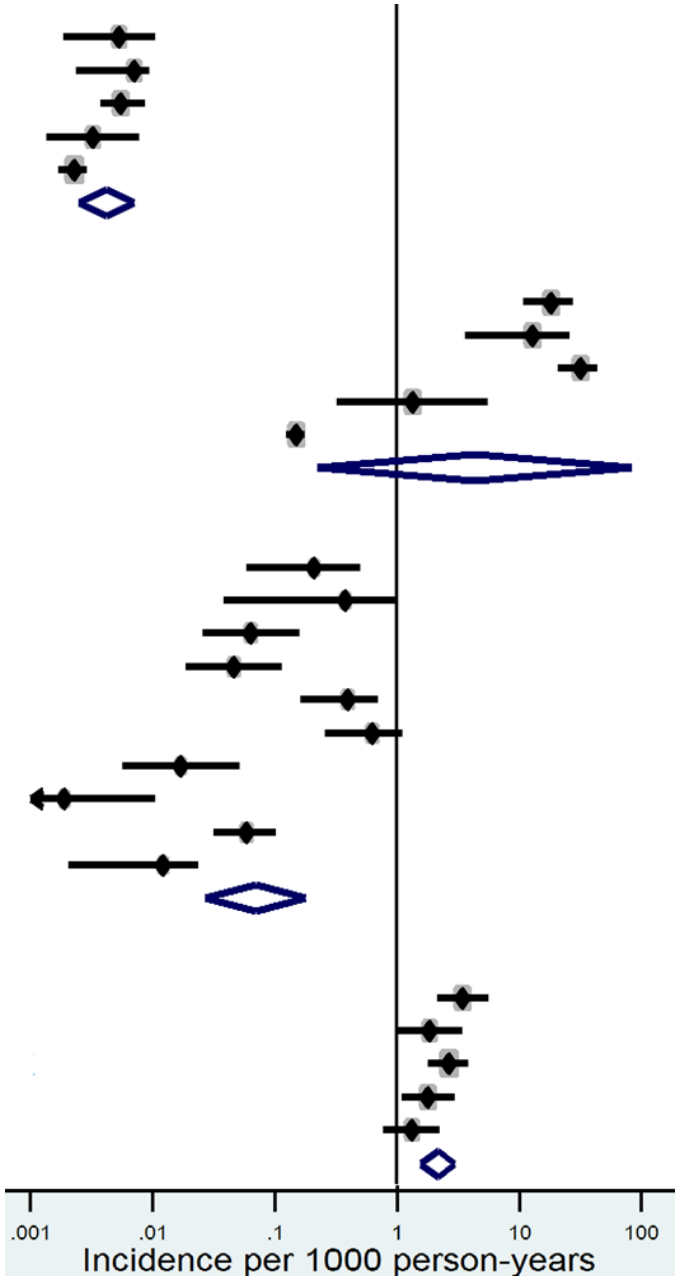
†The table only presents proportions attributed to the eight pathogens targeted in this review, and excludes proportions attributed to any other pathogens, including those of unknown aetiology. These figures are not directly comparable due to the differences in estimation methodology used in each study.

Figure 4: Meta-analysis of the five surveillance pyramid studies

Species	Country	Paper ID	Author	Rate	LCI	UCI	Weight
C.perfringens							
C. perfringens	US	27	Scallan, E	3.23	0.64	8.31	18.9%
C. perfringens	Australia	28	Kirk, M	0.75	0.12	2.37	15.9%
C. perfringens	Canada	29	Thomas, MK	5.45	2.93	8.31	33.2%
C. perfringens	UK	30	Adak, GK	1.19	0.27	5.30	15.9%
C. perfringens sp.	New Zealand	31	Cressey, P	3.77	0.57	11.09	16.0%
	Subtotal (I-squared = 54.1%, p = 0.069)			2.66	1.23	5.78	100.0%
Campylobacter							
Campylobacter sp.	US	27	Scallan, E	2.83	1.13	5.39	14.9%
Campylobacter sp.	Australia	28	Kirk, M	8.37	5.07	13.56	21.7%
Campylobacter sp.	Canada	29	Thomas, MK	4.47	2.94	6.55	24.2%
Campylobacter sp.	UK	30	Adak, GK	5.44	3.08	9.59	19.8%
Campylobacter sp.	New Zealand	31	Cressey, P	11.04	5.44	17.30	19.5%
	Subtotal (I-squared = 66.0%, p = 0.019)			5.93	3.91	9.01	
Cryptosporidium							
Cryptosporidium sp.	US	27	Scallan, E	0.19	0.04	0.56	18.5%
Cryptosporidium sp.	Australia	28	Kirk, M	0.08	0.01	0.29	14.1%
Cryptosporidium sp.	Canada	29	Thomas, MK	0.07	0.03	0.14	23.5%
C. parvum	UK	30	Adak, GK	0.04	0.01	0.16	18.4%
Cryptosporidium sp.	New Zealand	31	Cressey, P	0.39	0.24	0.62	25.5%
	Subtotal (I-squared = 81.0%, p = 0.000)			0.12	0.04	0.34	100.0%
Giardia							
G. intestinalis	US	27	Scallan, E	0.26	0.17	0.37	24.1%
G. lamblia	Australia	28	Kirk, M	0.17	0.04	0.50	10.7%
Giardia sp.	Canada	29	Thomas, MK	0.24	0.15	0.37	22.9%
G. duodenalis	UK	30	Adak, GK	0.04	0.02	0.09	18.3%
G. intestinalis	New Zealand	31	Cressey, P	0.24	0.15	0.34	23.9%
	Subtotal (I-squared = 79.9%, p = 0.001)			0.17	0.10	0.29	100.0%



Species	Country	Paper ID	Author	Rate	LCI	UCI	Weight
Listeria							
L. monocytogenes	US	27	Scallan, E	0.005	0.002	0.011	15.9%
L. monocytogenes	Australia	28	Kirk, M	0.007	0.002	0.009	18.8%
L. monocytogenes	Canada	29	Thomas, MK	0.005	0.004	0.009	23.6%
L. monocytogenes	UK	30	Adak, GK	0.003	0.001	0.008	15.8%
L. monocytogenes	New Zealand	31	Cressey, P	0.002	0.002	0.003	25.9%
	Subtotal (I-squared = 78.5%, p = 0.001)			0.004	0.002	0.007	100.0%
Norovirus							
Norovirus	US	27	Scallan, E	18.27	10.79	27.79	20.2%
Norovirus	Australia	28	Kirk, M	12.90	3.65	26.32	19.9%
Norovirus	Canada	29	Thomas, MK	32.24	20.91	44.12	20.2%
Norwalk-like virus	UK	30	Adak, GK	1.34	0.32	5.59	19.4%
Norovirus	New Zealand	31	Cressey, P	0.15	0.12	0.18	20.3%
	Subtotal (I-squared = 99.6%, p = 0.000)			4.35	0.22	84.44	100.0%
STEC							
STEC O157	US	27	Scallan, E	0.211	0.059	0.500	10.0%
STEC non-O157	US	27	Scallan, E	0.377	0.038	0.961	8.6%
STEC O157	Australia	28	Kirk, M	0.064	0.026	0.159	10.4%
STEC non-O157	Australia	28	Kirk, M	0.046	0.019	0.115	10.4%
VTEC O157	Canada	29	Thomas, MK	0.395	0.162	0.700	10.8%
VTEC non-O157	Canada	29	Thomas, MK	0.631	0.257	1.120	10.8%
VTEC O157	UK	30	Adak, GK	0.017	0.006	0.051	9.9%
VTEC non-O157	UK	30	Adak, GK	0.002	0.000	0.010	8.4%
STEC O157	New Zealand	31	Cressey, P	0.059	0.032	0.102	11.0%
STEC non-O157	New Zealand	31	Cressey, P	0.012	0.002	0.024	9.6%
	Subtotal (I-squared = 90.1%, p = 0.000)			0.070	0.027	0.180	100.0%
Salmonella sp							
S. enterica, non-typh	US	27	Scallan, E	3.44	2.16	5.62	20.8%
S. enterica, non-typh	Australia	28	Kirk, M	1.85	0.98	3.43	15.8%
S. enterica, non-typh	Canada	29	Thomas, MK	2.69	1.81	3.86	25.0%
S. enterica, non-typh	UK	30	Adak, GK	1.81	1.09	3.00	19.8%
S. enterica, non-typh	New Zealand	31	Cressey, P	1.32	0.77	2.25	18.6%
	Subtotal (I-squared = 54.1%, p = 0.069)			2.16	1.56	3.00	100.0%



3.5 Other studies

There were three studies that could not be grouped into the three study design groups; Havelaar *et al.* (The Netherlands)[21] , Kumagai *et al.* (Japan) [26] and O'Brien et al. (UK)[9] The Havelaar *et al.* study estimated the incidence of IID by pathogen using surveillance data, population based cohort studies [14] and published data. Specifically, the data from the Sensor study was used to estimate the incidence of IID for the population of Netherlands in 2009. Pathogen specific estimates were calculated using laboratory surveillance data for *Campylobacter* spp., *Salmonella* spp., *Cryptosporidium* spp., and *Giardia* spp. Data for norovirus was based on hospitalisations of viral gastroenteritis. For STEC O157, the incidence was calculated using data from active surveillance.

Kumagi *et al.* identified three common causes of foodborne disease (*Campylobacter, Salmonella* species and enterohaemorrhagic *Escherichia coli* (EHEC)) through expert consultation. Annual incidence of IID for these pathogens were calculated using food poisoning outbreak statistics, surveillance data on EHEC, national patient surveys recording patients in hospitals and clinics in a single day and registration records from the Ministry of Health. The proportion attributable to foodborne disease was estimated using an expert elicitation process[62]. The surveillance pyramid approach was also used to calculate the estimated number and incidence of cases in the population. The annual incidence was 92.5, 31.7 and 80.7 cases per 100,000 population for foodborne IID caused by *Campylobacter*, *Salmonella* and EHEC respectively [26]. This paper was excluded from the surveillance pyramid studies as it was not clear how the calculations were done in relation to the Scallan *et al.* approach and there were limitations with data; there were only surveillance data available for EHEC, while data for *Salmonella* and *Campylobacter* incidence were based on outbreak data and national patient surveys which recorded patients in hospitals and clinics on a single day in October.

The O'Brien *et al.* (IID2 extension study) estimated the proportion of IID attributable food and the burden of UK acquired foodborne disease. The authors created a model to estimate the number of cases, GP consultations, hospital acquired foodborne disease due to 13 enteric pathogens: *Clostridium perfringens*, *E.coli* O157, *Listeria, Salmonella* (non-typhoidal), *Shigella*, *Cryptosporidium*, *Giardia*, adenovirus, astrovirus, norovirus, rotavirus and sapovirus. Various data sources were used for the model parameters, these included; IID1 and IID2 studies, outbreaks in UK and published literature obtained from a systematic review. Two modelling approaches were used (Monte Carlo simulation and a Bayesian approach) with producing similar results [9]. *Campylobacter* was the most common foodborne pathogen in the UK at 280,000 cases of foodborne illness, followed by *Clostridium perfringens* (79000 cases), norovirus (73000 cases) and *Salmonella* (34,000 cases). Despite the high number of *Campylobacter* cases, only 562 cases were hospitalised, reflecting a lower disease severity, in contrast *Salmonella* caused the highest number of hospital admissions at 2490, followed by *E,coli* O157 at 2233 admissions (Appendix 5).

4. Discussion

Three large groups of studies were identified which have been used to estimate the rates of IID in different countries in the literature. These studies can provide information that cannot be ascertained through laboratory based surveillance data alone.

The results indicate that rates of IID are broadly similar across the countries that have conducted cross-sectional studies (Figure 2) except for France[37] and Sweden [20]. The Swedish study had the largest recall period (365 days) which may have accounted for the lowest reported rate of IID amongst the cross-sectional studies, as symptoms are likely to be underreported as participants are more likely to forget episodes that have occurred. France used the 'Burden of illness' case definition and had similar methods to that of other studies using the same case definition and it is not obvious other than higher number of exclusion cases as to why the incidence is so much lower than other countries. The considerable heterogeneity amongst the cross-sectional studies (I^2 98.7% p value <0.001) indicates that there are clear differences between the studies that cannot be due to chance.

The surveillance pyramid studies used the Scallan *et al.* and the Mead *et al.* approach to estimate the extent of under-ascertainment and underreporting to calculate the overall burden of foodborne illness. The heterogeneity in the surveillance pyramid studies is high for many pathogens, but less than the retrospective cross-sectional studies (Figure 3). The data for the surveillance pyramid method relies on the quality and representativeness of the surveillance system within the country to calculate the overall burden of foodborne IID. These data were not available in some studies and where data was unavailable for pathogens, estimates (multipliers and estimates for multipliers) were derived from other countries which may in reality have different estimates. For example, multipliers from both the IID2 study and the Scallan *et al*. study were used to calculate pathogen specific rates (*C. perfringens*, *Campylobacter*, STEC O157, *Cryptosporidium, Giardia intestinalis*, norovirus) in New Zealand, application of the two multipliers from the two different countries produced different estimates, [13] demonstrating the sensitivity of these models to the underlying parameters which are used to estimate the burden of foodborne IID. While, in the US and Australia, limited routine surveillance data were available for norovirus and the studies estimates were derived from studies in England and The Netherlands, which may not be transferrable to their contexts and therefore studies reporting norovirus as the highest proportion of foodborne IID must be interpreted with caution. Further in the US study, data was obtained from FoodNet sites which only accounts for 15% of the US population and may be not be representative at country level [30].

Another component to estimating the burden of foodborne illness is estimating the proportion of cases due to contaminated food i.e. foodborne IID versus zoonotic or human transmission. In the studies which entailed a surveillance pyramid method, *C.*

perfringens and *Campylobacter* had the greatest proportion attributed to bacterial foodborne transmission. While this relative burden is expected, there is unreliability in these estimates as data was often derived from different sources such as outbreak data, literature review and expert consultation.

Unknown pathogens are also likely to cause a proportion of IID due to contaminated food. For the surveillance pyramid studies, the calculations of the proportions of foodborne illness from unknown pathogens were based on the foodborne proportions of known pathogens, so studies assumed that the burden of foodborne acute gastroenteritis is similar amongst those with unknown aetiology as those for whom a pathogen has been detected. Further studies are needed to better understand the causes of acute gastroenteritis amongst those cases to further improve estimates of foodborne transmission of IID [63].

Most countries conducted retrospective, cross-sectional surveys to estimate the incidence of IID because they tend to be cheaper to conduct than prospective study designs. They can be quicker to conduct and are able to assess a wide geographical area. While they can give overall estimates of IID, a disadvantage is that they are unable to provide pathogen specific estimates. They are also subject to a higher likelihood of bias particularly in the form of telescoping, whereby study participants perceive their symptoms to have occurred more recently than they actually did [64]. Telephone surveys also have several advantages; research can be gathered quickly, can be cost effective compared with face to face interviewing, they allow a geographically dispersed sample particularly enabling those living in remote rural areas to be reached. Telephone surveys provide anonymity for respondents which can be useful to facilitate responses, particularly for sensitive topics [65]. Disadvantages of telephone surveys include a lack of representativeness, mainly as households with no landlines are not represented (often tend to be younger and of lower socio economic status) [6] and ethnic minorities are often underrepresented due to language barriers. Anecdotally, due to shifts in technology, specifically in communications, telephone surveys may become irrelevant, particularly with the lack of landlines in households. In addition, those with mobile phones were often excluded from studies included in this review. The IID2 study excluded mobile phones because many mobile phone users are children and it would be unethical for a researcher to contact a child. If researchers managed to find a way to include mobile phones, it would be very difficult to localise mobile phone numbers and select a representative sample. There are also the challenges with the saturation of market research companies and telephone calls may be received negatively by respondents which may hamper response rates [65].Online surveys could be an alternative method to telephone surveys, they would be less expensive to operate, quicker to conduct and participants are more likely to be honest however they can be prone to loss to dropouts especially with longer surveys and misinterpretation of questions without an interviewer to clarify a question.

Some studies reported a large proportion of cases reporting IID with associated respiratory symptoms [28, 29]. This is because IID symptoms can occur as a consequence of primary respiratory symptoms [36, 66] In this review, we found only one study had accounted for respiratory symptoms in their case definition. Thomas *et al*, used the 'Burden of illness' definition and reported an overall monthly prevalence of 0.77 per person year. After removal of respiratory symptoms, the prevalence was 0.57 episodes per person year. For future studies, respiratory symptoms should be considered in case definitions, as removing cases with respiratory symptoms creates a more specific definition attempting to exclude respiratory infections that may cause gastrointestinal symptoms such as vomiting and diarrhoea.

Prospective cohort studies are the most accurate way of estimating burden of illness by producing more reliable data due to reduced recall bias and with the advantage of being able to collect stool samples from people who report the illness to determine the pathogens causing illness. Few countries have conducted these studies, most likely because they are expensive, complex and take a longer time to conduct. Prospective cohort studies can be harder to standardise across settings with regards to case definitions, recruitment, participation and follow up. With longitudinal studies, there is a problem of sensitisation-fatigue, where the illness reporting is highest during the early weeks of follow-up and subsequently decreases [64].

The IID1 and IID2 study are the only prospective cohort studies with the same methodology repeated at different points in time in the same country. They are therefore the only two studies where the pathogen specific estimates can be compared over time. The IID studies provide the most reliable rates on the estimation on the burden of specific foodborne pathogens by direct measurement whereas the surveillance pyramid studies use extrapolation and inference to calculate their rates of foodborne IID.

4.1 Study limitations

The searches in the literature databases were performed in English language only due to time limitations and the costs of translating studies and it is possible that bias may have been introduced towards English language studies. In addition, we focused on a subset of pathogens and did not consider all foodborne pathogens.

Studies were conducted at different time periods and we haven't evaluated their comparability or if there is evidence of change in time. Healthcare utilisation can change over time for example the IID2 study reported that IID-related GP consultations declined since the 1990s and changes in healthcare usage, rather than increased use of telephone information and advice services, were hypothesised to drive that decline [6].

We did not evaluate the changes in microbiological and molecular methods used in diagnostic testing over time which may have had impact on the study investigators

ability to detect pathogens. Attributes of surveillance systems such as sensitivity and positive predictive values were not considered when comparing data between countries and this could influence numbers reported for each pathogen by country [63].

5. Conclusion

- Studies used to estimate foodborne illness fall within three categories; retrospective cross-sectional studies, prospective cohort studies and surveillance pyramid studies. The range of study methodologies vary among and within countries making any comparisons and interpretations of differences challenging.
- Cross-sectional retrospective studies are the most commonly conducted study, rates of self-reported illness ranged from 0.31 to 1.4 episodes per person year. However, differences in study design such as case definitions, recall periods and representativeness of population samples can affect the incidence rates and therefore comparing rates across studies can be difficult.
- Few prospective cohort studies have been conducted because they can be expensive to implement however they are the most accurate way of estimating IID rates (compared to surveillance pyramid and cross sectional studies) because samples from symptomatic patients are obtained to confirm aetiology.
- The IID1 and IID2 studies are the only prospective cohort studies using the same methodology repeated at different points in time in the same country. They are therefore the only two studies where the pathogen specific estimates can be compared over time.
- The surveillance pyramid studies used the Scallan *et al.* and the Mead *et al.* approach to estimate the extent of under-ascertainment and underreporting to calculate the overall burden of foodborne illness. However, the models (e.g. multipliers) are country specific and their application to other countries need to be made with caution as the disease burden of a specific pathogens may not be the same in another country. The quality and representativeness of the surveillance systems within countries must also be taken into account as the calculations to estimate foodborne IID are extrapolated from laboratory confirmed cases derived from the surveillance systems.

Recommendations

- Studies aiming to estimate the incidence of foodborne IID should consider the use of online surveys in place of telephone surveys due to the limitations of sampling from landlines (particularly in the UK, where the usage is in decline [67]) and mobile phone users.
- Studies should consider using the standard case definition recommended by Majowicz *et al*. In addition, future IID studies in the UK should also use this standard case definition alongside the Vivani *et al* case definition to enable comparisons with previous IID studies.
- Enhanced knowledge and published data of the microbiological and molecular methods used, and the coverage of diagnostic testing on a

population level may have beneficial impacts on the detection of foodborne pathogens.
- Greater understanding of the defining attributes of established surveillance systems using the surveillance pyramid approach.

Further work

- Additional work is required to understand and describe the use of modelling approaches as those demonstrated in the surveillance pyramid studies. Although this review provides an overview of the methods, we have not described how the multipliers were derived, the use of PERT distributions, and the uncertainty calculations.
- Further studies are needed to better understand the causes of acute gastroenteritis among cases of unknown aetiology to further improve estimates of foodborne transmission of IID.

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Appendix 1: Search terms

Scopus and Web of Science

- TITLE-ABSTRACT-KEYWORDS
- English only papers
- Limit to Humans
- 1990-2018

#1. (burden W/2 disease)
#2. “cost of illness”
#3. Morbidity
#4. Mortality
#5. QALY
#6. “Quality adjusted life year*”
#7. “Disability adjusted life year*”
#8. DALY
#9. Estimate*
#10. Surveillance
#11. Detect*
#12. Monitor*
#13. Model*
#14. “Global burden of disease/”
#15. “Cost of illness/”
#16. “Quality Adjusted life years/”
#17. Morbidity/ or incidence/ or prevalence/
#18. Mortality/
#19. Sequelae/
#20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

#1. Norovirus
#2. Calicivirus
#3. “Norwalk virus”
#4. “Acute gastroenteritis”
#5. “Infectious intestinal disease*”
#6. Gastroenteritis
#7. “Gastrointestinal infection*”
#8. “Gastrointestinal pathogen*”
#9. “Gastrointestinal bacteria”
#10. “Enteric infection*”
#11. “Haemorrhagic colitis”

#12. Diarrh*
#13. “Stomach flu”
#14. “Gastric flu”
#15. “Stomach bug*”
#16. “Stomach virus*”
#17. “Escherichia coli”
#18. {E.coli}
#19. "Enterobacteriaceae Infection*”
#20. Dysentery Bacillary
#21. “Yersinia enterocolitica”
#22. “paratyphoid fever”
#23. “typhoid fever”
#24. “Small round structured virus*”
#25. “Winter vomiting disease*”
#26. Sapovirus
#27. Caliciviridae
#28. Campylobacter*
#29. Cryptospor*
#30. Salmonell*
#31. Shigell*
#32. Giardia*
#33. Listeri*
#34. VTEC
#35. STEC
#36. “Foodborne Disease*”
#37. Botulism
#38. “Staphylococcal Food Poisoning*”
#39. “Food poisoning*”
#40. Scombro*
#41. “Clostridium perfringens”
#42. “Bacillus cereus”
#43. Bacillu*
#44. “Hepatitis A”
#45. “Hepatitis E”
#46. “Taenia solium”
#47. “Echinococcus granulosus”
#48. “Echinoccoccus multicularis”
#49. “Toxoplasma gondii”
#50. “Entamoeba histolytica”
#51. “Trichinella spiralis”
#52. “Opisthorchiidae”
#53. Ascaris*
#54. “Trypanosoma cruzi”

#55. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50

#56. 20 and 55

#1. Porcine
#2. Bovine
#3. cow*
#4. Pig*
#5. Hog*
#6. Cattle
#7. Calves
#8. Livestock
#9. Poultry
#10. Animal
#11. Drug*
#12. Vaccine*
#13. Sequencing*
#14. Genomic*
#15. Genome*
#16. PCR
#17. Polymerase*
#18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

#16. 56 and not 18

#1. “Cohort Stud*”
#2. “Prospective stud*”
#3. “Cross-sectional stud*”
#4. Outbreak*
#5. “Case control*”
#6. “Follow up stud*”
#7. “Longitudinal stud*”
#8. “meta-analys*”
#9. “Systematic review*”
#10. “Ecological stud*”
#11. {case case}
#12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

#11. 16 and 12

Medline:

1. (burden adj2 disease).tw,kw.
2. Morbidity.tw,kw.
3. Mortality.tw,kw.
4. DALY.tw,kw.
5. Estimate*.tw,kw.
6. Surveillance.tw,kw.
7. Detect*.tw,kw.
8. Monitor*.tw,kw.
9. Model*.tw,kw.
10. Global burden of disease/
11. Cost of illness/
12. Quality Adjusted life years/
13. Morbidity/ or incidence/ or prevalence/
14. Mortality/
15. Sequela*.tw,kw.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. infectious intestinal disease*.tw,kw.
18. gastrointestinal infection*.tw,kw.
19. acute gastroenteritis.tw,kw.
20. gastroenteritis.tw,kw.
21. norovirus.tw,kw.
22. exp norovirus/
23. diarrh*.tw,kw.
24. exp diarrhea/
25. gastrointestinal pathogen*.tw,kw.
26. gastrointestinal bacteria.tw,kw.
27. enteric infection*.tw,kw.
28. stomach flu.tw,kw.
29. gastric flu.tw,kw.
30. stomach bug*.tw,kw.
31. stomach virus*.tw,kw.
32. exp campylobacter/
33. exp escherichia coli/
34. exp "e. coli"/
35. enterobacteriaceae infection*.tw,kw.
36. exp enterobacteriaceae infection/
37. bacillary dysentery.tw,kw.
38. exp bacillary dysentery/
39. exp escherichia coli infections/
40. yersinia enterocolitica.tw,kw.
41. exp salmonella infections/
42. exp cryptosporidiidae/

43. exp salmonella/
44. exp shigella/
45. exp giardia/
46. salmonella infection*.tw,kw.
47. cryptosporid*.tw,kw.
48. salmonell*.tw,kw.
49. shigell*.tw,kw.
50. giardi*.tw,kw.
51. exp listeria/
52. listeri*.tw,kw.
53. small round structured virus*.tw,kw.
54. winter vomiting disease*.tw,kw.
55. sapovirus.tw,kw.
56. caliciviridae.tw,kw.
57. VTEC.tw,kw.
58. STEC.tw,kw.
59. exp STEC/
60. exp foodborne diseases/
61. food poisoning*.tw,kw.
62. scombro*.tw,kw.
63. clostridium perfringens.tw,kw.
64. bacillus cereus/
65. clostridium perfringens/
66. exp botulism/
67. taenia solium.tw,kw.
68. echinococcus granulosus.tw,kw.
69. echinococcus multicularis.tw,kw.
70. toxoplasma gondii.tw,kw.
71. entamoeba histolytica.tw,kw.
72. trichinella spiralis.tw,kw.
73. exp ascaris/
74. ascaris*.tw,kw.
75. trypanosoma cruzi.tw,kw.
76. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
77. 16 and 76
78. porcine.tw,kw.
79. bovine.tw,kw.
80. cow*.tw,kw.
81. pig*.tw,kw.
82. hog*.tw,kw.

83. cattle.tw,kw.
84. calves.tw,kw.
85. livestock.tw,kw.
86. poultry.tw,kw.
87. animal/
88. drug*.tw,kw.
89. vaccine*.tw,kw.
90. sequencing*.tw,kw.
91. genomic*.tw,kw.
92. genome*.tw,kw.
93. PCR.tw,kw.
94. polymerase*.tw,kw.
95. 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 88 or 90 or 91 or 92 or 93 or 94
96. 77 not 95
97. cohort stud*.tw,kw.
98. cohort studies/
99. prospective stud*.tw,kw.
100. prospective studies/
101. cross-sectional stud*.tw,kw.
102. outbreak*.tw,kw.
103. case-control studies/
104. case control stud*.tw,kw.
105. Follow-up stud*.tw,kw.
106. longitudinal stud*.tw,kw.
107. longitudinal studies/
108. meta-analysis/
109. meta-analys*.tw,kw.
110. systematic review*.tw,kw.
111. systematic review/
112. ecological stud*.tw,kw.
113. case-case.tw,kw.
114. 97 or 98 or 99 or 100 or 101 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 113
115. 96 and 114
116. limit 115 to (english language and humans and yr="1990 -2018")

Appendix 2 Data extraction headings used for cross-sectional, retrospective surveys

Source
Paper ID
First author
Title
Year of publication
Reviewer
Reason for exclusion
Type of publication
Aim/hypothesis
Study design
Country
Completed interviews
Study area population
Recruitment procedures used
Sampling method - household
Sampling method - individual
Sampling frame
Language
Timing of interviews
Observed number of cases
Study period
Age category
Study methodology
Contact attempts
Recall period
Illness term
Case definition inclusion criteria
Case definition Exclusion criteria
Type of case definition
Variables used in statistical weighting
Study limitations
Response rate
Incidence rate unit (e.g. years, 1000 person years)
Estimation methodology: observed incidence or adjusted for underreporting
Notes

Appendix 3: Data extraction headings used for prospective cohort studies and surveillance pyramid studies

Source
PaperID
First author
Title
Year of publication
Reviewer
Include?
Reason for exclusion
Type of publication
Aim/hypothesis
Study design
Country
Recruitment procedures used
Sample size
GI measure (pathogen)
Observed number of cases
Study period
Age
Age category
Methodology
Laboratory methods
Case definition
Exclusion criteria
Type of surveillance
Covariates controlled for
Type of analysis
Study limitations
Estimated incidence *Campylobacter*
Incidence rate lower 95%CI *Campylobacter*
Incidence rate upper 95%CI *Campylobacter*
Estimated incidence *Listeria*
Incidence rate lower 95%CI *Listeria*
Incidence rate upper 95%CI *Listeria*
Estimated incidence *Salmonella*
Incidence rate lower 95%CI *Salmonella*
Incidence rate upper 95%CI *Salmonella*
Estimated incidence STEC

Incidence rate lower 95%CI STEC
Incidence rate upper 95%CI STEC
Estimated incidence *Giardia*
Incidence rate lower 95%CI *Giardia*
Incidence rate upper 95%CI *Giardia*
Estimated incidence *Cryptosporidum*
Incidence rate lower 95%CI *Cryptosporidum*
Incidence rate upper 95%CI *Cryptosporidum*
Estimated incidence *Clostridium perfringens*
Incidence rate lower 95%CI *Clostridium perfringens*
Incidence rate upper 95% CI *Clostridium perfringens*
Estimated incidence Norovirus
Incidence rate lower 95% CI Norovirus
Incidence rate upper 95% CI Norovirus
Incidence rate unit (e.g. years, 1000 person years)
Estimation methodology: observed incidence or adjusted for underreporting
Notes

Appendix 4: Microbiological findings in cases and controls in the nested case control component, The Netherlands, December 1998 to December 1999 [14]

	Cases			Standardised %[1]	Controls		
	No. positive	No. tested	% positive		No. positive	No. tested	% positive
Salmonella[2]	3	700	0.4	1	2	665	0.3
Campylobacter[3]	9	700	1.3	2	4	665	0.6
Yersinia[4]	3	700	0.4	2	5	665	0.8
Shigella	0	700	0.0	0	0	665	0.0
VTEC[5]	2	699	0.3	<1	1	665	0.2
Bacterial pathogens	17	699	2.4	5	12	665	1.8
Rotavirus	52	709	7.3	4	5	672	0.7
Adenovirus	27	709	3.8	1	4	672	0.6
Astrovirus	14	709	2.0	1	4	668	0.6
NLV[6]	114	709	16.1	11	35	669	5.2
SLV[5]	43	687	6.3	2	11	625	1.8
Viral pathogens	232	693	33.5	21	57	624	9.1
Giardia lamblia	35	706	5.0	4	33	673	4.9
Entamoeba histolytica	1	706	0.1	<1	0	673	0.0
Cryptosporidium	14	706	2.0	2	1	673	0.1
Cyclospora	0	706	0.0	0	0	673	0.0
Pathogenic parasites	48	706	6.8	6	34	673	5.1

[1] The number in the subgroups for standardisation by age, gender and cohort were all very small, and therefore, these percentages can be interpreted only as indication and not as definite numbers.
[2] *Salmonella* typhimurium phage type unknown (one case), *Salmonella* typhimurium 506 (one case), *Salmonella* braenderup (one case), *Salmonella* infantis (one control), and *Salmonella* Thompson (one control).
[3] *Campylobacter jejuni* (eight cases and three controls), *Campylobacter* species (two cases and one control).
[4] *Yersinia enterocolitica* 1A,04 (one case), 1A,O6,31 (one case and one control), 1A,O6,30 (one control), 1A,O untypable (one case and one control), *Yersinia bercovieri* O16A,58 (one control), *Yersinia Frederiksenii*, untypable (one control)
[5] Verocytotoxin-producing *Escherichia coli* (VTEC) O5K (one case), O64K (one case).
[6] NLV, Norwalk-like virus; SLV, Sapporo-like virus

	Cases			Standardised %[1]	Controls		
	No. positive	No. tested	% positive		No. positive	No. tested	% positive
Clostridium perfringens toxin	7	306	2.3	3	3	307	1.0
Staphylococcus aureus toxin A-D[7]	17	306	5.6	5	18	307	5.9
Bacterial toxins	24	306	7.8	9	20	307	6.5
Bacillus cereus	11	603	1.8	1	21	581	3.6
Other Bacillus	3	603	0.5	1	5	581	0.9
Dientamoeba fragilis	102	706	14.4	20	72	673	10.7
Blastocystis hominis	144	706	20.4	30	139	673	20.7
Pathogen[8]			46.1	36			20.7

[7] Six times enterotoxin A (six cases and 13 controls, enterotoxin B (two cases and two controls), enterotoxin C (nine cases and three controls), and enterotoxin D (no cases and no controls).
[8] Excluding *Dientamoeba fragilis*, *Blastocystic hominis*, *Bacillus cereus*, and other *Bacillus*. Estimated by adding the percentages with only toxin as found in the subsample to the percentage with bacteria, viruses or parasites in the total sample.

Appendix 5 Estimates of food related cases, GP consultations and hospitalisations by pathogen, UK 2009 (Model 2 Bayesian approach) [9]

Organism	Cases	(95% CrI)	GP consultations	(95% CrI)	Hospital admissions	(95% CrI)
Bacteria						
C.perfringens	79570	30700-211298	12680	6072-27040	186	38-732
Campylobacter	280400	182503-435693	38860	27160-55610	562	189-1330
E.coli O157	9886	748-142198	342	37-3030	2233	170-32159
Listeria	183	161-217	183	161-217	-	-
Salmonella	33130	8178-128195	10060	4137-24710	2490	607-9631
Shigella	1204	181-8142	602	341-1060	33	4-270
Protozoa						
Cryptosporidium	2773	562-12200	800	233-2386	94	18-436
Giardia	7877	1467-36059	883	197-3288	47	4-332
Viruses						
Adenovirus	8253	4734-13780	677	345-1278	62	30-118
Astrovirus	3470	1368-9991	262	93-812	11	3-42
Norovirus	74100	61150-89660	3276	2240-4729	332	248-440
Rotavirus	10295	6049-16730	1102	629-1870	95	48-177
Sapovirus*	-	-	-	-	-	-
TOTAL	511141		69727		6145	

*For sapovirus, no data were identified in the literature review on the proportion of cases attributable to food, so this model could not be applied.

C.perfringens, Clostridium perfringens; E.coli, Esherichia coli, GP, general practice