A systematic review of waterborne disease burden methodologies from developed countries

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ABSTRACT

The true incidence of endemic acute gastrointestinal illness (AGI) attributable to drinking water in Canada is unknown. Using a systematic review framework, the literature was evaluated to identify methods used to attribute AGI to drinking water. Several strategies have been suggested or applied to quantify AGI attributable to drinking water at a national level. These vary from simple point estimates, to quantitative microbial risk assessment, to Monte Carlo simulations, which rely on assumptions and epidemiological data from the literature. Using two methods proposed by researchers in the USA, this paper compares the current approaches and key assumptions. Knowledge gaps are identified to inform future waterborne disease attribution estimates. To improve future estimates, there is a need for robust epidemiological studies that quantify the health risks associated with small, private water systems, groundwater systems and the influence of distribution system intrusions on risk. Quantification of the occurrence of enteric pathogens in water supplies, particularly for groundwater, is needed. In addition, there are unanswered questions regarding the susceptibility of vulnerable sub-populations to these pathogens and the influence of extreme weather events (precipitation) on AGI-related health risks. National centralized data to quantify the proportions of the population served by different water sources, by treatment level, source water quality, and the condition of the distribution system infrastructure, are needed.

Key words | acute gastrointestinal illness, drinking, estimate, review, water, waterborne disease

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INTRODUCTION

Waterborne illness continues to be a concern in industrialized countries. In Canada, since the Walkerton waterborne outbreak of *Escherichia coli* O157:H7 and *Campylobacter jejuni* in 2000, which resulted in seven deaths and >2,300 illnesses, more stringent regulations regarding water treatment and risk management have been developed and implemented in many municipal systems across Canada (Holme 2003; Rizak & Hrudey 2007). Municipal water treatment requirements in Canada are high; however, there are still thousands of small systems and private wells, some under the direct influence of surface water (GUDI), that are untreated and at risk for pathogen intrusion, and are serving populations who may be at risk for exposure to waterborne pathogens (Richardson *et al.* 2009; Charrois 2010; Hunter *et al.* 2011).

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The true burden of acute gastrointestinal illness (AGI) due to drinking water in Canada is currently unknown. AGI for the purpose of this review refers broadly to AGI associated with the consumption of drinking water associated with endemic and/or epidemic exposures. A few crude estimates of AGI incidence attributable to tap water consumption have been compiled. Payment (1997) estimated that the burden of tap water related waterborne disease could be costing Canadians several million dollars annually due to the costs associated with lost work days, hospitalizations and costs of medications. In 2008, Environment Canada estimated that as many as 90,000 cases of AGI and 90 mortalities may occur annually in Canada as a result of waterborne disease (Edge *et al.* 2001). These estimates were based on a previous Centers for Disease Control and Prevention (CDC) estimate of 900,000

cases of AGI and 900 mortalities annually in the United States as a result of waterborne microbial infections (ASM 1999). Vinson (2012) produced a crude annual burden estimate of $2.7 billion due to waterborne disease (not AGI-specific) in Canada from recreational and drinking water exposures. Estimating burden or source attribution of waterborne disease is challenging as there are numerous data and knowledge gaps.

In 2006, Messner *et al.* (2006), from the United States Environmental Protection Agency (USEPA), proposed a method for developing a national estimate of waterborne disease attributable to the consumption of drinking water. This approach focused on community drinking water supplies, predicting that 16.4 million cases per year of acute gastroenteritis are a result of the consumption of drinking water in the United States. Additionally, Colford *et al.* (2006) employed a simpler approach, estimating that between 4.26 and 11.7 million cases of AGI are attributable to public drinking water systems in the United States on an annual basis.

The purpose of this research was to systematically review the approaches that quantify the burden of waterborne illness published in the peer-reviewed and grey literature, and to identify key knowledge gaps and critical data requirements for waterborne disease attribution or burden estimates in developed countries.

METHODS

Definition of waterborne disease

For the purpose of this review, the definition of waterborne disease burden is: the burden of AGI attributable to drinking water exposures. No strict definition of AGI was applied to the specific gastrointestinal symptoms as the goal of the review was to capture all studies that examined AGI burden associated with drinking water. Figure 1 illustrates the main pathways of exposure related to waterborne AGI in Canada attributed to drinking water supplies.

Research questions

Three research questions were addressed in this review:

Q1 What waterborne disease estimates (or models) have been published to date in the context of the developed world?

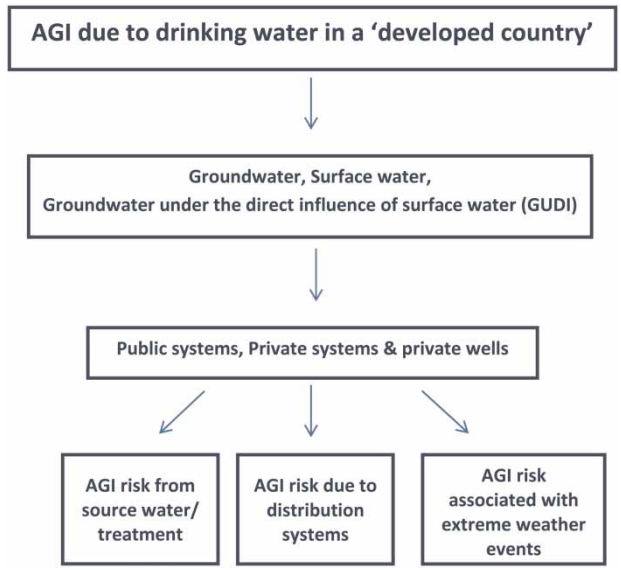

Figure 1 | Routes of exposure for drinking water related AGI in a developed country.

Q2 What epidemiological studies or risk assessments (quantitative studies) have been published to date that examine or quantify the risk of waterborne disease in the context of the developed world that could be used for a burden estimate?

Q3 What expert elicitation studies (qualitative studies) have been published to date that examine the risk of waterborne disease on populations in the context of the developed world that could be used for a burden estimate?

Review protocol

A review protocol was developed using the 'Cochrane Handbook for Systematic Reviews of Interventions' (Higgins & Green 2011). Literature was searched using the following electronic databases: PubMed/MEDLINE, CAB, and Scopus. Titles, abstracts and keywords were searched with relevant search terms (Table 1) using Boolean techniques. In an effort to capture grey literature and reduce publication bias, Google Scholar and ProQuest Dissertations and Theses were also used. The first 100 relevant articles based on inclusion and exclusion criteria (Table 2) retrieved in Google Scholar were exported to RefWorks (Freeman *et al.* 2009; Brooks *et al.* 2013).

A rapid review of the literature identified 1991 as the oldest relevant source year of publication; therefore, a date range of 1990 to present was selected. Only articles published

Table 1 | Search terms used in systematic review of literature on waterborne illness burden methodologies and data sources to support national burden of waterborne disease estimates, 1990–2013

Question	Water terms	Disease terms	Study terms
1. What waterborne disease estimates (or models) have been published to date in the context of the developed world?	Waterborne; 'waterborne disease'; drinking water	Pathogen; pathogens; gastroenteritis; 'AGI'; 'gastrointestinal disease'; diarrhea; diarrhoea	Estimate; estimates; model; models; burden; intervention; interventions; 'disability adjusted life years' (DALY); 'quality adjusted life years' (QALY); 'public health'; 'risk assessment'
2. What epidemiological studies or risk assessments (quantitative studies) have been published to date that examine/quantify the risk of waterborne disease in the context of the developed world?	Waterborne; 'waterborne disease'; drinking water; 'well water'; 'surface water'; groundwater; 'public water'; 'municipal water'	Pathogen; pathogens; gastroenteritis; 'AGI'; 'gastrointestinal disease'; outbreak; outbreaks; diarrhea; diarrhoea	Intervention; interventions; 'randomized control'; household; community; 'epidemiologic study'; 'epidemiologic studies'; 'public health'; 'attributed risk'; incidence
3. What expert elicitation studies (qualitative studies) have been published to date that examine the risk of waterborne disease on populations in the context of the developed world?	Waterborne; 'waterborne disease'; drinking water; 'well water'; 'surface water'; groundwater; 'public water'; 'municipal water'	Pathogen; pathogens; gastroenteritis; 'AGI'; 'gastrointestinal disease'; outbreak; outbreaks; diarrhea; diarrhoea	'Expert opinion'; 'expert elicitation'; estimate; estimates; model; models; 'qualitative method'; 'qualitative methods'; qualitative; 'public health'; survey; surveys

Table 2 | Inclusion/exclusion criteria for a systematic review of literature on waterborne illness burden methodologies and data sources to support national burden of waterborne disease estimates, 1990–2013

Criteria	Population	Study design	Disease estimates	Outcomes
Q1[a]	Must be representative of the Canadian context: a) Restricted to the following regions/countries: North America, Europe, New Zealand, Australia, Japan, Singapore; b) Using any drinking water source (private, public, regulated, unregulated etc …) – (exclude articles that only examine recreational water sources)	Any design (qualitative or quantitative data or mixed methods)	Waterborne disease (do not restrict studies that examine foodborne and waterborne in same study)	Proposes a model or methodology for estimating the burden of disease on a population
Q2	Must be representative of the Canadian context: a) Restricted to the following regions/countries: North America, Europe, New Zealand, Australia, Japan, Singapore; b) Using any drinking water source (private, public, regulated, unregulated etc …) – (exclude articles that only examine recreational water sources)	Any epidemiological studies, analysis of outbreak data	Waterborne disease (do not restrict studies that examine foodborne and waterborne in same study)	Calculate an attributable risk/ disease incidence as a result of drinking a particular water source
Q3	Must be representative of the Canadian context: a) Restricted to the following regions/countries: North America, Europe, New Zealand, Australia, Japan, Singapore; b) Using any drinking water source (private, public, regulated, unregulated etc …) – (exclude articles that only examine recreational water sources)	Any qualitative studies	Waterborne disease (do not restrict studies that examine foodborne and waterborne in same study)	Uses qualitative methods to estimate waterborne disease impact on a population

[a]Q1–Q3 refer to the questions outlined in Table 1.

in English were included. As suggested by Higgins & Green (2011), all relevant journals and conference proceedings that were cited numerous times during the search were hand-searched to ensure no articles were missed. In addition, the reference sections of all 'finalist' articles were hand-searched to identify any further relevant studies (Sargeant *et al.* 2006).

All articles recovered were saved and exported to RefWorks. The search results were merged and deduplicated. All titles and abstracts of articles/publications were preliminarily screened for relevance based on the inclusion/exclusion criteria specified in Table 2. Any title and/or abstract that did not clearly meet the criteria were eliminated in screen 1. Three rounds of relevance screening were performed by three independent researchers on titles and abstracts only. Disagreements were resolved via discussion among reviewers. After the third screen, full articles were examined for relevance. All relevant articles after this fourth screen proceeded to the data extraction phase.

Search terms and inclusion/exclusion criteria

The search terms (Table 1) were divided into three categories: water-related terms, disease terms and study terms. When performing the searches, these terms were separated by the Boolean terms OR/AND. Preliminary inclusion criteria for screen 1 are presented in Table 2. The screening process and results are illustrated in Figure 2.

After the third screen, extraction was based on two questions. If an article did not meet the requirements for these two questions it was excluded from data extraction.

Question 1: Does the article estimate or propose a method to calculate a disease burden due to drinking water? (Include any indicators of disease burden e.g., QALY, disability adjusted life years (DALY), cost, lost work days, risk of infection/illness, etc.) (Rice *et al.* 2006)

Question 2: Does the article fall under one of the seven categories for acceptable types of studies (Table 3)?

Data extraction/analysis

Data extraction focused on the following fields: primary results, methodology/study design, key data sources, study population, study location, drinking water sources, pathogens of concern, definitions of disease, water quality data collected and study limitations. The data extraction process involved categorizing the types of studies that estimate burden (Table 3). Once the articles were classified, a specific set of data extraction questions associated with each category were used to extract relevant information into an Excel database. Results from the data extraction process were analysed by category in a qualitative manner by comparing and contrasting the methods and results.

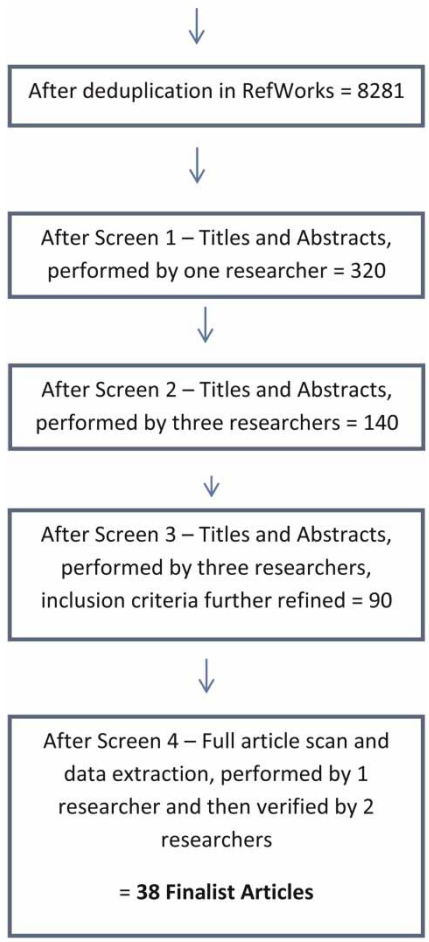

Figure 2 | Systematic review article screening process and results of screens 1–4 for the review of waterborne illness burden methodologies and data sources to support national burden of waterborne disease estimates, 1990–2013.

Qualitative evaluation of two US burden methodologies

Two burden methodologies (Colford *et al.* 2006; Messner *et al.* 2006) were compared to understand the different approaches, identify the main model assumptions and data gaps, and examine the sensitivity of the models to data inputs. Three scenarios were developed using the Messner

Table 3 | Finalist studies retained for data extraction in the systematic review of waterborne illness burden methodologies and data sources that could be used to support national burden estimates, 1990–2013

Category	Number of studies	Authors/publication year
1. Burden methodology: Proposes a methodology for a waterborne disease burden estimate (only methodology- no burden calculated)	3	Chick *et al.* (2003); Havelaar & Melse (2003); Soller (2006)
2. Burden estimate: Determines/calculates a waterborne disease burden estimate for a population using existing data (based on AGI or acute gastroenteritis)	8	Colford *et al.* (2006); Corso *et al.* (2003); Halonen *et al.* (2012); Laursen *et al.* (1994); Messner *et al.* (2006); Morris & Levin (1995); Payment *et al.* (1997); Vinson (2012)
3. Quantitative microbial risk assessment (QMRA)/Risk assessment: Include only QMRAs that use 'real' water quality or epidemiological data	14	Astrom *et al.* (2007); Cummins *et al.* (2010); Eisenberg *et al.* (2006); Hartnett *et al.* (2007); Hunter *et al.* (2011); Lambertini *et al.* (2012); Masago *et al.* (2006); Mena *et al.* (2008); Payment *et al.* (2000); Perz *et al.* (1998); Pintar *et al.* (2012); Ryu & Abbaszadegan (2008); Signor *et al.* (2007); Smeets *et al.* (2007)
4. Outbreak studies: Analyses a waterborne outbreak in a manner that provides a burden of disease (exclude all that do not calculate a burden or produce an OR only)	0	
5. Randomized controlled trials: Intervention study that provides a disease incidence rate and/or relative risk due to exposure to a drinking water source	7	Colford *et al.* (2002, 2005a, b, 2009); Hellard *et al.* (2001); Payment *et al.* (1991, 1997)
6. Sporadic/Endemic epidemiological studies: Studies that look at endemic waterborne disease to determine a disease burden estimate (exclude studies that only produce OR only)	6	Borchardt *et al.* (2003, 2012); Eisenberg *et al.* (2002); Frost *et al.* (2009); Nygard *et al.* (2007); Goh *et al.* (2005)
7. Qualitative methodology	0	

et al. (2006) and Colford *et al.* (2006) model frameworks (point estimate and stochastic models were produced). The scenarios were created using the Microsoft Excel Palisade @Risk Software (Version 5.7) add-on. Simulations were run with 10,000 iterations and the mean, upper and lower 90% credible bounds are presented. Sensitivity analyses were performed by examining the regression relationships between variable inputs and key outputs.

RESULTS

For the systematic review, the initial database searches yielded a total of 17,981 references. Thirty-eight articles met the selection criteria and were retained for data extraction (Table 3). The breakdown of articles by category was as follows: 14 quantitative microbial risk assessment (QMRA) articles, 13 epidemiological studies (seven randomized controlled trials (RCTs), six sporadic/endemic studies) and 11 burden estimates or methodologies.

Risk assessment and infectious disease transmission models

QMRA is a methodology that can be used to quantify and predict potential health risks and has been identified as a possible method to quantify the burden of waterborne disease (Soller 2006). In this review, 14 risk assessment studies and infectious disease transmission models were identified that quantified waterborne disease burden using site-specific water quality or epidemiological data (Perz *et al.* 1998; Payment *et al.* 2000; Eisenberg *et al.* 2006; Masago *et al.* 2006; Astrom *et al.* 2007; Hartnett *et al.* 2007; Signor *et al.* 2007; Smeets *et al.* 2007; Mena *et al.* 2008; Ryu & Abbaszadegan 2008; Cummins *et al.* 2010; Hunter *et al.* 2011; Lambertini *et al.* 2012; Pintar *et al.* 2012). All but one study collected or used water quality data as inputs into their assessments. In total, eight were single-pathogen studies, while six were multi-pathogen assessments (Table 4). Studies were performed in the USA, Canada, Ireland, Sweden, UK, France, Japan and Australia.

Table 4 | Risk assessment studies included in the systematic review of waterborne disease burden methodologies, organized by pathogen

Pathogen	Number of studies	Location of studies	References
Cryptosporidium	10	Australia	Signor *et al.* (2007)
		Canada	Hartnett *et al.* (2007); Pintar *et al.* (2012)
		England	Hunter *et al.* (2011)
		France	Hunter *et al.* (2011)
		Ireland	Cummins *et al.* (2010)
		Sweden	Astrom *et al.* (2007)
		UK	Smeets *et al.* (2007)
		USA	Perz *et al.* (1998); Eisenberg *et al.* (2006); Ryu & Abbaszadegan (2008)
Giardia	7	Australia	Signor *et al.* (2007)
		Canada	Payment *et al.* (2000); Hartnett *et al.* (2007)
		England	Hunter *et al.* (2011)
		France	Hunter *et al.* (2011)
		Sweden	Astrom *et al.* (2007)
		USA	Eisenberg *et al.* (2006); Ryu & Abbaszadegan (2008)
Enteric viruses (culturable and real-time polymerase chain reaction (qPCR) quanitified)	3	USA; Japan	Eisenberg *et al.* (2006); Lambertini *et al.* (2012); Masago *et al.* (2006)
Norovirus	3	Sweden; USA; Japan	Astrom *et al.* (2007); Lambertini *et al.* (2012); Masago *et al.* (2006)
Enterovirus	2	Sweden; USA	Astrom *et al.* (2007); Lambertini *et al.* (2012)
Rotavirus	1	Canada	Hartnett *et al.* (2007)
Campylobacter	1	Australia	Signor *et al.* (2007)
Salmonella	1	USA	Mena *et al.* (2008)
E. coli O157:H7	1	Canada	Hartnett *et al.* (2007)

Two of the studies focused on distribution system risk, while the remainder focused on risk due to the source/treatment component of water supply. *Cryptosporidium* and *Giardia* were the most common pathogens (12/14) identified in this review.

Nine of the 14 studies focused on public surface water supplies exclusively (Payment *et al.* 2000; Eisenberg *et al.* 2006; Masago *et al.* 2006; Astrom *et al.* 2007; Hartnett *et al.* 2007; Signor *et al.* 2007; Smeets *et al.* 2007; Ryu & Abbaszadegan 2008; Pintar *et al.* 2012). One study focused on the risk due to public groundwater supplies and the associated distribution systems (Lambertini *et al.* 2012). Mena *et al.* (2008) studied the risk associated with a cross-contamination event simulated in a pilot distribution system (pipe loop). One study focused exclusively on private groundwater supplies in the UK and France, where *E. coli* indicator data were used as a surrogate to estimate risk due to *Cryptosporidium* in these supplies (Hunter *et al.* 2011). An Irish study examined the risk due to private wells, public surface water and public groundwater supplies (Cummins *et al.* 2010). One final study of *Cryptosporidium* risk for New York City did not specify the nature of the water supply (Perz *et al.* 1998).

Epidemiological studies

Epidemiological studies were divided into three categories: RCTs, outbreak studies and sporadic/endemic epidemiological studies. Seven RCTs, six sporadic/endemic studies and zero outbreak studies were retained for data extraction in this review.

Randomized controlled trials

The RCTs included in this review are of published household drinking water intervention trials conducted in contexts relevant to Canadian drinking water systems. In

these trials, one group of households was randomly assigned to use an in-home intervention; in these studies, a household water filter was installed under the tap. The other group of households served as the control group and had no intervention. Theoretically, the two groups of households are representative of one another with the only difference being the intervention. Under this assumption, the researchers attribute detectable differences in self-reported illness between the two groups to the presence/absence of the household water intervention (Rothman 2012). However, household intervention trials assume all exposures to water are through a particular tap in the home, therefore failure to account for different exposures can tend to err on the side of no effect of the treatment device (null hypothesis). Consequently, water-attributed risk may be underestimated in these studies.

Five of the seven RCTs in this review were included in previous reviews by Colford *et al.* (2006) and Messner *et al.* (2006) as background to their USA burden estimates and therefore will not be discussed in detail here. In addition to these five trials, one trial conducted by Colford *et al.* (2005a) on HIV+ populations was included in the present review. Since 2006 when the USA burden estimates were published, Colford *et al.* (2009) conducted a trial on an older adult population that was also included herein. The trials were conducted on households served by community/municipal drinking water supplies using surface water or groundwater under the influence of surface water. No household RCT done on public groundwater sources or private wells was identified. All seven trials are described further in Table 5. These studies represent the only identified published household water intervention trials conducted in developed countries over the past three decades. This is not surprising since these studies are costly and time-consuming (Colford *et al.* 2006). The more recent trials by Hellard *et al.* (2001) and Colford *et al.* (2005b) were blinded and thus represent the 'gold standard' of RCTs. Both trials reported no significant difference between the intervention and control groups (Hellard *et al.* 2001; Colford *et al.* 2005b). The tap water leaving the plants and distributed throughout the water distribution system during both trials was reported to be of high quality (Hellard *et al.* 2001; Colford *et al.* 2005b). In the Colford *et al.* (2005b) study, the authors suggest that the lack of significant difference in illness rates observed between the control and intervention groups was attributed to the fact that more stringent water treatment regulations were in place. As a result, the authors concluded that the risk to tap water consumers in the system studied was limited. Both the Hellard *et al.* and Colford *et al.* studies noted that to detect an expectedly low attributable risk to treated drinking water, a much larger sample size would need to be used, and this would result in substantially greater trial costs (Hellard *et al.* 2001; Colford *et al.* 2005b).

Conversely, Payment *et al.* (1991, 1997) reported that both of their studies documented significant differences between intervention and tap water groups. These studies, however, were not blinded, potentially biasing the results (Noseworthy *et al.* 1994; Colford *et al.* 2002). At the time of the studies, it has been reported that the City of Laval distribution system was prone to more low pressure events and main breaks, and maintained a lower chlorine residual than what is generally applied today, potentially contributing to the higher attributable risk reported (Besner *et al.* 2010).

Sporadic/endemic epidemiological studies

Six epidemiological studies that focused on sporadic (endemic) disease were included in the review (Table 6). The studies vary in design, purpose, water source and target population (Table 6). All six studies estimated waterborne disease burden due to a water-related intervention (intentional or unintentional in the case of distribution system events) or the studies linked a particular water source to an increased incidence of illness at the community level (Eisenberg *et al.* 2002; Borchardt *et al.* 2003, 2012; Goh *et al.* 2005; Nygard *et al.* 2007; Frost *et al.* 2009). Sporadic/endemic disease studies tend to test various hypotheses until significance is found, consequently suggesting that publication bias may be an issue and that any review of the published literature may miss studies where no effect was observed (and thus not published).

Borchardt *et al.* (2003) links septic system density with diarrhoeal disease incidence in children. The study suggests that there is an independent relationship between the occurrence of diarrhoea in children and consumption of water

Table 5 | Summary of randomized controlled household drinking water intervention trials examined in the present systematic review of waterborne disease burden methodologies which could serve as potential data sources for a national burden estimate

Author/ publication date	Study area	Source water	Treatment	Use of blinding/ use of inactive (sham) treatment device	Study design	Recruitment and response rate	Study population	Study dates	Length of follow-up	Sample size (HH[a]/ individuals)	Drinking water treatment methods evaluated	Attributable risk % due to drinking water
Payment *et al.* (1991)	Laval, Canada	River water	Flocculation, rapid sand filtration, ozonation, chemical disinfection	No	RCT[b]	Randomly selected from study area directory and phoned; 3,741 households contacted/ 606 enrolled	General population: homeowners with one child 2–12 years old (did not exclude immunocompromised individuals)	Jan. 1988–June 1989	12 months	606/2,408	Reverse osmosis, tap water	AR[c] (% of all GI cases): 35% excess in tap water consumer group
Payment *et al.* (1997)	Laval, Canada	River water	Flocculation, rapid sand filtration, ozonation, chemical disinfection	No	RCT	Randomly selected from study area directory and phoned; 4,342 households contacted/ 1,590 enrolled		Sept. 1993–Dec. 1994	16 months	1,062/5,253	Tap water w/purge valve, bottled plant water, bottled purified water, tap water	AR: 12% excess cases in tap group
Hellard *et al.* (2001)	Melbourne, Australia	Surface water source from protected catchment	Chlorination	Yes[d]	RCT	Households were mailed invitations, they contacted researchers if they wanted to participate; 10,918 households mailed info/600 enrolled	General population: homeowners with one child 2–12 years old (excluding those with immunocompromising conditions)	May 2000–May 2001	12 months	714/988	UV and 1-micron filter, inactive device (control) UV and 1-micron filter, inactive device (control)	AR: 4% of all GI cases attributable to tap water No sig.[e] difference (IRR[f] = 0.99)
Colford *et al.* (2002)	Contra Costa County, USA	Surface water source	Conventional treatment and chlorination (ozonation added during study)	Yes[g]	RCT	Mailed flyer, households contacted researchers; 29,515 flyers mailed out/80 enrolled		March 1999–Oct. 1999	4 months	50 individuals		AR: 24% of all GI cases attributable to water; sample size too small to evaluate illness
Colford *et al.* (2005a, b)	Davenport, USA	River water	Conventional treatment with granular activated carbon/sand filters and chlorination	Yes[g]	RCT (with cross-over)	Solicitations sent out to 38,353 households; 1,421 households contacted researchers/ 456 enrolled		Oct. 2000–May 2002	12 months	456/1,296		AR: -0.008% to -0.08% of all GI cases attributable to water No sig. difference (IRR = 0.98)
Colford *et al.* (2005a)	San Francisco, USA	Surface water	Chlorination or filtration and chlorination in some cases (18% of the water supply is filtered)	Yes[g]	RCT	Mailed flyer, clinic visit or telephone calls made to recruit patients who were enrolled at Infectious Disease Clinic; 339 screened/50 enrolled	HIV+ patients, age >30 years old	May 2000–May 2001	4 months	?/50		AR: 70% (CI[h] 0–91%) Borderline sig. difference between groups, larger sample needed (OR = 3.34; CI = 0.99–11.21).
Colford *et al.* (2009)	Sonoma County, USA	GUDI[i] supply; chlorination		Yes[g]	RCT (with cross-over)	Mailed flyer to two groups (existing cohort of elderly and from study area); 4,391 households screened/714 enrolled	Elderly >55 years old (excluding immunocompromised individuals)	Apr. 2001–Jul. 2006	12 months	714/988		AR: 12% excess cases in tap water group

[a]HH = Households.
[b]RCT = Randomized controlled design.
[c]AR = Attributable risk.
[d]Double-blinded study (study subjects and analysts).
[e]sig. = significant.
[f]IRR = incidence rate ratio.
[g]Triple-blinded study (study subjects, analysts and plumbers that installed treatment devices).
[h]CI = Confidence interval.
[i]GUDI = Groundwater under the direct influence of surface water.

Table 6 | Summary of sporadic/endemic epidemiological studies examined in the present systematic review of waterborne disease burden methodologies which could serve as potential data sources for a national burden estimate

Author, publication date	Study area	Study design	Study population	Sample size	Water source(s)	Primary results (related to water exposure and health outcome)
Borchardt *et al.* (2003)	Wisconsin, USA	Case control trial	Children aged 1–18; immunocompetent only	Cases = 153; Controls = 274	Untreated private wells	Population AR[a]: 11% of diarrhoea in children attributable to drinking private well water positive with faecal enterococci
Borchardt *et al.* (2012)	Wisconsin, USA	Community intervention trial	Households, all ages except 13–18; immunocompetent only	440 HH[b] (413 adults, 765 children)	Public groundwater supplies	AGI AR due to viruses in groundwater = 6% and 22%, (authors suggest as high as 63% among children <5 years of age when NoV-GI was abundant in drinking water)
Eisenberg *et al.* (2002)	California, USA	Cross-sectional survey	HIV+ patients	226 HH/ 458 individuals	Boiled, bottled, tap water	AGI AR avoided from boiled water consumption = 64%; Result between always and never drinking boiled water; Adjusted RR[c] boiled = 0.61 (CI 0.29–1.31) AGI AR risk due to bottled water consumption = 26%; Result between always and never drinking bottled water was not significant; Adjusted RR bottled = 1.35 (CI 0.84–2.18)
Frost *et al.* (2009)	Northwest city, USA	Community interventional trial	Households with child 2–10 years old and/or adult >65	Controls = 164 HH/361 individuals intervention = 277 HH/711 iIndividuals	Unfiltered chlorinated surface water , surface water treated conventionally with 1 and 2 disinfection	GI AR~ 11%; Incidence rate ratio (IRR) for GI in intervention and control households = 1.12 (CI 0.87–1.43); no significant difference in illness as a result of intervention
Nygard *et al.* (2007)	Norway	Cohort study	Household; all ages	Exposed = 616 HH; Unexposed = 549 HH	Study of drinking water distribution system events; water sources not specified	AGI AR: 37% for households exposed to distribution system episodes compared to those that were not exposed
Goh *et al.* (2005)	UK	Case control trial	Individuals, all ages	Cases = 175; Controls = 537	Unfiltered chlorinated surface water, membrane treated chlorinated surface water	AGI AR ~ −79% (reduction due to membrane treatment); Adjusted IRR=0.207 (0.0099–0.431) of cryptosporidiosis for those exposed to improved water treatment compared to those that were not

[a]AR = Attributable risk.
[b]HH = Households.
[c]RR = Relative risk.

from private wells contaminated by faecal enterococci. The second study by Borchardt *et al.* (2012) was a large-scale study conducted on public groundwater systems in Wisconsin. The study examined virus occurrence in treated distributed drinking water and pooled AGI-incidence data collected from household surveys. Households were considered 'exposed' to viruses if one or more of their community samples were positive for enteric viruses. This is the first study that has attempted to quantify the burden of waterborne AGI due to untreated groundwater. It is also one of the few studies that has measured viruses in groundwater and linked virus occurrence to health (Locas *et al.* 2008).

In a cross-sectional study of HIV+ patients that reportedly consumed boiled tap water, tap water directly or bottled water, no significant findings were reported regarding disease reduction between the different groups (Eisenberg *et al.* 2002). Frost *et al.* (2009) conducted a community intervention trial on a municipal surface water system and did not report any significant findings with respect to disease reduction in the intervention group compared to the control group. Goh *et al.* (2005) conducted a study on the effect of membrane filtration on cryptosporidiosis in the United Kingdom. It was found that membrane filtration may be responsible for up to a 79% reduction of cryptosporidiosis cases (Goh *et al.* 2005). The study by Nygard *et al.* (2007) on drinking water distribution systems in Norway, examined the effects of distribution system events on gastrointestinal health. They reported that up to 37% of diarrhoeal illnesses were attributed to events in the distribution system such as main breaks or maintenance work.

Burden methodologies and estimates

This systematic review identified 11 publications that propose and/or produce a waterborne disease burden estimate (Laursen *et al.* 1994; Morris & Levin 1995; Payment 1997; Chick *et al.* 2003; Corso *et al.* 2003; Havelaar & Melse 2003; Colford *et al.* 2006; Messner *et al.* 2006; Soller 2006; Halonen *et al.* 2012; Vinson 2012). Three papers presented approaches (Chick *et al.* 2003; Havelaar & Melse 2003; Soller 2006), while eight presented a methodology and produced an estimate (Laursen *et al.* 1994; Morris & Levin 1995; Payment 1997; Corso *et al.* 2003; Colford *et al.* 2006; Messner *et al.* 2006; Halonen *et al.* 2012; Vinson 2012). A summary of the main components of each of the 11 studies is presented in Table 7. The studies are predominantly from the United States and were mostly published in the 2000s. There were two Canadian studies that quantified economic burden due to waterborne disease (Payment 1997; Vinson 2012). The studies, included in Table 7, focus primarily on waterborne disease due to tap water exposure and on pathogens that cause AGI. A variety of burden metrics including cases of illness/infection, lost work days, financial burden and DALY were used. Seven of 11 studies use a point estimate methodology to quantify burden, while four propose/use modelling techniques to formally capture the uncertainty and variability in the inputs and final estimates (Table 7).

Articles that focus solely on the method to quantify the burden of endemic human cases of AGI to the consumption of treated municipal tap water

Three papers proposed methodologies rather than produce a true burden estimate (Chick *et al.* 2003; Havelaar & Melse 2003; Soller 2006). Chick *et al.* (2003) proposed the use of a stochastic infection model to forecast infection probability of pathogens in treated drinking water in the United States. The model accounts for secondary transmission (person-to-person and recontamination of water by infected individuals and recreational water exposure, etc.) which is explained in more detail by Chick *et al.* (2001). They propose that endemic disease incidence data collected by the CDC along with water quality data collected by the USEPA could be used with stochastic methods to estimate secondary transmission parameters. *Cryptosporidium* exposure in New York City was used as a case study to verify the approximations in the model. The paper proposes a modelling approach rather than producing an actual estimate of the burden of waterborne disease in the United States (Chick *et al.* 2003).

In 2003, Havelaar and Melse published a methodology with the World Health Organization (WHO) to apply DALYs as a metric to illustrate the magnitude of disease burden attributed to treated drinking water (Havelaar &

Table 7 | Summary of published methodologies to attribute waterborne disease to treated drinking water supplies, including important data and knowledge gaps identified by the authors that will help inform future estimates

Author, publication date	Location	Measure of burden	Endemic/ outbreak	Type of water supply	Burden approach	Model data inputs	Data/knowledge gaps
Chick *et al.* (2003)	New York, USA	Risk of infection	Endemic	Community supplies	Propose the use of a stochastic/ dynamic model (including secondary infection)	Community intervention trial data; Water quality monitoring data	Secondary infection parameters for microbes; Data on shedding of microbes; Simultaneous illness prevalence rates and water quality monitoring data
Soller (2006)	USA	Risk of infection/ illness	Endemic	Community supplies	Proposes that a microbial risk assessment (MRA) model could be used to inform a national estimate	Pathogen occurrence data; Population at risk; Dose response; Relationships; Secondary infection rates	Not many MRAs on distribution systems; Risk associated with transient small water systems unknown
Havelaar & Melse (2003)	WHO, global level	Disability adjusted life years (DALYs)	Endemic and outbreak	Not specified	Proposes using DALYs as a measure for disease burden (calculated from number of cases, severity and duration of the specific illness); Final step in a disease model	Cases of infection(s); Duration of illnesses; Severity of illnesses	Need for quality epidemiological data; Severity weights lacking for drinking water-related illnesses; Guidance on how to use limited epidemiological data in MRA is needed
Colford *et al.* (2006)	USA	Annual cases of AGI	Endemic	Community supplies	Point estimates based on multiplication of inputs	% of community water systems at high and low risk	Distribution systems AGI; Groundwater-related AGI; AGI due to private wells/small unregulated systems; Missing data on vulnerable populations
Messner *et al.* (2006)	USA	Annual cases of AGI	Endemic	Community supplies; Groundwater and surface water	Monte Carlo modelling approach	Data from Payment RCTs; Expert opinion, USEPA water quality monitoring data	Distribution systems AGI; Groundwater-related AGI; AGI due to private wells/small unregulated systems
Morris & Levin (1995)	USA	Average number of GI infections (by pathogen)	Endemic and outbreak	All tap water	Burden calculated by pathogen (bacteria, viruses, protozoa) using point estimates	Literature data from past epi studies, outbreak data and CDC surveillance data	Large variability in point estimates; Unknowns regarding viral diseases and emerging pathogens such as *Cryptosporidium*
Payment (1997)	Canada	Cost associated with GI illness	Endemic	Community supplies	Point estimates based on multiplication of inputs (# cases * cost/case)	Proportion of AGI that is due to tap water (Payment RCTs); Cost per illness; # cases of AGI annually	Health risks due to ageing distribution and treatment infrastructure
Vinson (2012)	Canada	Cost associated with waterborne illness	Endemic and outbreak	All waterborne disease	Point estimates based on multiplication of inputs (# cases * cost/case)	Data from literature regarding # of cases; UK, US, Canadian healthcare costs; Canadian productivity costs	US data used for estimate
Corso *et al.* (2003)	Milwaukee, USA	Cost of illness	Outbreak	Community supply	Phone survey of households affected by outbreak; Point estimates based on multiplication of inputs	% population affected by diarrhoea (mild, moderate and severe) following an outbreak; Medical costs; Indirect costs (time lost due to illness; time lost due to caregivers to sick)	Inadequate data in hospital and financial records to account for all costs (e.g., physician visits, ambulance costs, self-medication); Illness among visitors not quantified; Data for costs to businesses, government, etc.
Halonen *et al.* (2012)	Nokia, Finland	Cost of lost work days	Outbreak	Community supplies (distribution system contamination)	Retrospective study of sick leave following a contamination event; Point estimate of burden (# cases * cost/case)	Sick leave data from workers before, during and following event; GPS coordinates of workers	Sick leave data could not be directly linked to GI incidence because these data were unavailable
Laursen *et al.* (1994)	Uggelose, Denmark	Cost of lost work days	Outbreak	Community supply (contamination of a well with sewage)	Retrospective household questionnaire following outbreak; Point estimate of burden (# cases * cost/case)	# lost days of productivity; Cost per lost day	Healthcare costs; Questions around heavy precipitation and onset of GI symptoms in the community

Melse 2003). The proposed approach was not country-specific, but rather offers a template for others to reproduce estimates for specific pathogens. They propose applying a DALY approach to the final step of a disease model by taking the final number of cases of illness (by pathogen) and multiplying them by severity weights and duration estimates, which they provide, for typically waterborne cases of AGI. This approach is therefore an add-on to the estimation of the cases of illness attributed to a treated drinking water supply, but provides a mechanism for quantifying the economic and public health impact of these cases of disease on a country.

In 2006, Soller proposed a microbial risk assessment (MRA) framework that could be used to inform a national estimate of drinking water-related AGI, provided all pathogens are accounted for in the risk assessment and summed to give an overall estimate. The proposed risk assessment approach involves dividing the model into a source/treatment component and distribution system component that can be modelled either statically or dynamically (including secondary infection).

Articles that present a burden methodology and produce a country-specific estimate of waterborne disease attributed to treated drinking water systems

Eight studies were identified that provide a methodology and produced an estimate for waterborne illness attributed to treated drinking water supplies in the USA, Canada, Finland and Denmark (Laursen *et al.* 1994; Morris & Levin 1995; Payment 1997; Corso *et al.* 2003; Colford *et al.* 2006; Messner *et al.* 2006; Halonen *et al.* 2012; Vinson 2012). Five studies quantify burden on a national level (Morris & Levin 1995; Payment 1997; Colford *et al.* 2006; Messner *et al.* 2006; Vinson 2012), while three quantify the burden attributed to specific outbreak situation in Denmark, the USA and Finland (Laursen *et al.* 1994; Corso *et al.* 2003; Halonen *et al.* 2012).

Five studies produced economic burden estimates (following the calculation of cases) and three provided a number of cases of illness or infection (Table 8). The economic measures included costs attributable to lost work days, lost productivity, and medical costs associated with

Table 8 | Summary of burden of waterborne disease estimates identified in this review

Author, publication date	Location	Illness	Burden indicator	Type of burden estimate	Burden estimate
Cases of illness					
Morris & Levin (1995)	USA	Pathogens that cause GI illness	Average number of infections (by type of illnesses)	National	Moderate to severe: 560,000 cases; Mild to moderate: 7,100,000 cases
Colford *et al.* (2006)	USA	AGI	Annual cases of AGI	National	4.26–11.69 million cases
Messner *et al.* (2006)	USA	AGI	Annual cases of AGI	National	16.4 million cases
Economic burden					
Corso *et al.* (2003)	Milwaukee, USA	*Cryptosporidium*-related GI illness	Cost associated with illness	Outbreak	96.2 million dollars (cost of Milwaukee outbreak)
Halonen *et al.* (2012)	Nokia, Finland	GI illness	Cost of lost work days	Outbreak	1.8–2.1 million Euros (due to outbreak)
Laursen *et al.* (1994)	Uggelose, Denmark	GI illness	Cost of lost work days	Outbreak	1.6 million Danish Kroner
Payment (1997)	Canada	AGI illness	Cost associated with illness	National	40.3–107.5 million dollars
Vinson (2012)	Canada	AGI illness and respiratory (Legionella)	Cost associated with illness	National	2.7 billion dollars

AGI illness. The studies were conducted in the USA, Canada, Finland and Denmark. The estimates for the United States ranged from 4.26 to 16.4 million cases of AGI attributable to tap water (Morris & Levin 1995; Colford *et al.* 2006; Messner *et al.* 2006). The economic burden estimates for Canada ranged from $40.3 million to $2.7 billion Canadian for tap water-related illnesses and all waterborne illnesses, respectively (Payment 1997; Vinson 2012). The remaining three articles estimated burden due to specific outbreak events. The burden due to outbreaks in the USA, Finland and Denmark were 96.2 million US dollars, 1.8–2.1 million Euros (~2.46–2.87 million US dollars) and 1.6 million Danish Kroner (~290,000 US dollars), respectively (Laursen *et al.* 1994; Corso *et al.* 2003; Halonen *et al.* 2012).

The three studies that calculated the number of cases of illness were produced by Morris & Levin (1995), Colford *et al.* (2006) and Messner *et al.* (2006). Morris & Levin (1995) calculated the number of illnesses by pathogen (*Salmonella, Shigella, E. coli, Campylobacter, Giardia*, *Cryptosporidium*, viruses), while Colford *et al.* (2006) and Messner *et al.* (2006), calculated the number of cases of AGI due to drinking water. Colford *et al.* (2006) and Morris & Levin (1995) produced crude point estimates in terms of cases of illness per year. Messner *et al.* (2006) refined the methodology by incorporating a Bayesian approach to estimating some of the data inputs, and used Monte Carlo simulation to account for the uncertainty and variability inherent in the data inputs used. Key aspects of each study, and inherent assumptions and knowledge gaps that were identified are presented in Table 7.

Morris & Levin (1995) developed an estimate using surveillance/outbreak case numbers, values from the literature and expert opinions. Values from the literature were used to inform any gaps in surveillance/outbreak data or to substantiate any assumptions. For instance, they used numbers from Britain to estimate the number of total cases of *Campylobacter* annually in the USA. Expert opinions were used from a study of experts at the CDC (Bennett *et al.* 1987) who estimated for various pathogens (*Salmonella, Shigella, E. coli, Campylobacter, Giardia*, *Cryptosporidium*, viruses) the per cent of cases that were attributable to different sources including water. For each pathogen included in the estimate, they present low, high and crude point estimates for the annual number of cases of illness due to drinking water in the United States. They also predict the number of mortalities for each pathogen based on published mortality proportions for each pathogen. In addition, the pathogens were grouped by the severity of the infection, where a moderate-to-severe infection was defined as 'case fatality rate of greater than or equal to 0.1%'. Moderate to severe illnesses included: *Salmonella, Shigella, E. coli and Campylobacter,* while mild to moderate cases included: *Giardia*, *Cryptosporidium*, and viruses. Within each category, the results were summed to give a total number of moderate-to-severe cases, and mild-to-moderate cases of illness due to drinking water.

The Colford *et al.* (2006) approach is based on the use of data from five randomized controlled trials (RCTs) that have estimated the proportion of cases of AGI attributable to drinking water (Payment *et al.* 1991, 1997; Hellard *et al.* 2001; Colford *et al.* 2002, 2005a, b). This proportion is then applied to the estimated number of cases of AGI per person annually in the USA. Using the percentage of the US population supplied by municipal systems and data on the number of systems that did not consistently meet regulatory requirements, they estimated a proportion of the population being served by 'high risk' and 'low risk' systems (a 10-fold difference in risk between these). Similar to the Soller (2006) approach, they separate risk into 'distribution system risk' and 'source/treatment risk'. Various scenarios are modelled by adjusting the risk attributed to the distribution system component and source/treatment component as well as the population exposed to high/low risk source waters. Colford *et al.* (2006) note that the approach could be refined to account for vulnerable populations (the young, elderly and immunocompromised) as data become available.

The Messner *et al.* (2006) approach is similar to the Colford *et al.* (2006) approach. Specifically, Messner *et al.* (2006) divide the estimate into a source/treatment component and a distribution system component. They also use data from two RCTs (Payment *et al.* 1991, 1997) to estimate the risk of AGI attributable to tap water consumption. Using expert opinion, they subsequently rank US community drinking water supplies with respect to the system studied in the RCTs to establish AGI incidence distributions. Examination of US monitoring data along with expert opinion is used to quantify the variability in

source/treatment and distribution system AGI risk. The final estimate is calculated by applying these inputs to a lognormal distribution (researchers assume AGI incidence is lognormally distributed) to produce an estimated number of cases per person-year of AGI due to drinking water. The number of cases per person-year is translated to the proportion of the population served by community water supplies (CWS) in the United States.

As presented in Table 5, five studies included in this review calculate the economic costs of waterborne disease (Laursen *et al.* 1994; Payment *et al.* 1997; Corso *et al.* 2003; Halonen *et al.* 2012; Vinson 2012). Laursen *et al.* (1994) conducted an historical follow-up study with a structured postal questionnaire following an outbreak in Denmark. The data collected from study participants included: demographic status, consumption of water, symptoms of gastroenteritis, physician contacts and sick leave taken during a specified time period following the outbreak incident. They found that 1,658 sick days were taken as a result of the outbreak. Payment (1997) used data from the literature and from his two RCTs (from Laval, Canada) to make assumptions regarding AGI attributable to tap water exposure and to subsequently estimate costs associated with waterborne illness in Canada. Vinson (2012) used data from predominantly grey literature, and made numerous assumptions to calculate a crude estimate of non-AGI specific waterborne disease (legionellosis, outbreak and endemic AGI cases, mycoplasma pneumonia and toxoplasmosis) due to all exposures (drinking, recreational exposure, premise plumbing). Following the Milwaukee outbreak, Corso *et al.* (2003) conducted a phone survey of 613 households to determine the number of people with mild, moderate and severe illness. Average cost of illness was determined by adding direct medical costs and indirect costs associated with loss of productivity. Total costs were determined by taking the average cost of illness multiplied by the burden of illness (mild, moderate and severe). Halonen *et al.* (2012) conducted a retrospective study of sick leave of Finnish public sector employees prior to, and following, a waterborne outbreak for those exposed and unexposed to the contaminated water. The difference in number of sick days used between the unexposed and exposed was assumed to be attributed to the outbreak and cost of lost work days was calculated accordingly.

Comparison of burden methodologies

The burden approaches presented by Colford *et al.* (2006) and Messner *et al.* (2006) for the United States were further explored. These approaches were compared using a US population of 182 million served by community surface water supplies and 90.5 million served by groundwater supplies (Colford *et al.* 2006). Some of the initial inputs used by Colford *et al.* (2006) and Messner *et al.* (2006) were modified to consider relevant data reported since 2006. In addition, a third estimate was produced by a stochastic approach to Colford *et al.* (2006) method to consider uncertainty and variability of the inputs and output.

All assumptions are outlined in Table 9 for each of the published approaches. Table 10 presents a comparison of the final results of the approaches by Colford *et al.* (2006) and Messner *et al.* (2006). In comparing the estimates, the mean number of AGI cases attributable to drinking water from CWS for the United States ranged from 3.09 to 18.48 million per year. This represents a mean value between 0.011 and 0.069 cases per person-year for those people on CWS. Colford *et al.* (2006) and Messner *et al.* (2006) reported ranges 0.0156 to 0.043 cases per person-year and 0.02 to 0.12 cases per person-year, respectively, among the population served by CWS in the United States. The low end of the scenario estimate was derived by applying the Modified Colford Approach. On the upper end, the scenario estimates exceeded the numbers produced by Messner *et al.* (2006) even though most of the same assumptions were used in the model. This occurred because, for the present analysis, the lognormal distribution was not truncated at two cases per person-year, as done by Messner *et al.* (2006). It was assumed that the extremes in the distributions modelled could represent vulnerable populations such as young children, the elderly and the immunocompromised and therefore truncating the model was not necessary.

The two Colford *et al.* (2006) approaches are most sensitive to the attributed risk due to drinking water (based on the values from Payment *et al.* 1991, 1997; Hellard *et al.* 2001; Colford *et al.* 2002, 2005a, b), the overall AGI incidence rate due to all causes and the per cent

Table 9 | Assumptions used to compare Colford *et al*. (2006) and Messner *et al*. (2006) approaches used to produce national waterborne disease burden estimates for the United States in terms of AGI attributable to community drinking water supplies

Key model elements	Colford *et al.* (2006)	Modified Colford approach	Messner *et al.* (2006)
Method applied	Point estimates	Stochastic modelling	Stochastic modelling
AGI AR[a] assigned to surface water	AR due to SW = 12%[b]	Surface water AR due to SW/TR[c]; PERT (Min 0%; Most likely 10.2%; Max 22.2%)[b]	Fraction of AGI due to SW/TR for SW systems = Uniform Distribution (0.20/0.26 to 0.24/0.26)
AGI AR assigned to groundwater	AR due to GW = 12.5%[d]	Groundwater AR due to SW/TR – PERT (Min 5.1%; Most likely 10.7%; Max 14.9%)[d,e]	Fraction of AGI due to SW/TR for GW systems = Uniform Distribution (0.065/0.17 to 0.255/0.256)
Population served by high risk surface water systems	7.6% of SW users consume water of high risk[f]	PERT distribution (similar to Beta distribution) for SW users at risk (Min 3.1%; Most likely 5.4%; Max 7.6%)[f]	Not applicable
Population served by high risk groundwater systems	5.4% of GW users consume water of high risk[f]	PERT distribution (similar to Beta distribution) for GW users at risk (Min 3.1%; Most likely 5.4%; Max 7.6%)[f]	Not applicable
Assigned risk between low and high risk systems	10-fold difference between systems of low and high risk	10-fold difference between systems of low and high risk	Log range in SW/TR[c] and DS[g] system risk variability = Uniform Distribution (2.0–5.0)
Ranking of the RCTs with respect to US Systems	Not applicable	Not applicable	Ranking of the Laval and Wisconsin systems (SW/TR risk) with respect to US systems = Uniform Distribution (0.90–0.995); Ranking of the Laval and Wisconsin DS risk = Uniform Distribution (0.70–0.99)
AGI AR assigned to the distribution system	AR varied between SW/TR and DS risk: 10% due to SW/TR; 90% due to DS; 10% due to DS; 90% due to SW/TR; 50% due to DS; 50% due to SW/TR	Distribution system AR – PERT (Min 0.1%; Most likely 1.8; Max 4.9%)[e]	Fraction of AGI due to DS = 1 - Fraction due to SW/TR

[a]AR = Attributable risk.
[b]Based on Colford *et al.* (2006) (mean of five randomized control trials and corresponding min and max values); in the Monte Carlo simulation these values were adjusted based on the AR% that could be due to the DS using values from Lambertini *et al.* (2012).
[c]SW/TR = Source water/treatment.
[d]Assumes AR% range of 10–15% (Mean 12.5%) for groundwater.
[e]Risk due to distribution system assumed based on finding from Lambertini *et al.* (2012).
[f]USEPA Regulatory monitoring (Colford *et al.* 2006).
[g]DS = Distribution system.

of the population consuming water of high risk ($r = 0.95$, 0.17, 0.16). In the Messner *et al.* (2006) approach, the model was most sensitive to the log range for source water/treatment variability and distribution system variability for both water types (surface water and groundwater) ($r = 0.33$, 0.29, −0.21, 0.16). In addition, the results were sensitive to the ranking of Laval (Payment *et al.* 1991, 1997) and Wisconsin (Borchardt *et al.* 2012; Lambertini *et al.* 2012) among the US population source/treated waters and distribution systems ($r = -0.31$, −0.32).

DISCUSSION

This review identified and compared all published methodologies that may help inform waterborne disease burden and source attribution estimates on a national level.

Table 10 | Comparison of Colford *et al*. (2006) and Messner *et al*. (2006) model results in terms of cases of AGI per year for a US population served by CWS

Approach	Estimated AGI cases due to groundwater	Estimated AGI cases due to surface water	Estimated total cases of AGI per year	Published US estimates[a] (cases of AGI per year)
1. Colford *et al.* (2006)	1.39 to 4.04 million	2.93 to 7.81 million	4.32 to 11.85 million	4.26 to 11.69 million
2. Modified Colford approach	Mean = 0.91 million. Upper and lower 95% credible bounds: 0.62–1.20 million	Mean = 2.18 million. Upper and lower 95% credible bounds: 1.64–3.10	Mean = 3.09 million. Upper and lower 95% credible bounds: 1.82–4.43	N/A
3. Messner *et al.* (2006)	Mean = 5.60 million. Upper and lower 95% credible bounds: 1.5–14.43 million	Mean = 12.88 million. Upper and lower 95% credible bounds: 3.6–30.5 million	Mean = 18.48 million. Upper and lower 95% credible bounds: 590,000–6,030,000	16.4 million

[a]Values refer to those published by Colford *et al*. (2006) and Messner *et al*. (2006).

Additionally, relevant epidemiological data from the literature were found and important knowledge and data gaps highlighted by various authors were identified. In Table 11, the authors compiled a global summary of knowledge gaps, which includes specific data needs that may contribute to filling these gaps and help further inform a national estimate of waterborne illness.

The review focused primarily on two recent burden methodologies produced for the United States, as they are the only methodologies to date that quantify waterborne disease burden on a national level (Colford *et al.* 2006; Messner *et al.* 2006). These methodologies rely on numerous assumptions with varying degrees of uncertainty, outlined herein, which require further refinement, as acknowledged by the authors. One advantage of both the Colford *et al.* (2006) and Messner *et al.* (2006) estimates is that as new data become available, the models can be updated in a transparent manner, to demonstrate progress in our understanding of the greatest sources of risk for waterborne AGI.

The Colford *et al.* (2006) and Messner *et al.* (2006) approaches are reliant on the use of data from randomized controlled trials over data produced in other epidemiological studies. These assumptions are justifiable, given the lack of epidemiological data available and given that randomized controlled trials are considered the 'gold standard' of epidemiological studies, to attribute risk to exposures. In the Colford *et al.* (2006) approach, the mean of the attributable risk due to drinking water from all trials (Payment *et al.* 1991, 1997; Hellard *et al.* 2001; Colford *et al.* 2002, 2005a, b) was used as the key illness rate input into the model. In the Messner *et al.* (2006) approach, the attributable risk due to drinking water from the Payment *et al.* (1991) trial(s) was applied. The Laval system studied in this trial was subsequently ranked among US systems based on expert opinion (Messner *et al.* 2006). Given the sensitivity around these inputs (attributable risk and ranking of Laval), it is important to ensure that the assumptions made are representative of the country context. In addition, the issue of study design and the lack of blinding in the original Payment *et al.* (1991, 1997) studies is worth considering, although it would be difficult to estimate the direction of bias that may be introduced in non-blinded studies.

Due to a lack of data on the potential health effects of consuming groundwater versus surface water supplies, the two water sources were treated equally in the Messner *et al.* (2006) analysis. Lack of data on the potential health effects related to the consumption of groundwater supplies was identified by both Messner *et al.* (2006) and Colford *et al.* (2006) as a significant knowledge gap in the literature. There is a need for both epidemiological data on the health impact of consuming groundwater as well as pathogen occurrence in these supplies. A recent community intervention trial, identified in this review, that focused on small groundwater systems in Wisconsin, USA, is one example of a project that will help fill this data gap (Borchardt *et al.* 2012). Additional epidemiological studies are required that quantify the risk due to groundwater systems, particularly private wells and small systems.

In the absence of epidemiological data, and based on the literature recovered in this review, QMRA could be used in the development of a national waterborne disease burden estimate for certain systems, such as private wells or smaller

Table 11 | Key knowledge gaps and specific data needs identified through this systematic review that would help inform a national waterborne illness burden or attribution estimate

	Specific data needs				
Knowledge gaps	**Epidemiological data**	**Source water quality data**	**Population served (by each type of water supply across a country)**	**State of drinking water infrastructure (treatment systems, distribution, reservoirs, etc.)**	**Climate-related impacts on disease estimates**
Community surface water supplies	Data exist; however larger scale RCTs would be beneficial to try and quantify AGI attributable to drinking water so that the results are statistically significant. Data on the health effects on vulnerable populations	Data exist; however not always centralized at the national level	Data exist; however not always centralized at the national level	Data exist; however not always centralized at the national level	Robust epidemiological studies that quantify the AGI risk associated with climactic events (e.g., rainfall, temperature changes) in all types of water supply systems (small, large, surface water and groundwater) as well as drinking water distribution systems. Water quality – data following extreme events
Community Groundwater supplies	RCTs or robust epidemiological studies that quantify risk due to consumption of water from groundwater systems. Data on the health effects on vulnerable populations	Groundwater pathogen data for pathogens linked to AGI (e.g., Norovirus, *Cryptosporidium, Giardia, Campylobacter, E. coli* O157)	Data exists; however not always centralized at the national level	Data exist; however not always centralized at the national level	
Private wells and private supplies			Population served by private wells is not always well defined on a national level	Knowledge around the state of well infrastructure, the presence/absence of treatment devices and the impact of these on AGI is not well defined	
Distribution systems	Robust epidemiological studies that quantify the health risks due to distribution system operation and failures are needed. Studies that examine risks associated with different system characteristics and events (e.g., pipe materials, pipe age, system size, disinfectant residual, loss of pressure, etc.). Data on the health effects on vulnerable populations	Some data exist; however it would be beneficial if water samples could be collected for detection of pathogens following events in the distribution system to see if there is an increase in pathogen load associated with these events	N/A; Linked to community supplies	Knowledge around the condition state of drinking water distribution systems is lacking (e.g., pipe material, age, leaks, main breaks, water age, etc.). Knowledge around the specifics of drinking water distribution system residence times and water age are lacking	

non-municipal systems (Soller 2006). One disadvantage of the QMRA approach is that it is pathogen-specific and in order to calculate an overall burden due to waterborne exposures, a risk assessment would need to be performed for all pathogens and for all exposure scenarios (water sources, consumption patterns, immunocompromised,

elderly, children, etc.) and then the results combined. This is both labour- and data-intensive, but is proposed as an alternative to the modelling approaches published by Messner *et al.* (2006) and Colford *et al.* (2006). In many cases, minimal data exist on the prevalence (and enumeration) of enteric pathogens in surface, groundwater, or groundwater under the direct influence of surface water (GUDI) waters. There are very little data on the concentrations of microbial pathogens in groundwater under non-outbreak conditions (Abbaszadegan *et al.* 2003; Pitkänen 2013; Hynds *et al.* 2014). This is particularly true for enteric viruses as the detection methods are labour-intensive and costly. Large volumes of water need to be concentrated to detect viruses in groundwater (Abbaszadegan *et al.* 2003). Enteric pathogen occurrence and concentration data are needed (at a minimum) for key AGI-related pathogens in groundwater: norovirus, *Campylobacter, E. coli* O157, *Cryptosporidium* and *Giardia* (Hynds *et al.* 2014).

Prevalence data are integral to the development of the exposure assessment component of a QMRA which is likely why only two of 14 studies in this review performed QMRAs on groundwater supplies (either private wells or public systems). One study by Hunter *et al.* (2011) used *E. coli* datasets from France and UK private water supplies to infer *Cryptosporidium* exposure in groundwater. The other (Lambertini *et al.* 2012) based their QMRA on results of water quality data collected during a community intervention trial in Wisconsin, USA, where virus samples were collected from wells prior to, and after, UV treatment at the wellhead and also at a number of households in the study communities. The samples were analysed using real-time polymerase chain reaction (qPCR) for enterovirus, norovirus GI and GII, adenoviruses, rotavirus and hepatitis A virus. The QMRA was performed using 'all viruses', enterovirus and norovirus data. Even in the absence of rigorous data, an advantage of the QMRA approach is that it formally addresses the uncertainty and variability inherent in the data inputs (Cummins *et al.* 2010).

The Messner *et al.* (2006) and Colford *et al.* (2006) approaches focus only on community water systems and neither approach considers the risk due to private wells and small private supplies. For an estimate to quantify burden due to all water supplies, a segmented approach by water system type should be considered. Reynolds *et al.* (2008), in their review of AGI and non-AGI waterborne burden estimates, suggest that groundwater supplies be addressed separately. In order for risk due to small private supplies to be quantified, information on the number of individuals served by these systems is necessary, in addition to the quality of water from these systems, and the subsequent attributable risk of AGI associated with consuming water from these supplies. Quantifying risk due to small water supplies and private wells is a challenge, given the lack of representative epidemiological data. The RCTs in this review were all performed on large municipal systems using surface water supplies; therefore, the results from these trials are not relevant for small systems and private wells. Only one of the 'endemic/sporadic' disease burden papers in this review had findings relevant to small systems, namely private wells (Borchardt *et al.* 2003). Given the lack of epidemiological data available, QMRA could be an appropriate approach to generate burden estimates for these types of systems.

In both US estimates, the authors quantify the burden due to source water/treatment and the distribution system. This approach is supported by the work of numerous other authors identified in this review (Payment *et al.* 1991, 1997; Nygard *et al.* 2007; van Lieverloo *et al.* 2007; Besner *et al.* 2010; Lambertini *et al.* 2012). Although both Messner *et al.* (2006) and Colford *et al.* (2006) identified that source/treatment risk and distribution system risk need to be treated separately, due to a lack of data, the authors made the same assumptions for distribution systems as they did for source water/treatment risk.

Since 2006, two studies have attempted to quantify the burden of disease due to drinking water distribution systems (Nygard *et al.* 2007; Lambertini *et al.* 2012). Drinking water distribution systems are ageing and there are different events in these systems under normal operation that could potentially cause risk to consumers, such as leaks in the system, main breaks and low pressure events (Kirmeyer *et al.* 2001; Nygard *et al.* 2007; Besner *et al.* 2010; Lambertini *et al.* 2012). These different types of events can allow the intrusion of pathogens from the surrounding environment into the drinking water distribution pipe network (Kirmeyer *et al.* 2001). Nygard *et al.* (2007) studied the health effects of distribution system events in a project in Norway. Lambertini *et al.* (2012) used a QMRA approach to quantify a

range of AGI attributable to drinking water distribution systems based on the results of the community intervention trial by Borchardt *et al.* (2012). Studies of this nature will help inform estimates of risk associated with drinking water distribution and the effects of ageing infrastructure. Although these studies are promising, more work is needed in this area to answer the questions around distribution system risk.

This review identified that North American studies that examine the health risks associated with different water distribution system characteristics, such as the effects of pipe materials, pipe age, system size, disinfectant residual, and water age are needed, particularly as our infrastructure systems below the ground age further. The Nygard *et al.* (2007) study was conducted in Norway on systems that do not maintain disinfectant residuals, and therefore are not representative of North American systems that do maintain residuals (Kirmeyer *et al.* 2001). In addition, the pipe materials of the systems studied by Nygard *et al.* (2007) were mostly constructed of steel and polyvinyl chloride (PVC) (Nygard personal communication 2013). It is unlikely that these systems would be representative of North American systems that are predominantly constructed of cast iron, ductile iron and PVC (Folkman 2012) and thus are not proposed for future waterborne disease burden estimation for North American systems.

During the review, numerous articles were retrieved that examined links between water-related illness and environmental factors, such as precipitation and temperature changes. Although this theme was not included in the review questions, weather can influence waterborne disease attribution methods. There are studies that link increases in precipitation to increases in waterborne disease occurrence. Curriero *et al.* (2001) and Thomas *et al.* (2006) found that increases in precipitation were linked to waterborne disease outbreaks in the United States and Canada over the previous 54 and 25 years, respectively. Curriero *et al.* (2001) found that 51% of outbreaks were preceded within a 2-month lag by extreme precipitation in the 90th percentile, while Thomas *et al.* (2006) linked rainfall greater than the 93rd percentile with a 2.283 odds increase in the chance of an outbreak. Drayna *et al.* (2010) found that any rainfall 4 days peviously was significantly associated with an 11% increase in children's AGI-related hospital visit. In a study in the north of Newfoundland and Labrador, Canada, high water volume (snowmelt and rainfall) 2 and 4 weeks previously significantly increased the number of weekly GI-related clinic visits by 1.34 and 1.31 times, respectively (Harper *et al.* 2011). Since extreme precipitation events are becoming more common as a result of changes in climate (IPCC 2007) and evidence linking increased precipitation with waterborne disease, researchers may need to consider how extreme precipitation events influence the attribution of waterborne disease to drinking water supplies, and how this may vary by type of water source, geographical regions of a country, and the susceptibility of treatment systems and distribution systems to weather events and public health risks.

In addition, this review did not include non-AGI illnesses attributed to water such as *Legionella*, *Naegleria fowleri* or *Pseudomonas aeruginosa*. It also did not examine illnesses related to recreational water exposures or exposures through premise plumbing. These pathogens and exposure routes contribute to overall waterborne disease burden in developed countries and are becoming increasingly important causes of outbreaks and endemic cases of disease as reported by US CDC surveillance data (CDC 2013). Consequently, for an all-encompassing burden of waterborne disease analysis, these pathogens and routes of exposure should be considered in future estimates.

Finally, vulnerable populations such as children, the elderly and immunocompromised individuals, is one important aspect that should be considered when quantifying burden of waterborne disease. Colford *et al.* (2006) pointed out that the estimate they produced did not account for vulnerable populations who are often more susceptible to waterborne disease. Consequently, more data are required regarding the susceptibility of these sub-populations. Colford *et al.* (2005a, 2009) have conducted two RCTs that focus on HIV+ individuals and the elderly, respectively, to try and fill this data gap.

CONCLUSIONS

The results of this review suggest that there are limited methods available to quantify the burden of AGI illnesses attributable to drinking water at a national level. These vary from simple point estimates, to QMRA, to Monte

Carlo simulations that rely on both assumptions and epidemiological data from the literature.

Additionally, this review highlighted a number of knowledge gaps and data needs that would help further refine inputs into the methodological approaches first proposed by Colford *et al.* (2006) and Messner *et al.* (2006). Knowledge gaps and data needs identified include the following.

1. Epidemiological studies that quantify:
   - the risk of AGI due to the consumption of water from small and private water systems;
   - the risk of AGI attributable to drinking water distribution system operation and events;
   - the risk of AGI due to the consumption of groundwater supplies.
2. Pathogen occurrence water quality data, particularly for groundwater supplies.
3. Centralized data on the population served by various water supplies (small systems, large systems, private supplies, transient systems).
4. Data on the state, condition and operation of drinking water infrastructure including:
   - treatment systems in place and treatment capabilities;
   - drinking water distributions' conditions (age, pipe material(s), frequency of main breaks and repairs, residence times, water age, etc.);
   - condition of private water supplies (quality of well construction, maintenance, etc.).
5. Water consumption-related health effects on vulnerable sub-populations such as children, the elderly and immunocompromised.
6. Research that quantifies the risk of AGI associated with the effects of changing climate (increased precipitation) on drinking water supplies.

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