Measuring sporadic gastrointestinal illness associated with drinking water – an overview of methodologies

John Bylund, Jonas Toljander, Maria Lysén, Niloofar Rasti, Jannes Engqvist and Magnus Simonsson

ABSTRACT

There is an increasing awareness that drinking water contributes to sporadic gastrointestinal illness (GI) in high income countries of the northern hemisphere. A literature search was conducted in order to review: (1) methods used for investigating the effects of public drinking water on GI; (2) evidence of possible dose–response relationship between sporadic GI and drinking water consumption; and (3) association between sporadic GI and factors affecting drinking water quality. Seventy-four articles were selected, key findings and information gaps were identified. In-home intervention studies have only been conducted in areas using surface water sources and intervention studies in communities supplied by ground water are therefore needed. Community-wide intervention studies may constitute a cost-effective alternative to in-home intervention studies. Proxy data that correlate with GI in the community can be used for detecting changes in the incidence of GI. Proxy data can, however, not be used for measuring the prevalence of illness. Local conditions affecting water safety may vary greatly, making direct comparisons between studies difficult unless sufficient knowledge about these conditions is acquired. Drinking water in high-income countries contributes to endemic levels of GI and there are public health benefits for further improvements of drinking water safety.

Key words | drinking water, gastrointestinal diseases, waterborne disease, water distribution systems, water microbiology, water treatment

John Bylund
Jonas Toljander (corresponding author)
Maria Lysén
Niloofar Rasti
Jannes Engqvist
Magnus Simonsson
National Food Agency,
Box 622,
Uppsala SE-751 26,
Sweden
E-mail: *jonas.toljander@slv.se*

INTRODUCTION

A number of pathogenic microorganisms in the form of viruses, bacteria and protozoa can spread via drinking water, causing illness in the population (Ashbolt 2015). Globally, contaminated drinking water is a large public health problem, especially in many low-income countries (WHO 2014). In high-income countries, drinking water safety problems are rarely acknowledged, except for in occasional events when larger outbreaks of gastrointestinal illness (GI) are linked to drinking water. Caliciviruses (e.g. norovirus) and *Campylobacter* are the major pathogens causing waterborne outbreaks of GI in high-income countries; however, pathogenic *Escherichia coli*, *Salmonella*, *Shigella*, rotavirus, *Giardia* and *Cryptosporidium* are also occasionally involved (Guzman-Herrador *et al.* 2015). To date, the largest outbreak linked to drinking water in high-income countries was caused by *Cryptosporidium*, with over 400,000 people becoming ill in Milwaukee, USA (Dunn *et al.* 2014). Waterborne outbreaks are generally caused by extraordinary events leading to large numbers of reported cases. However, even when water supplies are carefully managed and meet drinking water standards for microbiological quality, drinking water can still become contaminated. This may lead to a few cases

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that are apparently sporadic, most of which are exhibiting mild symptoms. These cases are never reported and are therefore harder to detect. Such sporadic cases may be caused by situations when microbiological barriers of a water treatment plant are insufficient for removing high levels of contamination. Pathogens might also be introduced into the distribution system if water pressure is low or temporarily lost. Contaminated drinking water causes sporadic cases of GI that, to some extent, contribute to the endemic burden of illness in high-income countries (Colford *et al.* 2006; Messner *et al.* 2006; Reynolds *et al.* 2008; Beaudeau *et al.* 2014a; Murphy *et al.* 2015). The true burden of disease due to drinking water is, however, difficult to measure (Tam *et al.* 2012). Contextual factors such as local variations in water sources and climate combined with methodological limitations have resulted in risk estimates that are generally associated with a high degree of uncertainty.

In order to reduce the burden of disease attributed to drinking water it is important to gain knowledge of factors that may affect – and to what degree they affect – the safety of drinking water. Certain aspects of the relationship between drinking water and GI have been the subject of several previous reviews. Household intervention trials (Colford *et al.* 2006), community interventions (Calderon & Craun 2006) and observational studies (Craun & Calderon 2006) of drinking water were reviewed in a special issue of *Journal of Water and Health* in 2006. Estimations of burden of illness from drinking water (Murphy *et al.* 2014), problems with water distribution (Ercumen *et al.* 2014) and the correlation between GI and water quality parameters, such as turbidity (Mann *et al.* 2007) and bacterial indicators (Figueras & Borrego 2010; Gruber *et al.* 2014) have also previously been reviewed.

The present review covers the drinking water system, from raw water source to distribution networks (source to tap) and its potential health effects on consumers. The review outline is based on the types of data and study designs used in different studies, and these are discussed in separate sections. The structure within each section is arranged roughly according to the source-to-tap concept. Our aim is to provide a broad, updated and critical overview of the existing scientific literature, focusing on methods that have been used to study public drinking water and its contribution to endemic gastroenteritis in high-income countries of the northern hemisphere.

METHODS

This review investigates the following questions:

1. What methods have been used to estimate the burden of GI caused by public drinking water?
2. Do studies report a dose–response relationship between GI and the amount of water intake, when water production and distribution are in normal operation?
3. Is endemic GI affected by raw-water quality, drinking water quality, water treatment methods, water distribution and/or weather events?

The search strategy was structured according to the Population-Exposure-Outcome model (Higgins & Green 2011). Using this model different terms representing the exposure are combined with terms representing the outcome (supplementary Table S1, available with the online version of this paper). Additional terms were used to limit the search with regard to geography, time period, type of publication, etc. Exposure was represented by terms concerning public drinking water and water quality, extreme weather events that are commonly associated with deterioration of the water quality, as well as incidents or other unwanted circumstances that may have a negative impact on the drinking water supply. The outcome section of the search was composed of terms representing GI. MeSH terms in PubMed were used in order to capture studies of GI in general as well as studies of GI caused by specific pathogens.

We searched for peer-reviewed papers recorded in PubMed between January 1990 and May 2016. A full set of search terms is available in Table S1. Two expert reviewers at the National Food Agency (NFA) independently assessed each study according to a list of pre-determined criteria (Table 1). Articles were initially screened according to title and abstract. Articles that were deemed eligible by either one or both reviewers during screening of abstracts were then reviewed in full text by both reviewers and were subsequently included only if both reviewers were in agreement. If consensus could not be reached by discussion, a third reviewer at the NFA assessed the article in full text. Additional papers that were identified in the reference list of the included articles were also included in the review, if they fulfilled our selection criteria.

Table 1 | Inclusion and exclusion criteria for reviewed articles

	Inclusion	**Exclusion**
Population	Resident population	Animals Travellers Underlying chronic disease
Exposure	Municipal drinking water systems Ground water Surface water Changes in water quality Weather Changes/disturbances in water production Changes/disturbances in water distribution	Private drinking water systems Recreational water Rain water Sea water
Outcome	Gastroenteritis	Outbreaks only Non-gastrointestinal diseases Diseases from a non-infectious source
Geographic area	North America Europe	Asia Africa South America Australasia
Language	English Swedish Danish Norwegian French	All other languages
Study type	Peer-reviewed articles	Reviews Risk assessments Grey literature[a] Other literature
Publication period	January 1990–May 2016	Pre- 1990

[a] Grey literature is that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers, i.e., where publishing is not the primary activity of the producing body (Schöpfel 2010).

This paper presents a qualitative overview of the included studies and no meta-analysis was carried out. While the search strategy and the selection process was systematic, no systematic evaluation of the quality of the studies was performed.

RESULTS AND DISCUSSION

Selection of articles

The PubMed database search yielded a total of 5,652 references. Additionally six articles were identified from reference lists and other sources. Seventy-four articles met the selection criteria and were included in this review (Figure 1).

Study designs and data types

Among the selected articles several different outcome measurements were used to study the effect of drinking water. Information about GI was collected via health-care systems, from proxy data or directly from studied cohorts. By proxy data we here refer to indicators which are likely to correlate with GI incidence in the community. Several of the included studies used internet search volumes or drug sales data. In the cohort studies GI was measured as self-reported symptoms. Different definitions of gastrointestinal disease were used in different studies and this may affect comparability between studies. For self-reported GI there is a higher degree of recall bias if longer recall periods are used. Some symptoms, such as nausea, can also be subjective and difficult to measure. Among the included papers

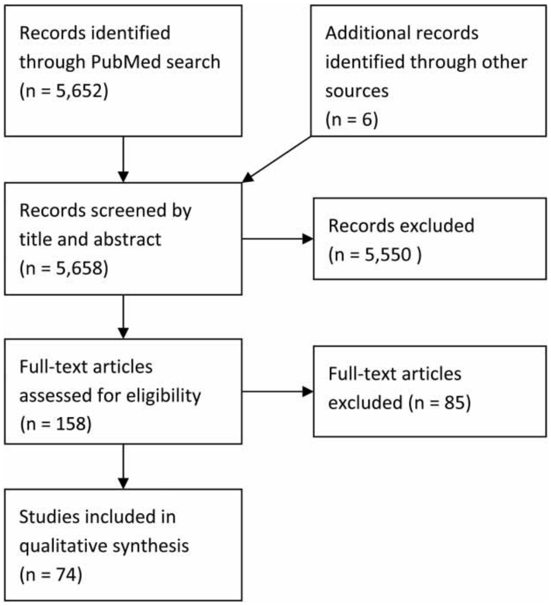

Figure 1 | Flow chart of selection of articles.

we identified two commonly used case definitions: acute gastrointestinal illness (AGI) and highly credible gastrointestinal illness (HCGI) (Table 2). The different methodologies and types of data are summarized in Table 3.

The systematic search resulted in articles representing both observational studies and intervention studies. In observational studies data collection is made without interfering with the studied population. Case-control studies, cohort studies, ecological studies and cross-sectional studies are all types of observational studies and all of these were also captured in our literature search (Table 3).

Table 2 | Case definitions of self-reported GI in different studies

Illness	Definition	References
AGI	Vomiting and/or diarrhoea with at least three loose stools during a 24-h time-period	Nygård *et al.* (2007), Febriani *et al.* (2010), Borchardt *et al.* (2012)
HCGI	Any of the following conditions: (1) vomiting, (2) watery diarrhoea, (3) soft diarrhoea and abdominal cramps, (4) nausea and abdominal cramps	Payment *et al.* (1991, 1997), Colford *et al.* (2002, 2005, 2009), Frost *et al.* (2009)

ECOLOGICAL STUDIES

Ecological studies using indirect measurements of GI

GI has been examined by using indirect measurements of GI. While such data do not give any information about the prevalence of GI per se, they correlate with the prevalence of GI and may therefore be used as a proxy to detect differences in the prevalence of disease. One example is the prescription or sales of drugs used for treatment of GI. Four French studies have used such data to analyse possible spatiotemporal correlations of GI with drinking water quality. Two studies conducted in the same city detected an increase in sales of drugs used for treatment of GI after sudden spikes in turbidity of both raw water and drinking water (Beaudeau *et al.* 1999, 2012). The city used ground water from a karstic aquifer susceptible to surface water contamination. Two water treatment plants supplied the city with drinking water, the first employing only chlorination and the second using filtration and chlorination. During rainy weather or elevated levels of raw water turbidity the first water treatment plant, using only chlorination, was closed while the second treatment plant implemented flocculation as an extra treatment before filtration. Sudden spikes in turbidity of both raw water and drinking water were associated with increased sales of drugs used for treatment of GI. The associations disappeared during long periods of increased raw water turbidity when flocculation was used (Beaudeau *et al.* 2012). Insufficient chlorination resulting in low free chlorine concentrations also increased the sales of drugs used for treatment of GI (Beaudeau *et al.* 1999). Data on drug sales were only available for a few pharmacies in the area and only a single pharmacy could provide information about sales without medical prescription which makes it difficult to assess if drug sales were representative for the whole city. In a third French study, high daily mean values of raw water turbidity were also found to correlate with increased prescriptions of GI-specific medical drugs to both children and adults (Beaudeau *et al.* 2014a). This study also detected a correlation with the number of pipe repairs and GI-specific medical drug prescriptions to children when pipe repairs were analysed as the only exposure variable. However, if the

Table 3 | Overview of methodologies and data sources for investigating relationship between drinking water and sporadic GI

Methodology	Definition	Data sources	Advantages	Limitations
Ecological study	Observational study of the correlation between risk factors and health outcomes based on populations defined geographically and/or temporally	Pharmacies	Available in most countries	Low correlation with sporadic GI
			International codes allow the use of data for specific drugs and facilitate comparisons between countries	No information about water consumption or confounders
				Affected by opening hours and holidays
		Telephone triage	Lots of data (high statistical power)	Only available in some countries
			High correlation with endemic GI	
			Description of symptoms	Reporting bias
			Seasonal and geographical variation	
		Health care	Available in most countries	High under-reporting
			Diagnosed cases	Mostly severe cases of GI
				Large study population required
Case-control study	Observational study in which two existing groups differing in outcome are identified and compared based on their association with hypothesized risk factors	Health care	Diagnosed cases	High under-reporting
			Allows identification of risk factors	Mostly severe cases of GI
				Selection bias
				Prone to recall bias
Cross-sectional study	Observational study that analyses data collected from a population, or a representative subset, at a specific point in time	Questionnaires	Possibility to collect detailed data on symptoms, water consumption and confounders	Only point estimate
		Interviews		Recruitment bias
				Low response rate
				Self-reporting may be subjective
Cohort study	Observational study that analyses data collected from a population, or a representative subset, over a period of time	Questionnaires	Possibility to collect detailed data on symptoms, water consumption and confounders	Expensive
			Collection of data over time	Labour intensive
		Interviews		Recruitment bias
		Health diaries		Low response rate

(*continued*)

Table 3 | continued

Methodology	Definition	Data sources	Advantages	Limitations
		Patient registers		Self-reporting may be subjective
Household intervention	An experimental study measuring changes in risk following a risk reducing measure in a population	Questionnaires	Possibility to collect detailed data on symptoms, water consumption and confounders	Expensive
		Interviews	Collection of data over time	Labour intensive
		Health diaries	Direct measurement of risk reduction due to intervention	Excludes non-home owners
				Different risk factors cannot be elucidated with point of use intervention

statistical analysis was adjusted for other exposures, such as drinking water turbidity, river flow and drinking water flow, the association between pipe repairs and drug prescription was no longer statistically significant (Beaudeau *et al.* 2014a).

In a fourth French study, Pirard *et al.* (2015) investigated the prescription of drugs following a storm that caused severe disruptions in drinking water production in several areas. No increase in prescriptions of drugs used for treatment of GI was observed during this event. The authors concluded that the storm affected the communities in several other ways that may have influenced health care seeking behaviour, for example, by making roads impassable (Pirard *et al.* 2015).

A single study used internet search volume as an indicator for GI. An increase in the weekly proportion of internet searches on the search engine Google including the words ‘vomiting’ and ‘diarrhea’, in two US cities was associated with the number of pipe breaks in the studied cities during the previous week (Shortridge & Guikema 2014).

Proxy data are often easy to collect and may give an indication of sudden changes in the prevalence of GI. Proxy data is, however, difficult to interpret because it is affected by other, often unknown factors; for example, opening hours of health facilities and impassable roads. The use of indicator data of GI could however be a useful method for monitoring trends or sudden changes of GI in the community.

Ecological studies using telephone triage data

Several studies have measured changes in the number of telephone calls to health information centres. Health information centres are often used as a means for triaging, giving advice for home treatment or, in case of more severe illness, directing the caller to primary health care or the emergency room. Such data can be considered as a form of health care data as the data are, at least in some countries, stored in the form of patient journals. A major difference however is that the prevalence data consist entirely of self-reported illnesses which may be more subjective than a medical diagnosis. In a Canadian area using river water treated with pre-chlorination, flocculation, filtration, ozonation and post-chlorination, an increase in drinking water turbidity was associated with an increased number of calls to a health information telephone centre (Gilbert *et al.* 2006). In a Swedish city, which is supplied by surface water from a river, high levels of precipitation were associated with increased numbers of GI-related calls to a nurse advice line (Tornevi *et al.* 2013). In the same city, a similar study investigated disturbances in either water production process or the number of pipe breaks. In this study there was, however, no significant correlation with GI-related calls (Malm *et al.* 2013). The lack of relationship in the latter study was likely to be due to the fact that most disturbances were low-risk events. Gilbert *et al.* (2006) concludes that the lag times between periods of high drinking water turbidity levels and increased number of GI-related calls correspond to the incubation time of *Cryptosporidium* and *Giardia*. On the other hand, Tornevi *et al.* (2013) found that a lag time between high precipitation events and increase in telephone calls corresponded to incubation times of waterborne viruses such as norovirus. The differences between these studies could reflect local variation in source water quality and different microbial barriers used in the waterworks.

Similarly to health care data, telephone triage data may be prone to reporting bias since most people do not seek advice for GI. People may also prefer seeking medical advice on certain days of the week. Tornevi *et al.* (2015) showed that people preferred to use nurse advice telephone lines during rainy days instead of visiting primary health care facilities. Telephone data have a potential to be useful in epidemiological research since the sheer amount of data over time provides high statistical power, facilitating the analysis of variables that may correlate with GI prevalence in the population.

Ecological studies using health care data

The majority of studies identified in this review use health care statistics for investigating differences in the incidence of GI in relation to drinking water. Information from health care is often reported through International Classification of Diseases (ICD) codes. Health care statistics can be based on laboratory-confirmed cases of specific pathogens or more general classifications based on gastrointestinal symptoms. Since the degree of under-reporting is high for GI, health care statistics underestimate the real prevalence of GI (FSA 2000). This is particularly the case with pathogens causing GI with short duration times, such as norovirus, for which people rarely seek medical attention. Due to under-reporting, large study populations are required for detecting potential relationships between GI and drinking water. One advantage of health care data is that information about the number of cases diagnosed with communicable diseases is easy to collect in many countries. Health care statistics are also very useful for detecting changes in the incidence of disease and to generate hypotheses about which factors may be important to drinking water safety.

The quality of the water source determines the need for microbiological barriers in water treatment plants. The most common types of raw water are ground and surface water sources. Surface water, typically lakes and rivers, generally has a poorer microbiological quality than ground water and is considered to require more treatment than ground water. Ground water production, on the other hand, could be more vulnerable to contamination because, if contamination occurs, few treatment plants have enough barriers for reducing it. In our review, several studies compared regions using different types of water sources. In a study from the USA, areas using municipal water from a mix of surface and ground water sources had an increased incidence rate of campylobacteriosis, cryptosporidiosis, giardiasis, salmonellosis and infections of shiga toxin-producing *E. coli* (STEC) when compared to areas supplied by municipal ground water. In this study, only a single city used municipal ground water while several other urban areas used mixed water sources. It is uncertain whether other differences between the cities may have confounded the results. A low number of cases also made the results uncertain (Uhlmann *et al.* 2009). In a Canadian study, comparing 257 water treatment plants, the risk for giardiasis was also higher with surface water compared to ground water (Odoi *et al.* 2004). An ecological study in Sweden did, however, not detect any differences in the rates of campylobacteriosis between ground and surface water areas (Nygård *et al.* 2004).

Different watersheds could not explain the spatial distribution of diagnosed cases of cryptosporidiosis in a study from the UK (Hughes *et al.* 2004). Only a small number of cases was however reported, which made it difficult to detect small differences between water supply areas. In a German ecological study, a higher incidence of diagnosed cases of GI was found in areas supplied by ground water compared to areas using surface water. This may be explained by the fact that most ground water treatment plants were small and only a few of them used disinfection barriers such as chlorination, while the surface water treatment plants generally had more microbiological barriers. Confounders such as socioeconomic factors and livestock production, which may affect the results, were however not analysed (Dangendorf *et al.* 2002). Since endemic GI may also be affected by many other different factors it is important to analyse a large set of confounders that may affect the results. When analysing the hospitalization rate of Canadian children for acute gastroenteritis, Febriani *et al.* (2009) found an increased rate of disease in municipalities with a surplus production of manure from animal production. This increase of risk was present in municipalities using mainly ground water or private wells, but not in municipalities using surface water. Several other factors such as education level and average income were, however, also different between communities with and without surplus manure, and this may have confounded the results. In a US study, the majority of drinking water-related GI was also estimated to be caused by contaminated private wells (DeFelice *et al.* 2016). It is well known that several zoonotic pathogens causing GI, such as *Campylobacter* and *Cryptosporidium*, can spread through drinking water. A large animal population, in combination with unprotected small-scale water supplies, may therefore increase the risk of drinking water-related illness.

A common route for zoonotic pathogens to contaminate drinking water is when periods of precipitation increase the run-off from pastures or farmland fertilized with manure. The run-off adds to the load of pathogens in water sources. This could potentially have more severe consequences for small water treatment plants or private wells which may lack sufficient microbiological barriers. Increased levels of precipitation have, indeed, been connected to an increase in GI health care visits among children in the USA (Drayna *et al.* 2010; Uejio *et al.* 2014), weekly rates of cryptosporidiosis in the UK (Naumova *et al.* 2005) and yearly rates of campylobacteriosis in Norway (Sandberg *et al.* 2006). Drayna *et al.* (2010) analysed cases living in areas mostly provided by surface water and detected an increase in GI health care visits 4 days after a day with precipitation. Uejio *et al.* (2014) detected an increase only in areas using untreated and undisinfected municipal water. In areas using treated municipal water no relation between precipitation and GI health care visits was detected.

Some studies have observed a lag time of 7 days or shorter between precipitation and contacting health care (Naumova *et al.* 2005; Drayna *et al.* 2010). Since it may take several days before the affected water reaches consumers there may be an underestimation of GI caused by pathogens that normally have long incubation times. Periods of wet weather for 7 days or longer, increased the number of visits to primary health care centres associated with GI in a Swedish city using surface water as a raw water source (Tornevi *et al.* 2015). In a British study, increased maximum river flows from April to November was also correlated with an increase in reported cases of cryptosporidiosis (Lake *et al.* 2005). During the winter months, between December and March, no correlation was detected. This may be due to the fact that many livestock animals are housed indoors during the winter, which may reduce the amount of *Cryptosporidium* contamination of raw water during these periods.

Other ecological studies in Sweden and the USA did not detect any correlation between mean monthly precipitation and campylobacteriosis (Nygård *et al.* 2004) or daily precipitation and hospital emergency admissions of elderly people diagnosed with gastroenteritis (Beaudeau *et al.* 2014b), respectively.

High precipitation may ultimately lead to flooding, which brings about many hygienic challenges to an affected community and its drinking water supply. Flooding increased the amount of emergency room visits for GI in Massachusetts, USA, during the first 4 days after the flooding event. However, it was not possible to determine if this increase was caused by contamination of drinking water or if it was caused by other effects of the flooding (Wade *et al.* 2014). Both river flow and hospitalizations for GI illnesses showed similar seasonal patterns in a study among elderly people (>65 years) living in large population centres in the USA, but the peak of hospitalizations preceded the peak of river flow. This could be because pathogens are flushed into the river before the level of river flow reaches its peak or that hospitalizations are affected by other confounding factors (Jagai *et al.* 2012).

Large amounts of precipitation may also cause sewage overflows into surface watersheds. After two events of extreme precipitation in the USA which resulted in bypass of a large amount of sewage into a river, an increase in emergency visits for diarrhoeal illness among children was detected in areas using the river as water source. No such increase was, however, detected during four smaller bypass events in the same study, and a general trend between sewage bypasses and emergency visits could therefore not be established (Redman *et al.* 2007). Drayna *et al.* (2010) also detected an increase of GI health care visits among children after a single sewage bypass event but did not detect a general trend. This may be because the water treatment plants in the studies may be able to sufficiently handle smaller amounts of contamination but may not have sufficient treatment to treat single events of heavy contamination. In addition, due to under-reporting only an extreme event may result in large enough numbers of illnesses to be detected using hospital records. Increased emergency department visits for GI in Massachusetts, USA was observed after extreme precipitation events. This correlation was only seen in regions using combined sewer and storm water runoffs connected to a river used for drinking water production (Jagai *et al.* 2015). In extreme weather situations, such as flooding, the risk for GI is however also increased by several other factors such as infection through flood water and difficulties in maintaining hygiene if potable water is not accessible.

Local climate may also influence hydrology and raw water quality. In Canada, different seasonality in the incidence of confirmed cases of GI was detected between regions dominated by either rainfall or snowfall (Galway *et al.* 2014). In cold regions, where snowfall during the winter is followed by large amounts of snowmelt in the spring, the rate of confirmed cases of GI increased in early spring and peaked during the summer. This could partly be due to high river flows, affecting raw water quality. On the other hand, in regions dominated by rain during winter, GI incidence started to increase during spring and peaked in September. Neither climate type nor raw water source were identified as significant risk factors for disease during the course of the study. Since only confirmed cases were analysed as an outcome, milder cases of GI such as norovirus infections may be underestimated in this study (Galway *et al.* 2014).

As discussed above, the quality of the water source may be influenced by the type of water source as well as various events and activities in the water catchment area. Changes in the turbidity of both raw water and drinking water are continuously monitored in most water treatment plants. Turbidity is a measurement of the amount of particles in the water and therefore serves as an indicator of disturbances and that additional water treatment is warranted. Increases in daily mean raw water turbidity have been connected to increases in GI-related emergency visits (Tinker *et al.* 2010; Hsieh *et al.* 2015) and emergency admissions of the elderly in the USA (Beaudeau *et al.* 2014b). Monitoring the turbidity of drinking water is useful for detecting problems in drinking water treatment. High drinking water turbidity was associated with increased numbers of GI-related visits to emergency departments in Philadelphia, USA for both children (Schwartz *et al.* 1997) and the elderly (Schwartz *et al.* 2000).

A massive increase in turbidity preceded the large outbreak of cryptosporidiosis in Milwaukee, USA affecting over 400,000 persons. A retrospective study during a 1-year period before the outbreak showed a correlation between increased drinking water turbidity and increases in emergency department visits and hospital admissions for GI among both children (Morris *et al.* 1996, 1998) and adults (Morris *et al.* 1998). In contrast, Tinker *et al.* (2010) did not detect any correlation between drinking water turbidity and emergency department visits for GI in another metropolitan area in the USA.

Several of the studies indicate that sudden increase in drinking water turbidity is an indicator for increased risk of GI. High turbidity in drinking water does, however, not always imply water contamination since most particles causing turbidity are not of pathogenic origin. High drinking water turbidity indicates problems in water treatment and particle removal that makes drinking water more susceptible for pathogen contamination from raw water.

Raw water quality differs between different water sources and accordingly requires different types of treatment. Different types of water treatment may also be efficient against different pathogens. For example, many waterborne bacterial pathogens are susceptible to chlorination while the parasite *Cryptosporidium* is highly resistant to chlorine.

Three Canadian studies investigated incidence rates of GI compared to raw water source and type of water treatments used. Levesque *et al.* (1999) found no correlation with the incidence of giardiasis. Kabore *et al.* (2010) detected a significant trend of increasing incidence of children diagnosed with non-viral gastroenteritis and giardiasis when surface water was used as raw water and with less rigorous water treatment processes. Kabore *et al.* (2013) defined very low risk areas as using purified ground water or chlorinated and UV-treated ground water. When they compared these areas with moderate risk areas (defined as ground water without disinfection or surface water with chlorination and UV treatment), they found a lower risk for non-viral GI, including campylobacteriosis, among children in areas classified as moderate risk. The results show that the very low risk classification underestimated the true risk. It is difficult to accurately classify different water treatments into single risk categories and such classifications may have a major impact on the results.

The efficiency of different water treatment barriers is highlighted in three articles. The incidence rate of campylobacteriosis in Norway was lower among residents supplied by drinking water from water treatment plants using a process considered able to remove or inactivate *Campylobacter* (Sandberg *et al.* 2006). In a US study, regions using municipal unfiltered water from a mix of surface water and ground water sources had a higher incidence rate of giardiasis and cryptosporidiosis compared with residents supplied by private wells or filtered water sources (Naumova *et al.* 2000). Odoi *et al.* (2004) detected a higher incidence rate of giardiasis in Canadian regions using unfiltered water. Chlorination did not affect the incidence of giardiasis in this study.

Studies conducted before and after changes in water treatment procedures can give a valuable insight into the efficiency of certain water treatment methods. Switching from chlorination and chloramination to ozone treatment and chloramination appeared to result in a reduction in GI hospital admissions for elderly people in an area using surface water in the USA (Beaudeau *et al.* 2014b). The incidence rate of cryptosporidiosis declined after installation of coagulation and filtration treatment at two different surface water treatment plants in Scotland (Pollock *et al.* 2008, 2014). Filtration of water appears to be an important method of decreasing the risk of GI, especially for surface water where no natural filtration occurs. Water management procedures have been indicated to be able to affect endemic GI. An Icelandic study compared water treatment plants with or without water safety plans. Areas implementing water safety plans had a lower incidence of GI health care visits (Gunnarsdottir *et al.* 2012).

Even though water treatment can be carefully controlled at a water plant, drinking water may still become contaminated during distribution. Pathogens may be introduced into the distribution system during episodes of low water pressure or may be present in the biofilm of water pipes. Areas with long water residence time had a higher incidence of emergency department visits for GI in a US study (Tinker *et al.* 2009). Nygård *et al.* (2004) also detected an increased risk for campylobacteriosis in Swedish municipalities categorized as having long water distribution networks, compared to municipalities categorized as having short distribution networks. There was, however, also an increased risk in rural regions with a high density of ruminants, which may be an important confounder. Rural regions are often sparsely populated and have longer distribution networks compared to urban regions.

Case-control studies

In the previous section we provided an overview of studies that use health care data to generate hypotheses about relationships between drinking water and sporadic cases of GI. A different approach for generating hypothesis commonly employed in epidemiology is the use of case-control studies. Case-control studies may also rely on health care data but compare the risk factors for a disease among confirmed cases and a healthy control population in order to assess if certain exposures, for example, drinking tap water, are more common among cases. In a Canadian study there was no relationship between raw water source and risk for acute gastroenteritis among children that were hospitalized for diarrhoea or diagnosed with a pathogen causing gastroenteritis (Levallois *et al.* 2014). Surface water was however identified as a risk factor for giardiasis among children in another Canadian case-control study (Gagnon *et al.* 2006). In a third Canadian study, campylobacteriosis was associated with tap water consumption, when tap water was analysed as the only risk factor. However, when several other risk factors were included into the statistical model, tap water was no longer statistically significant (Michaud *et al.* 2004). This indicates that there may also have been other confounding risk factors that influenced the risk.

Three other case-control studies compared cases of GI with persons utilizing health care for other types of illnesses. In the first study, children from areas using municipal or private ground water in the USA had a higher risk for GI compared to users of municipal surface water (Gorelick et al. 2011). In the second study, the risk for campylobacteriosis among users of municipal ground or surface water sources was investigated, however no difference was observed when cases were compared with patients that had been diagnosed with other GI pathogens (Galanis et al. 2014). In a third study, however, drinking municipal water was identified as a risk factor among patients compared to other diagnosed cases of GI (Pintar et al. 2009). Whether or not patients lived in urban or rural settings was not investigated, and this may have influenced the results since urban residents more often use municipal water.

Two case-control studies in the USA did not detect an association between drinking water and cryptosporidiosis, possibly due to a low number of study participants (Khalakdina et al. 2003; Valderrama et al. 2009). However, four case-control studies were conducted in the UK and observed a dose–response relationship between estimated daily consumption of unboiled tap water from public water supplies and the risk for cryptosporidiosis (Goh et al. 2004, 2005; Hunter et al. 2004) and giardiasis (Stuart et al. 2003).

In a case-control study, Hunter et al. (2004) did not present data on no correlation between problems with tap water pressure and cases of cryptosporidiosis. They later extracted data from the control group in this study and found a significant correlation between self-reported diarrhoea and low tap water pressure (Hunter et al. 2005). Even though statistically significant, the study was not designed to evaluate the effects of low tap water pressure in the control group. For instance, it was not known whether the low water pressure events actually preceded illness and the results were based on few cases.

Most of the case-control studies above do not investigate differences in raw water sources or water treatment methods and focus only on the consumption of municipal drinking water. Case-control studies can mainly be used to identify certain risk factors but are difficult to use in order to quantify the impact these risk factors have on the health outcome. Several case-control studies only report factors that were identified as significant risk factors and do not include the complete set of questions asked to study participants. This indicates that studies might have, indeed, investigated associations between drinking water and GI, but have only reported it when a statistically significant relationship was found. Such studies were therefore not captured in this review. Case-control studies may also suffer from selection bias, as identified cases are commonly recruited from diagnosed cases who have been seeking medical care and cases often suffering from severe symptoms. Pathogens which frequently cause mild symptoms or have short duration times may thus be more difficult to investigate using the case-control study design.

Cross-sectional studies

Cross-sectional studies measure the prevalence of an outcome, for example, GI at a single point in time. In contrast to case-control studies, which tend to use health care data with diagnosed cases, the cross-sectional design relies on self-reported illness. A disadvantage of this is that infections by particular pathogens cannot be studied. In addition, self-reported illness can be highly subjective and therefore it is important to use case definitions. An advantage, however, is the possibility to reduce recall bias and that cross-sectional studies may capture many of the cases that are otherwise unreported when using other methods. Since cross-sectional studies only measure a single point in time it is not possible to detect any trends in incidence or to evaluate the effects of seasonal variation. This limits the usefulness of cross-sectional studies when evaluating the relationship between drinking water and GI.

Using telephone interviews, St-Pierre et al. (2009) investigated the prevalence of diarrhoea in the previous 7 days. People using disinfected surface water or undisinfected ground water, had a lower prevalence of diarrhoea compared to other types of drinking water. No dose–response relationship between tap water consumption and diarrhoea was detected. The prevalence of diarrhoea was higher in areas supplied by water treatment plants that were categorized as low at risk for microbiological contamination. A possible reason for this is that the low risk category to a large extent comprised surface water treatment plants that, on the one hand, had an advanced water treatment process but, on the other hand, may be affected by heavily contaminated raw water.

Interviews in respondents' homes were used to investigate the rate of self-reported AGI in a socioeconomically challenged rural area in the USA. Households which had experienced quality problems such as low pressure, loss of service or taste and odour problems had a higher risk for AGI during the previous 7 days. Measured drinking water turbidity and water pressure was, however, not associated with risk for AGI (Stauber *et al.* 2016).

In a Norwegian study, using mail questionnaires, GI among children was shown to be lower among users of chlorinated drinking water compared with users of unchlorinated drinking water. No difference in risk for GI was detected among adults (Kuusi *et al.* 2003). The study was conducted on a national level and no information was collected about type of raw water, water treatment processes or water consumption. Since several different types of municipal water were included, it is difficult to assess whether chlorination or confounding factors such as raw water quality or other water treatment methods reduced the risk of GI.

Three cross-sectional telephone surveys, measuring water consumption and self-reported cases of GI, were performed in Canada. Jones *et al.* (2007) found an association between self-reported GI in the previous 28 days and the amount of unboiled tap water consumed in the last 24 hours, which was used as an indicator of habitual daily consumption. No association could, however, be established between GI and type of raw water source. In another telephone survey, self-reported AGI in the previous 28 days was not associated with raw water source, water consumption or in-home water treatment. Self-reported AGI was, however, related to precipitation and AGI increased after a period of very low precipitation during the summer, as well as following a period of high precipitation during the autumn among users of surface water. AGI was also more common among ground water users after high levels of precipitation during the summer (Febriani *et al.* 2010).

Cohort studies

While cross-sectional studies provide a snapshot of the GI prevalence, cohort studies are observational studies which follow a population over a period of time, sometimes many years. This allows for collecting more data, increasing the power of statistical analysis, and may also capture variations in prevalence over time. Cohort studies often use similar means for data collection (e.g., telephone interviews) as cross-sectional studies; however, they may also use patient registers.

In several studies the prevalence of antibodies against certain pathogens has been used as a measure of exposure to pathogens. Seroprevalence of *Giardia* and *Campylobacter* varies among users of different surface water sources. Isaac-Renton *et al.* (1996) found dissimilarities in seroprevalence of IgM antibodies against *Giardia* between regions using different water sources in Canada, but no statistical analysis was carried out and it is not possible to know if this could be attributed to differences between water sources or to other differences between the regions. In another study from the USA, higher seroprevalence of IgG antibodies against *Cryptosporidium* was detected among blood donors from a region with filtered and chlorinated surface water compared to residents from a region with chlorinated ground water (Frost *et al.* 2002). Blood donors living in the surface water region were also more exposed to other potential risk factors such as swimming and drinking untreated water.

In a French study, detection of astrovirus and *Giardia* in both raw water and tap water was associated with an increased risk of self-reported gastrointestinal symptoms (Gofti-Laroche *et al.* 2003). There was no relationship between gastrointestinal symptoms and the detection of *Cryptosporidium*, faecal coliforms or faecal streptococci in either raw water or drinking water. However, we identified several limitations in this study, such as small number of water samples and low sampling volumes, making the results uncertain.

Since cohort studies follow a population over a time period there is a possibility to study changes in water treatment methods that are being implemented during the study period. Implementation of changes in a water treatment plant can be viewed as a community-wide intervention and provides an opportunity for investigating the effects of different water treatment methods since the health effect on a large number of individuals can potentially be studied.

During a Canadian cohort study, hospital discharge records and billing records from physicians were analysed in relation to type of water source at the patients' addresses (Teschke *et al.* 2010). At the beginning of the study only a few surface water works used chlorination, but at the end of the study most surface water works had introduced chlorination. Unchlorinated water, both from surface and ground water sources, was identified as a risk factor for physician visits for GI. The effect of precipitation was also analysed among users of surface water but no statistically significant relationship between GI and precipitation was observed.

Using health diaries, the prevalence of GI was studied among the elderly or families with children in a study conducted in the USA. During the study the local water treatment plant changed from using unfiltered and chlorinated surface water to using coagulation, high-rate granular filtration with anthracite, ozonation and chlorination. No change in the incidence of self-reported GI could be detected after the installation (Frost *et al.* 2005, 2009). A reason for this could be that the raw water source was a well-protected watershed with low levels of microbiological contamination. The studies also had a small number of study participants and may have failed to detect small changes in the incidence of gastroenteritis.

Implementation of UV-disinfection at water production plants previously using undisinfected ground water was associated with a decrease in self-reported AGI (Borchardt *et al.* 2012). This was also correlated with a decrease of the number of water samples with detectable levels of adenovirus, enterovirus, norovirus (genogroup I and II), hepatitis A virus and rotavirus. Water samples were collected both directly after UV-disinfection and from taps in homes. UV-disinfection lowered the amounts of virus detected directly at the water treatment plant and there was also a dose–response relationship between virus loads in tap water and AGI, for total amounts of virus, norovirus genogroup I as well as enterovirus, indicating that UV indeed lowered the risk of viral GI in the population.

The incidence rate of cryptosporidiosis (Pollock *et al.* 2008, 2014) as well as seroprevalence of antibodies against *Cryptosporidium* (Ramsay *et al.* 2014) declined after installation of coagulation and filtration treatment at two different surface water treatment plants in Scotland. However, the authors argue that decreased levels of pathogens in the drinking water could also decrease protective immunity against *Cryptosporidium* on population level and thereby increase the risk of receiving cryptosporidiosis from other sources than drinking water (Pollock *et al.* 2008, 2014; Ramsay *et al.* 2014). After the introduction of new barriers, cases of *C. hominis* increased, although the total incidence of cryptosporidiosis declined. This suggests that protective immunity towards *C. hominis* infections declined when exposure to *Cryptosporidium spp*. via drinking water declined.

Cohort studies have also been employed to investigate the health effects of disturbances in the drinking water distribution systems. In a US study, individuals living in households that experienced more than 7 days of low water pressure or loss of water service had an increased risk for self-reported gastrointestinal symptoms (Gargano *et al.* 2015). There was also a trend for increasing risk of gastrointestinal symptoms during longer periods of low water pressure or loss of water service. This trend might however not directly be caused by contaminated drinking water as it is difficult to maintain basic hygiene during long periods without access to potable water. This increases the risk for transmission of infectious disease through other routes than drinking water. Although an increase in self-reported GI was detected, health care utilization did not increase in the area. This demonstrates that data from hospital care might not detect small increases in disease.

In a Norwegian study, households were interviewed by telephone about prevalence of AGI 8–14 days after a low-pressure event in their water distribution system (Nygård *et al.* 2007). Breaks and maintenance work in the water distribution systems were associated with a higher risk of AGI and risk was even higher for events when pressure was low for 6 hours or longer and for individuals drinking more than one glass of tap water per day. In addition, chlorination during pipe repairs lowered the risk. Altogether, the results from the study strongly indicated that breaks and maintenance work may give rise to sporadic cases of GI in the population.

Intervention studies

Intervention studies are cohort studies with a twist; by intervening with a risk reducing measure, researchers attempt to lower the risk and then compare the risk reduction with a control group that may be either unblinded or blinded. To date, several intervention studies have been conducted in Canada (Payment *et al.* 1991, 1997) and the USA (Colford *et al.* 2002, 2005, 2009; Wade *et al.* 2004) and these studies have previously been reviewed by Colford *et al.* (2006).

The first household intervention trial was conducted by Payment *et al.* (1991) in Canada. Homeowners with at least one child were recruited and a total of 606 households with 2,408 individuals completed the study. All of the study participants were supplied by water from the same water treatment plant that treated river water with pre-disinfection, flocculation, rapid sand filtration, ozonation, and final disinfection by chlorine or chlorine dioxide. Study participants were randomly assigned to using domestic reverse osmosis units attached to the cold water line. Participants in the control group received no treatment and also knew that their tap water was untreated. Tap water drinkers without treatment had a higher annual incidence of HCGI illness compared to filtered water drinkers and it was estimated that 35% of the reported HCGI among tap water drinkers was attributable to drinking tap water. A dose–response relationship between the amount of tap water drunk and incidence of HCGI was identified for the control group but not for the filtered water group. Although symptoms among cases of HCGI often were similar to norovirus infections there were no differences in seroprevalence of norovirus between unfiltered and filtered tap water drinkers (Payment *et al.* 1994).

A second Canadian household intervention trial was conducted on another study group in the same region (Payment *et al.* 1997). Homeowners with at least one child in the households were recruited. Over 1,000 households containing 5,253 individuals completed the study and participants were randomly assigned to one out of four treatment groups: (1) tap water, (2) tap water with a purge valve installed, (3) bottled water treated with reverse osmosis and ozonation, or (4) bottled water from the water treatment plant. The highest rates of HCGI were observed in the tap-valve group, followed by the tap group. This led the authors to conclude that the excess of HCGI may primarily have been due to distribution-related contamination rather than source water contamination. A positive dose–response relationship between daily water consumption and HCGI incidence was detected for tap water users older than 12 years, however in children aged 2–12 years, higher tap water consumption was negatively associated with HCGI incidence The authors speculate that this could be because individuals with a high consumption of drinking water at the beginning of the study could have acquired a protective immunity by exposure to low levels of pathogens in the drinking water. No relationship between water consumption and HCGI in the tap-valve group and no correlation between distance to the local water treatment plant and self-reported GI among tap water users was detected during the study. Bottled water from the water treatment plant had high levels of bacterial growth and half of the participants using this type of bottled water dropped out of the study, mainly due to complaints of water taste and odour. The study concluded that 14–40% of GI could be attributed to tap water.

The two studies conducted by Payment *et al.* were unblinded. In later US studies performed by Colford *et al.* (2002, 2005, 2009), the study participants were blinded by using externally identical active or sham devices. The active devices used a 1-micron filter and ultraviolet light treatment. In a pilot study with 77 households with at least one child, the rates of HCGI were slightly higher in the sham group compared to the active group, but the results were not statistically significant (Colford *et al.* 2002).

Following the pilot study, Colford *et al.* (2005) performed a full-scale intervention trial with 465 households and a total of 1,296 individuals. All of the study participants were supplied by the same water treatment plant using a river as raw water source and coagulation, sedimentation, sand filters, carbon filters and chlorination. Participants used an active or sham device for 6 months and then switched to the opposite device for 6 months. No significant difference in rates of HCGI was observed between the intervention and control group and the authors concluded that less than 10% of HCGI illness was attributable to drinking tap water. No dose–response relationship was detected between water intake and HCGI. During the study, in the spring of 2001, a severe flood occurred in the study area, whereby sewage water bypassed treatment and contaminated the source water supply. There was an increase in HCGI during this time among study participants, both in the intervention group and in the reference group, but no association with water consumption was observed (Wade *et al.* 2004).

Colford *et al.* (2009) performed another crossover intervention study similar to previous studies. This trial included 714 households with at least one person aged 55 years or older. Households were supplied by drinking water from induced ground water that had been treated with chlorination. The authors found evidence of reduction of 12% HCGI associated with use of the active device. No dose–response relationship between water consumption and HCGI was however detected.

The unblinded intervention studies that identified tap water as a risk for GI also identified a dose–response relationship between GI and tap water intake (Payment *et al.* 1991, 1997). In blinded intervention studies, however, the risk attributed to drinking water is smaller or not detected and a dose–response relationship cannot be established. All studies are performed on surface water, or induced ground water, and it is therefore uncertain whether there would be any risk differences if the studies had taken place in areas using ground water. Additional intervention studies among ground water users need to be carried out in order to evaluate the risk attributable to ground water. The drinking water complied with water regulations at the time of the study in all of the identified studies, although drinking water treatment plants used raw water from microbiologically challenged surface water sources. Intervention studies may provide a direct estimate of the prevalence of GI that can be attributed to drinking water. The studies have however produced highly varying estimates, perhaps partly due to local conditions and seasonal variation. In addition, intervention studies are expensive and point of use interventions do not give information as to which risk factors during production and distribution of drinking water contribute to the risk for GI.

Future research needs

Existing studies highlight that endemic spread of GI through drinking water is still a problem in high-income countries. The level of risk in many cases does not comply with WHO guidelines of a tolerable burden of disease of 10^{-6} disability-adjusted life year (DALY) per person per year (WHO 2011). Although the risk of acute disease associated with drinking water is usually low, most countries would probably benefit from increased research and development for improving water safety. Since GI infections may result in long-term sequelae (Batz *et al.* 2013; Rehn *et al.* 2015), the health benefits of reducing GI illness may be substantial. Children and the elderly have been shown in several studies to be more susceptible to GI compared to the general population. It is therefore important to include these age groups in order to increase the sensitivity of the studies and to assess the magnitude of disease burden in subpopulations at risk.

Due to their usually low concentration and heterogenic distribution of pathogens in drinking water, it is difficult to directly study pathogenic microorganisms in relation to sporadic cases of GI (Allen *et al.* 2015). To perform such studies vast amounts of data are needed and care must be taken to select appropriate indicators to represent the pathogen load in water. Another approach, circumventing this problem, is to study the dose–response relationship between drinking water intake and risk for illness. A dose–response relationship is biologically plausible since pathogens are unevenly distributed in drinking water at the point of use, and higher water consumption should therefore increase the risk of exposure to pathogens in the drinking water. A few of the reviewed studies did indeed report a dose–response relationship between drinking water and sporadic GI. Quantity of tap water intake is therefore an important variable to be included in epidemiological studies of drinking water-associated GI.

Extreme weather events such as large amounts of precipitation and flooding affects raw water quality and may increase the risk for GI. Surface water is most vulnerable to weather effects but ground water may also be affected. Climate change is estimated to result in more extreme weather events, which also may affect the safety of drinking water. It is therefore important that water treatment plants have sufficient treatment barriers to be able to produce safe drinking water, not only under normal circumstances, but also during more extreme weather situations. Knowledge about the efficacy of microbiological barriers during extreme weather events is, however, limited and needs to be further studied.

Ground water is often considered to require less treatment compared to surface water sources. Studies in this review, however, indicate that ground water production is not always safer with regards to GI. This is because ground water treatment plants often have fewer microbiological barriers, and therefore they are more vulnerable if the raw water becomes contaminated. It is however difficult to directly compare ground and surface water sources because different water treatment methods are used and water consumers often live in different locations with several other factors confounding any possible effects of drinking water. To evaluate the effects of ground water additional intervention trials comparing ground water and surface water are recommended.

A common problem with many of the studies included in this review is the local variations between studies and lack of statistical robustness, making meta-analysis difficult. In several of the included studies statistically significant relationships between GI and risk factors disappear when confounding factors are included in the analysis. Since GI is caused by several different pathogens and several routes of transmission, very large datasets are required to detect how drinking water affects the prevalence of GI. Intervention studies are useful for obtaining information about the contribution of drinking water to the endemic levels of GI. However, intervention trials are costly to conduct and since the studies included in this review mainly examined point of use interventions, it is not possible to assess which factors in drinking water production or distribution contributed to the risk for GI. In order to evaluate specific risk factors other types of studies, especially cohort studies, are more effective.

Health care data and other indirect measurements of GI are often easy to collect and can be used to detect differences in the incidence of GI. There is, however, a risk that pathogens with short duration times, such as norovirus, might be disproportionally under-reported in health care data because people rarely seek medical care for such diseases. This increases the risk for misinterpretation when only health care data is analysed.

We recently published a study correlating microbiological barrier efficacy at 21 water treatment plants with GI-related telephone triage data. We obtained results showing that, theoretically, lower barrier efficacy increased the incidence of GI symptoms (Tornevi *et al.* 2016). As a complement to the more general results obtained in intervention studies, telephone triage data or cohort studies appear to be cost-effective methodologies when assessing specific risk factors. This may be achieved by using such data before and after changes in water treatment or distribution.

CONCLUSIONS

- Drinking water in high-income countries contributes to endemic levels of GI. There are health benefits for further improvements of drinking water production, especially in view of ongoing climate changes which will put further stress on drinking water production due to more frequent extreme weather events.
- A common problem with many of the studies included in this review is the general lack of statistical robustness and large local variations between studies.
- The drinking water supply chain is complex and the safety of drinking water is affected directly or indirectly by a great number of local factors, such as type of raw water source, land use, climate, etc. This variation offers different challenges when it comes to processing the raw water into drinking water, and also makes it difficult to make a generalized assessment of how much drinking water contributes to endemic GI.
- In order to evaluate the effectiveness of specific water treatments, cohort studies or studies using telephone triage data before and after changes in water treatment or distribution may be a cost-efficient supplement to intervention studies.

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