WATER AND INFECTION.
EPIDEMIOLOGICAL STUDIES OF EPIDEMIC AND ENDEMIC WATERBORNE DISEASE

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SUMMARY

Infections transmitted by water continue to be a public health problem both in developing and in developed countries. In the developed countries, the classical waterborne diseases such as typhoid and cholera are almost eliminated, whereas other pathogens and challenges have emerged.

The overall aim of the thesis was to investigate and describe aspects of water-associated infections in a Nordic setting. Contaminated water may act as a transmitter of infectious disease by various routes. Examples of both traditional routes and more recently recognised routes are illustrated. In addition, the thesis describes and evaluates the use of different epidemiological tools and study designs in investigating waterborne illness, and demonstrates how the approach is guided by the outbreak setting and the purpose of the investigation.

This research focus on four areas; endemic waterborne disease, outbreaks caused by contaminated drinking water, outbreaks caused by produce irrigated with contaminated water and a description of an outbreak caused by inhalation of contaminated aerosolised water.

The disease burden caused by non-outbreak related waterborne illness is difficult to estimate. We describe two studies linking endemic illness to drinking water. The first was an ecological study on environmental risk factors for campylobacteriosis in Sweden. Areas with longer water-distribution network and higher proportion with private water supply was associated with a higher rate of infection than areas with shorter distribution networks and public water supply. The second study found an increased risk of gastrointestinal illness following an episode of maintenance work or mains repair on the water distribution network.

In the second part, we describe outbreaks caused by contaminated drinking water. Most waterborne outbreaks in Norway are linked to smaller waterworks with no or failing disinfection. We do, however, also experience larger outbreaks where the hygienic barriers are in place, exemplified by a Giardia outbreak linked to a waterworks supplying several thousand persons. Late detection lead to prolonged suffering and delay in treatment, and emphasizes the need for improved outbreak detection systems.

In the third part, we describe two outbreaks caused by produce irrigated with contaminated water. Both outbreaks were caused by imported lettuce, and the pathogens involved were not endemic in the importing countries. The outbreaks illustrates that water safety is not only a national concern, and that waterborne pathogens that are not endemic may be introduced in new

areas through imported produce. Due to increased trade and travel, international collaboration in infectious disease surveillance and control is important for effective prevention.

The fourth part describes a different aspect of waterborne transmission, illustrated in an outbreak of legionellosis caused by inhalation of contaminated aerosolised water. The investigation identified a new source of Legionella transmission; an industrial air scrubber. Technological developments used to improve living conditions, such as air conditioning systems, and protect the environment through "washing" polluted air in scrubbers, creates new ecological niches where aquatic microorganisms can multiply and be disseminated and cause disease. A thorough risk assessment needs to be carried out during the development and implementation of such systems, so that effective preventive measures can be put in place.

In the final chapter we give some general recommendations and suggest some further studies to better understand the burden of waterborne disease, and some approaches to improve outbreak detection and investigation.

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LIST OF PAPERS

This thesis is based on the following published papers. They will be cited by their Roman numbers:

I. Nygård K, Andersson Y, Røttingen JA, Svensson A, Lindback J, Kistemann T, Giesecke J. Association between environmental risk factors and campylobacter infections in Sweden. Epidemiol Infect 2004; 132: 317-25.

II. Nygård K, Wahl E, Krog T, Tveit OA, Bøhleng E, Tverdal A, Aavitsland P. Breaks and maintenance work in the water distribution systems and gastrointestinal illness: a cohort study. Int J Epidemiol 2007; 36: 873-80.

III. Nygård K, Gondrosen B, Lund V. [Water-borne disease outbreaks in Norway] In Norwegian. Tidsskr Nor Laegeforen 2003; 123: 3410-3.

IV. Nygård K, Schimmer B, Søbstad O, Walde A, Tveit I, Langeland N, Hausken T, Aavitsland P. A large community outbreak of waterborne giardiasis-delayed detection in a non-endemic urban area. BMC Public Health 2006; 6: 141.

V. Nygård K, Vold L, Halvorsen E, Bringeland E, Røttingen JA, Aavitsland P. Waterborne outbreak of gastroenteritis in a religious summer camp in Norway, 2002. Epidemiol Infect 2004; 132: 223-9.

VI. Nygård K, Andersson Y, Lindkvist P, Ancker C, Asteberg I, Dannetun E, Eitrem R, Hellström L, Insulander M, Skedebrant L, Stenqvist K, Giesecke JG. Imported rocket salad partly responsible for increased incidence of hepatitis A cases in Sweden, 2000-2001. Euro Surveill 2001; 6: 151-3.

VII. Nygård K, Lassen J, Vold L, Andersson Y, Fisher I, Löfdal S, Threlfall J, Luzzi I, Peters T, Hampton M, Torpdahl M, Kapperud G, Aavitsland P. Outbreak of Salmonella Thompson infections linked to imported rucola lettuce. Foodborne Pathog Dis 2008; (Accepted for publication)

VIII. Nygård K, Werner-Johansen Ø, Rønsen S, Caugant DA, Simonsen Ø, Kanestrøm A, Ask E, Ringstad J, Ødegård R, Jensen T, Krogh T, Høiby EA, Ragnhildstveit E, Aaberge IS, Aavitsland P. An outbreak of Legionnaires' disease caused by long distance spread from an industrial air scrubber. Clin Infect Dis 2008; 46: 61-9

LIST OF ABBREVIATIONS

AR	Attack rate
AR%	Attributable risk percent
ARI	Annual Risk of Infection
CI	Confidence interval
Enter-net	European surveillance network for human Salmonella and VTEC infections
EPIET	European Programme for Intervention Epidemiology Training
FAO	Food and Agriculture Organization of the United Nations
GIS	Geographical information system
GMP	Good manufacturing practices
IRR	Incidence rate ratio
MRA	Microbial risk assessment
MSIS	Norwegian Surveillance System for Communicable diseases
NA	Data not available
NIPH	Norwegian Institute of Public Health
NorPD	Norwegian Prescription Database
OR	Odds ratio
PAF	Population attributable risk percent
PFGE	Pulsed-field gel electrophoresis
PR	Prevalence ratio
RAPD	Randomly amplified polymorphic DNA
RASFF	European Commission's Rapid Alert System for Food and Feed
RFLP	Restriction fragment length polymorphism
RR	Risk ratio
SMI	Swedish Institute for Infectious Disease Control
WHO	World Health Organization

1. GENERAL INTRODUCTION

Water and humans

WATER IS ESSENTIAL FOR LIFE. Water is indispensable for human health and well-being, and is crucial for sustainable development. Throughout history, civilizations have flourished around rivers and major waterways. Although water is essential for life, it can also cause devastating effects as an effective carrier of pathogens, able to transmit disease to a large proportion of the population in a very short time span.

Waterborne illness has plagued humans throughout history. Cholera was a feared disease that caused large pandemics during the 19th century. John Snow, a physician working in London during the large cholera epidemics in the middle of the 18th century was sceptical to the then-dominant miasma-theory of transmission. He believed the disease was transmitted by water contaminated with faeces from cholera victims (1). By interviewing local residents and cholera victims, he studied the pattern of illness according to water supply, and managed to pinpoint one well located centrally in the cholera victims' neighbourhood – the Broad Street Pump. He later created a map to illustrate how the cases were clustered around this well. John Snow's work was an important event in the history of waterborne illness, and he is regarded as one of the founders of the science of applied epidemiology.

During the 20th century, global water use increased six-fold, more than twice the rate of population growth. In Europe, water consumption in private households varies around 100 – 250 litres per person-day (2). Norway is among the countries with the highest household water consumption per person, with an estimated 224 litres per person-day (2). Most of the water used in households is for toilet flushing, bathing and washing machines, and as little as 6% is for drinking and cooking. However, the largest personal water use is the "hidden water use" – the water needed for production of food and personal commodities (Table 1).

For human survival, the absolute minimum daily water requirement is only about five litres per day, whereas a total daily requirement, including water used for sanitation, bathing, and cooking, is estimated to be about 50 litres per person (3). In developing countries, 20-30 litres per person-day are considered enough to meet basic human needs (4).

In addition to private water consumption, a large amount of water is used for irrigation in agriculture, industrial processes and cooling of electric power plants. Lakes and rivers are

recipients of agricultural runoff and wastewater from communities and industry. Altogether an increasingly high pressure is put on the available fresh water sources.

Table 1 Water use in households and hidden water use by selected products

Household water consumption (5)	*NO-1981*	*SE-1995*	*DK-1997*	*FIN-1998*
Personal hygiene	31 %	44 %	38 %	49 %
Toilet flushing	23 %	29 %	28 %	15 %
Washing clothes	19 %	22 %	14 %	14 %
Dish washing	15 %	29 %	11 %	16 %
Drinking and cooking	6 %	7 %	8 %	3 %
Other uses	5 %	15 %	15 %	3 %

Hidden water use by product (6)	*Virtual water use for production (litres)*
1 glass of milk (200 ml)	200 l
1 cup of coffee (125 ml)	140 l
1 orange	50 l
1 slice of bread with cheese	90 l
1 hamburger (150 g)	2400 l
1 cotton T-shirt	2000 l
1 sheet of paper	10 l
1 microchip	32 l

In December 2003, the United Nations General Assembly proclaimed the years 2005 to 2015 as the International Decade for Action 'Water for Life'(7). The Millennium Development Goal number 7 on environmental sustainability includes a target of reducing by half the proportion of people without access to safe drinking water by 2015 and to stop unsustainable exploitation of water resources. Although waterborne diseases are typically considered to be a problem in developing countries, there is an increasing attention also in developed countries to the public health problem of waterborne illness. Here, outbreaks of the classical waterborne bacterial diseases, such as typhoid and cholera, no longer occur. However, other pathogens and challenges have emerged and waterborne infections continue to be a challenge to public health even in highly developed industrial countries at the beginning of the 21st century.

Infectious agents associated with water

> *"I discovered, in a tiny drop of water, incredibly many very little animalcules, and these of diverse sorts and sizes. They moved with bendings, as an eel always swims with its head in front, and never tail first, yet these animalcules swam as well backwards as forwards, though their motion was very slow."*
>
> *Antony van Leeuwenhoek (1632 –1723)*

Many infectious agents have water as their reservoir or are able to survive in water for some time, thus representing a potential threat to humans. Below I describe briefly some of the most important waterborne pathogens and the diseases they cause, with emphasis on those that are of main concern in the Nordic countries. Table 2 shows a more comprehensive list.

Bacterial infections

Campylobacteriosis

Campylobacter spp. is the most common cause of bacterial gastroenteritis in Norway (Table 2), and several waterborne outbreaks have been reported in recent time (8-11). The main reservoir is warm-blooded animals (including birds and humans). The common clinical picture is a self-limiting diarrhoea of 1-2 weeks duration, however some persons may develop post-infectious complications such as reactive arthritis and Guillain-Barré syndrome (12). Case-control studies have identified drinking untreated water as one of the risk factors for infection in Norway (13), and several waterborne outbreaks have been reported (8;9;14). *Campylobacter spp*. was commonly found in water samples in a survey of surface water sources in Norway, but was not isolated from well water samples (15)

Typhoid, paratyphoid and other salmonella infections

Salmonella Typhi and Paratyphi, the causes of typhoid- and paratyphoid fever respectively (also called enteric fever), have humans as the only reservoir. *S.* Typhi have historically caused many large waterborne outbreaks, however improved water hygiene and sanitary services have almost eliminated the problem in the developed world. In Norway, only a few cases are reported annually, and most are acquired during travel abroad (Table 2). Disease onset of typhoid fever is insidious with fever, general malaise, aches and flu-like symptoms. The lethality may be as high as 15% without adequate antibiotic treatment.

Non-typhoid *Salmonella spp.* are important causes of foodborne infections all over the world. Today, there are over 2500 known serovars of *Salmonella (16)*, and both warm- and cold-blooded animals can be carriers. In Norway, between 1500 and 2000 cases are reported

annually, most related to travel abroad (Table 2). Waterborne outbreaks have been reported, also in Norway (17-20). The main symptoms are self-limiting gastroenteritis, but salmonellae may occasionally cause more severe infections such as septicaemia or post-infectious reactive arthritis.

Yersiniosis

Yersinia enterocolitica is a relatively common cause of bacterial gastroenteritis in the Nordic countries. The illness is typical an acute febrile diarrhoea, which may be accompanied by severe abdominal pain (especially in children). Post-infectious immunological complications may include erythema nodosum and reactive arthritis, and these have predominantly been reported in Nordic countries (21-24). Drinking untreated water has been identified as one of the risk factors for yersiniosis in Norway (25). *Yersinia spp*. has been isolated in drinking water samples in Norway, however most were non-pathogenic variants (15;26)

Shigellosis (Bacillary dysentery)

There are four subgroups of shigella causing illness of varying severity; *Sh. dysenteriae, Sh. flexneri, Sh. boydii* and *Sh. sonnei.* Humans are the only known hosts, and while person to person spread is the predominant mode of transmission, both food- and waterborne outbreaks occur. *Sh. sonnei* cause a relatively mild and self limiting diarrhoeal illness, while the others cause more severe and often bloody diarrhoea. Systemic symptoms with fever, malaise and general pains may be present. Most shigella infections reported in Norway have been acquired during travel abroad (Table 2).

Cholera

Cholera was the first disease shown to be waterborne and has played an important role in the history of waterborne illness. Although the disease is very rare in the developed world today, it is still a major cause of illness and death in several parts of the world. Cholera is caused by *Vibrio cholerae*, and humans are the only known reservoir. The main clinical feature is watery diarrhoea, which may be life-threatening in severe cases due to rapid loss of fluid and electrolytes. Only sporadic imported cases are reported in Norway.

Infection caused by enteropathogenic *Escherichia coli*

The enteropathogenic *E. coli* are grouped based on their virulence properties. The most important are:

Enterotoxigenic *E. coli* (ETEC) is a common cause of travellers' diarrhoea, and an important cause of diarrhoea in children in developing countries.

Enteropathogenic *E. coli* (EPEC) mainly affects infants, and can cause watery, mucoid diarrhoea and fever.

Enteroinvasive *E. coli* (EIEC) causes illness similar to shigella dysentery.
Enterohaemorrhagic *E. coli* (EHEC) causes diarrhoea, which often is bloody. Some cases develop haemolytic uraemic syndrome, mainly children. Ruminants are the main reservoir for EHEC.

The enteropathogenic *E. coli* can be transmitted from person to person (or animals for EHEC and atypical EPEC) or through contaminated water and food. Both ETEC and EHEC is reported to have caused waterborne outbreaks (27-33), and in developed countries, EHEC is of major concern due to the severity of the illness. In Norway, ETEC and EIEC are rarely diagnosed, however cases with EPEC and EHEC-infections are reported annually (Table 2).

Tularaemia
Tularaemia is a zoonosis caused by the bacterium *Francisella tularensis*. Rodents and small mammals are the main reservoir, and transmission usually occurs through direct contact with infected animal tissue or through insect bites, but it may also be airborne or through food or water. The initial symptoms is typically influenza-like with fever and general body aches, and depending on the route of infection, the clinical disease may present in different forms; ulceroglandular, oropharyngeal or respiratory. In Norway, 10 to 20 cases are reported annually, and oropharyngeal have been the most common clinical manifestation (34). Water is considered an important mode of transmission (35). Waterborne outbreaks have been reported, both in Norway (36) and in other countries (37;38).

Legionellosis
Legionella spp. are naturally present in water environments. Several species are recognized, but human illness is mainly associated with infection with *Legionella pneumophila* serogroup 1. There are two typical disease syndromes; Legionnaires' disease, which is a severe pneumonia mainly affecting elderly, people with chronic heart or lung disease or smokers, and Pontiac fever, which is a self-limiting influenza-like illness that may affect also otherwise healthy people. The infection is mainly transmitted through inhalation of contaminated aerosols. Aspiration of contaminated water is reported in hospitals (39). Although most cases reported in Norway are travel-related, both outbreaks and sporadic cases occur (40).

Leptospirosis
Leptospirosis is a zoonosis caused by *Leptospira interrogans*. The most important human pathogenic serovars of *Leptospira interrogans* are *icterohaemorrhagiae*, *canicola* and *hardjo* associated with rats, dogs and cattle, respectively. Humans are infected through contact with animal urine or with water contaminated with animal urine, and transmission is mainly through abraded skin or mucous membranes; occasionally also through consumption of contaminated

food or water (41). The illness is often mild with flu-like symptoms. Some patients develop severe systemic symptoms, including fever, pains and hepatic and kidney failure. Leptospirosis is not endemic in Norway.

Parasites

Giardiasis

Giardiasis is caused by a protozoan parasite *Giardia lamblia* (syn. intestinalis or duodenalis) and is an important cause of gastrointestinal illness. Infection is transmitted by direct person contact or by contaminated food or water. The predominant symptoms are diarrhoea, bloating and flatulence. Some people may have symptoms lasting for years if not treated. Most cases reported in Norway are imported, however domestic cases may be underdiagnosed (42).

Cryptosporidiosis

Cryptosporidiosis is caused by a protozoan parasite, of which two species are of importance; *C. parvum* and *C. hominis*. Cattle are an important reservoir for *C. parvum*. Transmission is through direct contact with infected humans or animals, or through contaminated food and water. The illness is characterized by a self-limiting diarrhoeal illness, but may be severe and long-lasting in immunosuppressed individuals. Cryptosporidiosis is not a notifiable disease in Norway, and may be underdiagnosed in cases with gastroenteritis (42)

In a survey of Norwegian water sources in 1998-1999, *Giardia* cysts and *Cryptosporidium* oocysts in low concentrations was frequently identified. However, the viability or infectivity for humans of the identified parasites was not assessed (43).

Schistosomiasis

Shistosomiasis is a group of diseases caused by trematode flatworms. There are five species of importance to public health, with varying severity and geographical distribution. Swimmers' itch (schistosome dermatitis) is due to penetration of cercaria through the skin when swimming in contaminated water. Birds are the main hosts. The dermatitis is probably caused by an allergic reaction, and this form is present on all continents, and also a common problem in some fresh-water lakes in Norway. A more severe form of schistosomiasis, causing a severe systemic infection, is present in some more tropical areas of the world.

Toxoplasmosis

Toxoplasmosis is a zoonosis caused by the protozoo *Toxoplasma gondii*. In healthy persons the infection is usually asymptomatic or may present with mild influenza-like symptoms that can last for weeks. Infection during pregnancy may result in abortion, stillbirth or foetal abnormalities. Infection is usually transmitted by contact with cat feces, by consumption of food

or water contaminated with oocysts from cat feces or soil, or by eating raw or undercooked meat containing oocysts (41). Contaminated water has increasingly been recognized as an important route of transmission (44-47).

Viruses

Viral gastroenteritis

Several viruses may be transmitted by contaminated water, including norovirus, rotavirus, adenovirus and astrovirus. Of these, norovirus has been the most commonly reported in waterborne outbreaks (48). The symptoms are dominated by vomiting and diarrhoea, normally lasting for a few days.

Viral hepatitis

Two viruses have been associated with waterborne transmission of viral hepatitis; hepatitis A and hepatitis E virus. Initial symptoms are non-specific with general malaise, fever and pains. Jaundice develops after some days. Most people recover completely, and fulminant hepatitis and fatality are rare complications. Food- or waterborne hepatitis is not common in Norway, and the immunity in the population is low (49;50), however outbreaks have occurred among intravenous drug users and homosexual men (51-53).

The large variety of different microbes that are able to be transmitted by water is a challenge. However, although a diverse range of infectious agents are transmitted by water – both directly and indirectly – the investigation of outbreaks caused by waterborne pathogens are less dependent on which agent causes the outbreak than on the setting of the outbreak.

Table 2 Waterborne pathogens and their significance in water supplies in Norway [1]

Pathogen	Symptoms	Situation in Norway			Important animal source	Persistence in water supplies [3]	Resistance to chlorine [4]
		Endemic	Cases / year reported [2]	% imported			
Bacteria							
Campylobacter jejuni, C. coli	Diarrhoea (Guillain-Barre syndr.)	+++	2000-2500	50-60	Yes	Moderate	Low
Yersinia enterocolitica	Diarrhoea, reactive arhritis	++	100-200	20-30	Yes	Long	Low
Escherichia coli – Pathogenic [5]	Diarrhoea	+	50-100	50-70	Yes	Moderate	Low
Enteropathogenic	Diarrhoea	+	10-20	20-40	Potentially	Moderate	Low
Enterotoxigenic, Enteroinvasive	Diarrhoea, bloody diarrhoea	-	20-50	>90	No	Moderate	Low
Enterohaemorrhagic	Bloody diarrhoea, HUS	+	10-20	40-50	Yes	Moderate	Low
Salmonella Typhi	Typhoid Fever	-	10-20	>90	No	Moderate	Low
Other salmonellae	Gastroenteritis, reactive arthritis	+	1500-2000	80-90	Yes	May multiply	Low
Shigella spp.	Bacillary dysentery	-	100-200	80-90	No	Short	Low
Vibrio cholerae	Watery diarrhoea	-	0-2	100	No	Short to long[6]	Low
Fransicella tularensis	Tularaemia	+	10-20	0-5	Yes	Long	Low
Legionella spp.	Legionnaires' disease: pneumonia Pontiac fever: flu-like symptoms	+	20-30	50-60	No	May multiply	Low
Viruses							
Adenoviruses	Gastroenteritis, resp. infections	+++	NA		No	Long	Moderate
Enteroviruses	Various clinical manifestations	++	50-100	0-5	No	Long	Moderate
Astroviruses	Diarrhoea	++	NA		No	Long	Moderate
Hepatitis A viruses	Hepatitis	+	50-150	50-60	No	Long	Moderate
Hepatitis E viruses	Hepatitis	-	NA		Potentially	Long	Moderate
Noroviruses	Gastroenteritis	+++	NA		Potentially	Long	Moderate
Sapoviruses	Gastroenteritis	++ ?	NA		Potentially	Long	Moderate
Rotavirus	Gastroenteritis	+++	NA		No	Long	Moderate

Pathogen	Symptoms	Situation in Norway			Important animal source	Persistence in water supplies [3]	Resistance to chlorine [4]
		Endemic	Cases / year reported [2]	% imported			
Protozoa							
Cryptosporidium parvum	Diarrhoea	++?	NA		Yes	Long	High
Cyclospora cayetanensis	Diarrhoea		NA		No	Long	High
Entamoeba histolytica	Amoebic dysentery	-	NA		No	Moderate	High
Giardia intestinalis	Diarrhoea	+?	300-400	80-90	Yes	Moderate	High
Toxoplasma gondii	Miscarriage, birth defects	++	NA		Yes	Long	High
Helminths							
Dracunculus medinensis	Guinea worm disease: ulcerating skin infection	-	NA		No	Moderate	Moderate
Schistosoma spp.	Bilharziasis: systemic illness, liver and kidney damage	-	NA		Yes	Short	Moderate
	Swimmers itch: allergic dermatitis	++					

1) Adapted from table 7.1 in WHO Guidelines for drinking water quality (54)

2) Data from the Norwegian Surveillance System for Communicable diseases (MSIS) (55). NA: Data not available: the disease is not notifiable.

3) Detection period for infective stage in water at 20 °C: short, up to 1 week; moderate, 1 week to 1 month; long, over 1 month.

4) When the infective stage is freely suspended in water treated at conventional doses and contact times and pH between 7 and 8. Low means that 99% inactivation at 20 °C generally in <1 minute, moderate 1–30 minutes and high >30 minutes.

5) Includes enteropathogenic, enterotoxigenic and enteroinvasive.

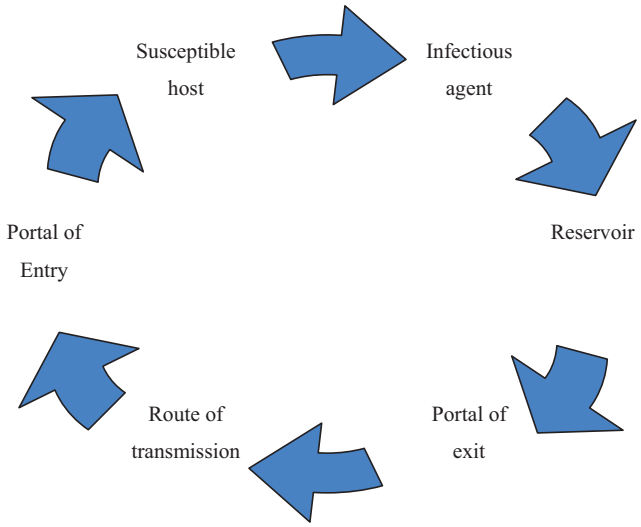
6) Vibrio cholerae may persist for long periods in association with copepods and other aquatic organisms.

The roles of water in disease transmission

Chain of transmission

The chain of transmission is a conceptual model for spread of infectious agents (Figure 1). The chain contains six links that all have to be present for the disease to spread. Thus, infectious disease control will be achieved by removing at least one of the links to break the chain.

Figure 1 The chain of transmission



The sources and routes of transmission for water-associated infectious agents

Infectious diseases related to water have been categorised in water-borne diseases (including food-borne disease caused by use of contaminated water, e.g. cholera, typhoid), water-washed diseases (also called “water-scarce” diseases, caused by lack of sufficient quantities of water for basic hygiene, e.g. intestinal helminth infections), water-based diseases (e.g. schistosomiasis, swimmers itch), water-related vector-borne diseases (e.g. malaria, filariasis and dengue), and water-dispersed infections (e.g. legionellosis). The present study focuses on the most relevant routes in the Nordic countries, where the water-washed, water-based and water-related vector-borne diseases are of less public health importance.

Some infectious agents may live and multiply in water (legionellae, vibrionaceae). In these cases, water is the reservoir of the infectious agent. For other agents, water is a merely a

temporary vehicle for the agents' spread from infected animals or humans (reservoirs) to susceptible humans. The transmission routes can be categorised in this way:

1) Direct transmission through drinking water:
Drinking water can be contaminated from infected humans or animals, either at the source or in the distribution pipelines. Both inadequate water protection, and inadequate treatment or maintenance of water pipelines are important contributing factors.

2) Indirect transmission through consumption of foodstuffs contaminated from water:

- Shellfish raised in contaminated water may concentrate pathogens (especially viruses) during the process.
- Irrigation of foodstuffs with contaminated water close to harvesting may lead to contaminated products reaching the consumer.
- Rinsing fresh produce or other foodstuffs with contaminated water before sale or serving may contaminate the food.

3) Direct transmission through contact with contaminated water:
Some parasites are able to penetrate intact skin and cause severe infections. In addition, some pathogens gain entrance through small cuts or breaks in the skin (e.g "swimmers ear").

4) Airborne transmission:
Aerosol producing devices may create aerosols that can be dispersed over large distances and then inhaled by humans. The environment in such devices may be favourable for growth of certain pathogens, a recognized problem with legionellae in cooling towers. In addition, some viruses may be transmitted by aerosols if the water in the devices is contaminated.

The portal of entry for water-associated infectious agents

The infectious agents have to gain access to the human body in order to cause disease, i.e. transgress the unspecific defence of the human body, such as skin, mucosa and nasal hair. Agents that contaminate water may gain access to the human body in numerous ways. The most common are:

- **Ingestion (mouth) by drinking** contaminated water. Several pathogens are able to survive for longer periods in water, and large outbreaks of both zoonotic and non-zoonotic pathogens have been reported all over the world (56-60)

- **Ingestion (mouth) by eating food** that has been washed in, sprayed by or irrigated by contaminated water. For instance, an outbreak of shigellosis caused by iceberg lettuce occurred in Norway in 1994 (61).
- **Ingestion (mouth) by using devices** (mouth swabs, tooth paste etc) that contain contaminated water. For instance, in 2002, 231 patients in Norwegian hospitals were infected with a strain of *Pseudomonas aeruginosa* that had contaminated several batches of a commercially available mouth swab (56;62).
- **Inhalation (mouth, nose)** of aerosolised contaminated water in the community or in hospital (through ventilator). For instance, in 1999, an outbreak of Legionnaires' disease affected many visitors to a flower show in the Netherlands, and the source was traced to whirlpool spa on display (63).
- **Skin penetration** (through intact skin) by bathing in or contact with contaminated water. A variety of parasites are able to penetrate intact skin, from the less severe illness swimmers itch caused by bird schistosomes, to more severe infections like bilharzias (schistosomiasis) causing a large public health problem in the developing world.
- **Wound contamination** (through damaged skin or mucosa) by bathing or washing of wound in contaminated water. For instance, following the 2005 tsunami in the Indian Ocean, there were several reports of wounds infected with a variety of seawater and freshwater bacteria, such as *Vibrio* and *Aeromonas* species (64).
- **Injection (through skin)** by the use of contaminated water in injected fluids. For instance, infusion of contaminated water for injection was the source of two outbreaks of bloodstream infections in Brazil (65).

Emerging challenges

The main challenge is that humans are dependent on water while water at the same time is an excellent environment for many infectious agents. Although improved sanitary practices for the disposal of sewage, source water protection, and filtration and chlorination of drinking water dramatically decreased the risk of waterborne infections in the developed world during the 20th century, new challenges related to waterborne pathogens have emerged.

Some pathogens have proved to be resistant to traditional drinking water treatment, and outbreaks caused by chlorine resistant parasites such as cryptosporidium and giardia is a major concern.

Increased globalisation of trade may lead to import of products contaminated with pathogens that are not endemic in the importing country. Low-grade contamination of products can cause widespread outbreaks that may be difficult to detect and investigate. Increased population

mobility due to migration and the popularity of travel to exotic travel destinations may change the presence and level of different pathogens in sewage. Outbreaks caused by non-endemic pathogens may occur, but the outbreaks may be detected late due to diagnostic limitations.

New technology aimed at improving living conditions such as air conditioning systems, or measures to protect the environment such as biological wastewater treatment and industrial air-washers has created new ecological niches and new mechanisms for transmission.

An ageing population and increased susceptibility in the population due to chronic illness or immunosuppression put high demands on the water quality, and is especially important in hospital settings. Additionally, increasing urbanisation and population density put a stress on the available water sources and sanitation systems. A continuous assessment of development- and maintenance requirements of the water distribution and sewage systems are therefore needed to prevent an increase in the risk of water contamination.

Epidemic and endemic waterborne disease

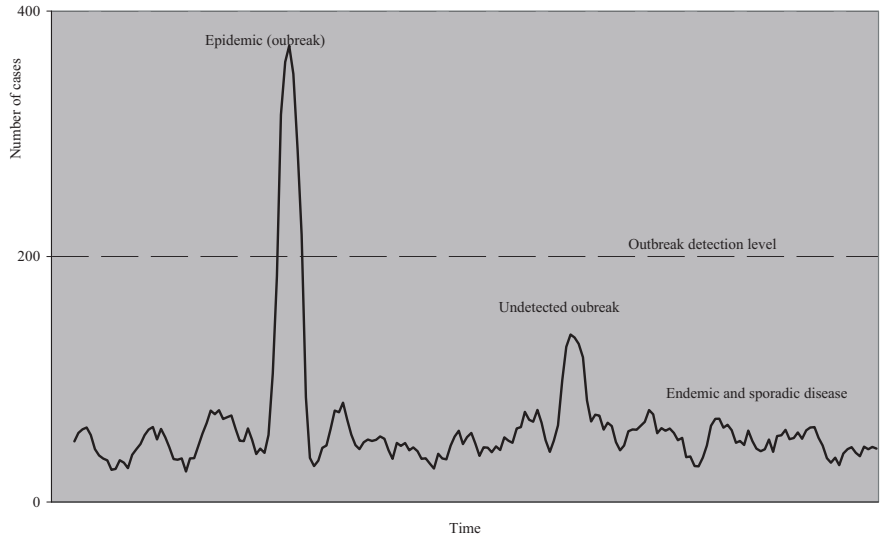
Poor water quality continues to be a major public health problem globally. According to the World Health Organization, diarrhoeal disease accounts for an estimated 4 % of the total global burden of disease measured in disability adjusted life years (DALYs) and around 1.8 million deaths every year (66). It has been estimated that almost 90% of that burden is attributable to unsafe water supply, sanitation and hygiene, mainly affecting children in developing countries.

In developed countries, waterborne disease is no longer considered a constant threat. However, waterborne diseases have not been eradicated, and every year some waterborne outbreaks occur. Outbreaks caused by contaminated drinking water may have substantial public health impact and will cause large concern in the affected community. In recent years, the importance of non-outbreak waterborne illness has gained renewed interest. The proportion of endemic gastrointestinal illness in the community that can be attributed to water is unknown. Probably, drinking water systems that fulfil the required standards can intermittently be contaminated by pathogens either through low-level contamination of source water, inadequate water treatment or deterioration of water quality in the distribution system (67). Although the concentrations of infectious organisms may be very low in these incidents, they may result in sporadic cases of illness that are not recognized or investigated as a possible outbreak (68)

Epidemic and endemic disease

The distinction between epidemic disease (or outbreaks) and endemic disease is illustrated in Figure 2. Epidemic disease is defined as a clear increase in number of cases with a specific illness compared with the normally expected in a given period and place. The recognition of an outbreak will depend on the sensitivity of the surveillance systems, which often depends on the severity and specificity of the symptoms, the normal background rate, the degree of exposure in the population and the proportion exposed that develop symptoms. Waterborne outbreaks are characterized by a high degree of exposure in the population, however the symptoms are often mild and non-specific (gastroenteritis), and not all exposed will develop symptoms. Short-lasting contamination events within the water distribution systems may cause smaller outbreaks that may pass undetected (see Figure 2). In contrast, endemic disease refers to the constant presence of an illness in an area or population group; the expected level of the illness in that population. Sporadic disease occurs irregularly and consists of seemingly unrelated cases.

Figure 2 Epidemic and endemic disease



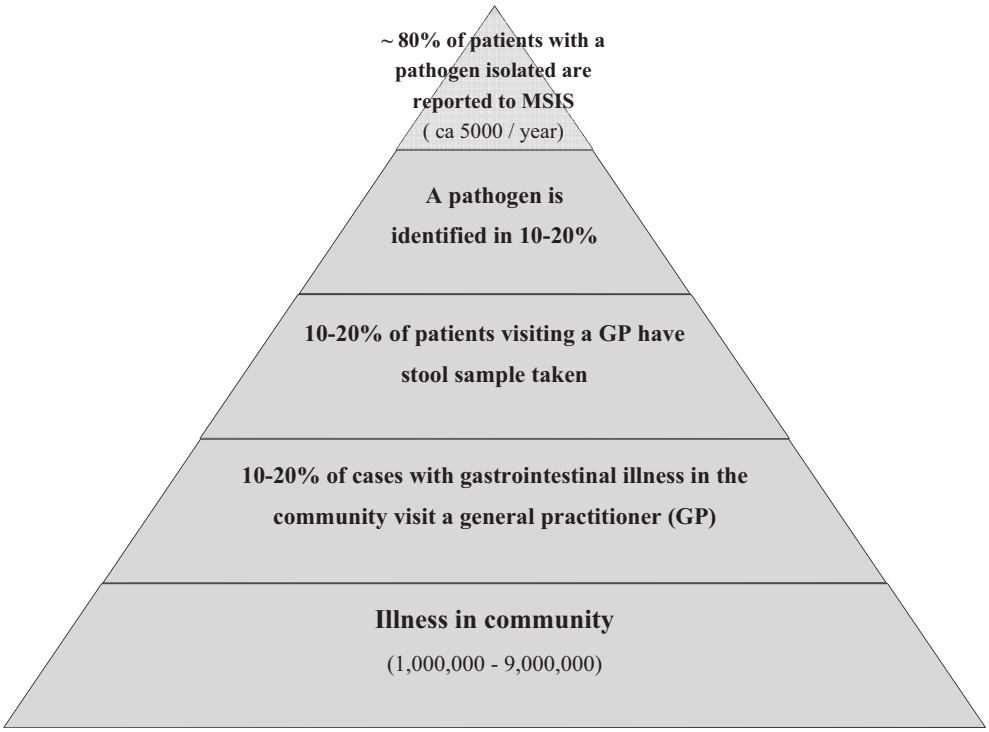
Burden of gastrointestinal illness

Although waterborne pathogens may cause a variety of illnesses, the most common clinical feature is acute gastrointestinal illness. Acute gastrointestinal illnesses may have a multitude of different aetiologies, both infectious and non-infectious, and with several transmission pathways, including person-to-person, contact with infected animals, and consumption of

contaminated food- and water. Figure 3 shows a conceptual pyramid of the occurrence of gastrointestinal illness and the proportion reported to national surveillance in a typical European country. The numbers in the figure are crude estimates calculated from population-based studies of gastrointestinal illness in the community and clinician surveys (69-73)(Table 3) The top of the pyramid represents the number of cases diagnosed with a notifiable gastrointestinal pathogens registered in the Norwegian Surveillance System for Communicable Diseases (MSIS)(55).

The figure illustrates the reasons for underreporting of gastrointestinal infections in national infectious disease surveillance: 1) Most persons with a gastrointestinal infection experience a relatively mild illness, and only few seek medical care (10-20%). 2) In only a proportion of patients will the physician request a stool sample (10-20%). 3) The sample is analysed for only a few pathogens, and is not 100% sensitive. 4) Not all infections are notifiable. The degree of underreporting varies between countries and between pathogens, both due to different health care seeking behaviour, different stool request practises among physicians, and differences in routine stool analysis and notification systems. In the UK, Wheeler et al estimated the underreporting for salmonella infections to be 1:3.2, while underreporting for norovirus infections was estimated to 1:1562 (70). In the USA the underreporting for salmonella infections was estimated to be 1:38 (74).

Figure 3 Under-reporting pyramid for gastrointestinal infections reported to the Norwegian infectious disease surveillance system (MSIS) *(rounded estimates based on international surveys, see text)*



Studies conducted during the last decades in developed countries have shown considerable variation in the incidence of gastroenteritis and consultation rate due to the illness. Incidence rates between 0.2 and 3 episodes of acute gastroenteritis per person-year have been reported (Table 3). Differences in case-definitions and study design may contribute to some of these differences, and it is difficult to say if they represent real differences in the disease burden in the population.

Recently, some countries have tried to estimate the burden of gastrointestinal illness attributed to tap water. In Canada, Payment et al. have conducted two household intervention trials, where the participating households where divided into groups either drinking water treated at the point of use (water treatment device installed within the households) or drinking ordinary tap water. They found that increased gastrointestinal illness was associated with drinking tap water from

major municipal water system that met current water quality criteria (75;76). In the USA and Australia, similar studies were conducted with no association between tap water consumption and illness (77;78). Differences in study designs as well as differences in water supply systems in the study areas may explain some of the variation.

Endemic gastrointestinal illness in Norway

As shown in Table 2 (waterborne pathogens) approximately 5000 cases of infections that may be water-associated are reported annually in Norway. However, the mode of transmission for most of the cases reported to national infectious disease surveillance is not known. Additionally, as mentioned above, the number of cases reported only represents a fraction of the illness that occurs in the community. In Norway, two population-based surveys have been done to estimate the burden of acute gastrointestinal illness. The first was done in august in 1986 among persons over 15 years of age. The interviewees were asked about symptoms of vomiting or diarrhoea in the previous two weeks, and the researchers found an incidence of acute gastroenteritis of 1.5 per person-year among people above 15 years of age, which means about 5 million episodes per year (79). The researchers also asked the cases about suspected cause of illness, and based on two of the cases (1.6 %) indicating drinking water as the possible source, they estimated that 50-100,000 cases of illness annually could be caused by drinking water in Norway. The second survey was conducted in 1999-2000 and included both children and adults. The interviewees were asked about symptoms of acute gastrointestinal illness in the four weeks prior to the interview. The results were similar to the results of the first survey, with an incidence rate of acute gastroenteritis = 1.2 per person-year. Among children aged less than 15 years, drinking water from a private water supply was associated with illness, while using chlorinated water was protective. In this second study, three respondents indicated drinking water as the possible source of infection (1.8%)(80).

In order to better target preventive measures we need more knowledge on which factors are contributing to the disease risk, and a better understanding of the role of water in transmission of infectious diseases. However, it is a challenge to obtain precise and reliable information on the true burden of waterborne disease.

Table 3 Selected studies of burden of gastrointestinal illness in developed countries [1]

Country	Study period	Design [2]	Case definition [3] (main components)	Sample size [4]	Episodes per person year	Reference
Retrospective data collection						
England	1993-96	CM (4w recall)	D or V	9776	0.55	(70)
USA	1996-03	CP (4w recall)	D	50323	0.6	(82)
USA	1996-97	CP (4w recall)	D D lasting >1d	8624	1.4 0.7	(83)
Norway	1999-00	CP (4w recall)	D or 3 of (V+N+AC+F)	1843	1.2	(80)
Ireland	2000-01	CP (4w recall)	D	9903	0.44	(84)
United States	2000-01	CP (4w recall)	D	14 647	0.99	"
Australia	2001-02	CP (4w recall)	D	6087	0.83	"
Canada (Hamilton)	2001-02	CP (4w recall)	D	3496	0.99	"
Canada (Hamilton)	2001-02	CP (4w recall)	D or V	3496	1.3	(85)
Prospective data collection						
Canada	1988-89	CBI (suburban)	D or V or N+AC	606hh - 2408p	0.76 [5]	(75)
Canada	1993-94	CBI (suburban)	D or V or N+AC	1062hh - 5253p	0.66 [5]	(76)
Canada	1995 (Apr-Jul)	CBC (rural)	D or V or N+AC	235hh - 619p	1.1	(86)
The Netherlands	1991 (Mar-Jul)	PBC	D or V+2 other symptoms	2257	0.63	(87)
England	1993-96	MBC	D or V	9776	0.19	(70)
France	1998-99 (Oct-Jun)	CBC (SE France)	D or V or N or AP D + 1 of the other	176hh - 544p	2.8 0.4	(88)
Australia	1997-99	CBI	D or V or N+AP	600hh - 2811p	0.82[5]	(78)
The Netherlands	1998-99	MBC	D or V (>3 times in 24h)	4860	0.28	(89)
USA	2000-02	CBI	D or V or N+AC D	456hh - 2811p	2.1[5] 0.64	(77)

1 Adapted from table 2 in Roy et al. (81)

2 CP: Cross-sectional population based surveys. CM: Cross-sectional medical-practice based surveys. CBI: community-based intervention trial.CBC: Community-based cohort. MBC: Medical-practice based surveys

3 D: diarrhoea, V: vomiting, N: nausea, US: upset stomach, AP/AC: abdominal pain/cramps.

4 p: persons, hh: households

5 Incidence in regular tap water- or sham-device group

Epidemiological study designs used in investigating waterborne disease

Epidemiology is defined as the study of distribution and determinants of health-related states or events in populations, and the application of this study to control of health problems (90). Epidemiological study designs can be broadly divided into two main groups; experimental studies and observational studies. Most studies investigating waterborne disease have been observational studies. Recently a few experimental studies have been conducted in Canada, the USA and Australia (75-78).

The design of experimental studies is aimed at reducing variation of extraneous factors in comparison with the factors that are being studied. The allocation or assignment of the study subjects to the exposure is under the control of the investigator, and can be randomized in order to obtain symmetry of potential unknown confounders.

Observational studies are used when experimental studies are not feasible for ethical, economical or practical reasons. The investigator cannot control the exposure, and therefore there is a potential for confounding bias if there is an association between the exposure of interest and an unknown risk factor for the outcome. The definition of the study population, the selection of study subjects and correction for possible confounders will therefore be crucial for obtaining valid results in observational studies (91).

An overview of study designs and examples of how they are used in investigating waterborne disease is shown in Table 4 and Table 5 respectively, and the concepts of some of the designs are shortly described below.

Cohort study

The purpose of a cohort study is to compare occurrence of illness in two groups of people – those who are exposed and those who are unexposed to a suspected risk factor. A direct estimate of the relative risk may be calculated by comparing the attack rates of illness in the two groups. Cohort studies are often used when the outcome of interest is relatively common, and a high number of cases will be expected in the study population during the study period. Cohort studies may be prospective or retrospective. In outbreak investigations, retrospective cohort studies are often used when there is a small and defined group at risk, such as in a local dinner arrangement or gathering.

Case-control study

The case-control study is an observational retrospective epidemiological study where the exposure status of people with the illness of interest (cases) is compared to the exposure status of a sample of people without the disease or a sample of the whole source population irrespective of disease status (controls). Cases and controls need to be selected from the same source population. Case-control studies are often used when investigating risk factors for rare diseases. In outbreaks, case-control studies will be used when the outbreak cannot be localized to a defined group and it is not feasible to interview the whole group at risk.

Ecological study

In an ecological (aggregated or group-level) study design, data on risk factor distribution and measures of disease in different populations is compared to explore associations. The groups under study can be defined by geography, by time or by profession or lifestyle.

Looking at the geographical distribution of diseases was one of the first methods used in epidemiology to study sources of transmission and rate of spread of disease, exemplified by the work on cholera in London by John Snow (92). The logic behind using geography to study risk factors for disease is to explore correlation between potential risk factors that have a spatial pattern and disease occurrence. Risk factors can include either physical and environmental factors, social, cultural and economic factors, or genetic factors. This method has become more available now, when the use of geographic information systems has made it easier to analyse routinely available surveillance data on a more detailed geographical level. In infectious diseases, such an ecologic design has mainly been applied for vector-borne diseases, but recently this approach has also been used to study risk factors for Enterohaemorrhagic *E. coli* (EHEC) infections in Canada and Sweden (93;94) and tuberculosis in Germany (95).

Time-series analysis is another example of ecological studies using time as the grouping variable. This method has been used in environmental epidemiology to study the effect of air pollution on health (96;97) and also in investigation of waterborne illness related to water turbidity (98;99).

Findings from ecologic analyses are not necessarily reflecting associations at the individual level. One major limitation is described as the ”ecologic fallacy”, where an association found between a potential risk factor and the outcome on the aggregated level does not reflect the biological effect on the individual level, due to within-group difference in exposure level and covariates (100). There may also be problems with availability of data necessary for adequate control of confounding in the analysis. Although ecologic studies may have several

methodological problems, the influence of environmental variables can often be difficult to assess on an individual basis, and an ecologic study may be one way to investigate the exposure effect. Ecological studies may be used as a relatively easy and inexpensive tool to assess associations that can be further investigated in more targeted studies (100).

Microbial risk assessment

A different approach to assess the likelihood of illness after exposure to pathogenic microorganisms is the microbial risk assessment (MRA). MRA is a scientific tool that can be used to evaluate the level of exposure and the subsequent risk to human health due to a specific pathogen or food product. Such techniques are becoming increasingly used in assessing risks associated with food or water because they facilitate scientific investigations of risks including quantification of uncertainty and prioritization of control strategies (101-104). In a quantitative risk assessment, information on pathogen distribution, exposure and dose-response is included as inputs in a mathematical model The outcome of the model expresses the risk of ilness or expected number of cases with level of uncertainty. Difficulties in MRA include limited data and approaches to assess risks to highly susceptible subpopulations.

Table 4 Overview of study designs used in investigating waterborne disease

Study design		Strengths	Limitations
Experimental - always prospective			
Clinical trials	Treatment	Strong evidence for causuality	Ethics
Field trials	Preventive measures, individual level	Control confounding	Cost and time
Community intervention trials	Preventive measures, community level		
Observational - often retrospective, sometimes prospective			
Cohort studies	Prospective	Measure incidence and relative risk	Limited power with rare diseases
		Time sequence: cause-effect	Cost and time
	Retrospective	Measure incidence and relative risk	Recall bias Cause-effect relationship
Case-control studies	Retrospective	Good for rare diseases Cheap and quick	Selection bias Recall bias Cause-effect relationship Unmeasurd confounding No direct measure of risk
Cross sectional studies	Population surveys Seroprevalence studies	Study of populations Generalizability Can be done quickly	Selection bias Recall bias Cause-effect relationship Not suitable for rare diseses
Ecological studies (group-level studies)	Geographical correlation Time-series analysis	Low cost, convenient	Ecological fallacy Confounding
Mathematical modelling			
Quantitative microbial risk assessment		Cheap and quick Estimate disease burden Scenarios – what if..	Large uncertainties

Table 5 Studies of endemic waterborne disease

Study design	Setting	Exposure	Outcome	Measure of risk	Reference
Observational					
Ecological studies					
Time-series analysis	Elderly(>65), Philadelphia	Water turbidity	Hospital admissions gastrointestinal illness	9% increase (95% CI 5.3%, 12.7%)	(98)
	Children, Philadelphia	Water turbidity	Hospital admissions gastrointestinal illness	> 2 years 31.1% increase (95% CI: 10.8, 55) < 2 years 13.1% increase (95% CI: 3.0, 24.3)	(99)
	Milwaukee	Water turbidity	Diagnosed gastroenteritis	Children RR 2.35 (95% CI: 1.34, 4.12) Adults RR 1.17 (95% CI: 0.91, 1.52).	(105)
		Tap-water quality	Anti-diarrheal drug sales		(106)
Geographical	Massachusetts	Unfiltered vs private groundwater	Cryptosporidiosis Giardiasis	IRR: 1.6 (95% CI:1.5, 1.7) IRR: 1.4 (95%CI: 1.3, 1.4)	(107)
	Vermont	Unfiltered vs filtered	Giardiasis	IRR: 1.9 (95%CI: 1.1-3.3)	(108)
Water treatment	Children, Melbourne	Before chlorination vs after	Hospital admissions gastroenteritis	OR 1.08 (95%CI 0,7-1.2)	(109)
	Lake district, UK	Membrane filtration	Cryptosporidiosis	IRR: 0.21 (95%CI 0.1-0.4)	(110)
Seroprevalence surveys					
	USA	Surface vs groundwater	Cryptosporidium	PR 1.36, P < 0.001 (72% vs. 52%)	(111)
	USA	Surface vs groundwater	Cryptosporidium	PR: 1.39 (1.2, 1.6) (54% vs. 38%)	(112)
Cross-sectional survey					
	HIV-positive, USA	never' vs 'always' drinking boiled water	Diarrhoea	0.68 (95% CI 0.45-1.04)	(113)
	Russian city	Residual chlorine level in distribution system	Gastrointestinal illness	RR 1.42 (95% CI 1.05, 1.91)	(114)
Cohort studies					
Community intervention studies	Massachusetts	From chlorination to ozone+filtration+ chlorination	Acute gastrenteritis	IRR: 1.8 (95%CI 1.5-2.1) AR%=34%	(115)
Time-series	Russian city	Water turbidity	Acute gastrenteritis	RR 1.47 (95% CI 1.16, 1.86)	(116)
Case-control studies					
	Norway	Undisinfected water	Campylobacteriosis	OR 1.9 (95%CI: 1.1- 3.3)	(13)
	Children, Sweden	Private well	Campylobacteriosis	OR 2.6 (95%CI: 0.9-7.4)	(117)
	Norway	Untreated water	Yersiniosis	OR 2.76 (95%CI: 1.2-6.4)	(25)
	New zealand	Nonurban water-supply	Campylobacteriosis	OR 2.7, CI 0.89-8,33	(118)
	Immunocompetent, San francisco	tap water vs filter or bottle	Cryptosporidiosis	OR 1.45 [95% CI: 0.4, 5.6].	(119)

Study design	Setting	Exposure	Outcome	Measure of risk	Reference
Experimental					
Intervention studies					
	Households Iowa	Home water treatment	Acute gastroenteritis	RR 0.98 (95% CI: 0.86, 1.10).	(77)
	Households, California	Home water treatment	Acute gastroenteritis	RR 1.32 (95% CI 0.8, 2.3)	(120)
	Households Melbourne	Home water treatment	Acute gastroenteritis	IRR 0.99 (95% CI 0.85-1.15)	(78)
	Households Montreal	Home water treatment	Acute gastroenteritis		(75)
	Households Montreal	- tap water - bottled at plant	Acute gastroenteritis	IRR=1.15 IRR=1.0	(76)
	HIV positive, San fransisco	Home water treatment	Acute gastroenteritis	RR 3.34 (95% CI: 0.99-11.21)	(121)
Mathematical modelling					
Quantitative microbial risk assessment					
	Sweden	Tap water normal operation	Cryptosporidium Rotavirus Campylobacter	ARI 48/100,000 ARI 400/100,000 ARI 16/100,000	(101)
	Pretoria, SA	Adenovirus in drinking water	Adenovirus infection	ARI: 1.0 - 1.7/10	(122)
	USA	systems using - polluted waters - pristine waters	Giardiasis	ARI with a 10(-3) treatment reduction. : 4.8/1000 1.3/10000	(123)

PR= prevalence ratio
OR= odds ratio
RR=relative risk /risk ratio
IRR= incidence rate rato
AR%=Attributable risk percent
ARI: Annual Risk of Infection

Statistical analysis - the use of regression models

"All models are wrong.
Some are useful."
- *George E. P. Box*

Both stratification and regression models can be used to present the effect of interaction or control for confounding. Historically, stratification has been the most common statistical approach for dealing with interaction and confounding, and is the most intuitive approach. In stratified analysis, the sample is separated into several subsamples according to specified criteria, such as age groups, socioeconomic status etc, and each subsample (=stratum) is analysed separately (90). The resulting estimate can either be interpreted within each stratum or pooled over the different strata if appropriate. However stratification is not a suitable choice if there are several exposures or factors that need to be controlled for simultaneously. Especially in outbreak investigations where the number of subjects in the study often is limited, stratification will often have limited value because of small numbers in each stratum giving unstable estimates. Rothman and Greenland refer to this as a point "when stratification has exceeded the limits of the data" (91).

Regression analysis examines the association between a dependent variable (response variable) to specified independent variables (explanatory variables). The regression equation contains estimates of one or more unknown regression parameters, which quantitatively link the dependent and independent variables. The parameters are estimated from the study data linking the dependent and independent variables.

The main uses of regression include 1) prediction of outcome based on risk predictors and 2) controlling for confounding when investigating associations between exposures and outcome. Depending on the purpose of the research – prediction or examining causal relationship - the considerations that apply when constructing a good model will differ. While parsimony is revered in predictive regression models, regression models studying associations between exposure and outcome often include several factors that may not explain a large amount of the variance in the outcome, but may be important confounders of the exposure of interest (91). For assessing causal effects of an exposure, the final model need to include all important confounders, not necessarily factors important for prediction.

Choice of model depends on the study design, the data characteristics and the aim of the analysis. In outbreak investigation, the main objective is to identify the exposure causing the outbreak, and the main rational for conducting a multivariate analysis is to control for possible confounders. For studies investigating general risk factors for disease, an additional objective may be to assess the increased risk associated with certain exposures.

Surveillance of outbreaks – epidemic intelligence

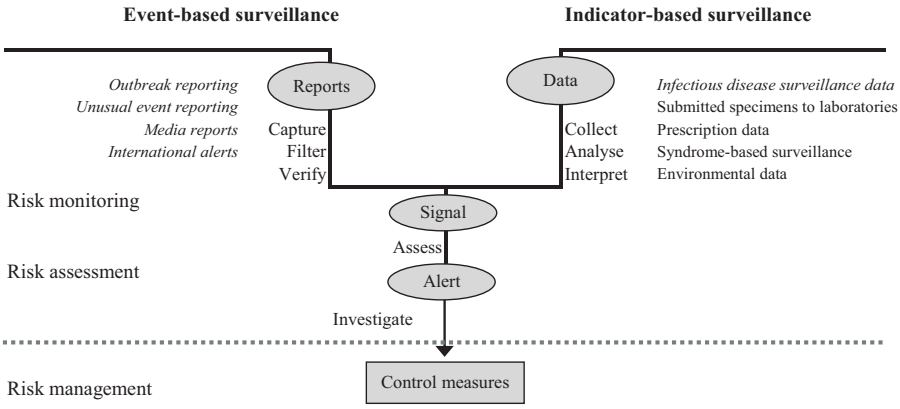
Information from waterborne outbreaks has provided new insights into waterborne pathogens and water system deficiencies, and has promoted changes in water regulations and water quality requirements. Rapid detection and thorough investigation is crucial for proper management of outbreaks, both in order to implement control measures to stop the current outbreak, but also to identify the deficiencies that make the outbreak possible so new outbreaks can be prevented. The term epidemic intelligence is used for the process of detection, verification, analyzing, assessing and investigating signals that may represent a threat to public health. It includes all activities related to early warning functions in addition to signal assessment and outbreak investigation. In risk analysis terminology, epidemic intelligence includes risk monitoring and assessment, but not risk management and communication (124).

There are two main data components in the epidemic intelligence framework for outbreak detection, as shown in Figure 4:

1) Event based surveillance: Outbreaks are detected through unstructured data gathered from different information sources, such as outbreaks or unusual events reported by health personnel or through media reports.

2) Indicator based surveillance: Unusual patterns or increases in number of specific diseases or syndromes are detected through monitoring of structured data collected through routine surveillance systems.

Figure 4 Epidemic intelligence framework (Italics represent systems already in place in Norway)



In Norway, the systems for outbreak detection in use today are the Norwegian Outbreak Surveillance System representing an event-based system and the Norwegian Surveillance System for Communicable Diseases (MSIS), representing an indicator-based system. Suspected or confirmed outbreaks should be notified immediately from the municipal medical officer to the Norwegian Institute of Public Health where the reports are collated in a national outbreak database. MSIS is the national infectious disease register, and all microbiological laboratories analysing specimens from humans, and all doctors in Norway, are required by law to notify cases of certain diseases to the MSIS central unit at Norwegian Institute of Public Health. Notification should be sent the same day as the case was diagnosed. Both systems will generate signals that need to be assessed, and then further investigated if the assessment so warrants.

It is always a challenge to get notification of outbreaks early in order to implement control measures to prevent further illness. For waterborne outbreaks, early identification is crucial, and in most outbreaks a large proportion of the population will probably already have been exposed before the outbreak is detected and measures can be implemented. However, electronic data transfer systems and new types of surveillance data may be better utilized to increase the timeliness in outbreak detection.

Investigation of outbreaks

In a research setting, it may take years to plan and conduct an epidemiological study. In an outbreak setting however, there is a need for rapid results. Even so, the investigators need to apply the same scientific methods and produce valid results in order to implement appropriate and timely public health measures to control the outbreak.

Due to the urgency of the situation there is a strong need for a structured approach to the investigation. In most outbreaks, the investigation will generally follow the same framework with three main components:

- Epidemiological investigation
- Microbiological investigation
- Environmental investigation and assessment

These components can be described in the following practical steps:

- Preparedness and planning
- Detect and verify
- Alert and inform stakeholders
- Define a case, identify and verify cases
- Describe the outbreak in terms of time, place, and person
- Generate hypotheses
- Test hypotheses
    - Epidemiological studies
    - Microbiological samples
- Perform environmental investigation and assessment
- Implement control and prevention measures
- Communicate findings

Detailed procedures for food- and waterborne outbreak investigations in Norway have been described in a manual used by the public health authorities and food safety authorities (125).

In practice, it may not be necessary to conduct all the steps for every outbreak investigation, and the steps may not be done in the order presented above. Control measures need to be implemented as soon as the source and mode of transmission are known, which may be early or late in any particular outbreak investigation.

All outbreaks are different, and adjustments need to be made during the investigation. Even if the framework is the same for all kind of outbreaks, some factors such as the illness, the outbreak setting, the source and the route of transmission may influence parts of the investigation.

There are several aspects of planning and conducting an epidemiologic study in an outbreak setting that differ from a planned and conducted epidemiologic study in a research setting. Some of these issues are:

- Limited time for planning and execution of the study
- The outbreak may evolve, and the study plan needs to be adapted accordingly throughout the investigation. Several methodological approaches may be used, and they may be changed during the investigation in response to preliminary results or changes in the outbreak situation
- No prior hypotheses – hypotheses need to be formulated and tested in an adaptive and sequential process
- Limited control over essential elements in the study design;
    - small number of cases early in the outbreak,
    - changing case definitions during time or case-definitions with several levels (probable, possible, confirmed) due to unknown aetiology or complicated diagnostic procedures
    - media attention may influence information from study subjects
- Preventive measures may need to be implemented when only preliminary results are available. The investigators need to balance the risk to the population against the level of confidence that the interventions are appropriate.

A major limitation that often is an issue in outbreak investigation is the question about the power of the study. In most outbreak investigations it will not be possible to plan and decide the number of subjects to include. The number of cases may be limited by the size of the outbreak, especially since it is important to start the investigation early in order to prevent more cases. However, outbreaks are mainly associated with one specific source, and a high measure of association is expected between exposure to the source of the outbreak and the risk of illness. Therefore, even small number of subjects in a study may give enough power to show an association between the source and the outcome in question.

In general, an outbreak investigation will never obtain the same quality as an experimental study. Still, the validity of the study need to be appropriate. There has been a perception that field investigation represent “quick and dirty” epidemiology. According to Goodman, a better descriptor for a good epidemiological field investigation would be “quick and appropriate”, reflecting the need for combining good science with rational judgements (126).

Investigation of waterborne outbreaks

In principle, the investigation of waterborne outbreaks follows the same approach as any other outbreak investigation as described above. However, there are some special challenges that need to be kept in mind during the investigation.

Exposure information

Water is the second most common exposure in a population next to air, and during one day nearly all people in a developed country will be exposed to tap water to some degree, either through drinking, washing or brushing teeth. Collection of exposure information need to take this into account since a simple dichotomous (yes/no) exposure variable may not be sufficient because everyone in practice will respond yes. Therefore, detailed information on places and sources of water consumption and amount consumed may provide more appropriate information to be able to detect an association between tap water and illness.

Information needs

Contaminated water may have an affect on the whole community supplied, and there will be a huge requirement for information from industry, catering businesses, health care institutions in addition to the mass media and the population. This may put a high pressure on the public health service, and may affect the time available for the outbreak investigation.

Technical investigation

Water supply systems are complicated technical systems. Involvement of technical personnel with knowledge of the water supply and distribution is essential in the investigation. Water works personnel may provide information of recent incidents or main breaks, and can give information on the water distribution in the area. Provision of maps of the water supply and distribution system is an essential part of the investigation when contaminated water is suspected. Over these maps one can quickly lay a map of the cases' residence and detect any obvious patterns.

Thorough investigation even if outbreak is over

In many cases, outbreaks are already over before they are detected. This is especially true for waterborne outbreaks. However, even if the outbreak is over, there is a need for a thorough investigation to verify the source and to identify the factors that caused the contamination in order to prevent future outbreaks. For effective prevention, both technical and managerial factors need to be assessed. The investigation is not complete by detecting a failure in disinfection; one needs to describe why this failure occurred, why it was not detected in time, whether it may happen again, and whether there is a need for an additional barrier.

Drinking water in Norway

Norway has an abundant supply of fresh water. Access to abundant and good quality water is often taken for granted and regarded as a basic right. Consumption of tap water at home is assumed to be safe and free from harmful pathogens, in contrast to what most people expect when travelling to more "exotic" destinations.

Traditionally, Norwegians lived in rural areas, and water was available through lakes and streams or in private wells. Low population density and climatic conditions contributed to the relatively low risk of waterborne infections. During the beginning of the 19th century, population growth and increased urbanization and industrialization required better water supply and sanitation services. In the middle of the century the building of water-works became a priority. The driving force behind the development of public water supplies was mainly the need for water for fire extinction, for industry and for practical reasons and convenience. The miasmatic theory of disease spread was then dominant, and water was not yet recognized as a route of transmission. It would last until the beginning of the 20th century before the need for water treatment was put on the agenda. In several places it was argued that there was not resources available for water treatment, and it was generally not needed since the water was considered of sufficient quality(127).

Provision of safe drinking water in Norway is based on water sources of high quality, source protection, and limited water treatment. The Norwegian drinking water regulations require at least two hygienic barriers against all physical, chemical and microbiological pollution that could possibly affect the potable water supply (128). Surface water is by far the most important source of drinking water in Norway, and supplies nearly 90% of the population. This is higher than in the other Nordic countries. In Sweden and Finland, 40-50% of the population is served by surface water sources, while in Denmark and Iceland more than 90% are served by groundwater (48;129). The water supply in Norway is dominated by many small waterworks. There are 1700 registered waterworks in Norway, of which 1200 serves less than 1000 persons and only five serves more than 100,000 people (130). In 2002, a total of 235 surface water waterworks in Norway, supplying 63 000 people (less than 2% of the population), lacked equipment for disinfecting water. These waterworks were generally small, serving from 30 to 3 800 people (131;131). For small water works it is a challenge to obtain sufficient resources for operation, for adequate maintenance of treatment and distribution system and for water quality control.

Even if the source water quality in general is good and the sanitary and water supply services are well developed and available to the entire population, waterborne outbreaks still occur and may have huge public health consequences. The general low level of infectious diseases in Norway may have lead to complacency among the water providers. Also, emerging pathogens such as *Cryptosporidium* pose challenges to existing water treatment technologies. Limited resources for maintaining the deteriorating water distribution systems are also factors that may influence the risk.

2. BACKGROUND AND OUTLINE OF THE THESIS

Background

This is an epidemiological study of infectious diseases that are associated with water. I have used several epidemiological designs to study both endemic disease and epidemic disease. The study of epidemic disease, or outbreaks, poses particular challenges as the investigations cannot be planned in advance; they are "acute research" of acute public health problems.

Setting

The setting of this study is Norway at the beginning of the 21st century, a Scandinavian country of 4.7 million inhabitants. In a survey in 2000, the World Bank ranked Norway among the ten wealthiest countries in the world (132). In the WHO world health report on health systems performance published in 2000, Norway ranked as number 11 among the 191 countries assessed (133). The average life expectancy was 80 years in 2004 (134). Two of the studies that comprise this thesis were conduced during my stay at the Swedish Institute of Infectious Disease Control in Sweden in 2001. Sweden is the closest neighbouring country, and shares many similarities with Norway regarding economical, health and social indicators and structure of the health care system.

Data for the study was collected during 2001 - 2006.

Most of the researchers behind the present study were based at the Norwegian Institute of Public Health (NIPH), a governmental non-regulatory institute mandated to conduct surveillance of infectious diseases, study the microbiology, immunology and epidemiology of infectious diseases and advice the health services and the public concerning infectious disease control and prevention. Some parts were conducted during my EPIET-training in 2001 in collaboration with researchers at the Swedish Institute for Infectious Disease Control (SMI), a government expert institute with a mission to monitor the epidemiology of infectious disease among Swedish citizens and promote control and prevention of these diseases.

Outline of the thesis

In chapter 1, I gave a brief overview of several challenges of water and infection. In the next chapter, I move from the general background to a presentation of the general objectives and the nine specific aims of the study. These are meant to answer some of the challenges that were presented in chapter 1.

Chapter 4 is a description of the data and the methods used to fulfil the aims of the study. In chapter 5, I present the main results of the study as they relate to the specific aims. Chapter 6 is a discussion of the findings of the study including a closer scrutiny of the methods. I try to put the results into perspective and consider what the study has added to our knowledge of the challenges presented in chapter 1.

In chapter 7 I will reiterate the main conclusions and suggest further studies in this field. References are in chapter 8, and the papers on which the thesis is based are appended.

3. AIMS OF THE STUDY

The overall aim of the study was to investigate and describe aspects of water-associated infections in a Nordic setting, and how water may act as a transmitter of infections by different routes; exemplified by drinking water, irrigated food and inhalation of aerosols. In addition, the study describes and evaluates the use of different study designs and epidemiological tools in investigating waterborne illness, and how the approach is guided by outbreak setting and purpose of the study. The specific aims are presented below.

A study in four parts

The thesis consists of four integrated parts. The first part includes studies of endemic disease associated with drinking water. The second part include outbreaks caused by drinking water. First I review outbreaks caused by drinking water in Norway, and then I present two examples of waterborne outbreaks, one large outbreak in Bergen caused by contamination of a public water works and one local outbreak at a camping site with a private well. In the third part, I study outbreaks associated indirectly with water, namely through food products that have been irrigated with contaminated water. Part four deals with an outbreak caused by aerosol spread of infectious agents.

Part 1. Investigating endemic waterborne disease

The general objective was to identify causes of endemic waterborne disease. Specifically, the study aimed to:

- investigate the geographical pattern of campylobacteriosis reported to the national surveillance system and evaluate the geographical association between climatic factors, agricultural data, and water-supply with disease incidence. The study was conducted in Sweden (paper I)
- measure how much the risk of gastrointestinal illness increases immediately following breaks and maintenance work in the water distribution system (paper II)

Part 2. Investigating outbreaks caused by contaminated drinking water

The general objectives was to describe and assess approaches of the investigation of outbreaks related to contaminated drinking water and show with two examples the diversity of such outbreaks and how various epidemiological designs can be used to verify water as the source. Specifically, the studies aimed to:

- review waterborne outbreaks reported in Norway in recent time, and describe the aetiology of and contributory factors in these outbreaks (paper III),
- identify the source of a large outbreak of giardiasis in Bergen in 2004 (paper IV),
- illustrate the usefulness of various data sources for outbreak detection and estimating extent of outbreaks (paper IV)
- identify the source of an outbreak of gastroenteritis in a summer camp in Norway in 2002 (paper V)

Part 3. Investigating outbreaks caused by produce irrigated with contaminated water

The general objective was to demonstrate that contaminated water may cause outbreaks indirectly through irrigation and to use two examples to demonstrate the complexity of such outbreaks and how the case control study is suited to identify the source. Specifically, the studies aimed to:

- identify the source of a nationwide outbreak of hepatitis A in Sweden in 2000-2001 (paper VI), and
- identify the source of a nationwide outbreak of *Salmonella* Thompson infections in Norway in 2004 (paper VII).

Part 4. Investigating an outbreak caused by inhalation of contaminated aerosolised water

The general objective was to demonstrate how aerosolised water may cause community wide outbreaks and to present tools to investigate such outbreaks. Specifically, the study aimed to:

- identify the source of a local outbreak of Legionnaires' disease in Norway in 2005 (paper VIII).

4. MATERIAL AND METHODS

All the studies in this thesis are observational studies.

Part 1. Investigating endemic waterborne disease

Risk factors for campylobacteriosis in Sweden (paper I).

Campylobacter sp. is the most common reported cause of acute bacterial gastroenteritis in Sweden and the incidence has been increasing. Case-control studies to identify risk factors have been conducted in several countries, but much remains unexplained. The geographical distribution of campylobacteriosis varies substantially, and many environmental factors may influence the observed pattern. We used an ecological study design to explore environmental risk factors for campylobacteriosis in Sweden.

The study was based on all domestic cases notified to the Swedish Institute for Infectious Disease Control (SMI) during the three years 1998–2000. As exposure variables, we included municipality level data on livestock density and water distribution and supply. To correct for possible climatic variations and other possible confounders that might be associated with urban or rural living conditions, we included variables for average temperature and annual precipitation and a variable for municipality class based on population size, degree of urbanization and production sector.

We imported data from the infectious disease register into a geographical information system (GIS) and mapped the individual cases based on their place of infection or place residence.

Breaks or maintenance work in water distribution system and gastrointestinal illness (paper II)

During maintenance work or breaks on the water distribution system, water pressure occasionally will be reduced. This may lead to intrusion of polluted water - either at the place of repair or through cracks or leaks elsewhere in the distribution system. The objective of this study was to assess whether breaks or maintenance work in the water distribution system with presumed loss of water pressure was associated with an increased risk of gastrointestinal illness among recipients.

We conducted a prospective cohort study among recipients of water from seven waterworks in Norway during 2003–04. One week after an episode of breaks or maintenance work on the water distribution system, a selection of ten exposed and ten unexposed households were interviewed about gastrointestinal illness in the week following the episode. A similar information-letter informing about the study and a questionnaire was sent to both the exposed and the unexposed households so as not to reveal the household's exposure status. Information was collected on age and gender of all household members, average tap water-intake at home per person in the household, travel history in the last month, children in day-care centre, and animal contact. In addition, they were asked if they had noticed any discoloration or strange taste of the tap water within the last 14 days, or if they thought there had been any work done on the water pipes recently. The person interviewed was also asked if there had been any episodes of acute gastrointestinal illness in the household during the week after the date of the break or maintenance work on the distribution system. Information about age, gender and symptoms of acute gastrointestinal illness of all household members was collected at the individual level.

Part 2. Investigating outbreaks caused by contaminated drinking water

Surveillance of waterborne outbreaks in Norway (paper III).

Outbreaks have been reported by different sources to different systems in Norway. We used these systems to review the number and characteristics of waterborne outbreaks reported in Norway over a 15 year period (1988-2002). Data for the review was collected from information on waterborne outbreaks reported to the Department of water hygiene and Department of Infectious Disease Epidemiology, NIPH and to the Norwegian Food Safety Authority. We included all events in which two or more people fell ill and water was the suspected source of infection. The data was collated and analysed in Excel.

Outbreak of giardiasis in Bergen in 2004 (paper IV).

In late October 2004, an increase in laboratory confirmed cases of giardiasis was reported in the city of Bergen. An investigation was started to determine the source and extent of the outbreak in order to implement control measures.

Source of the outbreak

As an initial assessment, we used an ecological study design to explore the association between drinking water supply and illness. We used a map of the six water supply zones serving the city and their number of recipients, to map the place of residence of each case and calculated attack

rates and risk ratio per water supply zone. After identifying one water supply area in the ecological study, we further conducted a case-control study limited to residents in the identified area. We defined a case of outbreak associated giardiasis as a person who had a stool sample positive for *Giardia* after September 1, 2004. Controls were selected from the city's population register, matched by gender and birth date. Both cases and matched controls were asked about the exposures in the same period; two weeks before symptom onset for the case. Persons with travel history to a country highly endemic for giardiasis during the incubation period were excluded. The information was collected by telephone interviews using a structured questionnaire targeted to exposures derived from trawling interviews of the first cases, including food and drinks consumed and quantity of water consumed, and different activities.

Outbreak detection

Epidemic intelligence is the process of detection, verification, analyzing, assessing and investigating signals that may represent a threat to public health. A key issue is to detect outbreaks early in order to rapidly implement control measures. Indicator based surveillance means to monitor structured data collected through routine surveillance systems to detect unusual patterns or increases in number of specific diseases or syndromes that can signal the start of an outbreak. Several sources may be used for this purpose, but they need to be evaluated for usefulness.

After the giardiasis outbreak in Bergen was over, several different data sources were assessed to see whether the outbreak could have been detected earlier by other means. The data sources were:

- the Norwegian surveillance system of communicable diseases (MSIS) on notified cases of giardiasis by day of diagnosis and day of notification,
- the Norwegian Prescription Database (NorPD) on number of prescriptions of metronidazol delivered from pharmacies to persons in Hordaland County per week
- data from Bergen emergency clinic on number of consultations for diarrhoeal illness per week
- data from the water works on results from routine water samples taken from the water source (number of indicator bacteria, turbidity etc)

Description and extent of the outbreak

We used the Norwegian Prescription Database (NorPD) to estimate the extent of the outbreak of giardiasis in Bergen in 2004. NorPD is a national health register that receive electronic data on all prescriptions, reimbursed and non-reimbursed, dispensed from all the five hundred pharmacies in Norway, however indications for treatment is not included in the register.

In the initial phase of the outbreak, the diagnostic capacity of the regional laboratory was insufficient, so physicians were recommended to start empirical treatment of all patients with clinical symptoms compatible with giardiasis. To assess the number of persons requiring treatment during the outbreak, we received data from NorPD on number of prescriptions of metronidazol delivered from pharmacies to persons in Hordaland County during January 1st 2004 to August 31st 2005. Metronidazole is normally prescribed for a variety of indications including giardiasis. The NorPD was established January 1st 2004, so the average monthly number of prescriptions during January 1st to August 31st 2004 was therefore used as the baseline, and the excess for the period September 1st 2004 to February 1st 2005 was assumed to be prescriptions to patients associated with the giardia outbreak.

The source of a gastroenteritis outbreak in a summer-camp (paper V)

In July 2002, an outbreak of acute gastroenteritis occurred in a camp facility in western Norway during a 10-day seminar, with around 300 guests staying overnight and several day-time visitors. Environmental and epidemiological investigations were conducted to identify and eliminate the source of the outbreak, prevent further transmission and describe the impact of the outbreak.

Due to the defined population it was decided to conduct a retrospective cohort study, and questionnaires were mailed to all families entered in the booking list of the organizers of the camp, asking about place and duration of stay, clinical symptoms, water and food consumed and about hygienic routines.

Part 3. Investigating outbreaks caused by produce irrigated with contaminated water

The source of an outbreak of hepatitis A in Sweden (paper VI)

An increased incidence of domestic hepatitis A cases without any obvious source of infection and a small outbreak in late spring 2001 spurred a national outbreak investigation. Hypothesis generating interviews of the first cases identified some common exposures that were investigated in a case-control study. Cases included in the study were all confirmed domestic cases of hepatitis A in Sweden with date of onset after 1 April 2001, when the outbreak started. Travel-related cases or cases with known contact with another confirmed case were excluded. Controls were selected from the Swedish national population register, matched for age, gender, and postal code. Both cases and controls were interviewed over the telephone.

The souce of an outbreak of salmonellosis (paper VII)

On November 15 2004, a cluster of three cases of *Salmonella enterica* serovar Thompson was reported by the National Reference Laboratory of Enteric Pathogens. In the following days further cases were detected from different parts of Norway. Based on information from hypothesis generating interviews with the first seven cases, we conducted a case control study in order to identify the source of the outbreak. A case was defined as a person with a laboratory confirmed infection with *S.* Thompson between October 1 and December 31, 2004 in Norway. Travel-related cases were excluded. All the cases came from cities of at least 5000 inhabitants. The source population was therefore defined to be all Norwegians living in such communities. From the source population two controls per case were selected from the Norwegian population register, matched by date of birth and gender. Both cases and controls were interviewed over the telephone. Cases were asked what they had consumed during the last three days before disease onset while controls were asked for the three days before the interview.

Part 4. Investigating an outbreak caused by inhalation of contaminated aerosolised water

The source of an outbreak of Legionnaires' disease (paper VIII)

Epidemiological study

On May 21, 2005, the Norwegian health authorities were alerted by a local hospital about several recent patients with Legionnaires' disease; all resided in two neighbouring municipalities. We investigated the outbreak to identify the source and implement control measures. To assess disease risk associated with exposure to each of several potential sources in the area of the outbreak we used a retrospective cohort study design. Information on patients' residences and movements, residences of all persons living in the two municipalities and location of suspected sources were included in a geographical information system (GIS). We calculated attack rates for residents living within and outside five circles of increasing radius, and calculated risk ratios for all circles around each potential source. In addition, we compared each "doughnut-shaped" rings formed by these circles to a reference rate defined as the attack-rate among residents living outside a radius of 10,000 m from the potential source. We assumed that only for the true source would the risk ratio diminish gradually with the distance from the source.

Aerosol dispersion modelling

The transport and dispersion of aerosols emitted from potential sources for the relevant time period was modelled. Inputs in the model were hourly meteorological information, including

wind direction and velocity, outdoor temperature at 25 m, and atmospheric temperature stability between 8 and 25 m. We assumed that the particle size of the aerosols were 2.5 μm, pipe diameter 1 m, output velocity 3 m/s, and emission rate 100 g/s. The model results were projected onto 1 km square grids, which give the average relative concentrations within that grid. The zones were calculated hourly, and were combined in the GIS for the relevant time period. The focus time period was back calculated based on the mid-time of illness onset using a 7-day incubation period. As the emission rates of aerosols from the various sources were not available, we interpreted the concentrations presented in the model on a relative basis. Also, the model did not represent the initial dispersion of the plume, due to effects of exhaust rates and building induced turbulence. The modeled plume distributions were included as layers in the GIS. We then measured the proportion of patients that would have been exposed to each of the sources by either living or visiting within the aerosol plume during the incubation period.

Statistical analysis

The statistical data analysis for the studies generally followed the same framework: First all exposures of interest were analysed in a univariate analysis and presented as matched odds ratios for case-control studies or attack rates and risk ratios for cohort studies, with 95% confidence intervals. The exposures of interest or exposures showing an association with illness were then further investigated in stratified analyses or multivariate regression models to assess interaction or confounding effects in order to get a true estimate of the independent effect of each exposure.

Stratified analysis

Breaks and maintenance work in the water distribution systems and gastrointestinal illness (paper II)

The main unit for analysis in this study was the household. A case household was defined as a household with at least one person with an episode of gastrointestinal illness during the observation period. The attack rate of gastrointestinal illness among exposed and unexposed households, the risk ratio and the risk difference with 95% confidence intervals (CI) were calculated. The attributable proportion among the exposed households was computed according to method described by Rothman(135). Stratified analyses with calculation of Mantel–Haenszel adjusted RRs were performed in order to assess possible confounders. Interaction was assessed by the likelihood-ratio test between logistic models with and without the interaction term. We assessed possible effect modifiers in a separate logistic regression model in the exposed group of households only. Variables with P-value <0.2 were evaluated in the model. The final model retained all variables with P-value <0.1.

Regression models

The regression models used in this thesis are presented in Table 6.

The statistical analyses were performed in EpiInfo, version 6.04 (CDC, Atlanta, GA, USA), LogXact-4 (version.4.1, Cytel Software) and STATA (STATA 8.0 Stata Corporation, College Station, TX, USA).

Table 6 Overview of regression models used

Regression model	Distribution	Link-function	Data	Effect measure	Suitable for	
Poisson	Poisson	Log	Count data	Incidence rate ratios	Count data over time or place	Paper I
Log-binomial	Binomial	Log	Binomial data	Risk ratios	Cohort studies	Paper V
Logistic	Binomial	Logit	Binomial data	Odds ratios	Case-control studies	Paper IV, VI, VII

Poisson regression

Environmental risk factors for campylobacteriosis in Sweden (paper I)

Poisson regression was used to estimate the relative risk of campylobacter infection associated with the environmental risk factors investigated. The expected number of cases occurring in a municipality was assumed to be proportional to the population size and the exponential of a linear combination of the environmental variables included in the analysis. STATA was used for the analysis.

Log-binomial regression

Waterborne outbreak of gastroenteritis in a summer-camp (paper V)

Univariate analysis and examination for a dose– response relationship for daily water intake was done by using EpiInfo. Significant risk factors were included in a multivariate generalized linear regression model for binomial data using log-link function in STATA. The significance level for exclusion of a variable from the model was set to 0.05. A variable for time of stay was also included in the model (present or absent after 16 July). Due to a suspected high degree of within family transmission, a second model was fitted where only index cases in each family (defined as all cases in each family occurring within 12 h of the first case in the family) were counted as cases. With this restricted case-definition, all remaining persons in the family were kept in the analysis as non-cases. Risk ratios (RR) from the multivariate model were used to calculate the population attributable risk per cent (PAF), defined as the proportion of the cases in the entire

population presumably attributable to the exposure: PAF = Pc(RR-1)/RR, where Pc=proportion of cases exposed (136).

Logistic regression

The same statistical approach was used in analysing the data from the case-control studies in the outbreak of giardiasis in Bergen, Norway (paper IV), the outbreak of hepatitis A in Sweden (paper VI) and the outbreak of Salmonella Thompson infections in Norway (paper VII).

To assess associations between consumption of specific food items or water and illness, conditional logistic regression was used to calculate food specific matched odds ratios (OR) and 95% confidence intervals (95% CI). Exposures associated with illness ($p < 0.1$) were included in a multivariable logistic regression model using the same regression procedure. The final model was obtained through stepwise deletion of variables on the basis of statistical and epidemiological criteria. Analysis of data was performed in STATA (paper IV and VI) and LogXact (paper VII).

Laboratory methods

In outbreaks associated with food or water, the microbiological investigation including environmental sampling is an essential part of the investigation. The microbial investigation includes three main components:

1. Assess indicators for faecal contamination of water or food
2. Analyse for the specific pathogen causing the outbreak
3. Use molecular typing methods to a) achieve a specific case definition; b) compare isolates from patients and the suspected source

Indicators of faecal contamination

In waterborne outbreaks, the contamination episode may be of short duration and the concentration of pathogens in the water may be low. Often isolation of the pathogen from random water samples is difficult. A more feasible approach is analysing water samples for indicators of faecal contamination, such as thermotolerant coliform bacteria, *E. coli*, faecal streptococci and *Clostridium perfringens* spores.

In the outbreak of giardiasis in Bergen (paper IV), results from routine water samples obtained during the period just before the outbreak started in August until it was detected in late October 2004 were reviewed and compared with results from 2003. The parameters investigated were

turbidity, total bacterial count and counts of thermotolerant coliform bacteria, *E. coli* and *Clostridium perfringens* spores. On the 7th and 11th of November, seven parallel samples were taken from the water source and investigated for presence of giardia cysts.

In the outbreak of gastroenteritis at the summer camp (paper V), water samples were examined for total coliforms, thermotolerant coliforms and faecal streptococci. Additionally, a few samples were also examination for presence of norovirus.

Molecular sub-typing methods

In two of the outbreak investigations, we compared pathogens isolated from patients and the suspected source with molecular sub typing tools. In the outbreak of *Salmonella* Thompson infections, pulsed-field gel electrophoresis (PFGE) was used to characterize and compare isolates from patients from several countries and from products (paper VII). In the outbreak of Legionnaires' disease, two different genotyping methods were used for characterization of both patient and environmental isolates: randomly amplified polymorphic DNA (RAPD) and restriction fragment length polymorphism (RFLP) (paper VIII).

Ethics

All studies in this thesis are observational studies, and no intervention or treatment is used in any of the studies.

The study presented in paper I was primarily based on epidemiological surveillance data collected in accordance with the Swedish communicable Diseases Act. Personal identifiers were omitted before analysing the data, and no additional information was collected from the cases.

The study presented in paper II was reviewed and approved by the Regional Committee for Medical Research Ethics. Study subjects were informed about the study in a letter sent one week before the interview.

Papers IV through VIII were outbreak investigations.

Ethics in outbreak investigations

Outbreak investigations have similarities with public health research. Although outbreak investigations may lead to generalizable information, the primary aim is to find the source in order to control the outbreak. It is virtually impossible to get ethical clearance in advance without causing undue delay in the investigation. The National Committees for Research Ethics

in Norway consider outbreak investigations as public health practice, and approval by the research ethical committee is not needed as long as the objective is to control the outbreak. This is in line with the 1991 International Guidelines for Ethical Review of Epidemiological Studies by the Council for International Organisations of Medical Sciences (CIOMS). Regarding outbreak investigation, the Council states “An exception is justified when epidemiologists must investigate outbreaks of acute communicable diseases. Then they must proceed without delay to identify and control health risks. They cannot be expected to await the formal approval of an ethical review committee. Nevertheless, in such circumstances the investigators will, as far as possible, respect the rights of individuals, namely freedom, privacy, and confidentiality”(137). The outbreak investigations follow the regulations on patient privacy and protection as stated in the Norwegian Law on Communicable Disease Control.

5. MAIN RESULTS

Part 1. Investigating endemic waterborne disease

Environmental risk factors and campylobacteriosis in Sweden (paper I)

During the three years of the study (1998–2000), there were a total of 23 481 campylobacter infections notified to the national infectious disease register in Sweden. Of these, 7280 (31%) were reported as acquired in Sweden, 13 715 (58%) were reported as acquired abroad, and for 2486 (11%) this information was missing. Only cases that had been acquired in Sweden and could be assigned to a municipality were included in the statistical analysis (7007 of the 7280 cases (96%)).

We assessed the association between various environmental factors and the reported incidence of campylobacteriosis in the 289 municipalities in Sweden, and found positive associations between campylobacteriosis incidence and municipal ruminant density (incidence rate ratio (IRR) 1.08, 95% CI 1.05–1.11), municipal average water-pipe length (meter/person) (IRR 1.12, 95% CI 1.08–1.16) and mean annual temperature (IRR 1.05, 95% CI 1.03–1.07). In a second model excluding the three largest cities (accounting for 1377 cases), the IRRs for ruminant density and water-pipe length increased, and having public water supply was associated with a decreased incidence (IRR 0.93, 95% CI 0.90–0.95).

Breaks and maintenance work in the water distribution systems and gastrointestinal illness (paper II)

The study was conducted among recipients of water from seven waterworks in Norway during 2003–4. One week after an episode of mains breaks or maintenance work on the water distribution system, exposed and unexposed households were interviewed about gastrointestinal illness in the week following the episode.

A total of 88 incidents of breaks or maintenance work in the water distribution system were included in the study, and 616 exposed and 549 unexposed households were interviewed. We found that 12.7% of the households exposed to breaks or maintenance work in the distribution system reported gastrointestinal illness in the household during a one-week period after the exposure compared with 8.0% in unexposed households in the same period (risk ratio (RR) 1.58, 95% confidence interval (CI) 1.1-2.3). The attributable fraction among the exposed households was 37% in the week following exposure. In the exposed households, a higher

average daily water consumption (>1 glass water per person per day) was strongly associated with gastrointestinal illness compared with a lower average daily water consumption (≤ 1 glass water per person per day) (RR 4.9, 95%CI 1.6-15.2). In the unexposed households, the amount of water consumed was not associated with gastrointestinal illness (RR 1.1, 95%CI 0.5-2.4).

The interviewed households included 3020 household members. The attack rate of gastrointestinal illness during the one-week period after break/maintenance work was 7.5% and 3.9% among persons in exposed and unexposed households, respectively. The highest attack rate was in the youngest children (0–5 years) in both the exposed and unexposed households. The highest RR, however, was observed in adults 20–39 years, where the attack rate was 10.2% and 1.8% among persons in exposed and unexposed households, respectively.

Part 2. Investigating outbreaks caused by contaminated drinking water

Waterborne outbreaks in Norway (paper III)

The review of waterborne outbreaks showed that during the 15-year period from 1988 to 2002, 72 waterborne outbreaks were reported in Norway affecting a minimum of 10 616 persons. Campylobacter and norovirus were the most common identified pathogens, causing 26% (19/72) and 18% (13/72) of the outbreaks respectively. The causative organism was unknown in 46% (33/72) of the outbreaks, probably many of which were caused by viral gastroenteritis. The water came from public waterworks in 32 of the 54 outbreaks for which this information was available (59%); and from a private supply in the remaining 22. In most of the outbreaks, the water was not disinfected. This was the case in 62% of the outbreaks related to waterworks and in all the outbreaks related to private water supplies. Over the last five years, there were more outbreaks related to small private water supplies (paper III).

Outbreak of giardiasis in Bergen 2004 (paper IV)

Description and extent of the outbreak

A total of 1300 cases of giardiasis were laboratory-confirmed in the outbreak. Data from the Norwegian Prescription Database gave an estimate of 2500 cases treated for giardiasis probably linked to the outbreak. The majority of the cases resided in the central parts of Bergen and there was a predominance of women aged 20–29 years, with few children or elderly.

Source of the outbreak

The ecological study showed that the risk of infection for persons receiving water from the water supply serving Bergen city centre was significantly higher than for those receiving water from other supplies. Of the first 795 cases registered by December 1st, 637 cases (80%) lived in the central part of the city, served by water supply A. During the months August to November, a total of 42,774 people received water from supply A. This yielded an attack rate in this supply zone of 149/10,000, compared to 8/10,000 in the other supply zones combined; RR 18 (95% CI: 15 – 22).

A total of 27 cases and 54 controls were included in the case-control study. In multivariable analysis, only drinking more than 5 glasses tap water at home (OR 5.9, 95% CI 1.7 – 21) or at a gym located in the city centre (OR 7.2, 95% CI 1.0 – 51) were independently associated with giardiasis.

Outbreak detection

The outbreak was recognized on October 29th 2004, when the municipal medical officer in Bergen was alerted by the university hospital to an increase of patients diagnosed with giardiasis; during the last two weeks there had been 27 laboratory confirmed cases among persons with unknown or no travel history.

The epidemic curve showed that the first cases fell ill in the end of August. Afterwards the number of cases increased gradually, and peaked in the middle of October (week 42) (Figure 1). Few people fell ill after the middle of November. Most of the cases have probably been infected during the period from the end of August until the beginning of October. Since Giardia cysts can survive in water for 1–2 months, the contamination may have occurred over a limited period in late August – early September. The detection in late October was then approximately two months after the outbreak started.

Information from some data sources that was assessed for outbreak detection are illustrated in Figure 5 and summarized below:

- Prescriptions for metronidazole started to increase in week 45.
- Number of laboratory-confirmed cases started to increase in week 44 – when the outbreak was detected. At the same time number of cases reported to the National Surveillance System for Communicable Diseases (MSIS) started to increase.
- Consultations for infectious gastroenteritis started to increase at the main acute care hospital in Bergen in the end of September; week 39.

- Routine samples from water supply A showed high amount of thermotolerant coliform bacteria and *E. coli* in untreated water in late August and September, with the highest values in samples taken on August 31 (week 36). This was considered to be common during that time of the year, and samples from treated water were within acceptable levels.

Outbreak of gastroenteritis at a summer camp (paper V)

The outbreak occurred during summer in a camp facility in western Norway during a 10-day seminar, with around 300 guests staying overnight and several day-time visitors. 205 persons filled out a posted outbreak questionnaire, of which 134 reported illness (attack rate, 65%). Multivariate analysis showed drinking water and taking showers at the camp-site to be associated with disease, with risk ratios of 1.8 (95%CI 1.1–2.8) and 1.5 (95% CI 1.2–1.9) respectively. Seven of the 11 cases that had not drunk any water from the water supply reported that they had taken showers at the centre. Using these figures to calculate the population attributable fraction, we calculated that approximately 41% of the cases could presumably be attributed to drinking water, and 23% to using the showers at the centre. Secondary person-to-person spread among visitors or outside of the camp was found. Norovirus was identified in several patient samples, and indicators of faecal contamination were found in samples from the private untreated water supply, but norovirus could not be identified.

Part 3. Investigating outbreaks caused by produce irrigated with contaminated water

Outbreak of hepatitis A in Sweden in 2001 (paper VI)

During winter and spring 2000-1, an increase was noted in the number of notified domestic hepatitis A infections in Sweden. Sixteen cases from six out of the 21 counties in Sweden were included in a case-control study to assess any common source. Median age of the cases was 42 years (range 27-69), and there was a predominance of women (nine women and seven men). Matched analysis showed that consumption of rucola salad was associated with disease (matched odds ratio 9.1, 95% confidence interval 1.5 - 69). Sixty-seven per cent of the patients recalled having eaten rucola salad in the two months before disease onset, compared with 32% of the controls. Several mentioned that the salad was imported, and some also mentioned that it was stated on the label that rinsing of the salad before consumption was not necessary.

Outbreak of *Salmonella* Thompson infections in Norway in 2004 (paper VII)

On November 15 2004, a cluster of three cases of *Salmonella* Thompson was detected by the National reference laboratory in Norway. The first case fell ill on October 24, and by December 31 2004, a total of 21 cases had been reported. The cases came from nine different counties. The median age was 49 years (range 12 - 81) and 76 % (16/21) were females.

The first 13 cases with 26 matched controls were included in the case-control study. In univariate matched analysis, chicken, soft-boiled eggs, mixed salad, iceberg lettuce and rucola lettuce were associated with disease. Because eating rucola and iceberg lettuce was nested in the mixed salad question, it was not possible to include all in the multivariable model. Therefore, rucola, iceberg lettuce and mixed salad were analysed separately in different multivariable models in which the other significant variables in the univariate analysis were included. Only eating mixed salad or eating rucola lettuce was significantly associated with disease (OR 8.8 [1.2-∞] and OR 5.0 [1.0-∞], respectively). After the results of the case-control study were ready, more detailed questioning of the cases identified that nine of ten cases recalled having consumed rucola lettuce, and almost all mentioned having eaten rucola from a pre-cut salad mix in pre-packed plastic bags of a specific brand. On November 26 2004, the Norwegian Food Safety Authority temporarily withdrew the incriminated product from the market based on evidence from the epidemiological investigation.

In response to an enquiry through the European surveillance network for human Salmonella and VTEC infections (Enter-net) some other European countries also reported an increase of cases,. Surveillance data from Enter-net demonstrated a general increase in reported *S.* Thompson isolates during October through December 2004, with an eight-fold increase in November.

Part 4. Investigating an outbreak caused by inhalation of contaminated aerosolised water

Outbreak of Legionnaires' disease (paper VIII)

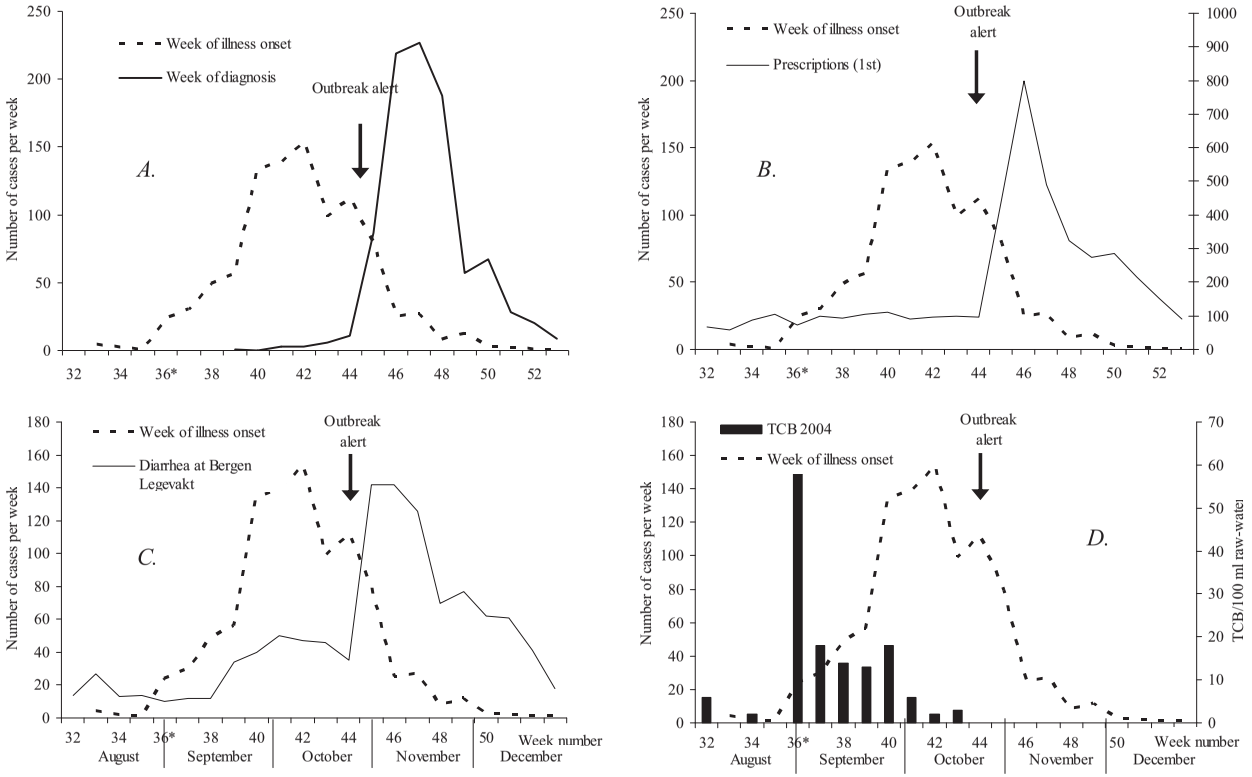
On May 21, 2005, the Norwegian health authorities were alerted by a local hospital about several recent patients with Legionnaires' disease; all resided in two neighboring municipalities. In total, 56 cases were identified during the outbreak, of which ten died. The cases fell ill during May 12-25. They resided up to 20 km apart, and had not visited any common places during the incubation period. Twenty-three companies or institutions with 41 aerosol-spreading installations were identified in the area; 31 cooling towers, 6 air scrubbers, three dry-coolers with spraying devices and one biological treatment plant. The environmental investigation

showed that fifteen of the 23 companies/institutions were unlikely to be a source of the outbreak, either because they were not operating during the outbreak, because their management and control regimen was considered of high standard, or because they were located far from the residency of most of the cases. The last eight were considered potential sources, and were evaluated further in a retrospective cohort study assessing the risk of living in the proximity of each of the sources. We found that those living up to 1 km from one particular air scrubber had the highest risk ratio, and only for this source did the risk ratio decrease as the radius widened. The plume modelled for the air scrubber also gave the best fit with the distribution of the cases. Genetically identical *L. pneumophila* serogroup 1 isolates were recovered from patients and the air scrubber.

The air scrubber is an industrial pollution control device that cleans air for dust particles by spraying with water. The circulating water had a high organic content, pH 8-9, and temperature 40°C. The air was expelled at 20 m/s and contained high amount of aerosolized water. The high velocity, large drift and high humidity in the air scrubber may have contributed to the wide spread of *Legionella*.

Figure 5 Cases of giardiasis by week of illness onset, Bergen municipality 1/9/2004 – 1/2/2005 (n = 963) and

A. cases of giardiasis by week of diagnosis.
B. prescriptions of metronidazol delivered from pharmacies to persons in Hordaland per week.
C. number of consultations for diarrhoeal illness per week at Bergen legevakt.
D. Thermotolerant coliform bacteria (TCB) in raw water samples from water supply A



6. DISCUSSION

This work illustrates the continued importance of water in transmission of infectious diseases in developed countries. We have demonstrated that both endemic and epidemic waterborne illness is an important public health issue in Norway and Sweden. A relatively low endemic level of infectious diseases in the Nordic countries may lead to complacency, and make upgrading of water systems a low priority issue. Outbreaks are more likely to be detected and investigated than endemic disease. Outbreaks often affect large numbers of people and cause great public concern, and have tended to drive changes in policy and water treatment practices. However, it is increasingly recognised that outbreaks comprise only a small fraction of waterborne illness, with endemic cases generally far outnumbering outbreak cases (138;139).

Endemic waterborne disease

(paper I, II)

Both studies presented in paper I and II showed an increased risk of endemic gastrointestinal illness associated with water distribution systems. In paper I, municipalities with longer water-pipe-distribution system averaged per person in the municipality showed a positive association with incidence of campylobacteriosis in the municipality. The study presented in paper II showed an increased risk of gastrointestinal illness after breaks and maintenance work on the distribution system.

Campylobacteriosis is an increasing public health problem, and several case-control studies have been conducted, primarily aimed at identifying risk factors for food borne infections (118;140-144). Some have identified untreated drinking water as a risk factor; however this has mainly been interpreted as drinking water outdoors (13;142). In rural areas in Sweden, dairy production, and swine and poultry farming are important agricultural industries. Contamination of water with agricultural waste is possible, especially when manure is used as fertilizer. These exposures may be difficult to assess in individually based studies, where cases and controls are often matched on geographical location. In our study, we used an ecological study design to investigate risk factors for endemic campylobacteriosis in Sweden (paper I). We used disease mapping and an ecological design to assess factors that may have a more indirect influence on the risk of infection, through contamination of water or the general environment. We found positive associations between campylobacter incidence and average water-pipe length per person, ruminant density, and a negative association with the percentage of the population receiving water from a public water supply. An association with length of the distribution

system may indicate that contamination occurring in the water distribution system might be an important contributing factor. In the study, we utilized data already available from the disease surveillance system and from various national databases. Thus, an ecological design may be a resource-effective method for a preliminary assessment of environmental risk factors. This is a new approach and few such studies have been conducted so far to study environmental risk factors for campylobacter infections.

We then conducted a cohort study to assess the risk of gastrointestinal illness associated with breaks or maintenance work in the water distribution system. The results showed an increased risk of illness in exposed households compared to unexposed households (Paper II). Endemic waterborne illness can either be caused by pathogens present in the water as it leaves the water treatment facility or by pathogens present or intruding in the water distribution system. It has been suggested that a substantial proportion of endemic acute gastrointestinal illnesses may be attributed to problems within the distribution system. An intervention trial by Payment et al. in Canada suggested that 14–40% of gastrointestinal illness was attributable to tap water meeting current standards, and that the distribution system appeared to be partly responsible for this increased risk. Pressure modelling found that the distribution system was prone to negative pressures (145). In the UK, a strong association between self-reported diarrhoea and low water pressure at the faucet was found in the control group in a case-control study on risk factors for cryptosporidiosis (146). However, the study was relatively small and due to study design the researchers were unable to confirm that the loss of pressure events preceded the diarrhoea.

During normal operation, the high pressure in the water distribution network prevents intrusion of external contaminants through leaks or cracks. A high amount of leakage makes the distribution system vulnerable to water intrusion when the pressure is reduced or reversed. This may happen when there are large water withdrawals such as during fire fighting, water shut off and other operations on the distribution system. Transient low and negative pressure events may occur in distribution systems because of a variety of system features and operations (e.g. power outages or pump stop/startup) (147). During these negative pressure events, pipeline leaks provide a potential portal for intrusion of contaminants into treated drinking water. Faecal indicator organisms and culturable human viruses have been shown to be frequently present in soil and water immediately exterior to drinking water pipelines (148). In Norway, between 34% of the total water produced is lost through leakage in the distribution systems (131). This is far more than what is reported in other Nordic countries (149). In other countries, where water shortage is a concern, there may be a higher priority in reducing water leakage and thereby also the risk of intrusion will be decreased.

Waterborne outbreaks associated with distribution system contamination is reported to have increased in importance in the USA in recent years (58). In Norway, increasing age of the water distribution systems, climatic conditions, common use of co-locating sewage pipes and water distribution pipes in the same ditch, high amount of leakage and pressure problems combined with limited resources and priority of upgrading the systems may further aggravate the problem.

There has been an increasing attention towards non-outbreak related waterborne illness in developed countries, and several studies have been conducted to estimate the burden of endemic waterborne disease. Some studies report a strong association, with up to 40% of endemic gastroenteritis attributable to drinking water (76), while other reports no evidence that drinking water is related to illness (78). Discrepancies between studies may be due to true differences in the quality of the water supply systems, but methodological issues may also influence the study results. Table 5 present some examples of study designs used in investigating endemic waterborne disease in developed countries and the main results.

The studies presented in this thesis were not designed to estimate the true burden of waterborne disease. Getting good disease burden estimates remains a challenge. It is recognized that pathogen-specific infectious disease surveillance systems have several limitations in assessing the burden of waterborne illness (150), both due to the large under-reporting of gastrointestinal illness and due to problems in assessing the source of infection for sporadic cases. Population-based randomized controlled household intervention trial where the participants are blinded to whether they receive a true water treatment device or a sham device is considered the "gold standard" to assess the risk of gastrointestinal illness associated with water exposure (151). However, these studies are very costly and time consuming, and the results will depend on the local conditions of the water supply at the site of the study. Several authors have proposed methods for estimating the risk of drinking water by quantitative microbial risk assessments, where the risk of illness is modelled based on probability distributions of the model parameters (101;104;152). Eisenberg et al (151) compared inferences drawn from a risk assessment with the results from a randomized household drinking water intervention trial, and concluded that the approaches are complementary in assessing the burden of illness attributable to drinking water exposure. Risk assessments can provide estimates of low-risk situations, which otherwise would have required a large number of study subjects, and may be used to identify high-risk conditions based on demographics, vulnerable populations, magnitude and sources of environmental contamination and failures in the supply system and types of treatment processes.

Outbreaks caused by contaminated drinking water

(paper III , IV, V)

The most important contributing factor to waterborne outbreaks in Norway in the review of outbreaks during the period 1988-2002 (paper III) was contamination of the raw water combined with missing or inadequate disinfecting procedures. In the outbreak of giardiasis in Bergen (paper IV), the water was disinfected by using chlorine. Chlorine disinfection is not sufficient for parasites such as *Giardia* or *Cryptosporidium* and therefore not considered an adequate hygienic barrier for these pathogens. Routine water sampling showed an increase in indicators for faecal contamination in untreated water, whereas samples of treated water were acceptable giving a false sense of security. The outbreak at the summer camp (paper V) illustrates the problem with small private water supplies.

Every year outbreaks caused by drinking water are reported in Norway. Although the true burden of waterborne illness is not reflected in the outbreak statistics, data from outbreak surveillance gives useful information about the important waterborne pathogens, the risks associated with different water sources, treatment processes, and distribution systems. Pathogens and water system deficiencies identified in outbreaks may also be important causes of endemic waterborne illness. For these reasons, it is important to thoroughly investigate and report all outbreaks in order to implement appropriate control measures and improve regulations and operation of water supply and distribution systems.

System deficiencies causing outbreaks

From the review of waterborne outbreaks in paper III, we found that the most important contributing factor to waterborne outbreaks in Norway was contamination of the raw water combined with missing or faulty disinfecting procedures. Contamination within the distribution system was the likely cause in about 10% the outbreaks with a known cause. A review of waterborne outbreaks in the Nordic countries revealed several similarities (48). From community systems supplied with surface water the following deficiencies were emphasized: Contamination of the raw water source in combination with disinfection deficiencies, no disinfection, cross-connections and regrowth in the distribution system. Similar occurrences were identified from outbreaks involving groundwater, with the most common problem being source water contamination through wastewater infiltration. Norway, Finland and Sweden had more outbreaks reported than Denmark and Iceland, and the authors discussed whether this was related to a higher proportion of the population being supplied by surface water, which is more

prone to accidental contamination. However, a review of waterborne outbreaks in Finland during 1998-1999 revealed that all except one of the outbreaks in that period were associated with groundwater (56). In the USA, the proportion of outbreaks associated with systems supplied by a groundwater source has increased during the last years, and problems in the distribution system were the most commonly identified deficiencies (58).

The outbreak described in paper V is a typical example of an outbreak associated with a private groundwater source. The requirements for smaller private supplies are often less strict than for public waterworks. As shown in this outbreak, inadequacies in private supplies can also have significant consequences when they supply water to large gatherings.

Pathogens involved in drinking water outbreaks

The most common identified pathogens in the outbreaks were *Campylobacter* and norovirus (paper III). This is similar to what is reported in the other Nordic countries (48;56) but differs from the UK and USA where *Giardia* and *Cryptosporidium* have been more common (59;60;153;154). A survey among microbiological laboratories in Norway showed that analysis for these parasites were rarely requested for patients with gastroenteritis that had not travelled abroad, and we discussed whether these parasites could be underdiagnosed in Norway (42). This was clearly illustrated in the outbreak described in paper IV. This was the first waterborne outbreak of giardiasis reported in Norway, and it was almost a two month delay before the outbreak was detected. Many patients contacted their physicians several times without being diagnosed with giardiasis. In almost half of the waterborne outbreaks described in paper III no pathogen was identified.

Route of transmission

In both outbreaks described in paper IV and V, there was a clear dose response with amount of water consumed, and drinking water was the most important route of transmission. However, in the outbreak of norovirus in the summer camp (paper V) there was also a significant risk associated with taking showers. This may be explained by swallowing water during showering, by transmission through aerosols or by contamination of hands followed by hand-to-mouth transmission. Standard recommendations to prevent illness during waterborne outbreaks are to boil water for food and drinking purposes and to enforce hygiene precautions to prevent person-to-person transmission. Our results show that this may not be sufficient to terminate outbreaks caused by norovirus. Although the association with showering was weak, the effect of using nonpotable contaminated water during norovirus outbreaks for other purposes than drinking needs to be taken into consideration.

Outbreaks caused by fresh produce irrigated with contaminated water

(paper VI, VII)

We have described two outbreaks associated with imported lettuce, one caused by hepatitis A virus (paper VI) and one caused by *S.* Thompson (paper VII). Both pathogens were non-endemic in the Nordic countries, and both outbreaks were due to imported products most likely contaminated with irrigated water. Using water of non-potable quality for irrigation of produce close up to harvest may lead to contamination of the products with a variety of pathogens. When the product is widely distributed and when only a few cases are falling ill with each pathogen in each community, even large outbreaks may go undetected. These outbreaks may also have gone undetected if the pathogens had been endemic in the country. It is likely that these outbreaks also involved several other countries, but were not detected or investigated as such.

During the last decades, several countries have reported an increase in outbreaks of infectious disease associated with consumption of fresh produce (155). As shown in Table 7, several different pathogens and a variety of vegetables and fruits have been involved. There may be several reasons for this observed increase, including consumer food preferences, food production practices, urbanisation and water scarcity, food distribution and globalisation of trade, emerging pathogens, and improved outbreak detection.

In the last 30 years, the consumption of fruits and vegetables has increased markedly in Norway (156), and a similar trend has been observed in other countries (157-159). While the domestic production has been relatively stable, there has been a steady increase in import of fresh produce (160). Due to the large and increasing global trade in fresh produce, contaminated batches have the potential to cause large international outbreaks. While the focus has been on harmonisation of monitoring pathogens in animal products, such as meat and eggs, less attention has been on good manufacturing practices for vegetables and fruits. There is therefore a need for increased attention on good manufacturing practices, especially for fruits and vegetables consumed raw.

Many foodborne outbreaks associated with imported products are detected when products are exported from a country where the endemic level of the contaminating pathogen is relatively high to a country where the endemic level is low. Imported lettuce has been implicated in hepatitis A outbreaks in other countries (161), and may represent an increasing problem when food items are imported from areas where this disease is endemic to countries where immunity

in the population is low. As described in the outbreak of *S.* Thompson (paper VII), a cluster of three cases with no travel history was enough to alert the public health authorities in Norway, while in the country of origin of the product, a few sporadic cases with this pathogen may not have signalled an outbreak.

Another reason for an observed increase in outbreaks related to fresh produce may be related to improved detection. New molecular typing tools and better international collaboration on surveillance of foodborne pathogens may have increased detection of widespread outbreaks due to low-grade contamination of fruits and vegetables. Often produce-related outbreaks are characterised by seemingly sporadic cases over a large area. If irrigation with sewage-contaminated water is the source of contamination, several pathogens may be involved, which will complicate outbreak detection. As was seen in the outbreak of *S.* Thompson infections (paper VII), several different pathogens were detected in the implicated product.

Fruit and vegetables - Water use from farm to fork

Water is used for several purposes in the production process of fruits and vegetables, including irrigation, applications of pesticides and fertilizers, cooling, and frost control. Post-harvest water use include produce rinsing, cooling, washing, waxing, transport, storing and spraying for freshness in shop displays.

It is often difficult to identify with certainty the source of microbial contamination for fresh produce. Sources of contamination include contamination by sewage used as fertilizer, from animals or birds, from irrigation water, from water used in packing or processing, or from handling by infected persons. It is not currently known what proportion of produce may become contaminated by water used in agricultural or packing facility operations. Pathogenic bacteria, parasites and virus have been found in irrigation water in several studies (162-164).

Numerous studies have investigated survival and growth characteristics of pathogens in fresh vegetables. Abdul-Raouf et al (165) demonstrated that *E. coli* O157 was able to grow on raw salad vegetables subjected to processing and storage conditions simulating those routinely used in commercial practice without any substantial influence on changes in visual appearance. Some pathogens grow more rapidly if the contaminated produce is first chopped, as was demonstrated in a study after an outbreak of *Salmonella* Thompson due to contaminated cilantro (166;167). For pathogens such as *Campylobacter*, norovirus, *Cryptosporidium* and verocytotoxin producing *E. coli*, the infectious dose is low, and therefore growth is not necessarily needed. Even small amounts of contamination with these organisms can result in foodborne illness (155).

In a survey of fruits and vegetables obtained in Norway in 1999-2001, 6%, mainly lettuce and sprouts, were found positive for *Cryptosporidium* oocysts or giardia cysts (168). A similar survey for bacterial pathogens concluded that the occurrence of pathogenic bacteria in Norwegian produce was low (169). In comparison, surveys conducted in some other countries have found a higher degree of faecal contaminants and pathogens in fresh produce (170-174). In 2005 the European Commission's Rapid Alert System for Food and Feed (RASFF) reported an increase in alerts regarding microbial contaminants in fresh produce, many related to fresh herbs imported from Thailand (175). The increase may also be partly caused by increased sampling as a result of reports of international outbreaks related to fresh produce. As mentioned in paper VII, several RASFF messages on contaminated rucola was posted in the period after the outbreak.

Problems linked with pathogenic microorganisms in fresh produce is of international concern, encompassing both public health and trade issues. Acknowledging this, the 38th Session of the Codex Committee on Food Hygiene in 2006 requested FAO and WHO to provide scientific advice to support the development of commodity specific annexes for the Codex Alimentarius "Code of Hygienic Practice for Fresh Fruits and Vegetables" (176)

Table 7 Outbreaks related to fresh produce 1990 – 2007 (outbreaks related to sprouts not included)

Year	Country	Product	Produce Source	Pathogen	Cases	Reference
1990	USA	Strawberries (frozen)	Domestic	Hepatitis A	28(+29 sec.)	(177)
1990	USA	Tomatoes	Domestic	S. Javiana	176	(178)
1991	Peru	Cabbage	Domestic	Vibrio cholerae	Unknown	(179)
1993	USA	Shredded carrots	Domestic	Escherichia coli (enterotoxigenic)	170	(180)
1993	USA	Tomatoes	Domestic	S. Montevideo	100	(178)
1994	International	Lettuce (iceberg)	Imported (Spain)	Shigella sonnei	>120	(61)
1995	USA	Raspberries likely	Imported (Guatemala?)	Cyclospora cayetanensis	87	(181)
1995	Canada	Iceberg lettuce	Imported	E. coli O157:H7	23	(182)
1995	USA	Lettuce	Domestic	E. coli O157:H7	70	(183)
1996	USA and Canada	Raspberries	Imported (Guatemala)	Cyclospora cayetanensis	1500	(184)
1996	USA	Mesclun lettuce	Domestic	E. coli O157:H7	54	(185)
1996	Japan	Radish sprouts	Domestic	E. coli O157:H7	10000	(186)
1996	Finland	Salad	Imported	Hepatitis A	30	(161)
1997	Canada	Raspberries (frozen)	Imported (Bosnia)	Calicivirus	>200	(187;188)
1997	USA and Canada	Raspberries	Imported (Guatemala)	Cyclospora cayetanensis	1000	(189)
1997	USA	Basil	Domestic	Cyclospora cayetanensis	341	(190)
1997	USA	Mesclun lettuce	Imported (Peru?)	Cyclospora cayetanensis	>100	(190)
1997	USA	Strawberries (frozen)	Imported (Mexico)	Hepatitis A	242	(191)
1998	Finland	Raspberries (frozen)	Imported (East Europe)	Calicivirus	> 500	(192)
1998	Canada	Raspberries	Imported (Guatemala)	Cyclospora cayetanensis	315	(190)
1998	USA	Green onion	Imported (Mexico?)	Hepatitis A	43	(193)
1998	USA	Mamey	Imported (Guatemala/Honduras)	S. Typhi	16	(194)
1998	USA	Tomatoes	Domestic	S. Baildon	85	(195)
1998	USA and Canada	Parsley	Imported (Mexico)	Shigella sonnei	500	(188;196;197)
1998	Finland	Iceberg lettuce	Domestic	Yersinia pseudotuberculosis	47	(198)

Year	Country	Product	Produce Source	Pathogen	Cases	Reference
1999	USA	Basil	USA/Mexico?	Cyclospora cayetanensis	62	(199)
1999	Canada	Blackberries suspected	Imported (Guatemala)	Cyclospora cayetanensis	100	(190)
1999	USA	Cilantro	Imported	S. Thompson	76	(166)
2000	USA	Raspberries	Imported (Guatemala?)	Cyclospora cayetanensis	54	(200)
2000	UK	Lettuce	Domestic	S. Typhimurium	361	(201)
2001	UK	Lettuce	Domestic(?)	S. Newport	19	(201)
2001	Canada	Thai basil	Imported	Cyclospora cayetanensis	17	(202)
2000	Germany	Lettuce	Imported (Spain/Italy)	Cyclospora cayetanensis	34	(203)
2002	USA	Tomatoes	Domestic	S. Javiana	82	(204)
2002	New Zealand	Blueberries	Domestic	Hepatitis A	81	(205)
2003	USA	Green onion	Imported (Mexico)	Hepatitis A	601	(206)
2003	Finland	Carrots	Domestic	Yersinia pseudotuberculosis	111	(207)
2004	UK	Lettuce		S. Newport	370	(208)
2005	Denmark	Raspberries	Imported (Poland)	Calicivirus	>1000	(209)
2005	France	Raspberries	Imported	Calicivirus	75	(210)
2005	Denmark	Carrots		Cryptosporidium hominis	99	(211)
2005	Sweden	Iceberg lettuce	Domestic	E. coli O157:H7	120	(212)
2005	Finland	Iceberg lettuce	Imported (Spain)	S. Typhimurium DT 104B	60	(213)
2005	USA (4 outbreaks)	Tomatoes	Domestic	S. Braenderup, S. Newport, S. Typhimurium	450	(214)
2006	Sweden	Raspberries	Imported (China)	Calicivirus	43	(215)
2006	USA	Spinach	Domestic	E. coli O157:H7	199	(216)
2007	Denmark/International	Baby corn	Imported (Thailand)	Shigella sonnei	120	(217;218)
2007	Sweden	Baby spinach	Imported	S. Java	107	(219)
2007	UK/International	Basil	Imported (Israel)	S. Senftenberg	>30	(220)

Outbreak caused by inhalation of contaminated aerosolised water

(paper VIII)

In paper VIII we describe the investigation of the largest outbreak of Legionnaires' disease in Norway. The source was an industrial air scrubber used as an industrial air purification device at a large industrial site for paper production and wood based chemicals. This is the first described outbreak associated with an air scrubber. Epidemiological and microbiological investigations, aerosol dispersion modelling and an assessment of the growth conditions for *Legionella* in the air scrubber all pointed to this source.

Previously, the maximum distance of transmission of *Legionella* was considered to be around 3 km (221). However, a cooling tower-related outbreak in France in 2003 showed a probable distribution over a distance of 6-7 km (222). In the outbreak described in paper VIII, eight cases stated they had not been closer than 10 km from the source, indicating a possibly larger transmission range from an air scrubber than from cooling towers. The incriminated air scrubber expelled air with a very high velocity and a large water drift, which may have facilitated the wide spread

Legionella bacteria are naturally present in aquatic environments such as rivers, lakes and reservoirs, usually in low numbers. To cause disease, the bacteria are introduced via water into artificial systems where favourable environmental conditions may facilitate growth and lead to high concentrations. This include a temperature in the range 20 to 55°C and a source of nutrients such as sludge, rust, algae and other organic matter. The presence of sediment or scales together with biofilms, are also thought to play an important role in harbouring and for providing favourable conditions. Finally, there must be a means of creating and disseminating inhalable aerosols that can reach a susceptible population.

Legionella is transmitted through inhalation of aerosolised contaminated water or soil or through aspiration. Community outbreaks of Legionnaires' disease have frequently been associated with cooling towers, and whirlpool spas, and less frequently with evaporative condensers, grocery store mist machines, respiratory or dental therapy equipment (223), potable water, and decorative fountains (Table 8). However, most cases are sporadic (80 – 90%) (224-226) and the source of *Legionella* for these cases is rarely known.

Outbreaks caused by *Legionella* is mainly a problem created by new technology. The ecological niches necessary for growth and dissemination is a result of demand of improved living

conditions (such as air conditioning systems or whirlpool baths), or – as shown in paper VIII – a result of a need for pollution control devices to reduce emissions to water and air. Studies of waste water treatment plants have also shown a high concentration of legionellae, and this was the suspected source of infection of a case of Legionnaires' disease in a worker at a waste water treatment plant in Sweden (227). However, if the plant does not have a device for wider aerosol dissemination , the risk of community-wide outbreaks is small.

All systems that use recirculating water in the temperature range facilitating growth of legionellae and have a possibility for disseminating aerosols should be considered as potential sources of infection. A risk assessment of the system will decide whether control measures are necessary.

Table 8 Examples of sources identified in outbreaks and sporadic cases of legionellosis

Date	Suspected Source	Cases	Deaths	Location	Ref
1976	Cooling Tower (widely accepted)	221	34	Philadelphia, PA, USA	(228)
1978	Evaporative condenser	8	0	Golfers, Country Club, USA	(229)
	Aerosolized tap water from jet nebulizers	5			(230)
1982	Contaminated potable hot water, potentially shower aerosols.	7	0	Community hospital, NY, USA	(231)
1983-88	Medication nebulizer	13	9	Community hospital, USA	(232)
1984-85	Distilled water used in respiratory therapy equipment and room humidifier (*L. dumoffii*)	5	3	Hospital, Quebec, Canada	(233)
1986	Exposure to excavation and construction activity	27	2	Retail store, Maryland USA	(234)
1989	Grocery store mist machine	33	2	Grocery store, Bogalusa USA	(235)
1989	Potable water, aspiration (?)	14		Military medical center, Texas USA	(39)
1992	Ice from ice machine	2	0	Hospital, Denmark	(236)
1994	Dental units	1	1	Dentist office, California, USA	(223)
1999	Whirlpool spa on display	188	21	Flower show, Netherlands	(63)
1999	Working with the pump of the ship's water system,	2	2	Cargo ship, Spain	(237)
2000	Outdoor fountain	11	0	Town square, Portugal	(238)
2001	Cooling tower	28	7	Stavanger, Norway	(40)
2001	Cooling tower	450 (800)	6	Murcia, Spain	(239)
2001	Cleaning line in automobile engine manufacturing plant	14	2	Ohio, USA	(240)
2003	Spa pool	8		Cruiseboat	(241)
2005	Indoor decorative fountain	18	1	Restaurant, Dakota USA	(242)
2006	Spa Pool	115	0	Sunderland, UK	
2007	Public hot water supply (after annual maintenance work)	175	4	Town in Sverdlovsk, Russia	(243)
2003-2004	Potable water (showering, bathing)	8	0	Hotel, Maryland USA	(244)

Outbreak detection

A crucial element in effective outbreak management is early detection. As described in the introduction, outbreak detection is based on two different approaches; indicator-based surveillance (case reporting) and event-based surveillance (outbreak reporting). Four of the five outbreaks described in this thesis were detected through event-based surveillance. However, all illustrates different aspects and problems with outbreak detection.

The outbreak of norovirus infections at the summer camp described in paper V shows how important it is to detect the outbreak early in order to limit the extent of the outbreak and avoid secondary transmission. Although, the closed setting facilitated early detection and reporting, the appropriate measures were not taken at this early stage, and the outbreak rapidly escalated.

Late detection contributed to the large public health impact of the outbreak of giardiasis (paper IV). Two years before the outbreak, a survey of laboratory practices had shown that clinicians rarely requested examination of stool samples for parasites when patients with gastroenteritis had no travel history (42). Relying on passive surveillance of laboratory-confirmed cases for detection of outbreaks is not sufficient when the pathogen is difficult to diagnose, or when the symptoms are common and the pathogen is non-endemic in the area and therefore not part of the routine diagnostic workup. Syndromic surveillance of gastrointestinal illness, or signals based on number of stool samples submitted for gastrointestinal pathogens may have led to earlier detection of the outbreak. However, due to a limited period of transmission and a delay in clinical consultations, the early warning system that would have been most timely in limiting the extent of the outbreak was a system based on water quality data. Clinical- or laboratory surveillance based outbreak detection would probably not had a large effect in limiting the extent of the outbreak, however earlier detection and identification of the aetiology would have caused more timely diagnosis of the patients, earlier start of treatment, less patient suffering and limited secondary transmission**.**

The only outbreak included in this thesis that was detected through indicator-based surveillance was the outbreak of hepatitis A described in paper VI. During winter and spring 2000 - 2001, there was an increase in domestic hepatitis A infections notified to the national infectious disease surveillance. During November 2000 to the end of June 2001, 80 domestic cases were reported, compared with 45 and 30, respectively, during the corresponding period in previous years. This was clearly more than expected, and an investigation was initiated.

The outbreak of *Salmonella* Thompson infections described in paper VII illustrates the usefulness of national reference laboratories in outbreak detection. Already at three cases with no travel history, the national reference laboratory raised an alert. If the isolates had not been submitted to a national laboratory, it is likely that the outbreak would have been detected at a much later state or maybe have passed undetected.

Alert clinicians and good communication between the hospital and the public health authorities facilitated the rapid detection and investigation of the outbreak of Legionnaires' disease described in paper VIII. The importance of the clinicians in early outbreak detection has been acknowledged in several occasions (245;246). The threshold for reporting suspected cases or clusters to the public health authorities should be low, and the public health authorities need to respond in an appropriate manner.

Public health authorities have traditionally relied on detection of outbreaks and rapid reporting by the primary health care providers. However, with an increased concern over bioterrorism attacks, new approaches for rapid outbreak detection are increasingly being investigated. One such approach is syndromic surveillance, which collects information on non-specific symptoms in order to detect an increase that may signal the start of an outbreak. In the USA, the BioSense system, developed by the Centers for Disease Control and Prevention at a cost of over $75 million (247), collects information on outpatient visits, pharmaceutical prescriptions, and laboratory requests in an attempt to detect disease outbreaks rapidly (248). Several similar systems are under development in other countries (249-252). However, the usefulness and cost-effectiveness of such systems have been discussed. An evaluation of syndromic surveillance effectiveness on detecting a covert anthrax attack concluded that the potential detection benefit of syndromic surveillance compared with clinical case finding depended critically on the specificity and sensitivity of the system and on the size of the outbreak (253). When syndromic surveillance was sufficiently sensitive to detect a substantial proportion of outbreaks before clinical case finding, it generated frequent false alarms.

A special issue of the journal Eurosurveillance in 2006 included three articles on recently established syndromic surveillance systems for the early detection of health threats (250-252). All concluded that the systems were helpful because they were able either to accurately reproduce data generated by existing specific systems or to document excess mortality following an already identified risk. However, none demonstrated a real added capacity to detect events that would otherwise have been missed (254).

Good communication and information sharing between health and water personnel, and a system integrating information from several data sources – including climatic, water quality, water complaints and syndromic health surveillance data - will probably achieve more timely and effective outbreak detection and management. More evidence-based research on the performance, management, effectiveness, cost-effectiveness and added value of non-etiological surveillance and new sources of health signals is needed before recommendations on resource-effective outbreak detection systems can be provided.

Study design

In the studies in this thesis, we have used ecological, case-control and cohort study designs. The choice of design in any study will be guided by the setting, the available resources and the purpose of the study.

In paper V, the outbreak occurred in a closed camp setting and the organisers had a list of names and addresses of all participants. Thus, a retrospective cohort study design was chosen, and a questionnaire was sent to all participants. The cohort design enabled us to estimate the total number of persons falling ill during the outbreak and investigate several exposures.

In the national outbreaks described in paper VI and VII, the source population was open, including the whole population. A case-control study design was chosen, where cases were identified from the national infectious disease registers, and appropriate controls were chosen from the population register.

In the outbreak of giardiasis described in paper IV, it was crucial to rapidly assess whether drinking water could be the source. A first assessment was done with an ecological study design, where attack rates in the different water supply zones in the municipality were compared. When this showed a strong indication of one central water supply zone, control measures were immediately implemented. To further verify this as the source, a case-control study was conducted with residents in the central water supply zone as the source population.

Methodological considerations

Ecological studies

In paper I and in the first study in paper IV we used an ecological study design, where the information is collected and analysed at population level rather than at individual level. One major limitation with this study design is described as the 'ecological fallacy', where an association between a potential risk factor and the outcome at the aggregated level does not

reflect the biological effect at the individual level, due to within-group differences in exposure level and covariates (100). Some argue that problems related to nondifferential exposure misclassification may be considered the strongest argument against the use of the ecologic studies as an inferential tool (255).

When ranking epidemiological study designs based on validity for etiologic inference of study results, ecologic studies rank low on the list while randomized trials are considered the best method. However, ecological studies have several advantages that warrant their use, as long as the methodological limitations are acknowledged. Individual-level studies are often very costly and time-consuming, while ecological studies may be quick to execute, do not require direct contact with large numbers of individuals in the population, and may utilise already existing data sets (256). This design has often been used as a primary assessment for generating hypotheses that can be further tested in individual-level studies. By its nature, ecologic methodology allows the study of large populations in ways that might not be feasible with any other design. Some environmental exposures may be difficult to measure on the individual level, and ecological studies or semi-individual studies may be a preferable approach (255).

In the investigation of the source of the outbreak of legionnaires' disease described in paper VIII, we used a retrospective cohort design. The exposed cohort was the population residing within circle-shaped zones around the potential sources, and the unexposed was the population living outside the zones. The exposure - place of residence – was used as a proxy for the concentration of contaminated aerosols disseminated from the potential source. It can be discussed whether this also could be classified as an ecological study, where the attack-rates within certain defined geographical areas are compared.

Bias in observational studies

All the studies in this thesis were observational studies. There are three main types of biases that are especially important to consider in observational studies; selection bias, information bias and confounding.

Selection bias occurs when there are systematic differences in characteristics between those who are included in the study and those who are not included, and they all belong to the defined study population (90). Studies where participation is based on self-recruitment may be prone to selection bias because the study subjects may have some special interest or worries regarding the study topic. The healthy worker effect is a recognized selection bias in studies on occupational exposures, where the exposed group of workers are generally more fit and healthy

enough to be employable, and has a lower morbidity and mortality than the population as a whole (257)

Information bias refers to errors in measuring exposure or outcome may cause. Non-differential misclassification is seen when the errors in classification of exposure or outcome are random. In contrast, differential misclassification in a cohort study is when the degree of misclassification depends on exposure status (90). The study participants' knowledge about their exposure may cause a different response about symptoms in those exposed than those not exposed, causing differential misclassification. In experimental studies, this is avoided by blinding the participants to their exposure status and standardize the outcome assessment. Non-differential misclassification will usually lead to bias towards the null, whereas differential misclassification can lead to bias in either direction (91).

Confounding is distinguished from selection and information bias in that when it is acknowledged and sufficient information is collected, statistical methods can be used during the analysis to correct the biased estimates. It is not possible to correct a biased estimate caused by selection or information bias during the analysis, and therefore, it is crucial that these issues are considered already at the design and execution stages of an observational study.

In the study of breaks and maintenance work in the water distribution systems and gastrointestinal illness (paper II) we tried to accomplish blinding of the participants regarding their exposure; however this was not completely successful. This may have led to some information bias among the participants in which those who believed they were exposed might have been more likely to report symptoms as compared to those who believed they were not exposed (also called awareness bias (258)). Non-blinding of the participants has been one of the main criticism of the water treatment intervention trials conducted by Payment in Canada (109;120). However, in our study when we stratified households according to whether they believed they had been exposed, the adjusted relative risk was only slightly lower than the unadjusted, thereby indicating that this did not have a large influence on the results. We further found an increased risk associated with higher average daily water intake, also supporting our conclusions that the association is causative.

Recall bias is one very common form of information bias. Cases will have a tendency to better recall past exposures than controls. Recall bias will therefore tend to overestimate the association of the outcome with exposure to a risk factor.

In the outbreak of giardiasis (paper IV), a boil-water notice was issued before the case-control interviews were conducted, and the outbreak created a massive mass media attention. This may have biased the results because the cases might have overestimated the amount of water consumed, while controls may have underestimated the amount. However, the questions were phrased as how much water they would usually drink during a normal day, which is less likely to be influenced by recall bias.

In paper VI and VII the cases were asked what they consumed in the time corresponding to the incubation period before disease onset, while the controls were asked for the same period before the interview. This will improve the recall for the controls, however, if there is a long time delay between disease onset for the cases and the interviews of cases and controls, some typical seasonal exposures may vary. This was discussed during planning of the studies, and the difference in time of exposures asked for was considered of less importance than to improve the sensitivity and specificity of recall of the controls.

7. MAIN CONCLUSIONS, PROPOSED ACTIONS AND FURTHER STUDIES

Main conclusions

Endemic waterborne disease

A large proportion of the waterborne disease burden arises outside detected outbreaks. We have studied two specific issues regarding endemic waterborne disease burden; the association between environmental factors and endemic campylobacteriosis and the association between maintenance work or main breaks in the water distribution system and gastrointestinal illness. Both studies indicated an increased risk related to water, and risk of contamination within the distribution system seems to be important. In Sweden, we found an association between average municipal water-pipe length and campylobacteriosis. Additionally, when excluding the three largest cities, we found that the proportion of people having a municipal water-supply was associated with a decreased incidence of campylobacteriosis in the municipality (paper I). Following incidents of breaks and maintenance work in the water distribution system in Norway, we found a 58% increase in the relative risk of acute gastroenteritis (paper II).

These studies were not designed to estimate the true burden of waterborne disease. Controlled trials randomised at household level where the participants are blinded to whether they receive a true water treatment device or a sham device is considered the "gold standard" to assess the risk of gastrointestinal illness associated with water exposure. However, these studies are very costly and time consuming, and the results will depend on the local water supply. An alternative approach is to conduct quantitative risk assessments, where the risk of illness is modelled based on probability distributions of the model parameters (101;151).

Investigating outbreaks caused by contaminated drinking water

Outbreaks caused by drinking water are a continuous problem even in developed countries with good infrastructure. Our review of waterborne outbreaks showed that during the 15 year period 1988-2002 there were 72 registered outbreaks affecting a minimum of 10 000 persons in total, and that most of these outbreaks occurred in small water works. The reason may be that these have limited resources for maintenance, lack or failure in disinfection and may be operated by personnel with only a limited amount of training. The outbreak of gastroenteritis in a summer camp described in paper V was traced to the local water supply and illustrates some of the

problems with small private water supplies. However, the largest outbreak of giardiasis recorded in Norway was traced to contaminated water from large waterwork serving ~50,000 persons (paper IV). This outbreak highlights the importance of non-complacency regarding provision of safe drinking water. Pathogens that are nonendemic in Norway, and that may be resistant to conventional water treatment, can become an increasing problem due to increased international travel and trade. Good communication between waterworks personnel, primary health care providers and public health personnel is important in order to detect outbreaks early so that appropriate measures can be taken. Electronic data transfer and data registers is increasingly used, both in monitoring of water quality and in the health care. Use of available electronic data sources may improve outbreak detection, can provide additional information on extent of the outbreak, as was demonstrated by the use of data from the prescription register in the outbreak in Bergen (paper IV). However, the cost effectiveness of such systems for outbreak detection has not been evaluated, and creation of many false signals may lead to unnecessary use of resources and fear in the population.

Thorough investigation of waterborne outbreaks to identify the pathogen and the deficiencies in the water supply system causing the outbreak is important, including both the technical failures, the operational and managerial issues, and legislative or regulatory issues. Good national surveillance of waterborne outbreaks is necessary in order to identify general areas were preventive measures or changes in legislation are needed.

Investigating outbreaks caused by produce irrigated with contaminated water

We identified imported rucola salad as the source of two foodborne outbreaks – one outbreak of hepatitis A in Sweden, and one outbreak of *Salmonella* Thompson-infections in Norway with international ramifications. In both outbreaks, irrigation water was suspected to be the source of contamination.

Due to the large and increasing global trade in fresh produce, contaminated produce may cause large international outbreaks. The setting up of national reference laboratories and increased use of harmonised typing tools will improve detection of national or international outbreaks caused by low-grade contaminated products.

Use of contaminated water for irrigation in the exporting country may introduce non-endemic pathogens such as hepatitis A virus in a susceptible population in the importing country and cause a re-emergence of pathogens that has been nearly eliminated. There is a need for higher emphasis on good manufacturing practices (GMP) for fruit and vegetables consumed raw. International collaboration in making GMP standards and rapid communication of information

through international networks is of great importance in preventing outbreaks and in the investigation and control of outbreaks caused by products on the global market.

Investigating an outbreak caused by inhalation of contaminated aerosolised water

We identified an air scrubber as the source of the largest outbreak of Legionnaires' disease ever recorded in Norway. An air scrubber has to our knowledge never previously been identified as the source of an outbreak of Legionnaires' disease.

Outbreaks of Legionnaires' disease are similar to waterborne outbreak in that a large proportion of the population will be exposed during a short period. However, only a small proportion of the population is susceptible to the disease. The ecology of *Legionella* bacteria needs to be taken into account in conducting risk assessments of aerosol producing devices. An air scrubber has never before been identified as the source of an outbreak of Legionnaires' disease, however an assessment of the environmental conditions in the scrubber was clearly favorable for facilitating growth of legionellae, and the emission of air at high velocity and high water content facilitated the wide dissemination of contaminated aerosols. Geographical tools such as mapping systems are important in the investigation of outbreaks of Legionnaires' disease, and knowledge of the location of potential devices is important for general preparedness and rapid investigation of outbreaks.

Proposed actions and further studies

Endemic waterborne disease

- For effective prevention of waterborne disease, it is important to gain more knowledge on the disease burden, the risks associated with the different parts of the water supply chain and where measures need to be implemented to prevent transmission. Microbial risk assessments adapted to different water supply systems may be used to estimate the risk of waterborne illness (151). We believe that population based surveys of gastrointestinal illness and surveys of general practitioners for practices for requesting stool specimens would provide better information for assessing the true burden of gastrointestinal illness, and for estimating underreporting in the current infectious disease surveillance system.
- The requirements for the water distribution system need to be assessed. The current legislation requires two hygienic barriers, however the specification for this requirement is targeted towards source water protection and water treatment and disinfection at the water treatment plant. The feasibility of developing more specific standards targeting also the

water distribution system (e.g. regarding leakages, pressure monitoring surveys) should be considered.

Investigating outbreaks caused by contaminated drinking water

- Rapid detection of outbreaks is needed in order to identify the source and contributing factors causing the outbreak, and to implement control measures. The usefulness of alternative outbreak detection tools, such as environmental indicator (climatic and water quality parameters), syndromic surveillance or surveillance of clinical samples submitted to laboratories needs to be evaluated.
- The risk of waterborne giardiasis and cryptosporidiosis in Norway is not known. Persons with gastrointestinal illness are rarely investigated for parasites if they have not been abroad. This may delay outbreak detection and underestimate the true public health burden of these parasites. Surveys of water sources have shown that both parasites are present in Norwegian surface water sources. Further studies to assess the true public health burden of endemic illness caused by these parasites in Norway are needed. With better knowledge of the burden of disease caused by these parasites and increased awareness, detection of future outbreaks might be more timely.

Investigating outbreaks caused by produce irrigated with contaminated water

- Increasing global trade in fresh produce will increase the risk of introduction of pathogens that is not endemic in the Nordic countries. The importers need to be aware of this risk, and should require that water used during production and processing in the exporting country is of sufficient quality to prevent contamination of the product. If this is not feasible, measures to decontaminate the final product before marketing need to be considered.
- National standards for water use in production and processing of fresh produce would be valuable, both for ensuring the safety of domestic produce and for enabling importers to require the same safety level for imported products. The Codex Committee on Food Hygiene acknowledges the problem and has currently requested FAO and WHO for scientific advice to address aspects related to the control of microbiological hazards in fresh produce (176). This could be used as a basis for developing national guidelines.

Investigating an outbreak caused by inhalation of contaminated aerosolised water

- Geographical tools are important in investigation of outbreaks with an environmental source, such as Legionnaires' disease. High risk devices, such as cooling towers and some industrial aerosol producing devices are required to be registered by the municipal health authorities. Already available geographical information could improve monitoring and

outbreak investigations. The usefulness of establishing a national geographical database containing basic information about cooling towers and similar installations should be evaluated.

- The industry is increasingly taking measures to control environmental pollution from industrial discharges to water and air. It is important that the risk of *Legionella* is taken into consideration during planning and implementation of pollution control devices.

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