Gastroenteritis in Norwegian primary care

Time trends and a large waterborne outbreak

Knut Erik Emberland

Thesis for the degree of Philosophiae Doctor (PhD)
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"(...) Once he got home Rieux telephoned his colleague Dr Richard,
one of the leading doctors in the town.
'No,' Richard said. 'I haven't seen anything out of the ordinary.'
'Not high temperature with local inflammation?'
'Well, yes, as it happens: two cases with very enlarged lymph nodes.'
'Abnormally so?'
'Huh!' said Richard. 'You know ... What's normal?' (...)"
Albert Camus, The Plague, 1947.

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As a researcher, you are expected to have a certain ability to criticize and look for improvements. But it is beyond my abilities to suggest points for improvement when it comes to the role of Guri Rørtveit and Knut-Arne Wensaas as supervisors: 'Real-time' without delays, based on trust, with genuine encouragement and support, and always improving both the quality and joy of my work. It has been a great pleasure working with you!

I have been in the fortunate situation of being part of several inspiring research environments, and these people have given me insights into topics far beyond my own research project. As an employee at the University of Bergen, my main affiliation has been with Section for General Practice at Institute of Global Public Health and Primary Care. I have also been affiliated with Research Unit for General Practice at NORCE Norwegian Research Centre. Additionally, I have been part of 'Epidemigruppen', a network of researchers who collaborate in various studies of epidemics.

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Lastly, I want to thank my wife Liv and our children Bjørn, Finn and Eva for all support and patience.

Contents

Summary

Gastroenteritis is a common term for acute infection of the gastrointestinal tract and includes several conditions and specific infections. Gastroenteritis has to a great extent caused disease and death in humans through our history. Even the very foundation of epidemiology can be traced back to John Snow's work on identifying drinking water as source of the cholera epidemic in London in 1854. Gastroenteritis still occurs frequently in the community, but most people in our part of the world experience self-limiting symptoms and therefore only a small proportion seek the health care services. Of those seeking medical attention, only a few submit stool samples for microbiological diagnostics, and only those who are diagnosed with a notifiable microbe are included in the statistics of the notification systems of infectious diseases. The clinical features of gastroenteritis vary from asymptomatic cases to fatal disease, but diarrhea is common in cases who develop symptoms.

The clinical features in the individual gastroenteritis patient can give a hint as to whether there is a viral or bacterial cause. Correspondingly, using existing knowledge about seasonal variation and the epidemiology of the specific infections may give an indication of probable microbiological cause in gastroenteritis patients at group level. This is useful knowledge because laboratory verified diagnoses are rare. Our study of consultations for gastroenteritis in Norwegian primary care during a 10-year period shows a contact pattern similar to what characterizes viral gastroenteritis: Most consultations took place in the winter and children and young adults dominated among the patients. The findings contribute to increased knowledge of the normal situation regarding gastroenteritis patients' use of health care services.

Since antibiotics became widely available in the years following World War II, antibiotic treatment has been central to the treatment of many infectious diseases. Gastroenteritis has been an exception, both because most are viral and because antibiotics only to a small extent have been shown to shorten the course of the disease and relieve symptoms also in most bacterial gastroenteritis. Antimicrobial resistance in bacteria causing gastroenteritis

represent a growing concern in a European and global context, although the current situation in Norway is more favorable. Transmission between animals and humans, either directly or indirectly via food, makes resistance in zoonoses and food-borne microbes particularly challenging. Our study of antibiotic use in gastroenteritis in the Norwegian primary health care service over a 10-year period shows that antibiotics are rarely used compared with other countries. Further, there has been an even more favorable development after 2012 with a decrease in the use of resistance-driving antibiotics such as fluoroquinolones and macrolides.

Gastroenteritis tends to appear as outbreaks of various magnitude and public health importance. The outbreaks occur and spread either via direct contact between humans, directly between humans and animals, or as food-borne outbreaks where the microbe spreads to humans via food or drinking water. Gastroenteritis caused by the foodborne infection campylobacteriosis is an example of the latter, and in June 2019, more than 1 500 in the community became acutely ill during a major waterborne outbreak of *Campylobacter* infection in Askøy. Our population-based study of acute gastroenteritis during the outbreak shows a broader spectrum of symptoms, with less bloody stools and more tiredness and joint pain than previously described in laboratory-verified sporadic cases of *Campylobacter* infection. The study sheds light on the cases of gastroenteritis that occur in the interface between how they appear in the community, in the health care services, in the notification systems, and not least in the research literature.

Norsk sammendrag

Gastroenteritter er en fellesbetegnelse på akutt infeksjon i mage-tarm-kanalen og omfatter flere tilstander og spesifikke infeksjoner. Gastroenteritter har i stor grad forårsaket sykdom og død hos mennesker opp igjennom vår historie, og selve opphavet til faget felt-epidemiologi føres tilbake til John Snows arbeid med å identifisere drikkevann som kilde til kolera-epidemien i London i 1854. Stadig forekommer gastroenteritter hyppig i befolkningen, men de fleste i Norge opplever selvbegrensende plager og derfor oppsøker kun en liten andel lege. Av de som søker lege blir et fåtall undersøkt med avføringsprøve for mikrobiologisk diagnostikk, og kun de som får påvist en meldingspliktig mikrobe inngår i statistikken til meldesystemene for infeksjonssykdommer. Sykdomsbildet ved gastroenteritt varierer fra asymptomatisk til dødelig sykdom, men diare er vanlig hos de fleste som utvikler symptomer.

Det kliniske bildet hos den enkelte gastroenterittpasient kan gi et hint om det foreligger en viral eller bakteriell årsak. I tillegg kan bruk av eksisterende kunnskap om sesongvariasjon og epidemiologi til de spesifikke infeksjonene si noe om sannsynlige agens hos pasienter på gruppenivå. Dette er nyttig kunnskap fordi man sjelden har laboratorieverifiserte diagnoser. Vår studie av legekonsultasjoner for gastroenteritt i norsk primærhelsetjeneste over en 10-års periode viser et kontaktmønster som likner det som kjennetegner virale gastroenteritter, hvor flest konsultasjoner fant sted på vinteren og hvor barn og unge voksne dominerte blant pasientene. Resultatene bidrar til en økt forståelse av normalsituasjonen for legesøkning ved gastroenteritter.

Etter at antibiotika ble allment tilgjengelig i tiden etter andre verdenskrig, har de stått sentralt i håndteringen av mange infeksjonssykdommer. Gastroenteritter har vært et unntak, både fordi de fleste er viralt betinget og fordi antibiotika i liten grad er vist å forkorte sykdomsforløp og lindre symptomer også for de fleste tilfellene av bakterielle gastroenteritter. Antibiotika-resistens hos bakterier som gir gastroenteritt er et økende problem i europeisk og global sammenheng, selv om situasjonen i Norge foreløpig er gunstig. Smitteoverføring mellom dyr og mennesker, enten direkte eller indirekte via

næringsmidler, gjør resistensproblematikken ved zoonoser og næringsmiddelbårne mikrober særlig utfordrende. Vår studie av antibiotikabruk ved gastroenteritter i norsk primærhelsetjeneste over en 10-års periode viser at antibiotika brukes sjelden sammenliknet med andre land. Det har vært en ytterligere gunstig utvikling etter 2012 med nedgang i bruk av særlig resistensdrivende antibiotika som fluorokinoloner og makrolider.

Gastroenteritter har en tendens til å opptre i større eller mindre utbrudd av ulik samfunnsmedisinsk betydning. Utbruddene oppstår og spres enten via direkte kontakt mennesker imellom, direkte mellom mennesker og dyr, eller som næringsmiddelbårne utbrudd der mikroben spres til mennesker via mat eller drikkevann. Gastroenteritt forårsaket av den næringsmiddelbårne infeksjonen campylobacteriose er et eksempel på sistnevnte, og i juni 2019 ble mer enn 1 500 personer akutt syke under et stort vannbårent utbrudd av *Campylobacter*-infeksjon på Askøy. Vår populasjonsstudie av akuttforløpet ved gastroenteritt under dette utbruddet viser et bredere spektrum av symptomer, med mindre blodig avføring og mer tretthet og leddsmerter, enn det som tradisjonelt er beskrevet for laboratoriebekreftede sporadiske *Campylobacter*-tilfeller. Studien belyser de tilfellene av gastroenteritter som opptrer i grenselandet mellom slik de forekommer i befolkningen, på legekontoret, i meldesystemene, og ikke minst i forskningslitteraturen.

List of publications

I. Emberland KE, Wensaas K-A, Litleskare S, Rortveit G. Consultations for gastroenteritis in general practice and out-of-hours services in Norway 2006–15. Fam Pract. 2019;36:614-20.

II. Emberland KE, Wensaas K-A, Litleskare S, Larsen L, Morch K, Ruths S, Rortveit G. Antibiotics for gastroenteritis in general practice and out-of-hours services in Norway 2006-15. Accepted for publication in Family Practice.

III. Emberland KE, Wensaas K-A, Litleskare S, Iversen A, Hanevik K, Langeland N, Rortveit G. Clinical features of gastroenteritis during a large waterborne Campylobacter outbreak in Askøy, Norway. Accepted for publication in Infection.

Abbreviations

AMR	Antimicrobial resistance
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CRP	C-reactive protein
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
GP	General practitioner
HELFO	Helseøkonomiforvaltningen
	(Norwegian Health Economics Administration)
ICPC	International Classification of Primary Care
KPR	Kommunalt pasient- og brukerregister
	(Norwegian Register of Primary Care)
KUHR	Kontroll og utbetaling av helserefusjon
	(Control and Payment of Health Reimbursements)
MSIS	Meldingssystem for smittsomme sykdommer
	(Norwegian Surveillance System for Communicable Diseases)
NIPH	Norwegian Institute of Public Health
NorPD	Norwegian Prescription Database
NorSySS	Norwegian Syndrome Suveillance System

OOH	Out-of-hours
PCR	Polymerase chain reaction
RR	Relative risk
WHO	World Health Organization
WONCA	World Organization of Family Doctors

1. Background

1.1 Gastroenteritis

1.1.1 Definitions and clinical features

Many different terms are used when referring to the condition that reflects an acute inflammation of the gastrointestinal tract which is caused by various microbes or toxins. In the literature of studies from primary care or population-based studies, terms such as 'diarrheal disease' (1, 2), 'infectious intestinal disease' (3), 'diarrheal disease' (4), 'acute gastrointestinal infections' (5-8), 'diarrhea' (9), 'acute diarrhea' (10, 11), and 'gastroenteritis' (12-14) are used for this condition, of which the latter is used in this thesis.

Gastroenteritis is a generic term referring to various clinical characteristics (such as 'winter-vomiting disease', 'dysentery', 'tourist diarrhea', 'food poisoning'), and specific infections with an identified microbe (e.g. 'campylobacteriosis' and 'giardiasis'). There exists no common definition of gastroenteritis, but there has been suggested a common symptom-based definition of a gastroenteritis *case*: An individual who experiences ≥ 3 loose stools, or any vomiting, in 24 hours, excluding cases where these symptoms are explained by known non-infectious reasons (15). However, this definition is not widely used in research without certain modifications, such as including additional symptoms among the criteria. The core element of the different definitions used in population-based studies or studies from general practice is the acute onset of enteric symptoms, most commonly loose stools or diarrhea (commonly defined as the passing of ≥ 3 loose stools in 24 hours) (3, 5-9, 11, 12, 14, 16). Additional symptoms often included in different gastroenteritis case definitions are nausea, abdominal pain, bloody stools, headache, fever, and joint pain.

The severity of gastroenteritis ranges from asymptomatic or self-limiting symptoms to illness leading to need of hospitalization, or death.

1.1.2 Epidemiology and microbiology

Gastroenteritis has been a leading cause of morbidity and mortality through the history of mankind. Even the very foundation of epidemiology can be traced back to John Snow's work on identifying drinking water as source of the cholera epidemic in London in 1854 (17, 18). Despite the progress of modern medicine, gastroenteritis is even today a leading cause of death in all ages globally, and the mortality among children under the age of 5 years is particularly high (2).

The burden of gastroenteritis is clearly highest in low-income countries, where many cases could have been prevented by improving access to safe water and health care, sanitation and childhood nutrition. In high-income countries gastroenteritis rarely causes death (3–5) but still causes significant socio-economic costs (6–9). Yet, while the mortality from most infectious diseases in the United States decreased from 1980 to 2014, there was an increase in mortality for diarrheal diseases which was the second leading cause of infectious diseases mortality in 2014 (1).

Gastroenteritis can be caused by a number of different agents such as toxins (produced by bacteria such as *Staphylococcus aureus*, *Clostridium perfringens and Bacillus cereus* (19)), viruses (e.g. norovirus, rotavirus, adenovirus, enterovirus and astrovirus (20)), bacteria (e.g. *Campylobacter spp.*, non-typhi salmonellae, *Vibrio cholerae*, *Yersinia spp.*, *Shigella spp.* and pathogenic *Escherichia coli* (19)), and parasites (e.g. *Giardia lamblia*, *Entamoeba histolytica* and *Cryptosporidium*).

Gastroenteritis can spread from person-to-person by fecal-oral transmission either by direct contact or indirectly by contaminated food, objects or surfaces. Specifically, norovirus can spread by direct or indirect contact with vomit from an infected person, even by ingesting small droplets of vomit spreading through the air (21, 22). Gastroenteritis cases are more likely to infect others when they have symptoms and 2-3 days after recovery, but also for a short period of time before symptom onset.

1.1.2.1 Diagnostics

During the last decade, polymerase chain reaction (PCR) diagnostics have become the primary method in routine microbiological investigation of stool samples from patients with gastroenteritis in Norway (23). This DNA-based method screens for a broad spectrum of viruses, bacteria and parasites (multiplex molecular panels) from one single rectal swab, with the results ready in just a few hours. Before PCR multiplex molecular panels were introduced, the primary investigation for gastrointestinal pathogens relied on a combination of different time consuming and labor-intensive methods such as culture, microscopy, and antigen detection (24). These methods also require that the clinician who requests the microbiological investigation selects the appropriate test for the suspected microbes.

The shift to PCR diagnostics, in turn, affects the epidemiology of laboratory confirmed infections. Previously, stool samples from patients with suspected gastrointestinal infection were routinely tested for *Salmonella*, *Campylobacter*, *Yersinia*, *Shigella* and *Vibrio*, but testing for viruses, parasites and pathogenic *E. coli* was done only when clinically or epidemiologically indicated and thus considerably underreported (23). Even the criteria for notification to the Norwegian Surveillance System for Communicable Diseases (MSIS) have changed from a culture verified diagnosis to also include PCR positive cases for certain infections. This was introduced in 2017 for the notification of campylobacteriosis (23). Further, PCR diagnostics is highly sensitive and does not need a viable microorganism but only remnants of DNA from the microbe in the feces for the test to be positive. Consequently, the positivity rates of gastrointestinal pathogens increase by 2- to 4-fold compared to diagnostics by conventional methods (24).

Thus, PCR diagnostics pose a risk of identifying microbes that are not of clinical or epidemiological importance. It is challenging for the clinicians to interpret the presence of organisms that have not been routinely tested for in the past (such as different viruses and enteroaggregative *E. coli* - EAEC) or decide whether microbes represent colonization or asymptomatic infections suggesting isolation and treatment (such as *Clostridioides*

difficile). It is also worth noting that the microbiological laboratories in Norway use different multiplex molecular panels with various repertoires of microbes being tested for. Positive results from PCR diagnostics should be interpreted with caution until results from the more thorough follow-up investigation by conventional methods are ready, including antibiotic susceptibility testing when applicable.

1.1.2.2 Stool samples: Who to be tested?

All patients with gastroenteritis should not submit stool samples for testing, as it would be neither socio-economically appropriate nor necessary or desirable for adequate management of most patients with gastroenteritis. Stool samples should be submitted only when clinically or epidemiologically indicated and followed by clinical information to the microbiologists. There exist no clear-cut national guidelines for when to submit stool samples from gastroenteritis patients in primary care. However, a summary of recommendations from guidelines for antibiotic treatment and management of gastrointestinal infections is as follows (25, 26): Stool samples should be limited to patients where the results are expected to be either useful for choosing treatment, or for epidemiological or infection control reasons. In addition, stool samples should be submitted from patients with severe symptoms (bloody stools, fever, severe abdominal pain, frequent passing of loose stools, dehydration), comorbidities or compromised immune system, duration of symptoms more than one week or recent travel abroad. Decisions about testing impacts in turn the epidemiology of the different infections in the surveillance systems.

The clinical features alone cannot be used to make certain inference about the causing organism. Still, the symptomatology can be of value to distinguish between suspected viral versus bacterial/protozoal cause: Symptoms of diarrhea but no vomiting, diarrhea lasting for more than 3 days, bloody diarrhea and fever are more common in bacterial or protozoal cause, whereas age < 5 years, onset in spring or winter and loss of appetite are more common in viral gastroenteritis (27, 28). Further, if known, information about suspected type of exposure (e.g. intake of particular food, contact with others with similar

symptoms) and time from exposure to symptom onset can contribute to suggest certain pathogens (28). The microbial cause can only be identified by microbiological investigation. However, a causing organism can be identified in less than 50% of stool samples from gastroenteritis patients presenting to primary care, and when identified it is most commonly viral (3, 11, 12, 14, 29).

1.1.2.3 Seasonality

Trends in seasonality are described for different microbes causing gastroenteritis (30-38), and the underlying mechanisms most probably vary for the different pathogens (34). The seasonality of common bacterial infections like salmonellosis and campylobacteriosis in Norway is distinct with peaking in August (36, 37), whereas the seasonality of common viral infections such as norovirus and rotavirus infection peak in December through February (30, 39) and March through May (32), respectively.

Possible factors contributing to seasonality are holiday travels abroad, variability in temperature and humidity, start of school year, geographical localization on either Northern or Southern Hemisphere and level of country development (33-35).

1.1.2.4 Viruses

Viral gastroenteritis in Northern Europe is most commonly caused by norovirus or rotavirus (in unvaccinated young children) and is popularly called ‘stomach flu’ or ‘winter vomiting disease’ as people have experience with their presence in the winter months, which is supported by the literature on seasonality (27, 30, 32, 39).

Rotavirus infection has been the most common cause of severe gastroenteritis among children under the age of five in Norway (18, 19). After the rotavirus vaccine was included in Norway’s Childhood Immunization Program in 2014, a 45% decrease in gastroenteritis-associated hospitalizations among children < 5 years and reductions in gastroenteritis contacts in primary care have been demonstrated (40, 41).

Norovirus is now the leading cause of gastroenteritis worldwide, and even emerged as the leading cause of severe gastroenteritis in young children in Finland and the United States

after implementation of rotavirus vaccination (20). Norovirus is highly infective and known to cause local outbreaks in institutions and in families with young children, and presents commonly as a self-limiting illness dominated by vomiting for 1-3 days (20, 28, 42). Due to the genetic and antigenic diversity within norovirus, the development of a norovirus vaccine is challenging, although clinical trials for some vaccine candidates are ongoing (8).

1.1.2.5 Bacteria and parasites

The bacterial gastrointestinal infections are subject to notification to MSIS and updated compilations of surveillance data for these are available at the Norwegian Institute of Public Health's (NIPH) online handbook on the prevention and control of infectious diseases ("Smittevernveilederen") (22): Campylobacteriosis is the most common with 2000-3000 cases annually, followed by salmonellosis (approx. 1000), *E. coli* enteritis (approx. 200-900), shigellosis (approx. 100) and yersiniosis (approx. 50-100). The parasitic infections giardiasis and cryptosporidiosis are notifiable in Norway, and in the recent years 300-500 cases of each have been reported annually. The majority of notified infections are acquired abroad. The proportion of domestically acquired infections differ, and is highest for yersiniosis (approx. 60%), enterohaemorrhagic E. coli enteritis (EHEC) (approx. 50%), campylobacteriosis and cryptosporidioisis (40-50%), giardiasis (20-30%), salmonellosis (approx. 20%). However, information on place of acquisition is missing for 10-20%.

Antibiotic-associated *C. difficile* infection has been notifiable to MSIS since 2012 (43) but is not readily considered gastroenteritis as it is an opportunistic and primarily nosocomial infection and a rare cause of diarrhea in the community (3).

1.1.3 Use of health care services and management

1.1.3.1 Use of primary health care services

Most people with gastroenteritis in high-income countries experience self-limiting symptoms and therefore rarely seek the health care services, although there might be

administrative reasons for the contact, such as need for sickness certification. Among those who seek health care services, most are managed in primary care. Of these, a small proportion is referred to hospital, and some submit stool samples for microbiological investigation. Consequently, the gastroenteritis cases with a laboratory verified pathogen, and thus subjects to being included in the surveillance statistics, represent only a fraction of cases in the health care services and in the population. These stages in reporting of cases with gastrointestinal infection to the surveillance system is often referred to as the 'notification pyramid' (3).

The incidence of self-reported gastroenteritis in the community varies between European countries. Although differences in methods and case definitions used make it difficult to compare the results of these studies directly, the incidence per person-year range from 0.19 and 0,27 in the United Kingdom (3, 44), 0.28 and 0.45 in the Netherlands (12, 45), 0.3 and 0.36 in Sweden (6, 7), 0.4 in Ireland (9), 0.9 in Poland (5), 1.2 Norway (16) and 1.4 in Denmark (8).

Studies from the United Kingdom and the Netherlands have identified the severity of illness and recent foreign travel to be the most important factors associated with gastroenteritis patients seeking their general practitioner (GP) (13, 46). Population-based studies from various European countries report that 0.9 - 30% of the gastroenteritis cases in the community contact the health care services (5-9, 13, 16, 45-47). In two Norwegian population studies from 1987 and 1999-2000, the proportion of gastroenteritis cases that consulted a doctor was 17% and 21%, respectively (16, 47).

1.1.3.2 Management, treatment, and infection control measures

Regardless the underlying pathogen, it is crucial in the treatment of gastroenteritis patients to ensure adequate compensation of fluid loss, and hospitalization for intravenous fluid therapy may be necessary. Symptoms like headache, joint- or muscle pain, or fever can be treated with analgesics/antipyretics, although antiemetics and antimotility agents

should be avoided in patients presenting to primary care with acute gastroenteritis, especially in children and cases with severe illness or bloody diarrhea (26, 48, 49).

To reduce the risk of further spread, patients should be informed about simple, individualized infection control advice, such as thorough hand washing, good routines for toilet visits and cooking, as well as short-term isolation of the sick for at least 48 hours after symptom relief. Sick leave used as an infection control measure may be relevant to patients who due to their work pose an increased risk for further spread of the infection (food handling and patient contact) regardless of the patient's clinical condition and functioning (50, 51). In Norway, updated details on general infection control advice and disease-specific control and follow-up regimens can be found at NIPH's website (52).

1.1.4 Public health aspects of gastroenteritis

1.1.4.1 Surveillance of gastrointestinal infections

Surveillance of gastrointestinal infections in Norway is primarily based on laboratory-confirmed cases, and the following gastrointestinal infections are subject to notification to MSIS (Communicable Diseases Notification System) when laboratory-confirmed: campylobacteriosis, enteropathogenic *E. coli* enteritis, salmonellosis, shigellosis, yersiniosis, cholera, giardiasis cryptosporidiosis and hemolytic-uremic syndrome (53, 54).

An obvious disadvantage of a laboratory-based surveillance system is the delay from time of infection and symptom onset until a laboratory confirmed diagnosis is notified (55). Norwegian Syndrome Suveillance System (NorSySS) was introduced in Norway in 2017 as a near real-time supplement to laboratory-based surveillance (56). The system is based on reimbursement claims data and shows the number of consultations in general practice and out-of-hours (OOH) services for the International Classification of Primary Care (ICPC) codes 'D11 Diarrhea', 'D70 Intestinal infection' and 'D73 Gastroenteritis suspected infectious' over a given period. The diagnoses are primarily based on the patient's symptoms and do not need to be laboratory confirmed.

1.1.4.2 Outbreaks

Gastroenteritis of any microbiological cause can appear as outbreaks. An outbreak can be defined as "two or more cases of a disease that is suspected to have a common source, or a number of cases that clearly exceed what one would expect (i.e. the endemic level - the normal background level of the disease) within an area in a given period of time" (57).

According to Norwegian regulations (MSIS-forskriften) and the International Health Regulations (IHR), all physicians in Norway have a duty to immediately send an early warning notification to the municipal public health officer if an outbreak of infectious disease is suspected, even when there is no laboratory-verified diagnosis (58). Early warnings of outbreaks related to food or drinking water are highlighted as of particular importance. Additionally, early warning notification also applies to isolated cases (one patient only) of cholera, diarrhea-associated hemolytic uremic syndrome (HUS) and enterohemorrhagic E. coli (EHEC) infection (58).

1.1.4.3 Public health and veterinary medicine

Many of the infections causing gastroenteritis are zoonoses (transmission between animals and humans) and foodborne diseases. Thus, public health and veterinary authorities are collaborating closely in the surveillance of foodborne illness and pathogens, both at a local (municipal public health officer and local Food Safety Authority), national (NIPH and Norwegian Food Safety Authority and Veterinary Institute) and a European level (European Centre for Disease Prevention and Control (ECDC) and European Food Safety Authority (EFSA)).

1.2 Campylobacter infections

A more detailed description of *Campylobacter* infections follows, as one part of this thesis (Paper III) is about a large waterborne *Campylobacter* outbreak that took place on the municipality Askøy outside Bergen in June 2019.

1.2.1 Microbiology

Campylobacter spp. are small, curved or spiral shaped Gram-negative bacilli (59). There are many species of *Campylobacter*, but *C. coli* and *C. jejuni* are causing most infections in humans, of which *C. jejuni* is the most common (59, 60). As of 2018, approx. 50% of all notified *Campylobacter* cases are PCR diagnosed only, without culture verification (23).

1.2.2 Epidemiology and outbreaks

Campylobacter was recognized as a human pathogen in the 1970s (59, 61), and is now the most common bacterial cause of gastroenteritis worldwide (62), in Europe (63), and in Norway (60). Annually, approx. 3000 cases in Norway are reported to MSIS of which more than 50% are infected abroad. The annual incidence of non-foreign travel related *Campylobacter* infections in Norway is estimated to 28.5 cases/100 000 during the years 2000-2014, but increasing after 2004, a trend also observed in Sweden, Finland (36) and the United States (64). The most common risk factors for domestically acquired *Campylobacter* infection in Norway are drinking untreated water, eating poultry, or eating and preparing barbeque meals (65, 66). Several waterborne outbreaks from Norway or other Nordic countries have been described (67-70).

The *Campylobacter* bacteria are found in Norwegian wildlife, most commonly in the guts of wild birds but can also be found in cattle, dogs and cats (60). As of 2019, the prevalence of *Campylobacter* in broiler flocks in Norway were 5.1%, which is low compared to other countries (60).

1.2.3 Clinical features

The clinical features of gastroenteritis caused by *Campylobacter* spp. are not different from other bacterial gastroenteritis. The most common symptoms include diarrhea (≥ 3 loose stools in 24 hours), nausea, vomiting, abdominal pain, and bloody stools (59, 61, 71-77). *Campylobacter* infection usually starts in the jejunum or ileum, and then progress

to affect colon, but in some the infection starts with symptoms of acute colitis such as frequent passing of watery stools or bloody diarrhea (71).

The illness is usually mild and self-limiting, but some experience severe illness with systemic illness or long-lasting frequent diarrhea leading to need for hospital care, or even lethal disease (59, 61, 71-77). Bloody stools and fever are considered markers of more severe infections (71, 76, 78, 79).

Campylobacter infection is known to have the ability to cause post-infectious complications such as the Guillain-Barré syndrome (acute immune-mediated polynevropathy), reactive arthritis, and irritable syndrome (IBS) (59, 80-84).

The studies comprising the literature on symptoms and clinical features of campylobacteriosis were predominantly published from 1970s to 2000 and are mostly based on either surveillance data or laboratory verified sporadic cases of infection (59, 61, 72-75, 78, 79). Such cases represent a selected group that may differ from the total symptomatic cases in the community (3, 44).

In the literature of epidemiological studies on *Campylobacter* infection, most are outbreak investigation studies with the aim to identify the source and the size of the outbreak. Outbreaks often happen without warning and there will always be some delay before it is acknowledged. It is difficult to plan research in advance and also to launch the study in the acute phase when focus is on managing the outbreak and its consequences. Hence, both comprehensive baseline data and data on symptoms and clinical features from outbreaks are relatively rare.

The description of antibiotic treatment of *Campylobacter* infections can be found in the following section ‘1.3.3 Antibiotic treatment of *Campylobacter*’.

1.3 Antibiotic treatment of gastrointestinal infections

Since antibiotics were commercialized in the years following World War II, antibiotic treatment has been, and still is, central to the treatment of most bacterial and parasitic

infectious diseases. However, antibiotics are less important for the treatment of gastroenteritis, and Norwegian guidelines and international recommendations state that antibiotics should be avoided for the treatment of gastroenteritis in primary care (25, 26). Norway generally has a low consumption of antibiotics compared to most other European countries (85). In high-income countries, gastroenteritis is rarely treated with antibiotics in primary care, with prescribing proportions ranging from 5 to 11% varying between countries (86-88). In contrast, a study from low- and middle-income countries found that approx. 50% of children under the age of 5 years with diarrhea who visited a health-care facility were treated with antibiotics (89).

1.3.1 Empiric antibiotic treatment

Empirical treatment with antibiotics (treatment without a verified microbe) seems particularly inappropriate in Norway as studies of gastroenteritis cases in primary care in countries from Northern Europe have shown that the infective agents are most commonly either viruses or cannot be identified (3, 11, 12, 29). Even in travel related gastroenteritis without a verified microbe, often referred to as 'tourist diarrhea', empiric antibiotic treatment should be avoided in primary care. This also applies to infections imported from parts of the world where bacterial and parasitic gastrointestinal pathogens are more prevalent, as imported infections more often are caused by antibiotic resistant microbes. Instead, patients with tourist diarrhea that present to primary care should be tested, and antibiotic treatment not considered before the results of the susceptibility tests are available. If the clinical condition requires urgent treatment, the patient should be hospitalized.

1.3.2 Specific antibiotic treatment

For most causal microbes, antibiotics are not shown to shorten the symptomatic phase of gastroenteritis, and in some cases could contribute to a more serious outcome in infections caused by *E. coli* and *Salmonella* (90, 91). However, specific antibiotic treatment is recommended for severe cases with certain symptomatic gastrointestinal infections such

as shigellosis, giardiasis and amoebiasis, although primarily in the hospital setting (25, 92).

Antibiotics approved for per oral treatment (thus can be used in the primary care setting) of specific gastrointestinal infections in Norway are macrolides, fluoroquinolones, tetracyclines, trimethoprim-sulphamethoxazole and vancomycin (25, 92).

1.3.3 Antibiotic treatment of Campylobacter

Antibiotics are usually not needed in treatment of campylobacteriosis but may be useful in the hospital setting in patients with severe illness or risk of severe illness (25, 71, 78, 79, 92-94). When antibiotic treatment of *Campylobacter* infection is indicated, macrolides (erythromycin or azithromycin) are the antibiotics of choice (71, 92, 93). There is an increase in fluoroquinolone resistance in *Campylobacter* species in many parts of the world, and macrolide resistance has also been reported in some countries although to lesser extent (71, 93).

1.3.4 Antimicrobial resistance

Antimicrobial resistance (AMR) is a major challenge to global public health (95). The ECDC has estimated that 33 000 patients died as a direct consequence of infections with antibiotic-resistant bacteria in the European Union (EU) and the European Economic Area in 2015 (96). As of today, the situation regarding resistant microbes in humans and animals in Norway is favorable (97). However, resistant microbes in zoonoses and foodborne illnesses are increasing in the EU (98), and fluoroquinolone-resistant *Campylobacter* spp., *Salmonella* spp., and *Shigella* spp. are on the WHO priority list of antibiotic-resistant bacteria (99).

One of the drivers of AMR is the antibiotic use itself through the process of selective pressure (100). In 2015, the Norwegian Government's Action Plan to Fight Antimicrobial Resistance in the Health Care Services (the Action Plan) launched a goal to reduce the total number of antibiotic prescriptions by 30% by the end of year 2020 as compared to

the level of prescriptions in 2012 (101). Measures to reduce inappropriate use of antibiotics is a contribution to this effort.

2. Aims of present study

This thesis is comprised by sub-studies of two research projects:

A) Antibiotic use in Primary Care in Norway (APRINOR), a registry-based project investigating the epidemiology and antibiotic treatment of infections in general practice and out-of-hours services in Norway.
B) Askøy *Campylobacter* Outbreak Study (ASCOS), a longitudinal cohort study following a large waterborne campylobacter outbreak in Askøy, Norway in June 2019.

The aims of the studies comprising this thesis were:

Paper I: To investigate the extent of, and explore characteristics associated with, consultations for gastroenteritis in primary care and to compare consultations in daytime general practice and out-of-hours services in Norway.

Paper II: To investigate time trends and patient characteristics associated with antibiotic treatment for gastroenteritis in Norwegian primary care in a 10-year period.

Paper III: To describe the clinical features of self-reported gastroenteritis in the Campylobacter outbreak setting, and to investigate factors associated with severe gastroenteritis.

3. Materials and methods

3.1 Paper I and II

Paper I and Paper II are presented together because the same design and data material were used for both. Paper I was a registry-based cohort study using reimbursement claims data, and in Paper II these data were linked to prescription data.

3.1.1 Setting and design

3.1.1.1 Norwegian primary care

As part of the national public health care system in Norway, all residents are entitled to sign up with a specific GP. As of 2015, 99% of the population was registered to this service (102). If medical care is needed either for acute or chronic illness, patients are supposed to contact their GP. Further, the GP has responsibility for long-term care for the patients on their list. Most consultations in primary care in Norway are carried out in the general practice opening hours, including daytime emergency consultations. Additionally, emergency medical services are organized as out-of-hours (OOH) services either with general practitioners on duty in the municipalities, or as 24-hour emergency services in some of the larger cities.

The traditional consultation by the patient's physical encounter with a doctor in the surgery represent a clinical situation enabling a proper examination and adequate treatment. This was the most common form of consultation in primary care, during the study period 2006-15 although video and e-consultations have become more common in recent years, especially during the ongoing SARS-CoV-2 pandemic. As opposed to consultations, 'simple contacts' are not face to face encounters but include telephone contacts and advice, and administrative requests for such as sickness certificates or prescribing of regular medication. GPs in Norway do home visits, but to a small extent and primarily for preventive purposes and follow up of frail and elderly patients with co-morbidity. In the OOH services, home visits constituted 3.2% of the consultations in 2015 and were almost exclusively to elderly patients (103). Commercial direct-to-consumer

services outside the national public health care services were not common in Norway in the study period 2006-15.

3.1.1.2 International Classification of Primary Care (ICPC)

Each contact in primary care is coded according to ICPC. The ICPC coding system was first published in 1987 by World Organization of Family Doctors (WONCA) (104), and is accepted by the World Health Organization (WHO) as a reason for encounter classification for primary care or general practice (105). Since 1992, Norwegian primary care doctors are required to use at least one ICPC-2 code on reimbursement claims (104).

Each ICPC code consist of one letter indicating organ chapter ('D – Digestive' etc.), and two digits where 00-29 indicate symptom diagnoses and 70-99 indicate disease diagnoses (106). The first two codes in the electronic medical records are automatically copied to the reimbursement claim for each contact.

3.1.1.3 Sickness certificates

Doctors in primary care play a key role in certifying sickness absence. Most employees need documentation from a physician for sick leave exceeding three days. Sickness certification are also used for infection control purposes in certain settings. As the GPs are responsible for long-term follow-up of the patients on their lists, GPs are particularly involved in the certification and follow-up of sick leave in Norway.

3.1.1.4 Point-of-care C-reactive protein tests

Point-of-care C-reactive protein (CRP) testing is a reimbursed procedure that is widely used in general practice and OOH services in Norway, and the use is particularly high in consultations where an infection is suspected and in the OOH services (107, 108).

3.1.1.5 Prescription of antibiotics

Antibiotics are subject to prescription in Norway, and more than 80% of all antibiotics are prescribed in primary care. Respiratory tract infections is the main reason for prescribing, and narrow spectrum antibiotics are most common (97). When a physician finds treatment with antibiotics indicated, the patient will receive a prescription and then get the

antibiotics dispensed from a pharmacy. Information about the indication for treatment (diagnosis or type of infection) is not included in the prescriptions for antibiotics.

3.1.2 Source of data

3.1.2.1 Reimbursement claims database (KUHR)

It is mandatory for doctors in general practice and OOH services to send electronically reimbursement claims for all contacts to the Norwegian Health Economics Administration (HELFO) at least every 14 days.

For each contact, the reimbursement claims include information about the patient (unique personal identifier, age, and sex), type of service (daytime general practice or OOH services), date, and diagnoses (ICPC-2 codes). In addition, the reimbursement claims contain information about reimbursed procedures such as point-of-care CRP testing and issuing of sickness certificates, but there exist no codes that specifically indicate microbiological testing of stool samples.

Data from these reimbursement claims are consecutively collected in the KUHR (Control and Payment of Health Reimbursements) database, primarily for administrative purposes although widely used for research on primary care activity. The KUHR database was not defined as a national health register during the study period but was later incorporated as a central part of the Norwegian Register of Primary Care (KPR) that was established as a mandatory national health register in 2017.

In Paper I and Paper II, we used KUHR data from all consultations by attendance in general practice and OOH services for the period 2006-15. Data from consultations made by telephone or electronically, and home visits were not included in the data set extracted from KUHR. For administrative reasons, daytime activity data from the 24-hour emergency services in Bergen (the second largest city in the country with 5% of the total population) are not registered in the KUHR database, and thus not part of these sub-studies.

3.1.2.2 Norwegian Prescription Database (NorPD)

NorPD is a registry of all prescription drugs dispensed from pharmacies and one of the mandatory national health registries in Norway. NorPD was established in 2004 and the data are complete and comparable for the years after 2005. Drugs used for treatment of inpatients in hospitals and nursing homes are not registered in NorPD as they are not dispensed from pharmacies.

For each dispensation, NorPD contains information about the patient (pseudonym personal identifier, age, sex), time for the dispensation, and information about the drug (Anatomical Therapeutic Chemical (ATC) classification system).

In Paper II, we used data from the NorPD for all prescribed systemic antibiotic courses dispensed from pharmacies in Norway during the 10-year period, 2006-15.

3.1.2.3 Linking of data sets

In Paper II, the data from NorPD was linked to the KUHR data set by the patients' pseudonym unique personal identifier and proximity in time for the registered events in the two data sets.

3.1.3 Definitions of variables

3.1.3.1 Variables used in both Paper I and Paper II

Focusing on clinical cases being eligible to further examination and treatment, a 'consultation' was defined as a patient's physical encounter with a doctor. Consultations made electronically, by home visits or telephone were not included in this study.

A 'gastroenteritis consultation' was defined as a consultation with one or more of the following ICPC codes: 'D11 Diarrhea', 'D70 Gastrointestinal infection' and 'D73 Gastroenteritis, presumed infection'. These ICPC codes are defining gastroenteritis in NorSYSS (109). D11 is a symptom diagnosis and the least specific of the three, whereas of the two disease diagnoses D73 includes a presumed unspecific (not verified)

gastrointestinal infection, and D70 include symptomatic cases of all specified gastrointestinal infections.

'Type of service' was predefined by the registry, and we categorized this variable into 'general practice' and 'OOH service'.

Patient sex was predefined in the registry. Patient age was categorized into the following ten categories: 0-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84 and ≥ 85 years. Analyses for the issuing of sickness certificates were restricted to patients aged 20-67 years only.

3.1.3.2 Time variables

The reimbursement claims data were extracted from KUHR at two different occasions: 1) delivered directly to us for the use in Paper I and 2) delivered via NIPH to be prepared for the purpose of linking to the NorPD. Due to privacy concerns, the Norwegian Data Protection Authority would not accept original dates coupled with patient data. These were therefore replaced by Statistics Norway with a random reference date unique for each patient, from which the time of each registration in this dataset refers to. However, year and quarter of a year were accepted as the most detailed level of the time variable. Quarter refers to time period of year for the consultations as follows: January-March, April-June, July-September and October-December. We further categorised time period into summer (combining April-June and July-September quarters) and winter seasons (combining October-December and January-March quarters).

Due to an error, the variable 'quarter' was not included in the data set extracted from KUHR to be linked to the NorPD. Consequently, year is the most detailed level of time in Paper II, in addition to the chronological variable 'reference date'.

3.1.3.3 Antibiotics related variables (Paper II only)

A 'course of antibiotics' was defined as a course of a prescribed systemic antimicrobial drug dispensed from a pharmacy and registered in the NorPD with the following ATC codes: "J01 Antibacterials for systemic use", "A07AA09 Vancomycin" or "P01AB01

Metronidazole". We further dichotomized the antibiotics due to their relevance in treatment of gastrointestinal infections according to Norwegian and international guidelines: 'gastroenteritis relevant' included fluoroquinolones, metronidazole, macrolides, tetracycline, trimethoprim-sulphamethoxazole and vancomycin, whereas all other antibiotics were defined as 'not gastroenteritis relevant'.

Antibiotics that have urinary tract infection (UTI) as the only indication were defined as 'UTI antibiotics' (pivmecillinam, mecillinam, trimethoprim, nitrofurantoin and metenamin).

The consultation data from the KUHR database were linked to the drug prescription data from NorPD by the patients' pseudonym unique personal identifiers and the reference date variable. We extracted for further analyses all gastroenteritis consultations, and considered a course of antibiotics that was dispensed from the pharmacy at the same day or the day after one of these consultations as linked to that gastroenteritis consultation.

Hence, antibiotics defined as 'gastroenteritis relevant' or 'not gastroenteritis relevant' were included as treatment for gastroenteritis in the analyses, provided they were dispensed as described above. The exceptions were the following two categories: 1) Courses of antibiotics (both 'gastroenteritis relevant' and 'not gastroenteritis relevant') linked to consultations with a co-diagnosis (other than D11, D70 or D73) likely to explain the prescription (see Supplementary Table S1 in Paper II), and 2) courses of 'UTI antibiotics.' These courses were excluded as treatment for gastroenteritis, and consultations linked to such courses were included as gastroenteritis consultations without antibiotic treatment for gastroenteritis in the analyses (see Figure 1 in Paper II).

3.1.4 Statistical methods

Descriptive statistics were calculated as the percentage of gastroenteritis consultations out of the total number of consultations for any diagnosis in Paper I, and as the percentage of gastroenteritis consultations that were followed by antibiotic treatment in Paper II.

Patient characteristics, use of CRP and issuing of sickness certificates were compared between gastroenteritis consultations and consultations for any diagnosis, between gastroenteritis consultations with and without antibiotic treatment, and between gastroenteritis consultations in general practice and in OOH services. We explored time trends in consultations, use of CRP testing, and the use of different antibiotics as treatment for gastroenteritis. Possible associations with patient age and sex, time of year for the consultations (Paper I only), use of point-of-care CRP testing and sickness certificate issuing in the consultations were investigated by bivariate statistics.

The high numbers of observations in the data material made even small differences and associations significant at the <0.05 significance level.

The data were analyzed using Stata/MP 15.0 and Microsoft Excel 2010 for Windows in Paper I, and StataSE 16.1 and Microsoft Excel for Windows 365 MSO in Paper II, for frequency and bivariate analyses. All data have been stored, processed, and analyzed on the University of Bergen's solution for secure processing of sensitive personal data in research (SAFE).

3.1.5 Ethical approval

Paper I and II were approved by Regional Committee for Medical and Health Research Ethics REC West (project number 2016/559) and The Norwegian Data Protection Agency (project number 16/01083).

3.2 Paper III

Paper III was a population-based cohort study using data collected using an online questionnaire during a large waterborne *Campylobacter* outbreak.

3.2.1 Setting and design

On 6 June 2019, an outbreak of gastroenteritis was detected on the island municipality Askøy, which has approx. 29 500 inhabitants. More than 1 500 inhabitants reported symptoms to the outbreak investigation team, who later concluded that the drinking water

had been contaminated by *Campylobacer jejuni* at some time in late May 2019 (110). Two deaths were related to the outbreak and 67 patients were admitted to hospital (110, 111). We established a large population-based cohort study and started to invite participants by text message (SMS) and collect data using a web-based questionnaire 14 days after the outbreak was acknowledged. Ethical approval was obtained before the invitations were sent out.

3.2.2 Participants

Text message was sent by the municipality of Askøy to approx. 1 600 mobile phones in Askøy on 20 June 2019, using the municipality's warning system. The text message encouraged all household members to answer the survey. Participants of all ages were included in the study. Inclusion was closed on 1 July 2019.

Participants were asked if they were ill during the outbreak, and participants who responded 'yes' were further asked about the symptoms, whereas those answering 'no' or 'uncertain' about acute illness did not receive these questions. The study population includes all participants who were ill during the outbreak, excluding those who had not been in Askøy at the time of the outbreak.

A 'case' was defined as a participant who reported being ill with gastrointestinal symptoms during the outbreak, with symptom onset in the study period, and who experienced at least one of the following symptoms (see Figure 1 in Paper III): loose stools, diarrhea, bloody stools, abdominal pain, vomiting and nausea. A 'non-case' was defined as a participant reporting not being ill during the outbreak *or* who reported being ill but did not fulfil the symptom criteria. An 'uncertain' was defined as a participant who was uncertain whether being ill during the outbreak *or* reported being ill and fulfilling the symptom criteria but with symptom onset either before the study period or missing.

3.2.3 The questionnaire

Paper III is based on data from the baseline survey out of totally four surveys in the Askøy ***Campylobacter*** Outbreak Study (ASCOS), a longitudinal cohort study following

the outbreak. The content of the questionnaire was based on existing literature and chosen to both describe the ongoing outbreak and to serve as baseline for topics in the follow-up surveys.

A paper version of the web-based questionnaire can be found in Appendix. In addition to status regarding illness and whereabouts during the outbreak (accounted for under the above section '3.3.2 Participants'), the following topics from the questionnaire were relevant to Paper III: the acute disease (symptoms, duration of each symptom, duration of disease and perceived severity), management (use of health care services and medication) and consequences of the disease (absence from work or school), age, sex, educational level, employment situation, marital status, household total income, self-reported previous diseases, intake of glasses with tap water during the week prior to outbreak, intake of alcohol units during a normal week and tobacco use.

3.2.4 Variables

We defined the outcome 'severe gastroenteritis' as cases reporting diarrhea for ≥ 5 days *and* at least one of either fever for ≥ 2 days or bloody stools. This outcome variable was based on existing literature (71, 76, 78, 79), as well as clinical experiences and expertise among members in the research group and aimed to capture a set of symptoms which indicated a greater extent of both local inflammation in the bowels and more generalized disease. Thus, the 'severe gastroenteritis' outcome was defined independently of the variable 'perceived severity' which covered self-assessed perceived severity at the worst time point during the acute illness.

We defined two different categorical variables for age, with three (0-24, 25-54 and ≥ 55 years) and 10 categories (0-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84 and ≥ 85 years), respectively. We categorized duration of illness into 0-3, 4-7, 8-14 and ≥ 15 days. Tobacco use was dichotomized, and alcohol units were categorized into the following six categories: 0, 1-2, 3-5, 6-9, 10-14 and ≥ 15 units per week. For the analyses of alcohol and tobacco use we included participants ≥ 16 years only, and the analyses of

educational level, employment situation and marital status, were restricted to participants ≥ 18 years.

There was a high proportion of missing data for the variables age and sex in the baseline survey (29% and 26% respectively). However, we were able to add data from the follow-up surveys for 580 and 507 participants, respectively. Thus, in the final study population there were 13% missing age and 12% missing sex information.

3.2.5 Analyses and statistical methods

Differences between proportions in cross tables were tested with Pearson's x^2-test for associations. For the outcome severe vs non-severe gastroenteritis, we estimated relative risks (RR) using a modified Poisson regression model (112) since this was a cohort design with a common outcome (23.7%). Confounding was investigated, and adjusted for when appropriate, in the regression models. Level of statistical significance was set at $p<0.05$.

We used the online questionniare tool SurveyXact by Rambøll. The software R, StataSE 16.1 and Microsoft Excel for Windows 365 MSO were used for processing and analyzing the data. All data have been stored, processed, and analyzed on the University of Bergen's solution for secure processing of sensitive personal data in research (SAFE).

3.2.6 Ethical approvals

Paper III was approved by Regional Committee for Medical and Health Research Ethics REC West (project number 2019/1086). Consent from parents was needed for participants under the age of 16 years.

4. Results

4.1 Paper I

Over the period 2006-15, there were 1 281 048 gastroenteritis consultations in Norwegian primary care of which 84.4% (n=1 081 774) were in general practice and 15.6 % (n=199 274) in the OOH services. This constituted 0.9% of all consultations for any diagnosis in primary care, and 0.5% and 1.6% of consultations in general practice and the OOH services, respectively.

The patients in the gastroenteritis consultations were dominated by young children aged 0-4 years (n=272 460, 21.3%) and young adults aged 25-34 years (n=210 226, 16.4%), which was also observed in both general practice and the OOH services.

Mean annual number of gastroenteritis consultations was 128 104. There was an overall 10.3% increase in number of gastroenteritis consultations from 120 624 in 2006, to 133 091 consultations in 2015. Due to an even higher increase in consultations for any diagnosis over the same period (25.3% increase), the proportion of gastroenteritis consultations decreased slightly from 1% in 2006 to 0.9% in 2015. The population of Norway increased by 11.3% from 2006 (n=4 640 219) to 2015 (n=5 165 802) (113).

We observed a bi-annual cycle of both the number and proportion of gastroenteritis consultations through the whole period, a pattern of variation most pronounced for the age category 0-4 years in both service types. After organizing the data according to winter and summer seasons, as the shift of the year split each winter season, these analyses did not show a similar bi-annual cycle from one winter season to the next.

We observed variations in gastroenteritis consultations frequencies peaking during January-March (29.3 %) followed by October-December (25.0 %), both in general practice and OOH services. This seasonal variation was most evident for the age categories 0-4 years, 5-14 and 25-34 years, whereas for other age groups the number of

gastroenteritis consultations in both service types were more equally distributed through the quarters.

Point-of-care CRP testing was used in 36.1% of the gastroenteritis consultations, 32.2% of the consultations in general practice and 57.4% in the OOH services.

Among patients in the working age (age group 20-67 years), sickness certificates were issued in 43.6% of the gastroenteritis consultations; 45.9 % in general practice and 24.6 % in OOH services.

4.2 Paper II

A course of systemic antibiotics was dispensed from the pharmacies within 1 day after 30 5054 of totally 1 279 867 gastroenteritis consultations in Norway in the period 2006-15. As mentioned in the methods section, we did not include the following linked antibiotic courses as treatment of gastroenteritis (see Figure 1 in Paper II): 1) gastroenteritis consultations with a co-diagnosis more relevant to the prescription (n=3 956) of which 2 076 were an R-diagnosis in ICPC-2, indicating a respiratory tract infection, and 1) gastroenteritis consultations linked to courses of UTI antibiotics (n=2 926). Consequently, there were a total of 23 663 gastroenteritis consultations with antibiotic treatment which constitutes a 1.8% antibiotic treatment proportion. In general practice the antibiotic treatment proportion of gastroenteritis consultations was 1.8% (n=19 617), and 2.0% (n=4 046) in the OOH services.

We observed an increase in the antibiotic treatment proportion of the gastroenteritis consultations from 1.4% in 2006 to 2.2% in 2012, then decreasing to 1.8% in 2015. A similar pattern was observed for the absolute number of gastroenteritis consultations with antibiotic treatment.

The lowest proportion of antibiotic treatment was observed in gastroenteritis consultations with the youngest children aged 0-4 years (1.0%), then increasing with increasing age up to the highest treatment proportions (3.0%) in gastroenteritis consultations with patients in

the two age categories 55-64 and 65-74 years. This trend was even more pronounced in the OOH-services, with a peak antibiotic treatment proportion of 4.6% in gastroenteritis consultations with patients aged 55-64 years.

CRP testing was used in 58.1% of the gastroenteritis consultations with antibiotic treatment, as compared to 35.7% without antibiotic treatment, and was more frequently used in OOH services than in general practice in both gastroenteritis consultations with (OOH services 72.4% vs. general practice 55.1%) and without (OOH services 57.1% vs. general practice 31.7%) antibiotic treatment.

We observed an increase in proportion of CRP testing in gastroenteritis consultations from 2006 (52.4%) to 2012 (60.8%), but then remained stable at approx. 61% until 2015.

The 23 663 gastroenteritis consultations with antibiotic treatment were linked to 25 956 antibiotic courses, as 90.3% (n=21 378) were linked to single courses, 9.6% (n=2 277) to two courses, and 0.03% (n=8) to three antibiotic courses.

Of these 25 956 antibiotic courses, the most frequently used were fluoroquinolones (28.9%), metronidazole (26.8%), beta-lactamase sensitive penicillins (10.8%) and macrolides (10.4%), although beta-lactamase sensitive penicillins were defined as 'not gastroenteritis relevant.'

From 2006-12, there was an increase in the number of courses of the 'gastroenteritis relevant' fluoroquinolones (128% increase), metronidazole (92.1% increase), sulfamethoxazole/trimethoprim (68.6% increase), tetracyclines (50.7% increase) and macrolides (64% increase). From 2012-15 there was a decrease in number of courses of all these antibiotics, except for metronidazole which continued a slight increase.

The most frequent combination among the 2 277 double courses was metronidazole and fluoroquinolones (38.1%, n=868), followed by metronidazole and extended spectrum penicillins (27.3%, n=621), metronidazole and tetracyclins (15.8%, n=359), and metronidazole and macrolides (9.5%, n=116).

4.3 Paper III

Of the 8681 individuals who accessed the web site with the questionnaire, 3885 answered the questionnaire (see Figure 1 in Paper III). Two-hundred-and-sixty-one participants who either stated they had stayed outside Askøy (n=209) or with missing information whether they had been ill during the outbreak (n=52) were excluded, leaving a study population of 3624 participants. Of these, 749 (20.7%) were cases, 2417 (66.7%) non-cases and 458 (12.6%) were uncertain.

The most frequently reported symptoms were tiredness (91.2%), loose stools (90.7%), abdominal pain (89.3%) and diarrhea (88.9%). Bloody stools (14.2%) was the least frequently reported symptom, and were most common in cases aged 0-25 years (25.6%) although none of these were under the age of 15 years. Joint pain was reported by 50.2%.

The duration of illness ranged from 0 to 24 days (median = 6 days). For treatment of the acute illness, paracetamol (62.8%) followed by non-steroidal anti-inflammatory drugs (NSAIDs) (31.8%) were the most commonly used medication. Twenty-one cases (n=21) had been treated with antibiotics, but none of these cases were under the age of 15 years. Antibiotic treatment was more common among hospitalized patients (30.3%, n=10) than those not hospitalized (1.5%, n=11).

Twenty-seven per cent (n=203) of the cases reported to have consulted a primary care doctor, and 4.2% (n=33) had been admitted to hospital. None of the hospitalized cases in the survey were under the age of 15 years.

Twenty-four per cent of the cases (n=177) fulfilled the definition of ‘severe gastroenteritis’. Cases with severe gastroenteritis more often reported drinking > 5 glasses of tap water (41.2% vs 30.4%, p=0.02), previous gastric ulcer disease (13.6% vs 2.3%, p=0.01) and previous depression (16.9% vs 10.3%, p=0.02), compared to cases with non-severe gastroenteritis. In the adjusted modified Poisson regression analyses, previous depression (RR: 1.61, 95% CI 1.16-2.24) and previous peptic ulcer disease (RR: 1.73, 95% CI 1.00-2.99) remained as statistically significant risk factors for severe

gastroenteritis. Further, age 55-64 years (RR: 0.62, 95% CI 0.41-2.46) and 35-44 (RR: 0.52, 95% CI 0.35-0.77), were associated with a lowered risk of severe gastroenteritis as compared to the reference age category 45-54 years, although the RR for age 55-64 years was not significant in the unadjusted regression model.

5. Discussion

5.1 Scientific theoretical considerations

The core of this thesis is 'gastroenteritis', which is a generic term that encompasses a variety of different infections and conditions. The variety in use of different generic terms (gastroenteritis, acute diarrhea, infectious diarrhea, infectious intestinal disease etc.) and in methodological approaches by infection specific studies (population-based, notified sporadic cases, outbreak investigation studies etc.) have made the comparison of our results with relevant background literature challenging.

Gastroenteritis occurs frequently in the population, and most of us have experienced at least one episode in our life. Thus, there is a common sense, both in the community and among health care professionals and researchers, of what gastroenteritis is, although not necessarily referring to the term. Consequently, it can be challenging to choose the best scientific documentation to refer to when it comes to matters that are largely common sense.

From a scientific theoretical point of view, it is interesting to note that most of the literature on clinical features of *Campylobacter* infections was published in the 1970s and through the 1980s, shortly after the bacteria was acknowledged as a pathogen to humans. These descriptions of clinical features define what is considered typical for *Campylobacter* infections, which in turn affects whether the clinicians' suspect the infection and thus becomes important for management when it comes to testing, notification, and treatment. A self-reinforcing process arises where you may find what you are looking for.

5.2 Methodological considerations

5.2.1 Paper I and Paper II

The main strength of these two registry-based cohort studies is the use of complete registry data for nearly all consultations in general practice and OOH services, and all

courses of systemic antibiotics dispensed from pharmacies in Norway during a ten-year period from 2006-15. This reduces selection bias considerably. The use of comparable data for a 10-year period provides a unique opportunity to study trends in contact patterns in primary care and use of antibiotics for gastroenteritis.

5.2.1.1 Two different data sets extracted from KUHR

The reimbursement claims data were extracted from KUHR at to different occasions, and this had some consequences. First, there is a discrepancy of 1 181 in total number of gastroenteritis consultations in the two data sets. We assume that the difference is either by corrections or adjustments in the KUHR data base between the two extractions, a result of randomly different outcomes of data management and processing (such as handling of duplicates), or a combination of the two. The discrepancy is relatively small (0.09%) and we could not identify any systematic differences or deviations between the two data sets. Second, the variable 'quarter of a year' was not included in the data set that was linked to the NorPD data. Consequently, we could not look at possible seasonal variation in prescribing.

5.2.1.2 Consultations in primary care

A part of the reimbursement claims from the 24-hour emergency services in Bergen (daytime consultations from workdays) are not included, leading to a minor underreporting of consultations in the OOH services. This study was designed to investigate the face-to-face consultation activity concerning gastroenteritis, focusing on clinical cases being eligible to further examination and treatment. Thus, claims from electronic/telephone consultations or home visits were not included in the current study. We expect that the use of telephone consultations is considerable, due to the nature of gastroenteritis as a contagious disease. But these are probably dominated by requests for sick leave or similar administrative purposes, and also more prone to misclassification of disease on reimbursement claims (114). The lack of telephone consultations and home visits may challenge the external validity specifically in the context of syndromic surveillance, as our findings do not reflect the total activity in primary care. However,

telephone contacts may be used in the follow up of patients, and if these contacts result in the prescription of antibiotics these courses would be missing in our study.

5.2.1.3 Precision of the time variable

Another limitation is the lack of precision in the time variable. For the analyses of seasonality in Paper I, we should ideally have had information about the exact date or week number for the consultations.

5.2.1.4 Classification of disease

Possible misclassification of the disease (gastroenteritis) may challenge the internal validity. Our definition of a gastroenteritis consultation included the two disease diagnoses D70 'Gastrointestinal infection' and D73 'Gastroenteritis presumed infection', and the symptom diagnosis D11 'Diarrhea'. This definition is in line with the Norwegian Syndromic Surveillance System (25), and was also used in a recently published study of antibiotic treatment for gastroenteritis in the Netherlands (88). The ICPC symptom diagnosis D10 'Vomiting' was not included in the definition, although it is a common symptom in gastroenteritis it is probably less specific. As a result, consultations for diarrhea of other causes than gastroenteritis are included, but gastroenteritis consultations coded with D10 'Vomiting' are missed. To my knowledge, studies on the validity of these diagnoses and the diagnostic algorithm are lacking. Reimbursement claims data have been shown to be informative in monitoring disease activity in primary care and promising in syndromic surveillance of gastrointestinal disease (29, 115, 116).

Incorrect diagnosis coding in primary care is common (104), but the ICPC diagnoses correspond better with the patient record notes for consultations than for simple contacts with issuance of prescriptions (114). Different coding behavior in general practice and OOH services, as well as specific diagnosis being chosen to justify actions such as issuing sickness certificates or prescribing antibiotics, may cause differential misclassification (117) which must be taken into considerations when interpreting the data.

5.2.1.5 Antibiotics as treatment for gastroenteritis

In Paper II, we used antibiotics data based on courses dispensed from the pharmacies (as registered in NorPD). We do not have access to information about prescriptions, and thus do not know the indications for the treatment. Consequently, the indirect linking of dispensing to consultations may lead to possible misclassification of antibiotics as treatment for gastroenteritis. As a measure to minimize this, we did not include the following dispensations as treatment for gastroenteritis: 1) courses of antibiotics linked to consultations with co-diagnoses more likely to represent the real indication for the prescription, 2) courses of UTI antibiotics. Despite these measures, we believe that our study will include dispensed antibiotics that have been misclassified as treatment for gastroenteritis. The reason for this is that relevant co-diagnoses may not have been registered in the consultation, or the course might have been prescribed in consultations not included in the data material, such as telephone consultations, home visits, consultations with doctors outside primary care, or in consultations taking place between the gastroenteritis consultation and the dispensation. Lastly, antibiotic courses may also have been incorrectly defined as treatment for gastroenteritis if the consultation was misclassified as a gastroenteritis consultation.

5.2.1.6 Gastroenteritis consultations instead of episodes

The entity in Paper I and Paper II was gastroenteritis consultation, not gastroenteritis patient/case or gastroenteritis event. As a patient could have had several consultations during one gastroenteritis event, the results cannot be used for estimating the prevalence of gastroenteritis in the Norwegian population nor in primary care, nor can they be used to precisely estimate the extent of absence from work due to gastroenteritis.

5.2.2 Paper III

The main strength of this population-based cohort study was that data were collected during the acute phase of a large outbreak. This reduces recall bias considerably and constitutes a solid basis for follow-up studies of post-infectious complaints after the outbreak.

5.2.2.1 Text message approach and selection bias

The text message was sent by the municipality of Askøy on behalf of our research group. We do not know the exact number of text messages sent, how many who received the text message or, even less, how many were presented with the content of the message as all household members of the text message recipients were invited to participate. Consequently, we were not able to calculate an exact response rate for our survey.

Selection bias is error due to systematic differences in characteristics between those who participate in a study and those who do not, and challenges the validity and generalizability of a study (118). Because the characteristics of non-participants are unknown to us, the presence of selection bias must be assumed (117). Selection bias leading to underrepresentation of children is suggested by our previous finding of 17 patients under the age of 16 years in the study that characterized hospitalized patients during the same outbreak (111), whereas the present study includes no hospitalized cases under the age of 15 years.

5.2.2.2 The consequences of time urgency

This study of acute disease during an unforeseen waterborne outbreak could not have been planned in advance. We set up the study, got ethical approval and started data collection within two weeks after the outbreak was publicly known. This is a major strength of this study, but we later discovered some errors or limitations in the questionnaire: 1) unprecise phrasing of the questions regarding use of medication prior to the outbreak, 2) participants who were uncertain whether they were ill during the outbreak were not asked questions about symptoms. Consequently, we could not use the data on previous medication, nor categorize the uncertain group as cases or non-cases based on symptoms, as planned.

5.2.2.3 Missing data

Participants were per protocol asked to provide their national identity number, to allow for linkage with national health registries. As this was optional it turned out that many

chose not to give this information. Consequently, information about age and sex were missing for a considerable proportion of participants, as these data were extracted from the national identity number. All participants were asked about age and sex in later follow-up and we were able to update our database based on those answers.

The group that was uncertain whether they had been ill had the greatest proportion of missing data for most variables, representing a group with more uncertain answers overall, whereas cases had the lowest proportion of missing data.

5.2.2.4 Lack of clinical and microbiological data

The study did not include any data from medical records or microbiological investigations. Thus, cases were neither verified by a clinician's diagnosis nor by laboratory results. Using this population-based approach made it possible to investigate a broad spectrum of symptoms of gastroenteritis during a *Campylobacter* outbreak, but there is a risk that some cases were misclassified. Still, we believe that the main findings describe acute campylobacteriosis, as we expect a low probability for other causes of the gastroenteritis symptoms experienced by the cases in our study.

Because we did not have variables to verify exposure to *Campylobacter*, such as detailed information on the drinking water supply, we could not investigate potential risk factors for developing acute disease during the outbreak.

5.2.2.5 Definitions of 'case' and 'severe gastroenteritis'

To our knowledge, there exist no common, symptom-based definitions of campylobacteriosis, gastroenteritis nor 'severe gastroenteritis' that are widely used for research purposes. Thus, our case definition was a modification of case definitions used in previous studies (15, 68, 69, 119), based on the participants' self-reported information about their geographical presence, onset of illness and symptoms related to the outbreak. The symptom criteria in the case definition were quite wide, enabling the investigation of a broad spectrum of illness during the outbreak. Although this likely led to high sensitivity, it may have resulted in a lower specificity.

The definition of 'severe gastroenteritis' was based on existing literature (71, 76, 78, 79), as well as clinical experiences and expertise among members in the research group, with the purpose to capture a greater extent of both local inflammation in the bowels (diarrhea for ≥ 5 days or bloody stools) and more generalized disease (fever > 2 days). We observed an association between this symptom-based 'severe gastroenteritis' outcome with both the self-reported perceived severity variable, and with the health care use variables, which to some extent suggests that our definition is valid.

As the two definitions are based on self-reported symptoms, and 12% of the study population were uncertain whether they had been ill during the outbreak, we acknowledge that some participants probably have been misclassified (non-differentially) as 'cases' and with 'severe gastroenteritis' in our study.

5.3 Interpretation of main findings

5.3.1 Paper I

The main findings in Paper I were that gastroenteritis consultations constitute 0.9% of all consultations in Norwegian primary care. There was a small increase in absolute number of gastroenteritis consultations, during the years 2006-15, that corresponds mainly with the increase in the Norwegian population during the same period. We observed a bi-annual variation in gastroenteritis consultations, but this was not seen when organizing the data according to winter-summer variation. This likely reflects whether the main impact of winter vomiting disease (probably norovirus) hit the population before or after the shift of each year.

Our study included consultations for gastroenteritis due to all possible pathogens. But the observed pattern of seasonality was in line with that known for norovirus infection on the European continent (120). The assumption that a majority of the consultations were due to norovirus infection, is supported by our findings of high consultation numbers for gastroenteritis among young children, and that the boys dominated in those under the age of 15 years, which are in line with a Dutch study of norovirus infection in primary care

(29). Studies from Sweden (6) and the UK (3, 121) also present highest consultation rates among the youngest children. Further, young adults were the second most common patient group, suggesting transmission between child and carer supported by findings from an Australian population-based study of the risk of gastroenteritis (34). Rotavirus infection should be considered as one major cause of gastroenteritis among children under 2 years of age, and a Norwegian study of hospitalized children reported rotavirus infections peaking in March through May (32). Rotavirus vaccination was introduced in Norway in 2014, at the end of our study period, thus we were not able evaluate any potential effect of the vaccine introduction based on one year of observations only.

5.3.2 Paper II

The main finding of Paper I was that the antibiotic treatment proportion in consultations for gastroenteritis in Norway was 1.8%. This is lower compared to findings presented in literature from other high-income countries (86-89, 122). Possible explanations for this may be low levels of bacterial and parasitic gastrointestinal infections in Norway, relative to viral infections (60, 123). Other explanations can be different health care seeking behavior, or that gastroenteritis cases with high risk of severe illness in Norway are hospitalized for treatment rather than managed in primary care. Of note, Norway generally has a low consumption of antibiotics (85).

The antibiotic treatment proportion was higher in the OOH services compared to general practice, corresponding with studies from other European countries indicating higher antibiotic prescription rates in OOH services than in general practice for several infections (124-126). Possible reasons for this may be that the OOH services to a lesser extent offer follow-up, see patients with more severe illness and patients who, for various reasons, to a lesser extent are followed up by a GP.

We observed a 16% reduction in antibiotic use in gastroenteritis consultations after year 2012. This trend coincides with an observed reduction in the total use of antibiotics (11%

reduction) in Norway during the same period (127), and is in accordance with the goals of the Norwegian Action Plan from 2015 (101).

Our finding of fluoroquinolones and metronidazole as the most frequently used antibiotics in the gastroenteritis consultations corresponds with findings in studies from primary care in the Netherlands, Switzerland and England (88, 122, 128). We have no explanations for the continuous increase in the use of metronidazole in gastroenteritis consultations after 2012. However, as *C. difficile* infection has been notifiable to the Norwegian notification system (MSIS) after 2012 (129), and metronidazole is the first line treatment in primary care (25, 92), one could speculate whether this could be a contributing factor. Indeed, the number of *C. difficile* cases notified to MSIS did increase from 2013 (n=351) to 2015 (n=2641), and appr. 35% were notified by GPs (129, 130). But still, the real incidence of *C. difficile* infections in Norway is uncertain due to non-compliance with the reporting obligation from the laboratories (43, 130).

We found a lower prescription proportion among the youngest patients, a finding in line with a recent study from the Netherlands (88). This may be explained by higher gastroenteritis consultation frequency, and the higher likelihood of viral aetiology in younger patients, as accounted for in Paper I.

Betalactamase sensitive penicillins were the third most frequently used, which may be surprising as they are not suitable for treatment of any gastrointestinal infections and thus defined as 'not gastroenteritis relevant' in our study. Compared to existing literature, a study of antibiotic treatment for gastroenteritis in primary care in the Netherlands did not include prescriptions of betalactamase sensitive penicillins (88), and betalactamase sensitive penicillins were found to account for 1.3% of antibiotic prescriptions for infections in the gastrointestinal tract in a study from the UK (128).

A highly probable explanation to the frequent use of 'not gastroenteritis relevant' in our study is misclassification of disease and/or antibiotic treatment for gastroenteritis. Further, as 50% of the treatments with betalactamase sensitive penicillins were linked to patients

under 15 years of age, this may reflect more misclassification of disease in these age categories: Children pose a greater diagnostic challenge with high levels of co-infections and uncertain symptoms and findings. However, we cannot rule out the possibility that some doctors inappropriately prescribed the drug as a first line drug with the intention to treat gastroenteritis, as they are strongly advocated as the first choice antibiotics in treatment for several other infections commonly seen in primary care.

Our finding of extensive use of CRP testing in gastroenteritis consultations with antibiotic treatment, adds to the findings in previous studies describing an extensive use of CRP testing in Norwegian primary care, especially in consultations with patients with suspected infection and in OOH services (107, 108, 131). Our study cannot explain this finding, as it did not include clinical information such as test results or information whether the tests affected the decision whether to prescribe antibiotics.

5.3.3 Paper III

The finding in Paper III of diarrhea and abdominal pain as the most common, and bloody stools and vomiting as the least common symptoms of acute gastroenteritis in the outbreak setting, is in line with previous literature on *Campylobacter* infection (59, 68, 70, 72, 73, 77). Tiredness is a symptom that is non-specific to gastroenteritis, but still frequently reported in our study. We could not find descriptions of tiredness in published studies, probably because it is unspecific to gastroenteritis or *Campylobacter* infection. However, documenting the baseline level of the symptom at the time of the outbreak is useful to follow-up studies of post-infectious complaints, and should perhaps be investigated further in future outbreaks.

We found a lower proportion of bloody stools among cases in our study (14%) compared to proportions ranging from 30-58% in studies of laboratory confirmed cases in general practice in the Netherlands (72), of sporadic notified cases in Norway (73), of laboratory confirmed cases aged 0-14 years in an outbreak in Greece (132), and notified cases in Australia, Canada and the United States (77). The latter study also reported association

between age and bloody stools, that corresponds to our finding, although their proportions of bloody diarrhea among the youngest (59% in age < 5 years, 49% in 5-24 years) were higher than in our study (25.6% aged < 25 years, but none < 15 years).

On the other hand, the proportion of bloody stools was higher in our study compared to two previous outbreak investigation studies: a population-based study of an outbreak in Røros, Norway (2%) (68), and in a study of cases included among patients seeking health care services (of which 16% were laboratory confirmed) during an outbreak in Finland (4%) (70). A reason for lower proportions of bloody stools reported in outbreak studies, including the present study, may be that they capture a broader scope of clinical features than represented by the laboratory confirmed cases. However, virulence factors associated with bloody stools of the different strains of *Campylobacter*, cannot be ruled out (111).

Additionally, our finding was higher compared to the two previously published studies of the Askøy outbreak: NIPH's population-based outbreak investigation study (6%) (68) and the study of hospitalized cases (9%) (110, 111). An explanation for a lower proportion of bloody stools observed in the latter study, can be a possible lowered threshold for referral due to fatal outcome in the initial phase of the outbreak, thus leading to hospitalization of less severe cases (111). The fact that NIPH's outbreak investigation study was conducted at the very beginning of the outbreak only, and started a week earlier than our study, may be partly explain why NIPH found lower proportion of bloody stools as this symptom usually develops during days after infection.

In our study, joint pain was more common compared to the findings in a Norwegian study of sporadic campylobacteriosis from 1992 (50% vs. 27%) (73), but otherwise seems to be scarcely described as a symptom during the acute phase of *Campylobacter* infection in existing literature.

Median duration of illness observed in our study (6 days) is consistent with what is commonly reported in previous studies (5-6 days) (68, 70, 77), except for the Norwegian study of sporadic cases from 1992 reporting median 11 days duration (73).

A total of three per cent, none under the age of 15 years, and 30% of the hospitalized cases in our study were treated with antibiotics, whereas the study of hospitalized patients during the same outbreak found that one in two of children and one in ten of adults received antibiotics (111). A Norwegian study from 1992 reported that 16% of 135 sporadic laboratory confirmed cases in Norway were treated with antibiotics (73), White et al. 2019 reported an antibiotic treatment proportion of 35% in culture confirmed cases in Australia, Canada and the United States (77). However, neither of these previous studies discriminated between treatment proportions in hospitalized and non-hospitalized patients. The low antibiotic treatment proportion found in our study is in line with the Norwegian recommendations, and with a generally cautious policy regarding use of antibiotics in Norway (25, 71, 92, 97).

In Paper III, we identified high consumption of tap water, having depression or peptic ulcer prior to the outbreak as risk factors associated with severe gastroenteritis, whereas being in the age category 35-44 seemed to be protective. The association between high consumption of tap water and severe gastroenteritis is not surprising as the outbreak was waterborne, and probably indicates a dose response relationship. The association between depression and severe gastroenteritis is supported by a previous study showing that psychological comorbidity increased susceptibility to develop gastroenteritis during a waterborne outbreak in Belgium (84). However, bias may lead to reporting of more severe symptoms in cases with self-reported depression, as the symptom pressure can be perceived as more burdensome in this patient group. Peptic ulcer as a risk factor for severe illness is reasonable, as a gastrointestinal disease, and not least presumably often treated with anti-acidic medication which may cause vulnerability to a more severe illness.

6. Conclusion

Through the three sub-studies that comprise this thesis, we have documented that gastroenteritis consultations in Norwegian primary care exhibit an epidemiological pattern and seasonal variation in line with a dominance of viral infections.

Antibiotic treatment is infrequently used in gastroenteritis consultations in Norway. There was a decrease in overall use of antibiotics in gastroenteritis consultations after 2012, which coincides with an observed reduction in the total use of antibiotics due to any cause in Norway during the same period.

The clinical features of self-reported acute gastroenteritis during a large waterborne *Campylobacter* outbreak exhibits a broader spectrum of symptoms than the descriptions in existing literature of *Campylobacter* infections.

7. Further research

Future research to further improve the understanding of management of gastroenteritis patients in primary care should include clinical data from consultations, such as symptoms and severity of illness, travel history, information about stool sampling and results and antibiotic prescribing.

Also, further research is needed to investigate any benefits of point-of-care CRP testing for management of gastroenteritis patients, including whether the tests affect the decision whether to prescribe antibiotics.

More detailed information about time and geography of the consultations would be useful in future studies of the syndromic surveillance and antibiotic treatment of gastroenteritis.

By including information that verifies exposure to the source of infection, research studies on future gastroenteritis outbreaks can investigate risk factors for developing acute illness in the outbreak setting.

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PAPERS I-III

Including supplementary material

PAPER I

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Health Service Research

Consultations for gastroenteritis in general practice and out-of-hours services in Norway 2006–15

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Abstract

Background. Most of the patients with gastroenteritis seeking health care services are managed in primary care; yet, little is known about these consultations. Syndromic-based surveillance of gastrointestinal infections is used in several countries, including Norway.
Aim. To investigate the extent of, and explore characteristics associated with, consultations for gastroenteritis in primary care and to compare consultations in daytime general practice and out-of-hours (OOH) services in Norway.
Design and Setting. Registry-based study using reimbursement claims data from all consultations in general practice and OOH services in Norway over the 10-year period, 2006–15.
Methods. The main outcome variable was whether the consultation took place in general practice or OOH services. Possible associations with patient age and sex, time and use of point-of-care C-reactive protein (CRP) testing and sickness certificate issuing were investigated.
Results. Gastroenteritis consultations (n = 1 281 048) represented 0.9% of all consultations in primary care (n = 140 199 637), of which 84.4% were conducted in general practice and 15.6% in OOH services. Young children and young adults dominated among the patients. Point-of-care CRP testing was used in 36.1% of the consultations. Sickness certificates were issued in 43.6% of consultations with patients in working age. Age-specific time variations in consultation frequencies peaking in winter months were observed.
Conclusions. The proportion of gastroenteritis consultations was higher in the OOH services when compared with daytime general practice. Young children and young adults dominated among the patients. The seasonal variation in consultation frequency is similar to that shown for gastroenteritis caused by norovirus.

Key words: Epidemiology, gastroenteritis, general practice, health services research, primary health care.

Background

Gastroenteritis is an inflammation of the gastrointestinal tract caused by a pathogenic microbe. A common, symptom-based definition of a gastroenteritis case is an individual who experiences ≥3 loose stools, or any vomiting, in 24 hours, excluding cases where these symptoms are explained by known noninfectious reasons (1). Gastroenteritis is one of the leading causes of morbidity and mortality in low-income countries (2). In high-income countries, gastroenteritis is rarely lethal, and most patients experience self-limiting symptoms without seeking medical care (3–6). Still, in these countries, gastroenteritis has considerable socioeconomic costs (3, 7) and is of public health interest as the condition tends to appear in outbreaks (8–10).

Key Messages

- Consultations for gastroenteritis represented 0.9% of all consultations.
- Young children and young adults were the most common patients.
- Number of consultations for gastroenteritis was higher in winter months.

The agents causing gastroenteritis include a variety of viruses, bacteria, parasites and toxins. Stool samples are generally not submitted from primary care as most infections resolve in a few days without treatment. When stool samples are submitted, the infective agent is most commonly either viral or not identified (11–14). Spread of infections through international travel is of concern (15), and several of the microbes known to cause gastroenteritis are on the WHO priority list of antibiotic-resistant bacteria (16). Previous studies describe trends in seasonality for different agents causing gastroenteritis (17–23), although studies of seasonal trends in gastrointestinal infections in primary care are lacking.

Infectious disease surveillance systems are traditionally based on laboratory-confirmed cases. However, near real-time syndromic-based surveillance systems based on data from primary care that are not laboratory confirmed are established in several European countries, including Norway (24, 25). In the Norwegian Syndrome Surveillance System (NorSySS), gastroenteritis is defined by the ICPC diagnoses 'D11 Diarrhoea', 'D70 Gastrointestinal infection' and 'D73 Gastroenteritis, presumed infection'.

Most of the consultations in primary care in Norway are carried out in the general practice surgery during opening hours, including daytime emergency consultations. Additionally, emergency medical services are organized as out-of-hours (OOH) services either with general practitioners on duty in the municipalities, or as 24-hour emergency services in some of the larger cities.

When individuals with gastroenteritis seek health care, they are generally managed in primary care. Yet, little is known about these consultations in terms of prevalence in primary care, patient characteristics and seasonal variations. Scientific knowledge about gastroenteritis in primary care is useful for clinicians, public health professionals interpreting surveillance data and for health service planners.

The aims of this study were to investigate the extent of, and explore characteristics associated with, consultations for gastroenteritis in primary care and to compare consultations in daytime general practice and OOH services in Norway.

Materials and methods

All residents in Norway are entitled to have a general practitioner (GP) as part of the national public health care system. The GPs are the first port of call, provide comprehensive care and act as gatekeepers to secondary care. Point-of-care C-reactive protein (CRP) testing is widely used in general practice and OOH services in Norway.

Doctors in general practice and OOH services send reimbursement claims electronically to the Norwegian Health Economics Administration (HELFO). The reimbursement claims include information about the doctor (ID-number) and patient (unique personal identifier and sex), date and time for the contact and diagnoses for each contact. The reimbursement claims also contain information on actions such as point-of-care CRP testing and issues of sickness certificate as part of the individual consultations, as these actions are reimbursed.

The data from the reimbursement claims are registered prospectively in real-time and collected in the national KUHR database. In this study, we used data from KUHR from all consultations by attendance in general practice and OOH services during the 10-year period, 2006–15. Daytime activity data from work days from the 24-hour emergency services in Bergen (the second largest city in the country) are not included in this study, as they are not registered in the KUHR database.

Variables

We defined a consultation as a patient's physical encounter with a doctor, focusing on clinical cases being eligible to further examination and treatment. Consultations made electronically, by home visits or telephone were not included in this study. We defined a 'gastroenteritis consultation' as a consultation with one or more of the following ICPC codes: 'D11 Diarrhoea', 'D70 Gastrointestinal infection' and 'D73 Gastroenteritis, presumed infection', which are the codes defining gastroenteritis in NorSYSS (25).

The registry predefines type of service, and we could further categorize this variable into 'general practice' and 'OOH service'. We categorized patient age into the following ten categories: 0–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years. Patient sex is predefined in the registry. Due to privacy concerns, the Norwegian Data Protection Authority would only accept quarter of a year as the most detailed level of the time variable for this study. Quarter refers to time period of year for the consultations as follows: January–March, April–June, July–September and October–December. We further categorized time period into summer (combining April–June and July–September quarters) and winter seasons (combining October–December and January–March quarters). For the analyses of sickness certificate issues, we included consultations with patients aged 20–67 years only.

Statistics

The data were analysed using Stata/MP 15.0 for Windows and Microsoft Excel 2010 for frequency and bivariate analyses.

We calculated the proportion of gastroenteritis consultations as the percentage of total consultations for any diagnosis. The main outcome variable was whether the consultations took place in general practice or in the OOH services. Possible associations with patient age and sex, time of year for the consultations, use of point-of-care CRP testing and sickness certificate issuing in the consultations were investigated by bivariate statistics. The high numbers of observations in the data material made even small differences and associations significant at the <.05 significance level.

Results

Over the 10-year period, 2006–15, there were 140 199 637 consultations in primary care in Norway. Of these, 127 389 382 (90.9%) were in general practice and 12 810 255 (9.1%) in OOH services. There were 1 281 048 gastroenteritis consultations: of these 1 081 774 (84.4%) were conducted in general practice and 199 274 (15.6%) in the OOH services. This constitutes 0.9% of all consultations in primary care, corresponding to 0.8% of consultations in general practice and 1.6% of consultations in the OOH services.

Female patients contributed to 57.9% of consultations for any diagnosis: 58.4% in general practice and 52.5% in OOH services. The sex difference was less pronounced in the gastroenteritis consultations, with 52.8% female patients: 53.2% in general practice and 50.5% in OOH services (Table 1).

Mean patient age was 46.1 years for consultations for any diagnosis: 47.2 years in general practice and 35.1 years in OOH services (Table 1). Patients aged 55–64 years had the highest number of consultations (14.2%). Mean age was 32 years for the patients in gastroenteritis consultations: 33.6 years in general practice and 22.8 years in OOH services (Table 1). Children aged 0–4 years accounted for the highest number of gastroenteritis consultations, followed by young adults aged 25–34 years, in general practice and OOH services (Fig. 1).

Sex distribution by age for consultations with any diagnosis in primary care showed a majority of boys in the two lowest age categories 0–4 years (54.3%) and 5–14 years (50.7%): 54.0% and 50.4%, respectively, in general practice, and 55.2% and 52.2%, respectively, in OOH services. This finding was also observed for the gastroenteritis consultations in primary care (55.5% and 55.6% for the two age groups, respectively): both in general practice (55.9% and 56.4%) and OOH services (54.5% and 52.9%).

The numbers of all consultations for any diagnosis increased steadily every year over the 10-year period, from 12 295 867 consultations in 2006 to 15 185 884 consultations in 2015 (23.5% increase). This increase was seen in both general practice and OOH services until 2012, but in the following years, there was a slight decrease in the number of consultations in OOH services. Mean annual number of gastroenteritis consultations was 128 104, and the overall trend in number of gastroenteritis consultations was an increase from 120 624 in 2006 to 133 091 consultations in 2015 (10.3% increase). However, the proportion of gastroenteritis consultations decreased from 1% in 2006 to 0.9% in 2015, due to an even higher increase in consultations for any diagnosis.

The number and proportion of gastroenteritis consultations showed a bi-annual cycle through the whole period. This pattern of

Table 1. Characteristics of consultations for any diagnosis and for gastroenteritis in primary care (general practice and OOH services) in Norway 2006–15

	Consultations for any diagnosis						Gastroenteritis consultations					
	GP + OOH		GP		OOH		GP + OOH		GP		OOH	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total	140199637	100[a]	127389382	90.9[a]	12810255	9.1[a]	1281048	100[a]	1081774	84.4[a]	199274	15.6[a]
Sex												
Male	59049592	42.1	52958422	41.6	6091170	47.6	604732	47.2	506176	45.8	98556	49.5
Female	81149996	57.9	74430921	58.4	6719075	52.5	676314	52.8	575597	53.2	10717	50.5
Missing	49		39		10		2		1		1	
Age (years)												
Mean age	46.1		47.2		35.1		32		33.6		22.8	
0–4	7469970	5.3	5699054	4.5	1770916	13.8	272460	21.3	197329	18.2	75131	37.7
5–14	8044813	5.7	6632863	5.2	1411950	11.0	99295	7.8	76687	7.1	22608	11.4
15–24	12912593	9.2	10962960	8.6	1949633	15.2	159053	12.4	134797	12.5	24256	12.2
25–34	17936332	12.8	16204321	12.7	1732011	13.5	210226	16.4	185194	17.1	25032	12.6
35–44	19466283	13.9	17906604	14.1	1559679	12.2	157587	12.3	142206	13.2	15381	7.7
45–54	19361034	13.8	18077251	14.2	1283783	10.0	121612	9.5	111026	10.3	10586	5.3
55–64	19962550	14.2	18834073	14.8	1128477	8.8	108508	8.5	99578	9.2	8930	4.5
65–74	16469661	11.8	15611736	12.3	857925	6.7	74381	5.8	67453	6.2	6928	3.5
75–84	13145913	9.4	12430614	9.8	715299	5.6	54530	4.3	48060	4.4	6470	3.3
85–	5430438	3.9	5029866	4.0	400572	3.1	23394	1.8	19443	1.8	3951	2.0
Missing	50		40		10		2	0	1	0	1	0
Season												
January–March	36239587	25.9	33101417	26.0	3138170	24.5	375655	29.3	315345	29.2	60310	30.3
April–June	34630198	24.7	31357589	24.6	3272609	25.6	296551	23.2	244100	22.6	52451	26.3
July–September	32226854	23.0	29069703	22.8	3157151	24.7	288290	22.5	246625	22.8	41665	20.9
October–December	37102998	26.5	33860673	26.6	3242325	25.3	320552	25.0	275704	25.5	44848	22.5
CRP												
Yes	21663935	15.5	17534547	13.8	4129388	32.2	462609	36.1	348200	32.2	114409	57.4
No	118535702	84.6	109854835	86.2	8680867	67.8	818439	68.9	733574	67.8	84865	42.6
Sickness cert.[b]												
Yes	20658152	23.1	19997369	24.2	660783	9.3	320313	43.6	300743	45.9	19570	24.8
No	68938272	76.9	62522490	75.8	6415782	90.7	414071	56.4	354848	54.1	59223	75.2
Total	89596424	100	82519859	100	7076565	100	734384	100	655591	100	78793	100

Distribution within sex, age, season, centrality, point-of-care CRP and sickness certificate is given by column if not otherwise stated.

[a]Distribution of service type (GP and OOH services) within consultations for any diagnosis and gastroenteritis consultations, respectively

[b]Analyses of sickness certificate are restricted to patients aged 20–67 years.

variation was observed for both general practice and OOH services (Fig. 2), and most pronounced for the age category 0–4 years in both service types (data not shown). To further investigate this pattern, we organized the data according to winter and summer seasons, as the shift of the year splits each winter season. These analyses did not show a similar bi-annual cycle from one winter season to the next (data not shown).

Quarterly distribution of consultations for any diagnosis in primary care was nearly equal throughout the four quarters, although slightly more of the consultations were observed during the months October–December (26.5%) and January–March (25.9%). In contrast, gastroenteritis consultations peaked during January–March (29.3%) followed by October–December (25.0%), both in general practice and OOH services (Table 1). This variation for gastroenteritis consultations by quarter was most evident for the age categories, 0–4, 5–14 and 25–34 years (Fig. 3). For other age groups, the number of gastroenteritis consultations in both service types was more equally distributed through the quarters.

Point-of-care CRP testing took place in 15.5% of the consultations for any diagnosis: in 13.8% of the consultations in general practice and in 32.2% of the consultations in the OOH services (Table 1). Among gastroenteritis consultations, point-of-care CRP testing was used in 36.1% of the consultations: in 32.2% of the consultations in general practice, when compared with 57.4% in OOH services (Table 1).

Among patients in the working age (age group 20–67 years), sickness certificates were issued in 23.1% of the consultations with any diagnosis: 24.2% in general practice and 9.3% in the OOH services (Table 1). Sickness certificates were issued in 43.6% of the gastroenteritis consultations: 45.9% in general practice and 24.6% in OOH services (Table 1). We observed an equal sex distribution among patients in gastroenteritis consultations with sickness certificates issued in both general practice and OOH services (data not shown).

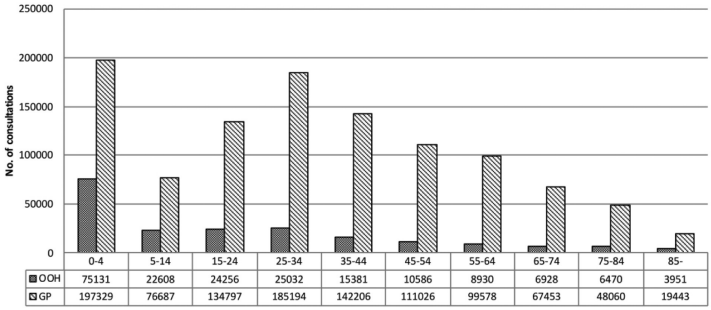
Discussion

Summary

Gastroenteritis consultations represented 0.9% of all consultations by encounter in primary care in Norway during the years 2006–15, of which 84.4% took place in general practice and 15.6% in OOH services. The number of gastroenteritis consultations was higher during the winter months with little change from one winter season to the next. The most common patient was either a young child or young adult, with young children dominating even more so in the OOH services. These two age groups also contributed the most to the observed peak in number of gastroenteritis consultations in the winter months.

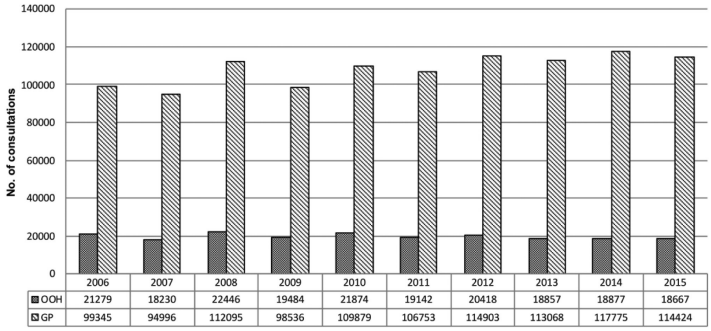
Strengths and limitations

A main strength of this study was the use of complete registry data from nearly all consultations in general practice and OOH services in



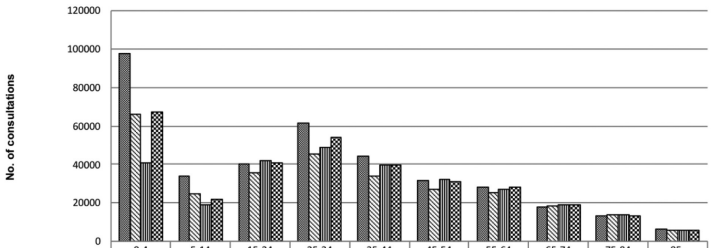
	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85-
OOH	75131	22608	24256	25032	15381	10586	8930	6928	6470	3951
GP	197329	76687	134797	185194	142206	111026	99578	67453	48060	19443

Figure 1. Number of gastroenteritis consultations in primary care by age group and service type [general practice (GP) and OOH services]. Norway, 2006–15. Total number of gastroenteritis consultations = 1281046 (2 missing).



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
OOH	21279	18230	22446	19484	21874	19142	20418	18857	18877	18667
GP	99345	94996	112095	98536	109879	106753	114903	113068	117775	114424

Figure 2. Gastroenteritis consultations in primary care by year and service type [general practice (GP) and OOH services]. Norway, 2006–15. Total number of gastroenteritis consultations = 1281048.



	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85-
January-March	97746	34184	40432	61663	44412	31486	28063	18104	13407	6157
April-June	66291	24712	35646	45725	34087	26772	25196	18247	13950	5925
July-September	40938	18744	41912	48994	39664	32502	27086	18756	13877	5817
October-December	67486	21655	41063	53844	39424	30852	28163	19274	13296	5495

Figure 3. Number of gastroenteritis consultations in primary care (general practice and OOH services) by age group and quarter of a year. Norway, 2006–15. *N* = 1281047 (1 missing).

Norway, thereby considerably reducing selection bias. Reimbursement claims data have been shown to be informative in monitoring disease activity in primary care, and promising in syndromic surveillance of gastrointestinal disease but yet having low sensitivity and low positive predictive value in detecting outbreaks (14, 26, 27). The current study has some limitations. A part of reimbursement claims from the 24-hour emergency services in Bergen (daytime consultations from work days) are not reported, leading to a minor underreporting of consultations in OOH services. Further, claims from consultations by e-mail, home visits and telephone were not included in the current study. Due to the nature of gastroenteritis as a contagious disease, we believe that the use of telephone consultations is considerable, but probably more for administrative purposes, such as sickness certificates, than for disease management. The lack of telephone consultations and home visits may challenge the external validity specifically in the context of syndromic surveillance, as our findings do not reflect the total activity in primary care. However, this study was designed to analyze the face-to-face consultation activity concerning gastroenteritis. Another limitation is the lack of precision in the time variable. Ideally for the analyses of seasonality, we should have had information about the exact date or week number for the consultations.

Possible misclassification of the disease (gastroenteritis) may challenge the internal validity. Awareness of different coding behaviour in general practice and OOH services, as well as specific diagnosis being chosen to justify actions (e.g. sickness certificate), is important in interpreting the data. Our definition of a gastroenteritis consultation including D11 'Diarrhoea', but not D10 'Vomiting', is not completely in line with a common definition (1), but was chosen to be in line with the definition used by the Norwegian Syndromic Surveillance System (25). As a result, consultations for diarrhoea of other causes than gastroenteritis are included, but gastroenteritis consultations coded with D10 'Vomiting' are missed. Studies on the validity of these diagnoses and the diagnostic algorithm are lacking.

The perspective of this study was from the health care services, and the entity in the study was the consultation for (not patients with) gastroenteritis. Thus, it cannot be used for estimating the prevalence of gastroenteritis in the Norwegian population nor in primary care. Also, it cannot be used to precisely estimate the extent of absence from work due to gastroenteritis.

Interpretation/comparison with existing literature

Many gastrointestinal infections exhibit some kind of seasonality (28) and the mechanisms of seasonality are thought to vary for the different pathogens (20), including factors such as variability in temperature and humidity, start of school year, geographical localization on either Northern or Southern Hemisphere and level of country development (19,21,23). Norovirus infections seem to have a seasonal pattern with peaks in the cooler months, i.e. December through February in the Northern Hemisphere and June through August in the Southern Hemisphere (17, 29). The present study includes gastroenteritis due to all possible pathogens, but the observed pattern of seasonality is in line with that known for norovirus infection on the European continent (30). Also, our findings of high consultation numbers for gastroenteritis among young children, and that the boys account for the majority of gastroenteritis consultations among those under the age of 15 years, are in line with a Dutch study of norovirus infection in primary care (14). Studies from Sweden (3) and the UK (13, 31) also present highest consultation rates among the youngest children. Our findings of young adults as the second most common patient group suggest transmission between child and carer supported by findings from an Australian population-based study of the risk of gastroenteritis (20). Rotavirus infection should be considered as one major cause of gastroenteritis among children under 2 years of age. In older children and in adults, rotavirus most often presents as asymptomatic or subclinical reinfections. A Norwegian study of hospitalized children reported rotavirus infections peaking in March through May (18). Rotavirus vaccination was introduced in Norway in 2014 (at the end of our study period); thus, we were not able to evaluate any potential effect of the vaccine introduction based on 1 year of observations only.

We observed a bi-annual variation in gastroenteritis consultations, but this was not seen when organizing the data according to winter–summer variation. This likely reflects whether the main impact of winter vomiting disease (probably norovirus) hit the population before or after the shift of each year.

During the 10-year period, there was a small increase in the absolute number of gastroenteritis consultations. This corresponds mainly with the increase in the Norwegian population during the same period.

Our finding of a higher proportion of point-of-care CRP testing in consultations for gastroenteritis in OOH services when compared with general practice has also been described in a previous Norwegian study (32). We find the use of CRP surprisingly high, but we do not have clinical information about the reason for the testing, nor the results of these tests.

Implications for clinical care and research

To the best of our knowledge, this is the first study to present complete national registry data on gastroenteritis patients' encounters with primary care doctors over a 10-year period. The results of this study are highly relevant when interpreting data for syndromic surveillance of gastroenteritis based on routine data from primary care. Increased knowledge of the typical patients (age and sex) expected to be seen in consultations for gastroenteritis throughout the year and service type would be useful for the doctors managing the patients in primary care. We think that our results are generalizable at least to countries in the Northern Hemisphere with a primary care system similar to Norway. Future research should study illness trajectories in patients with gastroenteritis managed in primary care. More detailed information about time and geography of the consultations would be useful in future studies of the syndromic surveillance of gastroenteritis. Adding clinical data from the consultations, such as symptoms and severity, and information about stool sampling and results, would further improve the understanding of gastroenteritis in primary care. Also, further research is needed to investigate any benefits of point-of-care CRP-testing for gastroenteritis.

In conclusion, the proportion of gastroenteritis consultations was higher in the OOH services when compared with daytime general practice. The most frequent patients with gastroenteritis in primary care were young children and young adults, with young children dominating even more so in the OOH services. The observed seasonal variation in consultations frequency is similar to that shown for gastroenteritis caused by norovirus on the Northern Hemisphere. These results should be useful for health service planners as well as surveillance systems and clinicians in countries with a comprehensive primary care system.

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Declaration

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Ethical approval: Regional Committee for Medical and Health Research Ethics, REC West (project number 2016/559). The Norwegian Data Protection Agency (project number 16/01083).
Conflict of interest: None.

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PAPER II

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Health Service Research

Antibiotics for gastroenteritis in general practice and out-of-hour services in Norway 2006–15

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Abstract

Background: When patients with gastroenteritis (GE) seek health care, they are generally managed in primary care. Little is known about the use of antibiotic treatment in these cases.
Objective: The aim of this study was to investigate time trends and patient characteristics associated with antibiotic treatment for GE in Norwegian primary care in a 10-year period.
Methods: We linked data from two nationwide registries, reimbursement claims data from Norwegian primary care (the KUHR database) and The Norwegian Prescription Database, for the period 2006–15. GE consultations were extracted, and courses of systemic antibiotics dispensed within 1 day were included for further analyses.
Results: Antibiotic treatment was linked to 1.8% (n = 23 663) of the 1 279 867 consultations for GE in Norwegian primary care in the period 2006–15. The proportion of GE consultations with antibiotic treatment increased from 1.4% in 2006 to 2.2% in 2012 and then decreased to 1.8% in 2015. Fluoroquinolones (28.9%) and metronidazole (26.8%) were most frequently used. Whereas the number of fluoroquinolones courses decreased after 2012, the number of metronidazole courses continued to increase until year 2015. The antibiotic treatment proportion of GE consultations was lowest in young children and increased with increasing age.
Conclusion: Antibiotic treatment is infrequently used in GE consultations in Norwegian primary care. Although there was an overall increase in use during the study period, we observed a reduction in overall use after year 2012. Young children were treated with antibiotics in GE consultations less frequent than older patients.

Key words: Antibiotics, consultation, gastroenterology, health services research, infectious diseases, primary care.

Introduction

Gastroenteritis (GE) is a common disease worldwide. In high-income countries, most episodes of GE are self-limiting without need of medical attention (1–4). Those seeking health care services are generally managed in primary care, accounting for about 130 000 consultations (0.9% of all primary care consultations) annually in Norway (5).

Studies from Northern European countries have shown that in primary care the infective agents are most commonly either viruses or cannot be identified (6–9). Norwegian guidelines and international recommendations state that antibiotics should be avoided for the treatment of GE in primary care (10,11). For most causal microbes, antibiotics are not shown to shorten the symptomatic phase of GE and, in some cases, could contribute to a more serious outcome (12,13). However, specific antibiotic treatment is recommended for certain gastrointestinal infections, especially in the hospital setting (11,14). In 2015, the Norwegian Government launched the Action

Key Messages

- Antibiotics for gastroenteritis are infrequently used in Norwegian primary care.
- Antibiotics usage increased from 2006 to 2012, followed by decrease through 2015.
- Metronidazole and fluoroquinolones were most frequently used.
- Children were least frequently treated with antibiotics for gastroenteritis.

Plan to Fight Antimicrobial Resistance in the Health Care Services (15), with the target of reducing total sales of antibiotics in human medicine by 30% within the year 2020 when compared with the level in 2012 (16). By 2015, an 11% reduction was already observed (17).

In high-income countries, GE is seldom treated with antibiotics in primary care, with prescribing proportions ranging from 5% to 11% varying between countries (18–22). In the current study, we use complete national registry data with the aim to investigate time trends and patient characteristics associated with antibiotic treatment for GE in Norwegian primary care from 2006 to 2015.

Materials and methods

Primary care in Norway

All residents in Norway are entitled to be on the patient list of a GP, and 99% of the population was registered to this service in 2015 (23). Most consultations in primary care, including daytime emergency consultations, are carried out in general practice surgeries during regular opening hours. In addition, emergency medical services are organized as out-of-hour (OOH) services with GPs on duty in the municipalities or as 24-hour emergency services in larger cities. In the management of infectious diseases, point-of-care C-reactive protein (CRP) testing is widely used in general practice and OOH services in Norway (24). GPs play a key role in certifying all sorts of sickness absence. Most employees will need documentation from a physician for sick leave exceeding three days. For infection control reasons, it is advised to issue sickness certificates to GE patients in specific work situations independent of the clinical manifestation and possible loss of function (food production and preparation, patient contact) (25).

We linked data from two national registries for the 10-year period 2006–15: Reimbursement claims data from Norwegian primary care (the KUHR database) and the Norwegian prescription database (NorPD).

The KUHR database

Reimbursement claims data from both daytime general practice and OOH services are registered in the national KUHR database. The reimbursement claims include information about service type (general practice or OOH service), patient (unique personal identifier defining age and sex) and time for the consultation and diagnoses (International Classification for Primary Care [ICPC-2] codes) for each contact. Reimbursed procedures, such as point-of-care CRP testing and issuing of sickness certificates, are also included in these data, whereas no specific codes exist for microbiological testing of stool samples.

In this study, we used data from all consultations by attendance in general practice and OOH services. Home visits, and consultations made electronically or by telephone, were not included in the data set extracted from KUHR. For administrative reasons, daytime activity data from the 24-hour emergency services in Bergen (the second largest city in the country with 5% of the total population) are not registered in the KUHR database, and thus not part of this study.

We defined a gastroenteritis consultation ('GE consultation') as a consultation with one or more of the following ICPC-2 codes: 'D11 Diarrhoea', 'D70 Gastrointestinal infection' and 'D73 Gastroenteritis, presumed infection'. 'D70 Gastrointestinal infection' represent the most detailed level of diagnostic codes for gastrointestinal infections. We categorized patient age in the KUHR database into the following 10 categories: 0–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84 and ≥85 years.

The Norwegian Prescription Database

The NorPD is a complete registry of all prescription drugs dispensed from pharmacies in Norway. Drugs used for treatment of inpatients in hospitals and nursing homes are not registered in NorPD. NorPD contains information about the patient (pseudonym unique personal identifier), time for dispensing and information about the drug [Anatomical Therapeutic Chemical (ATC) classification system code]. We used data from the NorPD for all prescribed systemic antibiotic courses dispensed from pharmacies in Norway during the 10-year period, 2006–15.

We defined 'course of antibiotics' as a course of a prescribed systemic antimicrobial drug dispensed from a pharmacy and registered in the NorPD with the following ATC codes: 'J01 Antibacterials for systemic use', 'A07AA09 Vancomycin' or 'P01AB01 Metronidazole'. We categorized antibiotics as either 'GE relevant' or 'not GE relevant', as we found it necessary to make this divide to further interpret the data. According to Norwegian and international guidelines, we defined the following antibiotics as relevant for treatment of gastrointestinal infections ('GE relevant'): fluoroquinolones, metronidazole, macrolides, tetracycline, trimethoprim-sulphamethoxazole and vancomycin. All other antibiotics were defined as 'not GE relevant'. When a GE consultation is linked to 'not GE relevant' antibiotics this can result from both inappropriate prescribing and misclassification in our data set (for example prescribing made for other diseases than GE). Additionally, we defined the following as urinary tract infection antibiotics ('UTI antibiotics'), as their only indication is UTI: pivmecillinam, mecillinam, trimethoprim, nitrofurantoin and metenamin.

Linking of data sets

The consultation data from the KUHR database were linked to the drug prescription data from NorPD by the patients' pseudonym unique personal identifiers.

Due to privacy concerns, the Norwegian Data Protection Authority would not accept original dates coupled with patient data. These were therefore replaced by Statistics Norway with a random reference date unique for each patient, from which the time of each registration in this dataset refers to.

A course of antibiotics was considered as linked to a consultation in primary care when the prescribed drug was dispensed from the pharmacy at the same day or the day after the consultation. We

extracted all GE consultations, and the courses of antibiotics linked to these consultations, for analyses. Both antibiotics defined as 'GE relevant' and 'not GE relevant' were included as treatment for GE in the analyses, except for the following two categories: (i) Courses of antibiotics (both 'GE relevant' and 'not GE relevant') linked to consultations with a co-diagnosis (other than D11, D70 or D73) likely to explain the prescription (Supplementary Table S1) and (ii) courses of 'UTI antibiotics'. These courses were excluded as treatment for GE, and consultations linked to these were included as GE consultations without antibiotic treatment in the analyses (Fig. 1).

Statistics

We calculated the proportion of GE consultations that were followed by antibiotic treatment. Patient characteristics, use of CRP and issuing of sickness certificates were compared between GE consultations with and without antibiotic treatment and between GE consultations in general practice and in OOH services. We explored time trends in the use of different antibiotics as treatment for GE. The data were analysed using StataSE 16.1 and Microsoft Excel for Windows 365 MSO.

Results

There were 1 279 867 GE consultations in Norway in the period 2006–15, of which 84.5% (n = 1 081 162) were in general practice and the rest in OOH services.

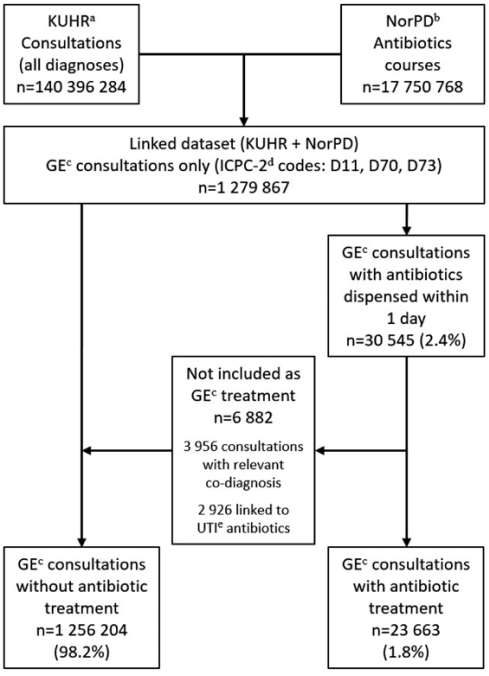


Figure 1. Flow chart of gastroenteritis consultations with and without antibiotic treatment in primary care. Norway, 2006–15. [a]KUHR: Reimbursement claims database (the KUHR database). [b]NorPD: The Norwegian Prescription Database. [c]GE: gastroenteritis. [d]ICPC-2: International Classification for Primary Care, version 2. [e]UTI: urinary tract infection.

Antibiotic treatment was linked to 1.8% (n = 23 663) of the GE consultations (Table 1), after excluding the following as GE consultations with antibiotic treatment not for GE: 3956 consultations with a co-diagnosis more relevant to the prescription (of these, 2076 were an R-diagnosis in ICPC-2, indicating a respiratory tract infection), and 2926 consultations linked to courses of UTI antibiotics (Fig. 1). In general practice, the proportion of GE consultations with antibiotic treatment was 1.8% (n = 19 617), and in the OOH services, the proportion was 2.0% (n = 4046).

The number of GE consultations with antibiotic treatment increased by 78.4% from 1636 in 2006 to 2918 in 2012, followed by a 16% decrease from 2012 until 2015. A similar pattern was observed for the proportion of GE consultations with antibiotic treatment, which increased from 1.4% in 2006 to 2.2% in 2012 and then decreased to 1.8% in 2015 (Fig. 2).

There was no difference between the sexes in proportions of GE consultations with antibiotic treatment (data not shown). The proportion of GE consultations with antibiotic treatment was lowest in patients aged 0–4 years (1.0%) and increased with increasing age up to the categories 55–64 and 65–74 years (3.0%). This trend was even more pronounced in the OOH services (Fig. 3).

CRP testing was used in 58.1% of the GE consultations with antibiotic treatment, when compared with 35.7% without antibiotic treatment (Table 1). CRP testing was used more frequently in OOH services than in general practice, this applied to both GE consultations with antibiotic treatment and without (Table 1). The proportion of CRP testing in GE consultations with antibiotic treatment increased from 52.4% in 2006 to 60.8 % in 2012 but remained stable for the years 2012–15 (data not shown).

Most of the GE consultations with antibiotic treatment were linked to single courses of antibiotics (90.3%, n = 21 378). A combination of two or three antibiotic courses was given following 9.6% (n = 2277) and 0.03% (n = 8) of GE consultations with antibiotic treatment, respectively. Thus, the 23 663 GE consultations with antibiotic treatment were linked to 25 956 antibiotic courses. Of these, the most frequently used 'GE-relevant' antibiotics were fluoroquinolones (28.9%), metronidazole (26.8%) and macrolides (10.4%). β-Lactamase-sensitive penicillins, defined as 'not GE relevant' antibiotics in this study, were third most frequent, accounting for 10.8%.

For the 'GE-relevant' antibiotics, we found an increase from 2006 to 12 in the number of courses of fluoroquinolones (128% increase), metronidazole (92.1% increase), sulfamethoxazole/trimethoprim (68.6% increase), tetracyclines (50.7% increase) and macrolides (64% increase), although there was a decrease in the number of courses of all these antibiotics from year 2012 to 2015, except for metronidazole (Table 2). For the 'not GE-relevant' antibiotics, an increase in the number of courses of penicillins with extended spectrum (70.8% increase) and β-lactamase-sensitive penicillins (40% increase) was found for GE consultations during the 10-year period (Table 2).

Metronidazole and fluoroquinolones (38.1%, n = 868) represented the most frequent combination among the 2277 double courses, followed by metronidazole and extended spectrum penicillins (27.3%, n = 621), metronidazole and tetracyclines (15.8%, n = 359), and metronidazole and macrolides (9.5%, n = 116).

Discussion

Summary

We found that 1.8% of the GE consultations in Norwegian primary care resulted in treatment with antibiotics during the years 2006–15.

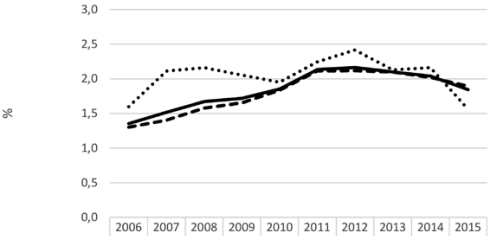
Table 1. Characteristics of gastroenteritis consultations without and with antibiotic treatment in primary care (daytime general practice and out-of-hour services) in Norway 2006–15 (N = 1 279 867)

	Without antibiotic treatment						With antibiotic treatment					
	DGP +OOH		DGP		OOH		DGP + OOH		DGP		OOH	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total	1 256 204	100	1 061 545	84.5[a]	194 659	15.5[a]	23 663	100	19 617	82.9[a]	4046	17.1[a]
Age (years)												
Mean age	31.8		33.5		22.6		40.2		41.4		34.6	
0–4	269 130	21.4	194 917	18.4	74 213	38.1	2679	11.3	2034	10.4	645	16.0
5–14	98 085	7.8	75 769	7.1	22 316	11.5	1061	4.5	824	4.2	236	5.8
15–24	156 270	12.4	132 689	12.5	23 581	12.1	2672	11.3	2068	10.5	604	14.9
25–34	206 649	16.5	182 321	17.2	24 328	12.5	3490	14.8	2820	14.4	669	16.6
35–44	154 164	12.3	139 375	13.1	14 789	7.6	3340	14.1	2800	14.3	539	13.3
45–54	118 360	9.4	108 258	10.2	10 102	5.2	3203	13.5	2739	14.0	463	11.5
55–64	105 307	8.4	96 810	9.1	8497	4.4	3223	13.6	2812	14.3	410	10.1
65–74	72 132	5.7	65 481	6.2	6651	3.4	2217	9.4	1959	10.0	255	6.3
75–84	53 231	4.2	46 926	4.4	6305	3.2	1281	5.4	1120	5.7	158	3.9
85–	22 874	1.8	189 98	1.8	3876	2.0	497	2.1	428	2.2	67	1.6
Missing	2	0	1	0	1	0	0	0	0	0	0	0
Sex												
Male	592 800	47.2	496 546	46.8	96 254	49.5	11 361	48.0	9319	47.5	2042	50.5
Female	663 402	52.8	564 998	53.2	98 404	50.6	12 302	52.0	10 298	52.5	2004	49.5
Missing	2	0	1	0	1	0	0	0	0	0	0	0
CRP												
No	808 174	64.3	724 745	68.3	83 429	42.9	9927	42.0	8809	44.9	1118	27.6
Yes	448 030	35.7	336 800	31.7	111 230	57.1	13 736	58.1	10 808	55.1	2928	72.4
Sickness certificate[b]												
No	402 727	56.1	345 790	53.8	56 937	74.9	10 941	69.1	8820	66.5	2121	82.0
Yes	315 560	43.9	296 477	46.2	19 083	25.1	4905	31.0	4438	33.5	467	18.0
Total	718 287	100	642 267	100	76 020	100	15 846	100	13 258	100	2588	100

Distribution within sex, age, point-of-care CRP testing and sickness certificates is given by column. DGP, daytime general practice; OOH, out-of-hour services.

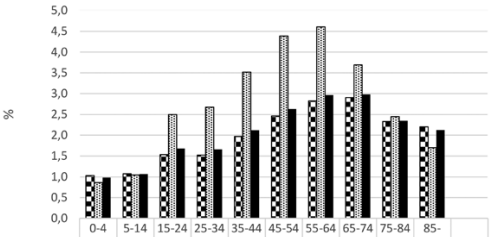
[a]Distribution of service types (daytime general practice and OOH services) within consultations without antibiotic treatment and with antibiotic treatment, respectively.

[b]Analyses of sickness certificates are restricted to patients aged 20–67 years.



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
DGP	1,3	1,4	1,6	1,7	1,8	2,1	2,1	2,1	2,0	1,9
OOH	1,6	2,1	2,2	2,1	2,0	2,2	2,4	2,1	2,2	1,6
DGP+OOH	1,4	1,5	1,7	1,7	1,9	2,1	2,2	2,1	2,0	1,8

Figure 2. Proportion of gastroenteritis consultations with antibiotic treatment by year and type of service, Norway 2006–15. *N* = 1 279 867. DGP, daytime general practice; OOH, out-of-hour services.



	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85-	
DGP	1,0	1,1	1,5	1,5	2,0	2,5	2,8	2,9	2,3	2,2	0,0
OOH	0,9	1,0	2,5	2,7	3,5	4,4	4,6	3,7	2,4	1,7	0,0
DGP+OOH	1,0	1,1	1,7	1,7	2,1	2,6	3,0	3,0	2,3	2,1	0,0

Figure 3. Proportion of gastroenteritis consultations with antibiotic treatment by age category and type of service, Norway 2006–15. *N* = 1 279 867. DGP, daytime general practice; OOH, out-of-hours services.

Young children were treated with antibiotics less frequent than older patients. Fluoroquinolones and metronidazole were most frequently used, followed by β-lactamase-sensitive penicillins and macrolides. The proportion of GE consultations resulting in antibiotic treatment increased until 2012, after which it declined. The same trend with initial increase and later reduction in treatment was not seen for metronidazole.

Strengths and limitations

The main strength of this study was the use of linked complete registry data from nearly all consultations in general practice and OOH services, and all courses of systemic antibiotics dispensed from pharmacies in Norway during a 10-year period. A limitation is that a part of the reimbursement claims from the 24-hour emergency services in Bergen (daytime consultations from workdays) are not included, leading to a minor underreporting of consultations in the OOH services. Furthermore, claims from electronic/telephone consultations or home visits were not included in the current study. We expect that the use of telephone consultations is considerable, due to the nature of GE as a contagious disease. But these are probably dominated by requests for sick leave or similar administrative purposes, and also more prone to misclassification of disease on reimbursement claims (26). However, telephone contacts may be used in the follow up of patients, and if these contacts result in the prescription of antibiotics, these courses would be missing in the current study. On the other hand, this may lead to an even greater underreporting of consultations without treatment. Hence, we do not think the study is subject to underestimation of antibiotic treatment in Norwegian primary care.

Possible misclassification of the disease (GE) may challenge the internal validity. Our definition of a GE consultation including 'D11 Diarrhoea' but not 'D10 Vomiting' is in line with the definition used by the Norwegian Syndromic Surveillance System (27), and a recent Dutch study on antibiotic treatment of GE in primary care (21). As a result, consultations for diarrhoea of other causes than GE are included, whereas GE consultations coded with 'D10 Vomiting' are missed. To our knowledge, studies on the validity of the diagnostic algorithm are lacking. Our calculation of treatment proportion was based on GE consultations, not GE cases or GE events. This implies that each case could have had several consultations during one GE event, leading to the possibility of an underestimation of the treatment proportion.

The data on antibiotics were based on courses dispensed from pharmacies, not prescriptions. The indirect linking of dispensing to consultations may lead to possible misclassification of antibiotics as treatment for GE. We sought to minimize this by excluding courses linked to consultations with co-diagnoses more likely to represent the real indication for the prescription, as treatment for GE. We also excluded courses of UTI antibiotics as treatment for GE for the same reason. Still, we believe that our study will include dispensing of courses misclassified as GE treatment. This could be because relevant co-diagnoses were not registered in the consultation or the course might have been prescribed in consultations not included in the data material, such as telephone consultations, home visits, consultations with doctors outside primary care, or in consultations taking place between the GE consultation and the dispensation. Antibiotic courses may also have been incorrectly defined as treatment for GE if the consultation was misclassified as a GE consultation.

Interpretation of results

The antibiotic treatment proportion in our study was lower (1.8%) than presented in literature from other high-income countries (18–22). This can be explained by low levels of bacterial and parasitic gastrointestinal infections in Norway, relative to viral infections (28,29). Other possible explanations can be that Norway generally has a low consumption of antibiotics (30), different health care seeking behaviour, or that GE cases with high risk of severe illness are hospitalized and thus not included in the study. The observed declining trend in antibiotic use in GE consultations after 2012 (16% reduction) coincides with an observed reduction in the total use of antibiotics (11% reduction) in Norway during the same period (17) and is in accordance with the goals of the Norwegian Action Plan (15).

Due to lack of clinical and microbiological data, we do not know the real indications for the antibiotic courses, and even less whether the treatment was empirical or specific. Our finding of relatively infrequent use of antibiotics in GE consultations indicates a restrictive use of antibiotics in the treatment of GE, as recommended by guidelines. The most frequently used antibiotics in the GE consultations in our study were fluoroquinolones and metronidazole, which are antibiotics shown to be commonly prescribed for gastrointestinal infections in studies from primary care in the Netherlands, Switzerland and England (21,22,31). We have no explanations for the continuous increase in the use of metronidazole after 2012.

We found a lower prescription proportion among the youngest patients, a finding in line with a recent study from the

Table 2. Types of antibiotic courses for gastroenteritis treatment by year, Norway 2006–15 (*N* = 25 956)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Fluoroquinolones	447	480	677	685	753	866	1019	976	886	701
Metronidazole	418	488	633	599	694	736	803	845	895	845
β-Lactamase-sensitive penicillins	225	201	311	222	328	323	312	296	281	315
Macrolides	222	218	240	197	284	325	364	289	317	241
Penicillins with extended spectrum	144	138	200	170	207	222	248	243	288	246
Tetracyclines	140	174	176	160	155	203	211	206	165	167
Trimethoprim-sulphamethoxazole	86	107	127	115	131	139	145	121	136	109
Other[a]	24	23	34	37	45	45	45	50	71	43
β-Lactamase-resistant penicillins	18	12	20	32	33	33	41	28	50	21
Cephalosporines	23	18	29	26	30	21	18	20	16	14
Total	1747	1859	2447	2243	2660	2913	3206	3074	3105	2702

List by total number of courses during the period.
[a]'Other' include vancomycin, clindamycin, fidaxomicin and fusidic acid.

Netherlands (21). This may be explained by higher GE consultation frequency, and the increased likelihood of viral aetiology in younger patients (5).

The frequent use of the 'not GE relevant' β-lactamase-sensitive penicillins may be surprising as they are not suitable for treatment of any gastrointestinal infections, although they are strongly advocated as the antibiotics of choice in treatment for several other infections commonly seen in primary care. A study from the UK found β-lactamase-sensitive penicillins account for 1.3% of antibiotic prescriptions for infections in the gastrointestinal tract, while a Dutch study of antibiotic treatment for GE in primary care did not include prescriptions of β-lactamase-sensitive penicillins (21). A proportion of the use of 'not GE relevant' antibiotics is probably related to misclassification of disease and/or antibiotic treatment for GE. Fifty percent of the treatments with β-lactamase-sensitive penicillins in the present study were linked to patients under 15 years of age. This may reflect a greater diagnostic challenge in consultations with children, with high levels of co-infections and uncertain symptoms and findings, leading to more misclassification of disease in these age categories. However, we cannot rule out the possibility that some doctors inappropriately prescribed the drug as a first-line drug with the intention to treat GE.

Previous studies from other European countries have indicated higher prescription rates in OOH services than in general practice for several infections (32–34), which corresponds to our finding of higher antibiotic treatment proportion in GE consultations in the OOH services.

The extensive use of CRP testing in Norwegian primary care, especially in consultations with patients with suspected infection and in OOH services, is described in previous studies from Norway (24,35,36). We do not have clinical information about the reason for our finding of extensive use of CRP testing in GE consultations with antibiotic treatment, nor the results of the tests, or if the tests affected the decision whether to prescribe antibiotics.

Conclusions

Antibiotic treatment is used in a very small proportion of GE consultations in Norwegian general practice and OOH services. Although there was an overall increase in use during the study period, there was a reduction in overall use after year 2012. There was a reduction in use of fluoroquinolones and macrolides, but an increase in metronidazole used also after 2012. The antibiotic treatment proportion of GE consultations was lowest in young children and increased with increasing age.

Supplementary material

Supplementary material is available at *Family Practice* online.

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Declaration

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Ethical approval: Regional Committee for Medical and Health Research Ethics, REC West (project number 2016/559); the Norwegian Data Protection Agency (project number 16/01083).
Conflict of interest: none.

Data availability

The data underlying this article cannot be shared publicly due to limitations given by the ethical approval and the data license granted by the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Protection Agency, respectively.

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TABLE S1 SUPPLEMENTARY. International Classification for Primary Care, version 2 (ICPC-2) co-diagnoses (other than D11, D70 and D73) more likely representing the indication for prescription of systemic antibiotics in primary care. List by order of appearance in ICPC-2.

General and unspecified	
A78	Infectious disease other
Eye	
F72	Blepharitis
F73	Eye infection/inflammation other
Ear	
H01	Ear pain
H29	Ear symptom/complaint other
H70	Otitis externa
H71	Acute otitis media
H72	Serous otitis media
H73	Eustachian salpingitis
H74	Chronic otitis media
Cardiovascular	
K70	Infection of circulatory system
K71	Rheumatic fever
Musculoskeletal	
L70	Infections musculoskeletal system
Neurological	
N71	Meningitis/encephalitis
N73	Neurological infection other
Respiratory	
R05	Cough
R09	Sinus symptom/complaint
R21	Throat symptom/complaint
R25	Sputum/phlegm abnormal
R71	Whooping cough
R72	Strep throat
R73	Boil/ascess nose
R74	Upper respiratory infection acute
R75	Sinusitis acute/chronic
R76	Tonsillitis acute
R77	Laryngitis/tracheitis
R78	Acute bronchitis/bronchiolitis
R79	Chronic bronchitis
R81	Pneumonia
R82	Pleurisy/pleural effusion
R83	Respiratory infection other
Skin	
S09	Infected finger/toe
S10	Boil/carbuncle
S11	Skin infection post-traumatic
S13	Animal/human bite
S73	Pediculosis/skin infestation other
S76	Skin infection other

S84	Impetigo
S94	Ingrowing nail
S96	Acne
Urological	
U01	Dysuria/painful urination
U07	Urine symptom/complaint other
U13	Bladder symptom/complaint other
U29	Urinary symptom/complaint other
U70	Pyelonephritis
U71	Cystitis
U72	Urethritis
U99	Urinary disease, other
Pregnancy, Childbearing, Family Planning	
W29	Pregnancy symptom/complaint other
W70	Puerperal infection/sepsis
W71	Infection complicating pregnancy
W94	Puerperal mastitis
Female Genital	
X14	Vaginal discharge
X15	Vaginal symptom/complaint other
X17	Pelvis symptom/complaint female
X23	Fear of sexually transmitted disease (f)
X29	Genital symptom/complaint female other
X70	Syphilis female
X71	Gonorrhoea female
X73	Genital trichomoniasis female
X74	Pelvic inflammatory disease
X92	Chlamydia infection genital female
X99	Genital disease female, other
Male Genital	
Y02	Pain in testis/scrotum
Y03	Urethral discharge
Y04	Penis symptom/complaint other
Y05	Scrotum/testis symptom/complaint other
Y06	Prostate symptom/complaint
Y25	Fear of sexually transmitted disease male
Y29	Genital symptom/complaint male other
Y70	Syphilis male
Y71	Gonorrhoea male
Y73	Prostatitis/seminal vesiculitis
Y74	Orchitis/epididymitis
Y75	Balanitis
Y99	Genital disease male, other

PAPER III

Infection
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ORIGINAL PAPER

Clinical features of gastroenteritis during a large waterborne *Campylobacter* outbreak in Askøy, Norway

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Abstract

Purpose Outbreaks of *Campylobacter* infection are common, but studies exploring the clinical features of acute illness in the outbreak setting are scarce in existing literature. The main purpose of the present study was to investigate the clinical features of self-reported acute illness in gastroenteritis cases during a large waterborne *Campylobacter* outbreak in Askøy municipality, Norway, in 2019.

Methods A web-based self-administered questionnaire, and invitation to participate was sent by the municipality of Askøy as text message to mobile phones using the municipality's warning system to the inhabitants during the ongoing outbreak.

Results Out of 3624 participants, 749 (20.7%) were defined as cases, of which 177 (23.6%) reported severe gastroenteritis. The most common symptoms were loose stools (90.7%), abdominal pain (89.3%) and diarrhea (88.9%), whereas 63.8% reported fever, 50.2% joint pain and 14.2% bloody stools. Tiredness, a symptom non-specific to gastroenteritis, was the overall most common symptom (91.2%).

Conclusion About one in four of the cases reported symptoms consistent with severe gastroenteritis. We found more joint pain and less bloody stools than reported in published studies of laboratory confirmed campylobacteriosis cases. Tiredness was common in the current study, although rarely described in previous literature of acute illness in the outbreak setting.

Keywords Campylobacter infections · Disease outbreaks · Gastroenteritis · Waterborne diseases

Introduction

Campylobacter spp. is considered the most common bacterial cause of gastroenteritis worldwide, as well as in Europe and Norway [1–3]. Approximately 3000 cases are reported annually in Norway, of which more than 50% are acquired abroad. The domestically infected cases are either sporadic or associated with smaller outbreaks, most commonly waterborne [4, 5].

Common symptoms of gastroenteritis caused by *Campylobacter* include loose stools, diarrhea (≥ 3 loose stools in 24 h), nausea, vomiting, abdominal pain, bloody stools and fever, and the severity varies from mild and self-limiting symptoms (most common) to lethal disease [6–14]. Bloody stools and fever are considered markers of more severe infections [6, 13, 15, 16]. Several studies report symptoms and clinical features of campylobacteriosis, but these studies were predominantly published in the period from late 1970s to 2000, and based mainly on surveillance data or sporadic cases of laboratory confirmed infection [7–12, 15, 16]. Such cases represent a selected group that may differ from the total symptomatic population in the community [17, 18]. During large outbreaks of gastrointestinal infections, many cases are not tested and thus not registered. Most epidemiological studies on campylobacteriosis outbreaks

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aim to identify the source of the outbreak and rarely include detailed descriptions of clinical features.

In some cases, campylobacteriosis is complicated with joint symptoms, or post-infectious neuropathy or irritable bowel syndrome (IBS) [8, 19–23]. Antibiotics are usually not needed in treatment of campylobacteriosis but may be useful in patients with severe disease [6, 15, 16, 24–27]. The burden of symptoms during an outbreak, including the extent of more severe disease is difficult to investigate since research cannot be planned in advance. Hence, comprehensive baseline data from outbreaks are relatively rare.

In June 2019, there was a large community-wide waterborne *Campylobacter* outbreak in the island municipality Askøy (population 29,500) in Norway. The outbreak was detected on 6 June 2019, and the outbreak investigation team consisting of the municipality of Askøy and the National Institute of Public Health's (NIPH) later concluded that the drinking water had been contaminated by *Campylobacter jejuni* sometime in late May 2019 [28]. The outbreak investigation findings were published in a report stating that more than 1500 inhabitants were ill during the outbreak [28]. Further, 67 patients were admitted to hospital and 2 deaths were related to the outbreak [28, 29]. Our group has long experience with research on clinical manifestations and complications of gastroenteritis in an outbreak setting [30, 31] and established a large cohort study within days after the outbreak was acknowledged. The primary aim of this study was to describe the clinical features of self-reported acute gastroenteritis in a *Campylobacter* outbreak setting. Secondary aims were to investigate factors associated with severe gastroenteritis.

Methods

The current paper is based on data from the baseline survey out of totally four surveys in the Askøy *Campylobacter* Outbreak Study (ASCOS), a longitudinal cohort study following the outbreak. Households in Askøy received an invitation to participate in the study on 20 June 2019. Invitations and a webpage link to the survey were sent by the municipality of Askøy by one text message (SMS) to approximately 16,000 mobile phones using the municipality's warning system, encouraging as many household members as possible to answer a questionnaire. Information was also presented in public meetings arranged by the municipality, on the municipality's web site, and on posters in municipality and GP offices during the study period. Participants of all ages were included in the study. Consent from parents was needed for participants under the age of 16, and parents were asked to answer the questionnaire on behalf of younger children. Inclusion was closed on 1 July 2019.

Participants were asked if they were ill during the outbreak. Participants responding 'yes' were further asked about the acute disease (symptoms, duration of disease and perceived severity), management (use of health care services and medication) and consequences of the disease (absence from work or school). Participants answering 'no' or 'uncertain' about acute illness did not receive these follow-up questions. Furthermore, all participants were asked if they had stayed continuously outside Askøy from 31 May up to the time for answering. The study population consists of all participants who answered the question whether they were ill during the outbreak, excluding those reporting that they had not been in Askøy during the outbreak (Fig. 1).

We defined a 'case' as a participant who reported being ill with gastrointestinal symptoms during the outbreak, with symptom onset in the study period, and who experienced at least one of the following symptoms: loose stools, diarrhea, bloody stools, abdominal pain, vomiting and nausea. A 'non-case' was a participant reporting not being ill during the outbreak *or* who reported being ill but did not fulfill

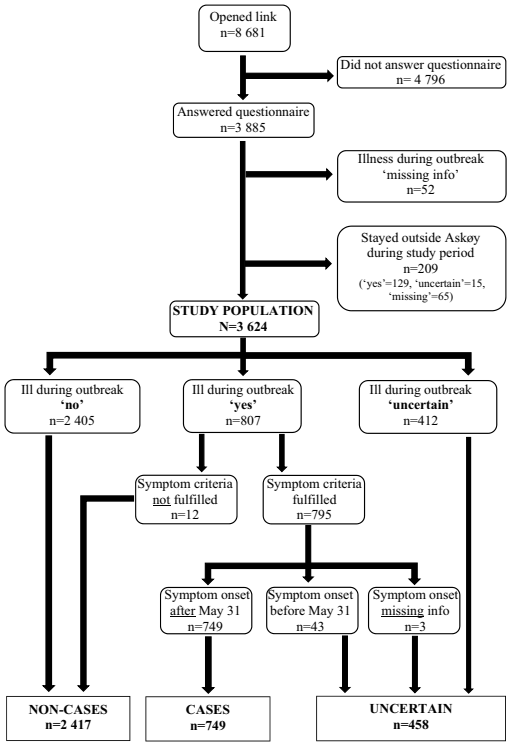


Fig. 1 Flow chart of inclusion and exclusion of the study population, and of the cases, non-cases and the uncertain group, during the *Campylobacter* outbreak in Askøy

the symptom criteria. Participants reporting that they were uncertain whether being ill during the outbreak *or* reported being ill and fulfilling the symptom criteria but with symptom onset either before the study period or missing, were assigned to the 'uncertain' group (Fig. 1). The participants were not asked whether they had submitted stool samples for laboratory verification of *Campylobacter* infection, as the aim of the study was to study self-reported gastroenteritis in the population during the *Campylobacter* outbreak.

Participants were asked to report 'perceived severity' at the worst time point during the acute illness, using a scale from 1 (well) to 9 (life-threatening illness). In addition, we defined the outcome 'severe gastroenteritis' as cases reporting diarrhea for ≥ 5 days *and* at least one of either fever for ≥ 2 days or bloody stools. Cases not fulfilling these criteria were defined as having 'non-severe gastroenteritis'.

Duration of each of the following symptoms were specified by the predefined categories 1–2, 3–4 or 5–7 days, or 1–2 or > 2 weeks: loose stools, diarrhea, bloody stools, nausea, vomiting, abdominal pain, fever, joint pain, tiredness and other symptoms, in addition to total duration of illness (number of days). Questions whether still being ill and whether each symptom was still present at the time of answering the survey were also included. The study questionnaire furthermore included questions about age (number of years), sex, educational level (elementary school, high school, and college/university), employment situation (student/pupil, worker, self-employed, unemployed, on welfare, and pensioner), marital status (single, married, divorced/separated, and widow/widower), household total income in Norwegian kroner (< 250,000, 250,000–499,999, 500,000–749,999, 750,000–1,000,000, and > 1,000,000), self-reported previous diseases (diabetes, ulcerative colitis, Crohn's disease, esophagitis, irritable bowel syndrome (IBS), celiac disease, peptic ulcer, anxiety, depression, and rheumatic disease), intake of glasses with tap water during the week prior to outbreak (0, 1–2, 3–5, > 5), intake of alcohol units during a normal week (number of units) and tobacco use (daily, sporadic, former daily smoker, and never smoked). Participants registered by their e-mail address, and were asked to voluntarily state their name, national identity number, telephone number and postal address for the purpose of follow-up studies and possibility/opportunity to be invited into adjacent research studies. All personally identifiable information were deidentified prior to analyses.

Two different categorical variables were made for age, with three (0–24, 25–54 and ≥ 55 years) and 10 categories (0–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84 and ≥ 85 years), respectively. Duration of illness was categorized into 0–3, 4–7, 8–14 and ≥ 15 days. Alcohol units were categorized into the following six categories: 0, 1–2, 3–5, 6–9, 10–14 and ≥ 15 units per week. Tobacco use was dichotomized. Analyses of alcohol and tobacco use were restricted to participants ≥ 16 years. Analyses of the variables educational level, employment situation and marital status, were restricted to participants ≥ 18 years. There was a high proportion of missing data for the variables age and sex in the baseline survey (29% and 26%, respectively), but we were able to add data from the follow-up surveys for 580 and 507, respectively, giving a final of 13% missing age and 12% missing sex information in the study population.

The data were collected online using SuveyXact by Rambøll. All data have been stored, processed, and analyzed on the University of Bergen's solution for secure processing of sensitive personal data in research (SAFE). The software R, StataSE 16.1 and Microsoft Excel for Windows 365 MSO have been used for processing and analyzing the data.

Descriptive statistics and Pearson's x^2-tests for associations were used to examine the distribution of different characteristics by two outcomes: (1) cases, non-cases and the uncertain group, and (2) cases with severe gastroenteritis vs. non-severe gastroenteritis. For the outcome severe gastroenteritis vs non-severe gastroenteritis, we further explored the associations by estimating relative risks (RRs) with 95% confidence intervals using a modified Poisson regression model [32], adjusting for sex and age. Distribution of symptoms, illness duration, management, and short-term consequences of the acute disease by sex and age were explored using descriptive statistics and Pearson's x^2-tests for associations. Level of statistical significance was set at $p < 0.05$.

Results

During the study period, 8681 individuals accessed the web site, of which 3885 answered the questionnaire (Fig. 1). Of these, 261 were excluded because information about whether they had been ill was missing (n = 52) or because they had stayed outside Askøy (n = 209). In the study population of 3624 participants, 749 (20.7%) were cases, 2417 (66.7%) non-cases and 458 (12.6%) were uncertain. Tables 1 and 2 show the distribution of characteristics by cases, non-cases, and the uncertain group. The proportion of missing data for most variables, including sex and age, was highest in the uncertain group, followed by non-cases.

The most common symptoms reported by the 749 cases were tiredness (91.2%), loose stools (90.7%), abdominal pain (89.3%) and diarrhea (88.9%) (Table 3 and Fig. 2). Bloody stools (14.2%) and vomiting (24.0%) were the least frequently reported of the listed symptoms. Nausea and joint pain were reported by 74.0% and 50.2%, respectively, whereas 63.8% of the cases reported fever. There were no sex differences in the prevalence of symptoms, except for nausea (78.9% in females vs. 67.7% in males, $p < 0.01$). Vomiting, fever, and tiredness were more commonly reported among the youngest and the oldest, compared to those aged

Table 1 Demographic characteristics of the study population, by cases with self-reported gastroenteritis, non-cases and the uncertain group, during the *Campylobacter* outbreak in Askøy

		All		Cases		Non-cases		Uncertain		x^2
		n	%	*n*	%	*n*	%	*n*	%	p^a
Total		3624	100	749	20.7*	2417	66.7*	458	12.6*	
Sex										0.73
	Male	1358	37.5	303	40.5	904	37.4	151	33.0	
	Female	1842	50.8	393	52.5	1209	50.0	240	52.4	
	Missing	424	11.7	53	7.1	304	12.6	67	14.6	
Age range (years)		1–91		1–82		1–91		1–81		
Age										< 0.01
	0–4	22	0.6	6	0.8	12	0.5	4	0.9	
	5–14	30	0.8	8	1.1	14	0.6	8	1.7	
	15–24	236	6.5	72	9.6	136	5.6	28	6.1	
	25–34	483	13.3	112	15.0	296	12.2	75	16.4	
	35–44	701	19.3	159	21.2	460	19.0	82	17.9	
	45–54	691	19.1	171	22.8	427	17.7	93	20.3	
	55–64	477	13.2	101	13.5	328	13.6	48	10.5	
	65–74	445	12.3	52	6.9	349	14.4	44	9.6	
	75–84	82	2.3	10	1.3	67	2.8	5	1.1	
	≥ 85	2	0.1	0	0.0	2	0.1	0	0.0	
	Missing	455	12.6	58	7.7	326	13.5	71	15.5	
Education level**										< 0.01
	Elementary school	175	4.9	47	6.4	102	4.3	26	5.9	
	High school	1192	33.6	299	40.9	748	31.5	145	32.7	
	University/college	1431	40.4	290	39.7	981	41.4	160	36.0	
	Missing	748	21.1	95	13.0	540	22.8	113	25.5	
Employment**										< 0.01
	Student/pupil	146	4.1	34	4.7	95	4.0	17	3.8	
	Worker	1879	53.0	459	62.8	1193	50.3	227	51.1	
	Self-employed	94	2.7	20	2.7	62	2.6	12	2.7	
	Unemployed	89	2.5	22	3.0	52	2.2	15	3.4	
	On welfare	177	5.0	55	7.5	95	4.0	27	6.1	
	Pensioner	423	11.9	50	6.8	336	14.2	37	8.3	
	Missing	738	20.8	91	12.4	538	22.7	109	24.5	
Houshold income										0.28
	< 250,000	86	2.4	23	3.1	51	2.1	12	2.6	
	250,000–499,999	393	10.8	89	11.9	254	10.5	50	10.9	
	500,000–749,999	609	16.8	130	17.4	388	16.1	91	19.9	
	750,000–1,000,000	683	18.8	171	22.8	437	18.1	75	16.4	
	> 1,000,000	900	24.8	191	25.5	621	25.7	88	19.2	
	missing	953	26.3	145	19.4	666	27.6	142	31.0	
Marital status**										< 0.01
	Single	440	12.4	131	17.9	251	10.6	58	13.1	
	Married/cohabitant	2152	60.7	459	62.8	1446	61.0	247	55.6	
	Divorced/separated	153	4.3	40	5.5	93	3.9	20	4.5	
	Widow/widower	61	1.7	9	1.2	45	1.9	7	1.6	
	Missing	740	20.9	92	12.6	536	22.6	112	25.2	

Distribution within characteristics is given by column unless stated by *

*Distribution by row, i.e., within study population

**Analyses restricted to participants ≥ 18 years

[a] *P* values from Pearson's x^2-test of association calculated from cross tables not including missing values and 'uncertain group'

Table 2 Characteristics of the study population, by cases with self-reported gastroenteritis, non-cases, and the uncertain group, during the *Campylobacter* outbreak in Askøy

		All		Cases		Non-cases		Uncertain		x^2
		n	%	*n*	%	*n*	%	*n*	%	p^a
Total		3624	100	749	20.7*	2417	66.7*	458	12.6*	
Tap water (glasses/day)[b]										< 0.01
	0	225	6.2	21	2.8	183	7.6	21	4.6	
	1–2	963	26.6	158	21.1	664	27.5	141	30.8	
	3–5	1450	40.0	319	42.6	952	39.4	179	39.1	
	> 5	976	26.9	247	33.0	612	25.3	117	25.5	
	missing	10	0.3	4	0.5	6	0.2	0	0.0	
Alcohol (units/week)**[c]										< 0.01
	0	1396	39.1	328	44.6	894	37.5	174	39.0	
	1–2	999	28.0	191	26.0	682	28.6	126	28.3	
	3–5	539	15.1	100	13.6	375	15.7	64	14.3	
	6–9	191	5.4	45	6.1	126	5.3	20	4.5	
	10–14	81	2.3	15	2.0	57	2.4	9	2.0	
	≥ 15	26	0.7	4	0.5	18	0.8	4	0.9	
	missing	336	9.4	52	7.1	235	9.8	49	11.0	
Tobacco**										0.75
	Yes	1602	44.9	322	43.8	1076	45.1	204	45.7	
	No	1895	53.1	401	54.6	1260	52.8	234	52.5	
	Missing	71	2.0	12	1.6	51	2.1	8	1.8	
Previous diseases										
	None	1860	51.3	332	44.3	1329	55.0	199	43.4	< 0.01
	Diabetes	142	3.9	22	2.9	105	4.3	15	3.3	0.09
	Ulcerative colitis	50	1.4	6	0.8	34	1.4	10	2.2	0.20
	Crohn's disease	16	0.4	4	0.5	7	0.3	5	1.1	0.32
	Oesophagitis	150	4.1	41	5.5	88	3.6	21	4.6	0.03
	Irritable bowel syndrome	318	8.8	76	10.1	187	7.7	55	12.0	0.04
	Celiac disease	35	1.0	12	1.6	17	0.7	6	1.3	0.02
	Peptic ulcer	93	2.6	24	3.2	51	2.1	18	3.9	0.09
	Anxiety	325	9.0	83	11.1	187	7.7	55	12.0	< 0.01
	Depression	344	9.5	89	11.9	207	8.6	48	10.5	< 0.01
	Rheumatic/inflammatory	207	5.7	54	7.2	121	5.0	32	7.0	0.02

Distribution within characteristics is given by column unless stated by *

*Distribution by row, i.e., within study population

**Analyses restricted to participants ≥ 16 years old

[a] *p* values from Pearson's x^2-test of association calculated from cross tables not including missing values and 'uncertain group'

[b] Average daily number of tap water glasses during week before outbreak

[c] Units of alcohol during a normal week

25–54 years, whereas diarrhea was most common in age category 25–54 years. Bloody stools were most frequently reported by cases in the age category 0–24 years (25.6%); however, none of these was under the age of 15 years. In age category 25–54 years, bloody stools were reported in 14.7%, and in 8.6% of those 55 years or older.

Illness duration ranged from 0 to 24 days, with a median at 6 days (interquartile range: 4–9 days) (Table 3). Nine percent (n = 68) reported still being ill at the time of answering the survey (data not shown). Slightly more men than women reported illness duration of 0–3 days (16.8% vs. 14.0%, $p = 0.04$) and ≥ 15 days (5.6% vs. 3.8%, $p = 0.04$), while an illness duration of 8–14 days was more common in women than men (27.5% vs. 18.2%, $p = 0.04$). For illness duration of 4–7 days, no sex difference was observed. No significant differences across age were observed for the illness duration distribution (Table 3).

Table 3 Symptoms, management, and consequences of illness during the *Campylobacter* outbreak in Askøy, by age

Age category (years)		All		0–24		25–54		≥55		Missing		x^2
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*p***
Total		749	100	86	11.5*	442	59.0*	163	21.8*	58	7.7*	
Symptoms												
	Loose stools	679	90.7	77	89.5	408	92.3	144	88.3	50	86.2	0.73
	Diarrhea	666	88.9	70	81.4	408	92.3	138	84.7	50	86.2	0.04
	Bloody stools	106	14.2	22	25.6	65	14.7	14	8.6	5	8.6	< 0.01
	Nausea	554	74.0	71	82.6	321	72.6	120	73.6	42	72.4	0.12
	Vomit	180	24.0	31	36.0	93	21.0	40	24.5	16	27.6	0.01
	Abdominal pain	669	89.3	78	90.7	400	90.5	142	87.1	49	84.5	0.94
	Fever	478	63.8	69	80.2	271	61.3	107	65.6	31	53.4	< 0.01
	Joint pain	376	50.2	40	46.5	225	50.9	84	51.5	27	46.6	0.22
	Tiredness	683	91.2	82	95.3	396	89.6	151	92.6	54	93.1	< 0.01
Illness duration (days)												0.43
	0–3	120	16.0	13	15.1	75	17.0	16	9.8	16	27.6	
	4–7	316	42.2	40	46.5	196	44.3	53	32.5	27	46.6	
	8–14	171	22.8	22	25.6	108	24.4	33	20.2	8	13.8	
	≥15	33	4.4	6	7.0	16	3.6	10	6.1	1	1.7	
	Missing	109	14.6	5	5.8	47	10.6	51	31.3	6	10.3	
Consulted doctor		203	27.1	31	36.0	109	24.7	53	32.5	10	17.2	0.01
Hospitalized		33	4.4	3	3.5	16	3.6	12	7.4	2	3.4	0.12
Absence school/work		414	55.3	59	68.6	281	63.6	46	28.2	28	48.3	< 0.01
Medication												
	None	184	24.6	21	24.4	109	24.7	42	25.8	12	20.7	0.03
	Antibiotics	21	2.8	2	2.3	10	2.3	8	4.9	1	1.7	0.12
	Loperamide	93	12.4	7	8.1	49	11.1	35	21.5	2	3.4	< 0.01
	Tramadol	13	1.7	1	1.2	5	1.1	6	3.7	1	1.7	0.10
	Codeine + paracetamol	41	5.5	3	3.5	24	5.4	8	4.9	6	10.3	0.39
	Paracetamol	470	62.8	59	68.6	281	63.6	92	56.4	38	65.5	0.58
	NSAIDs	238	31.8	41	47.7	156	35.3	21	12.9	20	34.5	< 0.01
	Probiotics	167	22.3	17	19.8	101	22.9	35	21.5	14	24.1	0.02

Distribution within characteristics is given by column unless stated by *

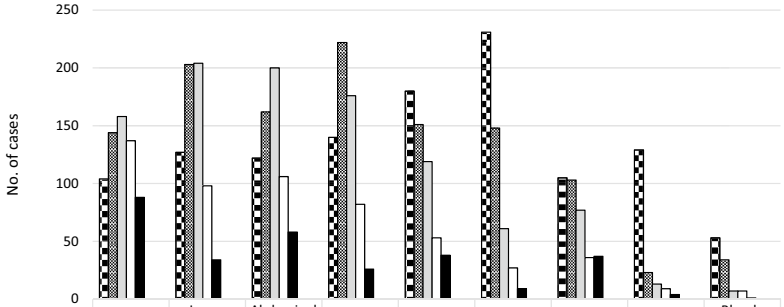
*Distribution by row

** p value from Pearson's x^2-test of association calculated from cross tables not including missing values

Each symptom's duration turned out to fit into one of to two main patterns (Fig. 2): symptoms with (1) an approximate bell-shaped distribution where most cases reported either 3–4 days or 4–7 days duration (tiredness, loose stools, abdominal pain and diarrhea), and (2) symptoms most frequently reported to last for either 1–2 days or 3–4 days with a subsequent decrease (nausea, fever, joint pain, vomiting and bloody stools). At the time of answering the survey, the proportions of cases reporting each symptom being 'still present' were: tiredness 15.9%, abdominal pain 9.0%, joint pain 8.5%, nausea 6.1%, diarrhea 6.0%, loose stools 5.9%, fever 1.3%, bloody stools 1.2%, and vomiting 0.5% (data not shown).

Paracetamol (62.8%) was the medication most frequently reported for treatment of the acute illness, followed by non-steroidal anti-inflammatory drugs (NSAIDs) (31.8%) (Table 3). Antibiotics use was reported by 2.8% (n = 21) of the cases, of which none were under the age of 15 years. Among the hospitalized cases, 30.3% (n = 10) reported antibiotics use, compared to 1.5% (n = 11) of those not hospitalized. Loperamide was reported by 12.4% ($n = 93$) of the cases, most commonly used by those aged ≥ 55 years (21.5%) and least common in age category 0–24 years (8.1%). No cases under the age of 15 years reported use of loperamide. No significant differences between the sexes were observed for consulting a doctor, hospitalization, or any medication (data not shown).

Twenty-seven percent ($n = 203$) of the cases reported to have consulted a primary care doctor, which was more common among the youngest and oldest compared to the



	Tiredness	Loose stools	Abdominal pain	Diarrhoea	Nausea	Fever	Joint pain	Vomit	Bloody stools
1-2 days	104	127	122	140	180	231	105	129	53
3-4 days	144	203	162	222	151	148	103	23	34
5-7 days	158	204	200	176	119	61	77	13	7
1-2 weeks	137	98	106	82	53	27	36	9	7
≥2 weeks	88	34	58	26	38	9	37	4	1
Missing	52	13	21	20	13	2	18	2	4
Total	683	679	669	666	554	478	376	180	106

Fig. 2 Duration of symptoms reported by cases with self-reported gastroenteritis, during the *Campylobacter* outbreak in Askøy. N = 749

middle-aged cases (Table 3). Four percent had been admitted to hospital, most commonly in the age category ≥ 55 years (Table 3). No cases below 15 years of age reported being admitted to hospital.

Twenty-four percent of the cases (n = 177) fulfilled the definition of 'severe gastroenteritis', and Supplementary tables 1 and 2 show the distribution and characteristics of these patients. There were significant positive associations between the outcome 'severe gastroenteritis', and the reported perceived severity at the worst time point of the illness (Table 4). Furthermore, cases with severe gastroenteritis more often had been in contact with a primary care doctor or were hospitalized (Table 4).

Compared to the others, cases with severe gastroenteritis more often reported drinking > 5 glasses of tap water (41.2% vs 30.4%, $p = 0.02$), previous peptic ulcer (13.6% vs 2.3%, $p = 0.01$) and previous depression (16.9% vs 10.3%, $p = 0.02$) (Supplementary table 2). In the adjusted regression analyses, previous depression (RR: 1.61, 95% CI 1.16–2.24) and previous peptic ulcer (RR: 1.73, 95% CI 1.00–2.99) remained significant (Table 5). Further, age 55–64 years (RR: 0.62, 95% CI 0.41–2.46) and 35–44 (RR: 0.52, 95% CI 0.35–0.77), were associated with a lowered risk of severe gastroenteritis as compared to the reference age category 45–54 years, although the RR for age 55–64 years was not significant in the unadjusted regression model.

Discussion

The typical gastroenteritis cases during the *Campylobacter* outbreak in our study were adults experiencing illness lasting for 4–7 days, with diarrhea, abdominal pain, and tiredness as the most common symptoms. About one in two of the cases reported fever or joint pain, whereas bloody stools and vomiting were less common. One in four of the cases fulfilled our definition of severe gastroenteritis. Risk factors associated with severe gastroenteritis were having depression or peptic ulcer prior to the outbreak, in addition to high consumption of tap water. Approximately 1 in 4 had consulted a doctor, and 4% had been hospitalized.

A main strength of this study was that data were collected during the acute phase of a large outbreak, which increases statistical power and reduces recall bias considerably. This also constitutes a solid basis for follow-up studies of post-infectious complaints after the outbreak.

Invitations to participate in the study were sent by the municipality of Askøy as text message to mobile phones using the municipality's warning system, an approach that had recently been used by the municipality and the Norwegian Institute of Public Health as part of their outbreak investigation [28]. Askøy municipality has 29,500 inhabitants, and not all could be reached by this approach.

Table 4 Health care seeking and perceived severity of illness during the *Campylobacter* outbreak in Askøy, by cases with severe or non-severe gastroenteritis

		All		Non-severe		Severe		x^2
		n	%	*n*	%	*n*	%	p^a
Total		749	100	572	76.4*	177	23.6*	
Contacted doctor								< 0.01
	Yes	203	27.1	117	20.5	86	48.6	
	No	539	72.0	450	78.7	89	50.3	
	Uncertain	5	0.7	3	0.5	2	1.1	
	Missing	2	0.3	2	0.3	0	0.0	
Hospitalized								0.01
	Yes	33	4.4	16	2.8	17	9.6	
	No	715	95.5	555	97.0	160	90.4	
	Missing	1	0.1	1	0.2	0	0.0	
Perceived severity[b]								< 0.01
	1 well	8	1.1	6	1.0	2	1.1	
	2	39	5.2	37	6.5	2	1.1	
	3	125	16.7	118	20.6	7	4.0	
	4	152	20.3	133	23.3	19	10.7	
	5	157	21.0	133	23.3	24	13.6	
	6	160	21.4	99	17.3	61	34.5	
	7	83	11.1	37	6.5	46	26.0	
	8	21	2.8	8	1.4	13	7.3	
	9 life threatening	4	0.5	1	0.2	3	1.7	

Distribution within characteristics is given by column unless stated by *

*Distribution by row

[a]*p* values from Pearson's x^2-test of association calculated from cross tables between cases with non-severe and severe gastroenteritis

[b]Self-reported perceived severity at worst time point of illness. Scale from 1 (well) to 9 (life threatening)

Information about age and sex were extracted from the national identity number, for those who had stated this. Using this procedure secured precise information for those who responded to this request, but resulted in missing data for those who did not want to give this information.

As many as 458 participants, 12.6% of the study population, were uncertain whether they had been ill with acute gastrointestinal infection during the outbreak. Many persons in this group were likely having incident diffuse symptoms of other causes, but the size of the groups suggests that a fraction represents the less severe end of the spectrum of *Campylobacter* infection. As this group was not asked questions about symptoms, we could not categorize them as neither cases or non-cases based on such information. The uncertain group had the greatest proportion of missing data for most variables, representing a group with more uncertain answers overall. Since the cases were not laboratory confirmed nor did we have variables to verify exposure to *Campylobacter*, such as detailed information on the drinking water supply, we could not investigate potential risk factors for developing campylobacteriosis during the outbreak.

Cases were not verified by a clinician's diagnosis or by laboratory information. Using this population-based approach, we were able to investigate a broad spectrum of symptoms during the outbreak. However, this also introduces some limitations. By use of a self-administered online questionnaire, we defined a 'case' based on the participants' self-reported information about their geographical presence, onset of illness and symptoms related to the outbreak. There exist no common, symptom-based definitions of campylobacteriosis or gastroenteritis that are widely used for research purposes. Thus, our case definition was a modification of case definitions used in previous studies [33–36].

Our definition of 'severe gastroenteritis' was based on existing literature [6, 13, 15, 16], as well as clinical experiences and expertise among members in the research group, and aimed to capture a set of symptoms which indicated a greater extent of both local inflammation in the bowels (diarrhea for ≥ 5 days or bloody stools) and more generalized disease (fever > 2 days). We observed an association between 'severe gastroenteritis', and perceived severity at the worst time point during the illness, and health care use, which to some extent suggests validity to the definition.

Population-based cohort studies describing the clinical features of *Campylobacter* infection during an ongoing outbreak, are scarce in existing literature. The proportion of

Table 5 Severe gastroenteritis by characteristics, during the *Campylobacter* outbreak in Askøy. Unadjusted and adjusted relative risks (RR) with 95% confidence intervals (CIs)

		Unadjusted		Adjusted[a]	
		RR	CI	RR	CI
Sex					
	Male	1.14	0.89—1.48	1.29	1.00—1.66
	Female	Reference		Reference	
Age group (years)					
	0–4	1.02	0.32—3.22	1.23	0.35—4.37
	5–14	0.38	0.06—2.42	0.35	0.05—2.26
	15–24	0.89	0.59—1.36	0.77	0.50—1.20
	25–34	0.85	0.59—1.22	0.76	0.52—1.11
	35–44	0.54	0.36—0.80	0.52	0.35—0.77
	45–54	Reference		Reference	
	55–64	0.67	0.43—1.02	0.62	0.41—0.94
	65–74	0.65	0.37—1.14	0.62	0.36—1.10
	75–84	0.92	0.35—2.42	0.89	0.32—2.46
	≥ 85	NA		NA	
Tap water (glasses/day)[b]					
	0	0.83	0.34—2.06	0.76	0.32—1.81
	1–2	0.72	0.48—1.08	0.73	0.49—1.09
	3–5	Reference		Reference	
	> 5	1.29	0.98—1.71	1.29	0.97—1.71
Diseases					
	None	0.84	0.65—1.10		
	Diabetes	1.56	0.89—2.76		
	Ulcerative colitis	2.14	0.95—4.81		
	Crohn's disease	1.06	0.19—5.81		
	Oesophagitis	1.37	0.86—2.19		
	Irritable bowel syndrome	1.26	0.86—1.84		
	Celiac disease	0.35	0.05—2.29		
	Peptic ulcer	2.00	1.27—3.16	1.73	1.00—2.99
	Anxiety	1.32	0.92—1.89		
	Depression	1.51	1.09—2.09	1.61	1.16—2.24
	Rheumatic/inflammatory	0.94	0.56—1.57		

[a]Adjusted for sex, age, intake of tap water, peptic ulcer and depression

[b]Average daily number of tap water glasses during week before outbreak

NA not applicable

children with acute gastroenteritis was lower in our study compared to previous studies of *Campylobacter* infections [9, 10]. Selection bias may have led to underrepresentation of the elderly and children. The latter is suggested by our previous finding of 17 patients under the age of 16 years in the study that characterized hospitalized patients during the same outbreak [29], whereas the present study found no hospitalized cases under the age of 15 years.

Our finding of diarrhea and abdominal pain as the most common, and bloody stools and vomiting as the least common symptoms of acute gastroenteritis in the outbreak setting, is in line with previous literature on *Campylobacter* infection [8–10, 14, 34, 37]. The proportion of cases reporting bloody stools were 14% in the present study, which is higher compared to the findings in two previous outbreak investigation studies: a population-based study of an outbreak in Røros, Norway (2%) [34], and in a study of cases included among patients seeking health care services (of which 16% were laboratory confirmed) during an outbreak in Finland (4%) [37]. The two previously published studies of the Askøy outbreak; NIPH's population-based outbreak investigation study (6%) [34] and the study of hospitalized cases (9%), also found lower proportions of bloody stools than the present study [28, 29]. Higher proportions of bloody stools, ranging from 30 to 58%, are reported in a study of laboratory confirmed cases in general practice in the Netherlands [9], of sporadic notified cases in Norway [10], of laboratory confirmed cases aged 0–14 years in an outbreak

in Greece [38], and notified cases in Australia, Canada and the United states [14]. The latter study also reported association between age and bloody stools, in line with our finding, although their proportions of bloody diarrhea among the youngest (59% in age < 5 years, 49% in 5–24 years) were higher than in our study (25.6% aged < 25 years, but none < 15 years). The reason for lower proportions of bloody stools reported in outbreak studies, including the present study, may be that they capture a broader scope of clinical features than represented by the laboratory confirmed cases. The corresponding low proportion of bloody stools observed in the study of hospitalized patients during the Askøy outbreak, can be explained by a possible lowered threshold for referral due to fatal outcome in the initial phase of the outbreak, thus leading to hospitalization of less severe cases [29]. However, virulence factors associated with bloody stools of the particular strain of *Campylobacter jejuni* cannot be ruled out [29].

Joint pain was more common in our study compared to a Norwegian study of sporadic campylobacteriosis from 1992 (50% vs. 27%) [10], but otherwise seems to be scarcely described in existing literature as a symptom during the acute phase of *Campylobacter* infection. Tiredness was not a case-defining symptom, but still the most frequently reported in our study. We could not find descriptions of tiredness in published studies, probably because it is unspecific to gastroenteritis or *Campylobacter* infection. However, documenting the baseline level of the symptom at the time of the outbreak is useful to follow-up studies of post-infectious complaints, and should perhaps be investigated further in future outbreaks. Our findings of more common joint pain and less bloody stools in these cases with self-reported gastroenteritis than previously reported in studies of laboratory confirmed *Campylobacter* cases, may reflect that the population-based approach may capture a broader spectrum of clinical features of acute gastroenteritis during in the *Campylobacter* outbreak setting.

Median duration of illness observed in our study (6 days) is in line with what is commonly reported in previous studies (5–6 days) [14, 34, 37], except for the Norwegian study of sporadic cases from 1992 reporting median 11 days duration [10].

A total of 3%, none under the age of 15 years, and 30% of the hospitalized cases in the current study received antibiotic treatment. The study of hospitalized patients during the same outbreak found that one in two of children and one in ten of adults received antibiotics [29]. Kapperud et al. reported in 1992 that 16% of 135 sporadic laboratory confirmed cases in Norway were treated with antibiotics [10], and White et al. 2019 reported an antibiotic treatment proportion of 35% in culture confirmed cases in Australia, Canada and the United States [14], although neither discriminated between hospitalized and non-hospitalized treatment proportions. Our finding of low antibiotic treatment proportion is concordant with the recommendations, and with a generally cautious policy regarding use of antibiotics in Norway [6, 24, 25, 39].

Risk factors associated with severe gastroenteritis were high consumption of tap water, having depression or peptic ulcer prior to the outbreak, whereas being in the age category 35–44 seemed to be protective. As the outbreak was waterborne, the association between high consumption of tap water and severe gastroenteritis probably indicates a dose–response relationship. Psychological comorbidity has previously been shown to increase susceptibility to develop infectious gastroenteritis [23], but bias may lead to reporting of more severe symptoms in cases with depression, as the symptom pressure can be perceived as more burdensome in this patient group. However, this effect should have been reduced because the outcome 'severe gastroenteritis' in these analyses was defined by reported symptoms rather than the cases' own assessment of perceived illness severity. Peptic ulcer as a risk factor for severe illness is reasonable, as a gastrointestinal disease, and not least presumably often treated with anti-acidic medication which may cause vulnerability to a more severe illness.

Conclusions

We present clinical features of self-reported acute gastroenteritis in a population during a large waterborne outbreak of *Campylobacter* infection. The most common symptoms were loose stools, abdominal pain, and diarrhea. About one in four of the cases reported symptoms consistent with severe gastroenteritis. Although not a gastroenteritis specific symptom, tiredness was the overall most common symptom, but is rarely described in previous studies of acute campylobacteriosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s15010-021-01652-3.

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Data availability The data underlying this article cannot be shared publicly due to limitations given by the ethical approval by the Regional Committee for Medical and Health Research Ethics.

Declarations

Conflict of interest None.

Ethical approval Regional Committee for Medical and Health Research Ethics, REC West (project number 2019/1086).

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Supplementary table 1. Demographic characteristics of cases with self-reported gastroenteritis, by severe and non-severe gastroenteritis, during the campylobacter outbreak in Askøy.

	All		Non-severe		Severe		x^2
	n	*%*	*n*	*%*	*n*	*%*	p^b
Total	749	100	572	76.4*	177	23.6*	
Sex							0.31
male	303	40.5	221	38.6	82	46.3	
female	393	52.5	300	52.4	93	52.5	
missing	53	7.1	51	8.9	2	1.1	
Age range (years)		1-82		1-82		1-79	
Age							0.11
0-4	6	0.8	4	0.7	2	1.1	
5-14	8	1.1	7	1.2	1	0.6	
15-24	72	9.6	51	8.9	21	11.9	
25-34	112	15.0	81	14.2	31	17.5	
35-44	159	21.2	131	22.9	28	15.8	
45-54	171	22.8	115	20.1	56	31.6	
55-64	101	13.5	79	13.8	22	12.4	
65-74	52	6.9	41	7.2	11	6.2	
75-84	10	1.3	7	1.2	3	1.7	
≥85	0	0.0	0	0.0	0	0.0	
missing	58	7.7	56	9.8	2	1.1	
Marital status**							
single	131	17.9	92	16.5	39	22.4	0.50
married/cohabitant	459	62.8	343	61.6	116	66.7	
divorced/separated	40	5.5	31	5.6	9	5.2	
widow/widower	9	1.2	8	1.4	1	0.6	
missing	92	12.6	83	14.9	9	5.2	
Education level**							0.31
elementary school	47	6.4	36	6.5	11	6.3	
high school	299	40.9	214	38.4	85	48.9	
university/college	290	39.7	223	40.0	67	38.5	
missing	95	13.0	84	15.1	11	6.3	
Employment**							0.06
student/pupil	34	4.7	22	3.9	12	6.9	
worker	459	62.8	346	62.1	113	64.9	
self employed	20	2.7	16	2.9	4	2.3	
unemployed	22	3.0	16	2.9	6	3.4	
on welfare	55	7.5	33	5.9	22	12.6	
pensioner	50	6.8	42	7.5	8	4.6	
missing	91	12.4	82	14.7	9	5.2	
Household income							0.44
< 250000	23	3.1	15	2.6	8	4.5	
250000-499999	89	11.9	71	12.4	18	10.2	

500000-749999	130	17.4	91	15.9	39	22.0
750000-1000000	171	22.8	129	22.6	42	23.7
> 1000000	191	25.5	142	24.8	49	27.7
missing	145	19.4	124	21.7	21	11.9

Distribution within characteristics is given by column unless stated by *.
* Distribution by row.
** Analyses restricted to participants ≥18 years old.
[a] P-values from Pearson's x^2-test of association calculated from cross tables that do not include missing values.

Supplementary table 2. Characteristics of cases with self-reported gastroenteritis, by severe and non-severe gastroenteritis, during the campylobacter outbreak in Askøy.

	All		Non-severe		Severe		x^2
	n	*%*	*n*	*%*	*n*	*%*	p^a
Total	749	100	572	76.4	177	23.6	
Tap water (glasses/day)[b]							0.02
0	21	2.8	17	3.0	4	2.3	
1-2	158	21.1	132	23.1	26	14.7	
3-5	319	42.6	246	43.0	73	41.2	
>5	247	33.0	174	30.4	73	41.2	
missing	4	0.5	3	0.5	1	0.6	
Alcohol (units/week)**[c]							0.44
0	328	44.6	255	45.5	73	42.0	
1-2	191	26.0	151	26.9	40	23.0	
3-5	100	13.6	75	13.4	25	14.4	
6-9	45	6.1	30	5.3	15	8.6	
10-14	15	2.0	11	2.0	4	2.3	
≥15	4	0.5	4	0.7	0	0.0	
missing	52	7.1	35	6.2	17	9.8	
Tobacco**							0.23
yes	322	43.8	240	42.8	82	47.1	
no	401	54.6	314	56.0	87	50.0	
missing	12	1.6	7	1.2	5	2.9	
Previous diseases							
none	332	44.3	261	45.6	71	40.1	0.20
diabetes	22	2.9	14	2.4	8	4.5	0.15
ulcerative colitis	6	0.8	3	0.5	3	1.7	0.13
Crohns disease	4	0.5	3	0.5	1	0.6	0.10
oesophagitis	41	5.5	28	4.9	13	7.3	0.21
IBS	76	10.1	54	9.4	22	12.4	0.25
celiac disease	12	1.6	11	1.9	1	0.6	0.21
peptic ulcer	37	4.9	13	2.3	24	13.6	0.01
anxiety	83	11.1	58	10.1	25	14.1	0.14
depression	89	11.9	59	10.3	30	16.9	0.02
rheumatic/inflammatory	54	7.2	42	7.3	12	6.8	0.80

Distribution within characteristics is given by column unless stated by *.
* Distribution by row.
** Analyses restricted to participants ≥16 years old.
[a] P-values from Pearson's x^2-test of association calculated from cross tables that do not include missing values.
b Average daily number of tap water glasses during week before outbreak.
c Units alcohol during a normal week.

APPENDIX

Paper version of web-based questionnaire for Paper III

Spørreundersøkelse om mageinfeksjonutbruddet på Askøy i juni 2019

Takk til alle som svarte på Askøy kommune og Folkehelseinstituttet sin spørreundersøkelse nylig. Det gav nyttig informasjon om utbruddet, og bidro til å vurdere tiltakene som ble iverksatt.

Vi ønsker at ALLE som mottar denne henvendelsen svarer, også om du IKKE var syk under utbruddet. Undersøkelsen tar ca 12 minutter å gjennomføre. Vi setter pris på om du svarer så snart som mulig, men innen 30. juni.
I denne undersøkelsen spør vi etter helse- og personoppysninger som er nyttige for forskningsformål, blant annet for å følge opp Askøys befolkning i tiden etter utbruddet.
Dette er en oppfølging av den undersøkelsen, samtidig med en forespørsel til deg om å delta i et forskningsprosjekt der Universitetet i Bergen i samarbeid med Askøy kommune, Folkehelseinstituttet, NORCE Norwegian Research Centre og Helse Bergen undersøker omfanget og alvorlighetsgraden av mageinfeksjonsutbruddet på Askøy og konsekvensene for folks helse på sikt. Prosjektet vil kunne bidra til å danne grunnlag for bedre behandling og oppfølging av pasienter rammet av slike infeksjoner.
Trykk HER for å lese utdypende informasjonsskriv med følgende tema (blir åpnet i eget vindu).

- Hva innebærer prosjektet?
- Mulige fordeler og ulemper
- Frivillig deltakelse og mulighet for å trekke sitt samtykke
- Hva skjer med prøver og opplysninger om deg?
- Oppfølgingsprosjekt
- Godkjenning
- Kontaktopplysninger

Du beveger deg frem og tilbake i spørreskjemaet ved å klikke på pilene nederst på siden. Svarene dine mellomlagres i systemet og du kan til enhver tid avbryte din besvarelse, for senere å gå inn i spørreskjemaet og fullføre besvarelsen ved å klikke på linken i e-posten. De fleste spørsmål er frivillige å svare på.

Dersom du har spørsmål til prosjektet kan du ta kontakt med.
Prosjektleder og professor Guri Rørtveit, tlf. 55 58 61 41, e-post guri.rortveit@uib.no.

Personvernombud ved Universitetet i Bergen er:
Janecke Veim, e-post janecke.veim@uib.no

Har du fylt 16 år?

- ☐ Ja
- ☐ Nei

Vi vil gjerne at du fyller ut spørreskjemaet, men siden du er under 16 år, krever norsk lov at vi får skriftlig samtykke av en av dine foresatte. Vennligst trykk her for å laste ned samtykkeskjema som du kan fylle ut og returnere til oss enten ved å

1) skanne og sende på mail til prosjektleder og professor Guri Rørtveit, tlf. 55 58 61 41, e-post guri.rortveit@uib.no.

eller

2) sende som brevpost til
Universitetet i Bergen
Institutt for global helse og samfunnsmedisin
Guri Rørtveit
Postboks 7804
5020 BERGEN

Vennligst bekreft at du har samtykke fra en av dine foresatte til å fortsette undersøkelsen

- ☐ Ja, jeg har samtykke
- ☐ Nei, jeg har ikke samtykke

Svar på spørsmålene i denne undersøkelsen regner vi som et samtykke til at vi kan bruke svarene dine til forskning. Dersom du ikke ønsker å delta kan du lukke nettleseren nå.

Har du blitt syk under dette mageinfeksjonsutbruddet?

- ☐ Ja
- ☐ Nei
- ☐ Usikker

Når ble du syk under dette utbruddet?

_____

Angi hvilke symptomer du har hatt, og i så fall antall dager symptomet varte. Hvis du fortsatt opplever symptomer kan du oppgi dette. Hvis du ikke har opplevd et symptom, kan du svare "ingen symptom".

	Nei, ikke hatt dette symptomet	1-2 dager	3-4 dager	5-7 dager	1-2 uker	Over 2 uker	Fortsatt tilstede
Løs/vandig avføring	☐	☐	☐	☐	☐	☐	☐
3 eller flere avføringer per dag	☐	☐	☐	☐	☐	☐	☐
Blod i avføringen	☐	☐	☐	☐	☐	☐	☐
Kvalme	☐	☐	☐	☐	☐	☐	☐
Oppkast	☐	☐	☐	☐	☐	☐	☐

Magesmerter	❑	❑	❑	❑	❑	❑	❑
Feber	❑	❑	❑	❑	❑	❑	❑
Leddsmerter	❑	❑	❑	❑	❑	❑	❑
Slapphet	❑	❑	❑	❑	❑	❑	❑
Andre	❑	❑	❑	❑	❑	❑	❑

Hvis du hadde andre symptomer, vennligst angi hvilke (adskilt med komma)

Hvor mange dager var du syk totalt sett?

Hvor syk var du da du var på det sykeste?
Svar på en skala fra 1-9 der 1 er frisk og 9 er livstruende syk.

- ❑ 1. Frisk
- ❑ 2
- ❑ 3
- ❑ 4
- ❑ 5
- ❑ 6
- ❑ 7
- ❑ 8
- ❑ 9. Livstruende syk

Er du fortsatt syk?

- ❑ Ja
- ❑ Nei
- ❑ Usikker

Var du hos lege (fastlege/sykehjemslege/legevaktlege) for plagene?

- ❑ Ja
- ❑ Nei
- ❑ Usikker

Ble du innlagt i sykehus for den aktuelle sykdommen?

- ❑ Ja
- ❑ Nei

Har du hatt fravær fra jobb, skole eller barnehage i perioden grunnet mageinfeksjonsutbruddet?

- ❑ Ja
- ❑ Ja, men fraværet skyldes ikke mageinfeksjonutbruddet
- ❑ Nei
- ❑ Ikke relevant

Er du fremdeles fraværende fra jobb, skole eller barnehage?

- ❑ Ja
- ❑ Nei

Angi periode du var fraværende fra jobb eller skole

Fra dato

Til dato

Har du brukt medikamenter for mageinfeksjonen under utbruddet?

	Ja	Nei	Vet ikke
Ingen	❑	❑	❑
Antibiotika	❑	❑	❑
Imodium/loperamid	❑	❑	❑
Tramadol/Nobligan	❑	❑	❑
Paralgin forte/Pinex forte	❑	❑	❑
Paracet/Pinex/Panodil/paracetamol	❑	❑	❑
Ibux/ibuprofen	❑	❑	❑
Probiotika, f.eks. Biola, Cultura, Idoform	❑	❑	❑

Brukte du andre medisiner for mageinfeksjonen?

Skriv hvilke medisiner, skilt med komma

Du får noen ekstra spørsmål fra Folkehelseinstituttet siden svarte at du ble syk etter 12. juni

Hva tror du selv er årsaken til sykdommen?

Kjenner du til andre personer som har, eller har hatt, samme symptomer som deg i uken før eller uken etter at sykdommen din startet?

- ☐ Ja
- ☐ Nei

Er vedkommende medlem av samme husholdning som deg?

- ☐ Nei
- ☐ Ja

Ble vedkommende syk før eller etter at sykdommen din begynte?

- ☐ Før
- ☐ Etter
- ☐ Samtidig

Hvor mye vann har du drukket daglig fra springen hjemme (inkludert saftblanding) siden torsdag 13. juni?

- ☐ 0 Glass
- ☐ 1-3 glass
- ☐ 4-6 glass
- ☐ > 6 glass

Har du fulgt kokeanbefalingene siden 13. juni 2019?

- ☐ Ja
- ☐ Nei

Hvorfor valgte du ikke å følge kokeanbefalingen(e)? Flere kryss mulig.

- ☐ Glemte det
- ☐ Vannet var klart og ok
- ☐ Kjøpte vann på flaske
- ☐ Tenkte det var liten eller ingen risiko for å bli syk
- ☐ Drikker ikke/generelt lite vann fra springen
- ☐ Vet ikke/husker ikke

Til hvilken bruk valgte du å koke vannet? Flere kryss mulig.

- ☐ Drikke
- ☐ Matlaging
- ☐ Tannpuss
- ☐ Isbiter
- ☐ Blande saft
- ☐ Vaske frukt/grønnsaker
- ☐ Annet
- ☐ Husker ikke/vet ikke

Hvor mange glass vann fra springen drakk du daglig i gjennomsnitt den siste uken før utbruddet?

- ☐ Ingen
- ☐ 1-2
- ☐ 3-5
- ☐ Flere enn 5

I hvor mange dager drakk du vann fra springen etter at du ble syk?

_____

Hvor mange glass drakk du i gjennomsnitt per dag etter at du ble syk?

- ☐ Ingen
- ☐ 1-2
- ☐ 3-5
- ☐ Flere enn 5

Har du drukket vann fra Kleppe vannverk?

- ☐ Ja
- ☐ Nei

- [ ] Usikker

Har du hatt nærkontakt med andre som kan ha vært syke med mageinfeksjon i perioden?
- [ ] Ja
- [ ] Nei
- [ ] Vet ikke

Har du oppholdt deg sammenhengende utenfor Askøy kommune i hele perioden fra 31.mai og til i dag?
- [ ] Ja
- [ ] Nei
- [ ] Usikker

Hvor mange enheter alkohol drikker du vanligvis i løpet av en uke (1 enhet: 0,33l øl, 1 glass vin, 4cl brennevin)?

_____

Hva er ditt forhold til tobakksrøyking?
- [ ] Nåværende daglig røyker
- [ ] Sporadisk røyker
- [ ] Tidligere daglig røyker
- [ ] Aldri røykt

Har du eller har du hatt noen av disse sykdommene før utbruddet? Flere kryss mulig.

- [ ] Ingen av disse
- [ ] Diabetes
- [ ] Ulcerøs colitt
- [ ] Crohns sykdom
- [ ] Spiserørsbetennelse
- [ ] Irritabel tarmsyndrom
- [ ] Cøliaki
- [ ] Magesår
- [ ] Angst
- [ ] Depresjon
- [ ] Leddgikt/leddbetennelse
- [ ] Andre

Ved avkryssing av "andre" over, vennligst skriv hvilke, skilt med komma

Hvilke av disse medisinene har du brukt siste måned? Flere kryss mulig.

- [ ] Ingen
- [ ] Magesyredempende medisiner (eks: Nexium/esomeprazol, lansoprazol, Losec/omeprazol, Somac/pantoprazol, novalucid, titralac, Zantac/ranitidin, cimetidine)
- [ ] Immundempende medisin (eks: prednisolon, imurel, methotrexate, cellegift)
- [ ] Probiotika (eks: Biola, Cultura, Idoform)
- [ ] Medisin mot diaré (eks imodium, loperamid)
- [ ] Kvalmedempende(eks: afipran/metoklopramid, zofran/ondansetron)
- [ ] Betennelsesdempende (eks: ibux, ibuprofen, voltaren/diklofenac, celebra/celecoxib, napren/naproxen, Brexidol/piroxicam)
- [ ] Paracet, Paracetamol/panodil
- [ ] Acetylsalisylsyre (eks: Albyl-E, Dispril, Aspirin)
- [ ] Antibiotika

Vi ønsker nå at du svarer på noen spørsmål om din helse fra før utbruddet startet, det vil si før 31.mai.

I løpet av siste tre måneder før utbruddet, hvor ofte har du hatt ubehag eller smerter noe sted i magen?
- [ ] Aldri
- [ ] Mindre enn 1 dag i måneden
- [ ] En dag i måneden
- [ ] 2-3 dager i måneden
- [ ] En dag i uka
- [ ] Mer enn en dag i uka
- [ ] Hver dag

I løpet av siste tre måneder før utbruddet, hvor ofte hadde du smerter og ikke bare ubehag noe sted i magen?
- [ ] Aldri

- [ ] Mindre enn 1 dag i måneden
- [ ] En dag i måneden
- [ ] 2-3 dager i måneden
- [ ] En dag i uka
- [ ] Mer enn en dag i uka
- [ ] Hver dag

For kvinner: Har du kun hatt dette ubehaget eller smerten i forbindelse med menstruasjons-blødning og ikke til andre tider?
- [ ] Nei
- [ ] Ja
- [ ] Ikke aktuelt fordi jeg ikke har menstruasjon

Har du hatt dette ubehaget eller smerten i 6 måneder eller lenger?
- [ ] Nei
- [ ] Ja

Hvor ofte ble ubehaget eller smerten i magen bedre eller forsvant etter at du hadde hatt avføring?
- [ ] Sjelden/aldri
- [ ] Noen ganger
- [ ] Ofte
- [ ] Det meste av tiden
- [ ] Alltid

Når dette ubehaget eller smerten begynte, hadde du hyppigere avføring?
- [ ] Sjelden/aldri
- [ ] Noen ganger
- [ ] Ofte
- [ ] Det meste av tiden
- [ ] Alltid

Når dette ubehaget eller smerten begynte, hadde du sjeldnere avføring?
- [ ] Sjelden/aldri
- [ ] Noen ganger
- [ ] Ofte
- [ ] Det meste av tiden
- [ ] Alltid

Når dette ubehaget eller smerten begynte, hadde du løsere avføring?
- [ ] Sjelden/aldri
- [ ] Noen ganger
- [ ] Ofte
- [ ] Det meste av tiden
- [ ] Alltid

Når dette ubehaget eller smerten begynte, hvor ofte hadde du hardere avføring?
- [ ] Sjelden/aldri
- [ ] Noen ganger
- [ ] Ofte
- [ ] Det meste av tiden
- [ ] Alltid

I løpet av de siste tre måneder før utbruddet, hvor ofte har du hatt løs, grøtete eller vandig avføring?
- [ ] Sjelden/aldri
- [ ] Ca. 25% av tiden
- [ ] Ca. 50% av tiden
- [ ] Ca. 75% av tiden
- [ ] Alltid, 100% av tiden

I løpet av siste tre måneder før utbruddet, hvor ofte har du hatt hard eller klumpete avføring?
- [ ] Sjelden/aldri
- [ ] Ca. 25% av tiden
- [ ] Ca. 50% av tiden
- [ ] Ca. 75% av tiden
- [ ] Alltid, 100% av tiden

Fra tiden før utbruddet: Reagerte du med plager fra magen dersom du inntok spesiell mat eller drikke?
- [ ] Nei, ingen plager
- [ ] Lette plager
- [ ] Middels store plager

☐ Store plager

Hadde du leddplager i løpet av den siste måneden før utbruddet?

Smerter i ledd

☐ Nei
☐ Ja, i 1 ledd, hvilket _____
☐ Ja, i flere ledd, hvilke _____

Hevelse i ledd

☐ Nei
☐ Ja, i 1 ledd, hvilket _____
☐ Ja, i flere ledd, hvilke _____

Stivhet i ledd

☐ Nei
☐ Ja, i 1 ledd, hvilket_____
☐ Ja, i flere ledd, hvilke_____

Har du revmatisk sykdom?

☐ Nei
☐ Ja, evt hvilken_____
☐ Usikker

Slitenhet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måneden FØR utbruddet. Vennligst besvar ALLE spørsmålene ved å krysse

Hadde du problemer med at du følte deg sliten?

☐ Mindre enn vanlig
☐ Ikke mer enn vanlig
☐ Mer enn vanlig
☐ Mye mer enn vanlig

Trengte du mer hvile?

☐ Nei, mindre enn vanlig
☐ Ikke mer enn vanlig
☐ Mer enn vanlig
☐ Mye mer enn vanlig

Følte du deg søvnig eller døsig?

☐ Mindre enn vanlig
☐ Ikke mer enn vanlig
☐ Mer enn vanlig
☐ Mye mer enn vanlig

Hadde du problemer med å komme i gang med ting?

☐ Mindre enn vanlig
☐ Ikke mer enn vanlig
☐ Mer enn vanlig
☐ Mye mer enn vanlig

Manglet du overskudd?

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Mer enn vanlig
☐ Mye mer enn vanlig

Hadde du redusert styrke i musklene dine?

☐ Ikke i det hele tatt
☐ Ikke mer enn vanlig
☐ Mer enn vanlig
☐ Mye mer enn vanlig

Følte du deg svak?

☐ Mindre enn vanlig
☐ Som vanlig
☐ Mer enn vanlig
☐ Mye mer enn vanlig

Hadde du vansker med å konsentrere deg?

- ☐ Mindre enn vanlig
- ☐ Som vanlig
- ☐ Mer enn vanlig
- ☐ Mye mer enn vanlig

Forsnakket du deg i samtaler?

- ☐ Mindre enn vanlig
- ☐ Ikke mer enn vanlig
- ☐ Mer enn vanlig
- ☐ Mye mer enn vanlig

Var det vanskeligere å finne det rette ordet?

- ☐ Mindre enn vanlig
- ☐ Ikke mer enn vanlig
- ☐ Mer enn vanlig
- ☐ Mye mer enn vanlig

Hvordan var hukommelsen din?

- ☐ Bedre enn vanlig
- ☐ Ikke verre enn vanlig
- ☐ Verre enn vanlig
- ☐ Mye verre enn vanlig

Når du følte deg sliten før utbruddet, omtrent hvor lenge hadde det vart?

- ☐ Mindre enn en måned
- ☐ Mellom en og seks måneder
- ☐ Seks måneder eller mer

Når du følte deg sliten før utbruddet, omtrent hvor mye av tiden kjente du det?

- ☐ 25 % av tiden
- ☐ 50 % av tiden
- ☐ 75 % av tiden
- ☐ Hele tiden

Søvn

Spørsmålene under besvares i antall dager per uke du har opplevd følgende problemer, hvor 0 er ingen dager i løpet av en uke, 7 er alle dager i løpet av en uke.

I løpet av de siste tre månedene, hvor mange dager per uke har du:

	0	1	2	3	4	5	6	7
Brukt mer enn 30 minutter for å sovne etter at lysene ble slukket?	☐	☐	☐	☐	☐	☐	☐	☐
Vært våken mer enn 30 minutter innimellom søvnen?	☐	☐	☐	☐	☐	☐	☐	☐
Våknet mer enn 30 minutter tidligere enn du har ønsket uten å få sove igjen?	☐	☐	☐	☐	☐	☐	☐	☐
Følt deg for lite uthvilt etter å ha sovet?	☐	☐	☐	☐	☐	☐	☐	☐
Vært så søvnig/trett at det har gått ut over skole/jobb eller privatlivet?	☐	☐	☐	☐	☐	☐	☐	☐
Vært misfornøyd med søvnen din?	☐	☐	☐	☐	☐	☐	☐	☐

Opplever du at du før utbruddet hadde søvnproblemer?

- ☐ Nei
- ☐ Litt
- ☐ Noe
- ☐ Mye
- ☐ Veldig mye

Bruker du sovemedisiner på resept?

- ☐ Nei
- ☐ Av og til
- ☐ 1-2 dager per uke
- ☐ 3-6 dager per uke
- ☐ Daglig

Trivsel og helse

Her kommer noen spørsmål om hvordan du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret - de spontane svarene er best.

Jeg føler meg nervøs og urolig

- Mesteparten av tiden
- Mye av tiden
- Fra tid til annen
- Ikke i det hele tatt

Jeg gleder meg fortsatt over ting, slik jeg pleide før

- Avgjort like mye
- Ikke fullt så mye
- Bare lite grann
- Ikke i det hele tatt

Jeg har en urofølelse, som om noe forferdelig vil skje

- Ja, og noe svært ille
- Ja, ikke så veldig ille
- Litt, bekymrer meg lite
- Ikke i det hele tatt

Jeg kan le og se det morsomme i situasjoner

- Like mye som før
- Ikke like mye som før
- Avgjort ikke som før
- Ikke i det hele tatt

Jeg har hodet fullt av bekymringer

- Veldig ofte
- Ganske ofte
- Av og til
- En gang i blant

Jeg er i godt humør

- Aldri
- Noen ganger
- Ganske ofte
- For det meste

Jeg kan sitte i fred og ro og kjenne meg avslappet

- Ja, helt klart
- Vanligvis
- Ikke så ofte
- Ikke i det hele tatt

Jeg føler meg som om alt går langsommere

- Nesten hele tiden
- Svært ofte
- Fra tid til annen
- Ikke i det hele tatt

Jeg føler meg urolig, som om jeg har sommerfugler i magen

- Ikke i det hele tatt
- Fra tid til annen
- Ganske ofte
- Svært ofte

Jeg bryr meg ikke lenger om hvordan jeg ser ut

- Ja, jeg har sluttet å bry meg
- Ikke som jeg burde
- Kan hende ikke nok
- Bryr meg som før

Jeg er rastløs, som om jeg stadig må være aktiv

- Uten tvil svært mye
- Ganske mye
- Ikke så veldig mye
- Ikke i det hele tatt

Jeg ser med glede frem til hendelser og ting

- Like mye som før
- Heller mindre enn før
- Avgjort mindre enn før

☐ Nesten ikke i det hele tatt

Jeg kan plutselig få en følelse av panikk

☐ Uten tvil svært ofte
☐ Ganske ofte
☐ Ikke så veldig ofte
☐ Ikke i det hele tatt

Jeg kan glede meg over gode bøker, radio og TV

☐ Ofte
☐ Fra tid til annen
☐ Ikke så ofte
☐ Svært sjelden

Vi ønsker flere samtykker fra deg for å kunne få best mulig kunnskap om utbruddet og konsekvensene av dette. Dette vil kunne bidra til bedre oppfølging av de som ble rammet.

Jeg samtykker til:

Vennligst kryss av ved alle du samtykker til

☐ innhenting av opplysninger om meg hos fastlege, legevakt eller sykehus (evt. sykehjem)
☐ videre analyser av allerede innhentede prøver
☐ at det kan tas kontakt med meg for å få tatt nye prøver
☐ at data om meg kan kobles til helseregistre som nevnt i informasjonsskrivet

Lenke til infoskriv her.

Navn på legesenteret du bruker. Flere kryss mulig.

☐ Fenring legesenter
☐ Florvåg legesenter
☐ Fromreide legesenter
☐ Kleppestø legekontor
☐ Strand legesnter
☐ Strusshamn legesenter
☐ Askøy legevakt
☐ Andre_____

Personlige opplysninger

Hva er navnet ditt?

Fornavn _____
Etternavn _____

Hva er ditt fødsels- og personnummer?
ddmmååxxxxx (f.eks. 03129811111)

_____

Hva er din alder?

_____

Hva er ditt kjønn?

☐ Mann
☐ Kvinne

Hva er din kontaktinformasjon?

Gateadresse _____
Postnummer _____
Mobilnummer _____

Sivilstand

☐ Enslig
☐ Gift/samboer
☐ Skilt/separert
☐ Enke/enkemann

For kvinner: Er du gravid?

☐ Ja
☐ Nei

- [ ] Vet ikke
- [ ] Ikke aktuelt

Hva er det høyeste utdanningsnivået du har fullført?

- [ ] Grunnskole
- [ ] Videregående skole/yrkesskole
- [ ] Universitet eller høyskole

Hva beskriver best din situasjon rett før utbruddet?

- [ ] Student/elev
- [ ] Arbeidstaker
- [ ] Selvstendig næringsdrivende
- [ ] Arbeidssøkende/arbeidsledig
- [ ] Ufør
- [ ] Pensjonist

Hvor mange voksne personer (18 år eller eldre) bor i din husstand?

____

Hvor mange barn/ungdommer (yngre enn 18 år) bor i din husstand?

____

Hva er samlet årsinntekt for husstanden?

- [ ] Mindre enn 250 000
- [ ] 250 000 - 499 999
- [ ] 500 000 - 749 999
- [ ] 750 000 - 1 000 000
- [ ] Over 1 000 000

Du har svart at du er under 16 år og at du *ikke* har samtykke av en av dine foresatte til å delta i undersøkelsen. Undersøkelsen avsluttes derfor.

Når du trykker "avslutt" blir svaret ditt lagret og du blir tatt med til informasjonssiden for denne undersøkelsen.

Takk for at du tok deg tid til å svare på undersøkelsen.

Når du trykker "avslutt" blir svaret ditt lagret og du blir tatt med til informasjonssiden for denne undersøkelsen.

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