The incidence and transmission of infectious gastroenteritis in English care homes

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Abstract

Background

Gastrointestinal infections are common in care homes for the elderly and frequently lead to outbreaks. Norovirus is a frequent cause of this illness. In this thesis I quantified the incidence of infectious gastroenteritis cases and outbreaks in care homes, in order to understand the epidemiology of these outbreaks and the proportion caused by norovirus.

Methods

I conducted a systematic review of the literature on community-based surveillance of norovirus disease. I then conducted a prospective cohort study to investigate the epidemiology of infectious gastroenteritis in care homes. I also analysed the care home outbreak surveillance data of two areas: I used Cheshire and Merseyside data to analyse the characteristics of outbreaks and North East England data to understand the proportion of outbreaks caused by norovirus. Finally, I estimated the burden of gastroenteritis outbreaks across England using available surveillance data.

Results

I found few papers describing community-based surveillance for norovirus disease. From the prospective cohort study I estimated the rate of infectious gastroenteritis to be 133.7 cases per 1,000 person-years at risk. I estimated the incidence of outbreaks (per 100 care homes per year) in four chapters, these estimates were: 76.4, 37.1, 38.1 and 22.5 in Chapters 4, 5, 6 and 7, respectively. I found that norovirus was detected in 64% of outbreaks with a pathogen identified. I estimated that there were 14,146 care home gastroenteritis outbreaks in England during 2014-2016; 47% more than the reported total.

Conclusions

I found that the current surveillance arrangements in England, based on outbreak reports, underestimate the incidence of outbreaks in care homes. Outbreak detection is likely to be the best method of surveillance, capturing the majority of cases. Norovirus is the most frequently detected pathogen in this setting, but other viral infections such as sapovirus and rotavirus are also important. Based on my findings, I have made recommendations for changes in the way that public bodies operate and avenues for future research.

Table of Contents

List of figures

List of tables

List of abbreviations

AIC	Akaike Information Criterion
aOR	adjusted Odds Ratio
AR	Attack Rate
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
CIPCP	Community Infection Prevention and Control Practitioner
CIPCT	Community Infection Prevention & Control Team
CMHPT	Cheshire and Merseyside Health Protection Team
CQC	Care Quality Commission
DALY	Disability Adjusted Life Year
EEA	European Economic Area
EIA	Enzyme-linked Immunosorbent Assay
EM	Electron Microscopy
EU	European Union
GP	General Practitioner
GPS	Global Positioning System
HPT	Health Protection Team
IID	Infectious Intestinal Disease
IQR	Interquartile Range
IRR	Incidence Rate Ratio
LCHT	Liverpool Community Health Trust
LTCF	Long-Term Care Facility
NOIDs	Notification of Infectious Disease
OR	Odds Ratio
OTU	Operational Taxonomic Unit
PCR	Polymerase Chain Reaction
PHE	Public Health England
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTAR	Person-time at Risk
QALY	Quality-Adjusted Life Years
REC	Research Ethics Committee
RFID	Radio-frequency identification
RT-PCR	Real-Time Polymerase Chain Reaction

R_0	Basic reproduction number
SD	Standard Deviation
SGSS	Second Generation Surveillance System
SQL	Structured Query Language
STEC	Shiga Toxin-Producing *E. coli*
TESSy	The European Surveillance System
UK	United Kingdom
US	United States
UoL	University of Liverpool
WHO	World Health Organisation

Chapter 1 - Introduction

In this chapter I will introduce information necessary to give the reader a general background to the research presented in this thesis. The first section of this chapter is centred on care homes, the primary setting for my research. Further to this, I will outline the background to infectious gastroenteritis, with a separate and more detailed section focussed on norovirus due to the importance of this pathogen in care home settings. I will introduce concepts regarding the history, biology, mechanisms of transmission, burden of disease and infection control practices. In the following section I will outline concepts of surveillance and how these are implemented in the surveillance of infectious gastroenteritis in care homes. For each of these topics, I will contextualise them within the care home setting, identifying important gaps in the evidence base. Building on this, I will outline the research questions I aim to answer in this thesis and how each of the subsequent chapters address these questions.

1.1 Care homes

1.1.1 Care home background

In 2017 there were 11,300 care homes for the elderly in the United Kingdom (UK), operated by 5,500 different providers. These care homes have approximately 410,000 residents.[1] The structure of care homes varies considerably. Some occupy converted housing and accommodate a small number of residents, while others may have several purpose-built units to provide different levels of care on the same site (an example is shown in Figure 1.1). A care home is defined by the Care Quality Commission (CQC) as “a place where personal care and accommodation are provided together.” All care homes will have elderly people residing there who require care and staff who provide caring duties, cleaning, catering and administrative services. Many also provide nursing care and have qualified nursing staff working in the care home. Residents may be visited by other healthcare staff such as physiotherapists and general practitioners (GPs). In addition, care homes are normally open and residents can be visited by friends and family.

In the UK, the mean size of a care home (number of beds in use) is 33 for those without nursing care, and 39 for those providing nursing care.[2] According to detailed data

collected by NHS Scotland, the mean care home occupancy percentage in 2017 was 88% for resident spaces, with residents having a median age of 81 years and a median stay of 18 months.[3] The same census found that the costs in 2017 averaged £659 per resident per week without nursing care, compared with an average of £749 when nursing care was included.[3] Data from 2009 show that care homes had an average of 1.8 qualified nurses, with an average of 5.2 healthcare assistants during the day and 2.8 during the night. This translated to an average of 4.2 residents per member of nursing staff during the day, and 8.6 during the night.[4] However, there is currently no national guidance in the UK on staffing levels, nurse to patient ratios or staff skill mix in care homes.

Throughout this thesis I will refer to care homes as a shorthand for residential care homes for the elderly, including those that provide nursing care. Such facilities may be referred to alternatively as nursing homes or long-term care facilities (LTCFs) in other publications.

Figure 1.1: Depiction of a typical modern care home

Image from Mike Coates, released under CC 1.0 Universal Licence

1.1.2 Care home regulation

In England the registration and operation of care homes is regulated by the Care Quality Commission (CQC). Under the Health and Social Care Act 2008 (Regulated Activities)

Regulations 2014, care home operators have requirements regarding the suitability of premises and staffing provision, among other requirements. Under the Care Quality Commission (Registration) Regulations 2009, providing residential accommodation together with personal care or nursing care (e.g. a care home with nursing) is a regulated activity in England. Under this legislation, each care home must have a registered provider and a registered manager who is responsible for managing the regulated activity at each premises. A registered manager is a person who is in day-to-day charge of the delivery of a service provider's regulated activity.

In England it is, therefore, mandatory for care homes to apply for registration with the CQC. The CQC then assess the service provider's compliance with the legal requirements before granting registration. Once registered, care homes are monitored and inspected by the CQC for compliance with their standards. During an inspection, care homes are assessed against five domains: Are they safe? Are they effective? Are they caring? Are they responsive to people's needs? Are they well-led? Under each domain is a series of statements which are referred to as their "key lines of enquiry". Only one of these lines of enquiry relates to infection or communicable disease, it states: "The home is kept clean and hygienic to prevent any risk of infection to you or other residents." Following the inspection, a report is written up by the CQC and each care home is given a rating. This rating is one of four categories: "Outstanding", "Good", "Requires Improvement" and "Inadequate". Care homes rated as "Requires Improvement" are given a list of areas to improve in; for those rated "Inadequate", the CQC can take a range of actions, from issuing requirement notices, placing the provider in special measures or prosecuting the provider.

1.1.3 Population vulnerability

Recent government policy in the UK has aimed to develop new models for providing enhanced healthcare in care homes. Older people are entering care homes later in life, with more co-morbidities and with complex needs such as dementia.[5] The proportion of residents with dementia increased from 36% in 2003 to 44% in 2009, with this trend likely to have continued.[6] Some elderly people currently residing in care homes receiving nursing care may have previously been hospitalised for treatment.[6]

Care homes provide an environment that is vulnerable to the acquisition and spread of infection.[7] They contain residents who are susceptible to infection who are in relatively

close proximity to one another in a semi-enclosed institutional setting, with staff, visitors and residents who enter frequently, providing an opportunity for introducing pathogens from the community and hospitals. Additionally, in care home residents, diagnosing infections may be more challenging because of subtle or atypical presentations, the presence of co-morbidities which obscure the symptoms, treatment with antibiotics which can cause loose bowel movements and the lack of available diagnostic facilities.[8] Any delay in diagnosis, treatment or implementation of preventative measures caused by these factors can allow transmission of pathogens within the facility. Pathogens being transmitted through a care home may cause cases of infectious gastroenteritis.

1.2 Infectious gastroenteritis

1.2.1 What is infectious gastroenteritis?

Gastroenteritis is an inflammation of the gastrointestinal tract, the organ system which takes in food and drink, extracts nutrients and expels waste as faeces. This inflammation can lead to a clinical presentation which includes symptoms such as diarrhoea, vomiting, nausea and abdominal pain. Gastroenteritis can be caused by a broad range of infectious and non-infectious causes. Otherwise healthy people with infectious gastroenteritis commonly present with an acute episode of diarrhoea and vomiting.

Gastrointestinal infections are responsible for a substantial proportion of morbidity and mortality across the world. Globally, the greatest burden of illness is suffered by young children, with diarrhoea being a common cause of death in children under 5 years old.[9] In healthy adults, this illness is usually short-lived and self-limiting, but older people and the immunocompromised are at greater risk of severe disease. For mild to moderate diarrhoea, a generally effective treatment is the use of oral rehydration therapy. Severe or complicated infectious gastroenteritis may require further treatment, with the precise treatment dependent on the pathogen responsible.

The nomenclature of infectious gastroenteritis can be confusing; there are several gastrointestinal infections such as *Helicobacter pylori* and poliomyelitis which do not necessarily cause symptoms of gastroenteritis. Alternatively, some non-infectious agents such as histamine and mercury can cause gastroenteritis. Foodborne gastroenteritis covers these non-infectious agents, along with a range of infections. For the purposes of this thesis

I will refer to infectious gastroenteritis. This is functionally synonymous with the term "infectious intestinal disease" (IID) which is also used in relevant literature.[10]

1.2.2 Historical context of infectious gastroenteritis

Gastroenteritis was recognised in ancient Greece, when it was believed to be associated with changes in the weather and with weaning of infants. In ancient China diarrhoea was recognised and treated using a naturally occurring clay.[11] Treatment for gastroenteritis was recorded in the 15th Century by the renowned English surgeon John Arderne in his text "*De Arte Phisicali et de Cirurgia*" (Figure 1.2). In this, he recommended treatments such as a mixture of hyssop, absinthe, dill and wine for nausea, and for diarrhoea a mixture of water, honey and berries.

Figure 1.2: Illustration of acute diarrhoea from *De Arte Phisicali et de Cirurgia* (1412) by John Arderne

Reproduced courtesy of the National Library in Stockholm (Kungliga Biblioteket)

It took until the second half of the 19th Century for gastrointestinal pathogens to start to be identified; with the isolation of organisms such as *Campylobacter*,[12] *Entamoeba*

histolytica[13] and *Shigella dysenteriae*.[14] By the middle of the 1970s the medical community started to obtain a fuller understanding of the pathogens which cause infectious gastroenteritis, with the discovery of pathogens such as Enterotoxigenic *Escherichia coli* (ETEC),[15] rotavirus[16] and norovirus.[17]

1.2.3 Transmission of infectious gastroenteritis

Infectious gastroenteritis can be caused by a number of different viral, bacterial or protozoal pathogens. These enteric pathogens are mainly transmitted between humans by the faecal-oral route. This route of transmission is where pathogens excreted in faecal matter pass from one person to the mouth of another person. This pathogen is then ingested by the recipient and they may become infected with the pathogen. This transmission can be through direct contact, or mediated by contaminated food, water or objects and materials (known as fomites). Infectious gastroenteritis caused by contaminated food is usually referred to as foodborne, and forms a subset of all such illnesses.

There are broad heuristics that can be used to understand the routes of transmission used by different groups of pathogens. For example, protozoa such as *Giardia* and *Cryptosporidium* are generally transmitted through contaminated water. Common bacterial causes of gastroenteritis such as *Campylobacter*, *Salmonella* and *E. coli* are frequently transmitted through contaminated food, though direct contact and contaminated fomites do transmit these bacteria. *Vibrio cholerae* is an outlier as a bacterial gastrointestinal infection which is almost exclusively transmitted through contaminated water. Viral pathogens such as norovirus and rotavirus are commonly transmitted through direct contact, fomites and contaminated surfaces, though transmission in food is a recurrent issue.[18]

Once initially exposed to a gastrointestinal pathogen, the probability that a person will be successfully infected depends on a range of factors such as their immune system function, residual immunity they have to the organism and the infectious dose of the organism. For example, some pathogens such as Shiga toxin-producing *E. coli* (STEC) can cause illness with as few as 10 organisms, whereas *Vibrio cholerae* requires at least 1,000 organisms to successfully infect a person.[19] The presence of symptoms such as diarrhoea and vomiting can increase the risk of transmission as they can facilitate pathogen spread on to fomites

and surrounding surfaces.[20] Due to such risks, there is substantial transmission in community household settings; a study found a household secondary attack rate of 8.8% (95% Confidence Interval 7.9% – 9.7%) for infectious gastroenteritis, with children having 2- to 8-fold greater risk than adults.[21]

1.2.4 Burden and aetiology of infectious gastroenteritis in the community

Due to the challenges inherent in the surveillance of infectious disease, it is difficult to produce accurate estimates of the burden of infectious gastroenteritis in the community. Studies which produce burden estimates, adjusted for under-reporting in general practice and to national surveillance, are largely from the US and western Europe. The variation in these estimates, and the pathogens causing illness, reflects factors such as differences in study methods, the adoption of new laboratory methods and underlying variances in the epidemiological situation in each area.

In England, a study of incidence and aetiology of cases of infectious intestinal disease in the community (IID study) during 1993-1996 found that the incidence rate in the community was 194 per 1,000 person years (95% Confidence Interval 181 – 208).[22] Using the laboratory methods at that time, a pathogen was detected in 24% of samples and the most frequent infections were *Campylobacter* spp. and *Salmonella* spp. A subsequent study in the United States (US) which used retrospective self-reported symptom information from 1996-1997 estimated the community incidence of infectious gastroenteritis to be substantially higher, at 790 per 1,000 person-years.[23] However, this rate is likely to have been an overestimate due to the biases known to affect studies which use retrospectively collected self-reported symptom data.

Following this, a prospective population-based cohort study was conducted in the Netherlands in 1998-1999. In this study, the community incidence rate of infectious gastroenteritis was found to be 283 per 1,000 person-years, higher than the previous UK estimate.[24] This study used reverse transcriptase-polymerase chain reaction (RT-PCR) tests, which at that point had been newly developed, for detecting sapovirus and norovirus. As a result of using these new diagnostic methods, this study found that viral pathogens were the most common, with norovirus being the leading single cause of disease. A similar finding came from a population-based study in north-west Germany which collected data during 2004. In this, they estimated that norovirus was the predominant pathogen, causing

6.26 cases per 1,000 person-years.[25] Due to the study design, the authors were not able to estimate directly the incidence rate of infectious gastroenteritis in the community, but did find the incidence of general practice consultation was 40.2 per 1,000 person-years.

Subsequent to the IID study from the mid-nineties, a similarly comprehensive longitudinal study of intestinal infectious disease (IID2 study) took place in the UK from April 2008 to August 2009. In this, the overall incidence rate in the community was 274 cases per 1,000 person-years (95% Confidence Interval 254 – 296).[26] This incidence was higher than the community incidence rate from the first IID study (194 per 1,000 person-years). The IID2 study tested for a range of viral, bacterial and protozoal pathogens. An adapted list of incidence rates by pathogen from this study is shown in Table 1; norovirus was the most common in the community, with 47 cases per 1,000 person-years. *Campylobacter* was the most frequently identified bacterial pathogen, with 10.9 cases per 1,000 person-years. Other commonly identified pathogens included sapovirus (26.1 cases per 1,000 person-years) and rotavirus (12.7 case per 1,000 person-years). The increased detections of norovirus and sapovirus in the IID2 study compared with the earlier IID study are most likely to be due to the adoption of PCR testing to replace electron microscopy, leading to increased testing sensitivity.[27] These findings from the IID2 study are the most recent comprehensive data on the pathogens causing infectious gastroenteritis in the community in England, but are now 10 years old.

Table 1: Incidence rates of infectious gastroenteritis in the community, April 2008 to August 2009, UK

Organism		Rate per 1,000 person-years	(95% Confidence Interval)
Viruses			
	Adenovirus	10.2	(6.8 - 15.4)
	Astrovirus	5.3	(3.0 - 9.4)
	Norovirus	47.0	(39.1 - 56.5)
	Rotavirus	12.7	(8.7 - 18.4)
	Sapovirus	26.1	(20.1 - 33.8)
Bacteria			
	C. perfringens	1.5	(0.5 - 3.9)
	Campylobacter spp.	10.9	(7.4 - 15.9)
	E. coli O157 VTEC	0.3	(0 - 4.3)
	Enteroaggregative *E. coli*	5.9	(3.4 - 10.2)
	Salmonella spp.	0.6	(0.2 - 2.4)
Protozoa			
	Cryptosporidium	1.2	(0.4 - 3.9)
	Giardia	2.0	(0.7 - 5.6)
	All IID	274.1	(253.8 - 295.8)

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The IID2 study also conducted a retrospective cross-sectional telephone survey, the results of which were published separately to the prospective cohort.[28] In this, the authors estimated the UK community incidence to be 533 cases per 1,000 person-years (95% CI: 377–778), a substantial increase in the figure reported to that from the prospective cohort. There were two other European studies which were contemporary with the IID2 study, both of which also used retrospective self-reported symptom information. A cross-sectional survey conducted in Germany in 2008-2009 estimated 950 cases per 1,000 person-years[29] and a similar cross-sectional survey in Sweden in the same time period estimated 310 cases per 1,000 person-years.[30]

To summarise these findings, a World Health Organisation (WHO) systematic review and data synthesis of this topic in 2015 estimated that globally, in 2010 there were 2 billion (95% Uncertainty Interval 1.5 – 3.0 billion) illnesses; 39% (95% Uncertainty Interval 26 – 53%) of which were in children under 5 years old.[31] This study estimated that norovirus was the most common cause of infectious gastroenteritis cases (685 million per year), with this also being the most frequent cause of infectious gastroenteritis deaths (212,489 cases per year), followed by *Salmonella enterica* serotype Typhi (144,890 cases per year).[31]

1.2.5 Infectious gastroenteritis in care homes

Gastrointestinal infections are one of the most common types of infection in care homes. A study based in UK care homes in 2006 found that there were 0.41 gastrointestinal infections per 1,000 bed-days, with other common infections being respiratory (2.52 infections per 1,000 bed-days), urinary (1.87 infections per 1,000 bed-days) and skin and soft tissue (1.57 infections per 1,000 bed-days).[32] Another study in the US found that the infections most frequently causing epidemics in care homes included gastroenteritis, influenza and skin infections.[33]

A global estimate of the incidence of infectious gastroenteritis among elderly people living in care homes has been synthesised using a systematic review of published surveillance. From this meta-analysis the pooled incidence estimate was 0.40 episodes per 1000 bed-days (95% Confidence Interval 0.27 – 0.56).[34] This systematic review found 15 studies, none of which were recent published estimates from the UK. There was considerable heterogeneity between studies. The highest incidence (1.9 episodes per 1,000 bed-days) was reported from a German study using electronic health records[35] and the lowest incidence (0.04 episodes per 1,000 bed-days) was reported from a small Canadian study with an unclear definition of gastroenteritis.[36]

In line with transmission in the community, a review of enteric outbreaks of all causes in care homes, published in 2008, found that transmission in this setting was mainly person-to-person during viral outbreaks. Recommended control measures included restricting visitors, excluding ill staff, encouraging effective hand hygiene, and effective environmental cleaning and disinfection.[37] Official guidance on the prevention and control of infection in care homes in the UK was published in 2013.[38] This details eight aspects of a simple, consistent and effective approach to infection prevention and control, which are hand hygiene, use of gloves, personal protective equipment, use of aprons, safe handling of sharps, safe handling of waste, safe handling of soiled linen and environmental cleaning. The registered manager in each care home is responsible for developing appropriate infection prevention and control policies and procedures that are readily available and appropriate to the home, and understood by all members of staff. Infection control measures impose substantial costs on each home. In Japan the economic burden was estimated to be approximately $182.6 per resident per year at 2015 prices.[39]

In England, Community Infection Prevention and Control Practitioners (CIPCPs) are commissioned by local authorities to provide advice, education, training, policy development and audit functions to care homes as part of their work in the wider community. Ideally, all infection control recommendations would rely on empirical evidence but a number of challenges, including the inability to culture some viral pathogens in the laboratory and the challenges of outbreak management in complex environments, has made it difficult to garner clear evidence of efficacy in certain areas of infection control.[40]

Viral pathogens have previously been found to cause the majority of infectious gastroenteritis in care homes. There are few studies which explore the pathogens causing non-outbreak gastroenteritis in care home: most focus on outbreaks. A study in England and Wales between 1992 and 1994 attributed 57% of outbreaks in residential facilities where a sample was submitted to viral causes and 29% to bacterial causes.[41] This is consistent with the findings of a systematic review of such outbreaks published between January 1997 to June 2007, which assigned 69% to viral causes and 31% to bacterial causes.[37] Of these viral causes, evidence from multiple studies suggests that norovirus is the most frequently identified pathogen in care home outbreaks. Norovirus was identified in 77% of outbreaks in Oregon,[42] 78% of outbreaks in the Netherlands,[43] 74% from south west England,[44] 36% of outbreaks in France,[45] and 40% of outbreaks in Australia.[46] However, the most recent study on the proportion of care home outbreaks caused by norovirus in the UK included data from 2002-2003 and no contemporary data have been published in the last 16 years.

Sapovirus is known to cause infectious gastroenteritis in care homes, having been identified in 66% of norovirus-negative outbreaks in one study in the US.[47] However, the burden of sapovirus in care homes is not well understood. It was not detected at all in one study of care home outbreaks in The Netherlands [43] and it has not been tested for during several other studies in similar populations.[44, 46] Rotavirus has also been found to cause gastroenteritis outbreaks in care homes,[43, 46] although, as with sapovirus, testing for this pathogen is inconsistent in this setting. Regarding foodborne gastroenteritis outbreaks in care homes, a study from the early 1990s in England and Wales found that 43% of these were caused by *Salmonella* and 40% were caused by *C. perfringens*.[41] This study found that 21% of gastroenteritis outbreaks in this setting were foodborne.

Clostridium difficile can be a major cause of antibiotic-associated diarrhoea in care home residents, with a study in the US estimating an incidence rate of 0.17-0.29 cases per 1,000 bed-days.[48] *C. difficile* can also cause outbreaks in care homes. One review of pathogens causing infectious disease outbreaks in care homes found that *C. difficile* was the cited pathogen in 11% of published gastrointestinal outbreaks included in this review.[49] Despite the availability of these studies on pathogens causing gastroenteritis outbreaks in care homes, due to different methods of outbreak surveillance, varying stool sampling rules and different pathogens being tested for using a range of methodologies, there are no recent, comprehensive estimates of the burden of gastrointestinal outbreaks caused by each pathogen.

From this section I have identified three key gaps in the literature related to infectious gastroenteritis in care homes: (a) the lack of recent estimate of the incidence of individual illness in care home residents (b) the lack of contemporary data to estimate the burden of outbreaks in care homes (c) the absence of current data on the epidemiological characteristics of care home outbreaks in England.

1.3 Norovirus

1.3.1 Norovirus biology

Although a condition called winter vomiting disease had originally been described by Zahorsky in 1929,[50] the first evidence that illness characterised by sudden onset of vomiting and diarrhoea might be caused by a non-bacterial infectious agent came following an outbreak that occurred in Norwalk, Ohio, USA in 1968.[51] Following the Norwalk outbreak, Kapikian *et al.* used immune electron microscopy to visualise viral particles in the samples of challenge study volunteers.[52] This virus was initially classified as small round structured virus (SRSV) and the only method for diagnosis was electron microscopy.[53] The later development of RT-PCR enabled norovirus to be detected with much greater sensitivity in stool and vomit.[54]

Noroviruses are classified into 10 genogroups, which are then further classified into 49 genotypes.[55] However, only three genogroups (I, II and IV) have been found to cause illness in humans.[56]. Multiple norovirus genotypes co-circulate simultaneously with continuous and rapid changes in the norovirus genetic diversity worldwide. This process

underlies the regional differences in norovirus genetic diversity.[57] The most common norovirus genotype reported in outbreaks is genogroup II genotype 4 (or genotype GII.4) which has multiple variants.[58] It is hypothesised that GII.4 is better at infecting humans than other genotypes based on its association with increased norovirus transmissibility observed in Japan from 2000-2016.[59] The evolution of GII.4 is affected by multiple mechanisms, including host herd immunity that drives antigenic drift in the hypervariable P2 domain.[60]

1.3.2 Norovirus symptoms, transmission and treatment

Norovirus infection generally causes self-limited gastrointestinal illness. Common symptoms include diarrhoea, vomiting and abdominal pain. In norovirus cases the mean number of bowel movements in 24 hours is 4.5 (standard deviation ± 3.5); the mean number of vomiting episodes is 3.7 (standard deviation ± 2.5).[61] Other symptoms include nausea, fever, headache, myalgia (muscle pain) and malaise.[61] The median incubation period is 24 to 48 hours [62] and the median duration of norovirus illness is 12 to 60 hours.[63] Although normally a self-limiting disease, norovirus can cause sequelae such as chronic diarrhoea in primary immune deficient, oncologic and transplant patients.[64] Norovirus can also be a cause of death, with a recent systematic review finding that deaths associated with norovirus infection are most commonly described amongst the elderly population and are acquired in healthcare facilities. Many norovirus-related deaths are in patients with varying degrees of immunosuppression.[65]

People ill with norovirus disease shed norovirus viral particles in stool and vomit.[66, 67] Typically, a very large number of viral particles (9.5 billion per gram of faeces) are shed in each stool movement.[68] This makes norovirus highly infectious as the infectious dose is estimated to be as low as 10-100 viral particles.[69] Despite the symptoms generally resolving within three days, virus particles can be shed from asymptomatic individuals for weeks after the original illness. [68] However, in the absence of a reliable and reproducible culture method, questions remain over whether these particles are viable virons and what role asymptomatic shedding plays in norovirus transmission. Susceptibility to norovirus is thought to vary between individuals, with evidence that persons with inactivated FUT2 genes (which encode H type 1 histo-blood group antigens) may be protected against several norovirus genotypes.[70, 71] Immunity to norovirus infection following infection is comparatively short-lived; human challenge studies in the 1970s found immunity to last

between two months and two years,[69] whereas a recent modelling study based on norovirus incidence data found immunity to last between 4.1 and 8.7 years.[72] Because of this short-lived immunity, previously infected and immune persons frequently re-join the pool of susceptible persons in the population.

The basic reproduction number (R_0) is defined as the expected number of secondary infections per generation if one infected individual is introduced into an entirely susceptible population. The R_0 for norovirus has been calculated in multiple studies and estimates range from 1.1 to 7.2.[18] The lower estimates of norovirus R_0 would not be consistent with the observed epidemic spread of new genotypes, whereas the higher estimates of norovirus R_0 would be consistent with the very large numbers of viral particles shed by norovirus, the low infectious dose and potentially long shedding durations.

Contaminated hands can transmit norovirus directly to others, or indirectly through contaminated surfaces or food. In a recent review, the main risk factor identified for norovirus illness was contact with a person with symptoms of infectious gastroenteritis. Infectious contacts account for 54% of norovirus cases in young children and 39% of norovirus cases in older children and adults. For young children, contacts outside the household presented the highest risk; for older children and adults, the highest risk was associated with child contacts inside the household.[73] Other notable transmission routes for norovirus are fomites and food.[74] Transmission of norovirus via contaminated surfaces is augmented by the resistance of these viral particles to hypochlorite cleaning solutions and the possibility of cleaning cloths transferring the virus.[75] Norovirus contamination of food can occur at the source of production or by infected food handlers during preparation. Oysters are an example of a food that are frequently contaminated with norovirus and cause outbreaks.[76] Globally, only 18% (95% uncertainty interval 11-30%) of norovirus infections are thought to be foodborne.[31] The contamination of food by infected food handlers during preparation or serving has been implicated in outbreaks involving a diverse range of foodstuffs and in a wide range of settings, including military establishments and weddings.[77]

Prompt assessment of dehydration status and appropriate treatment with fluids are key to preventing severe outcomes.[78] Inadequate access to healthcare explains why nearly all norovirus mortality in children occurs in developing countries. Treatment is primarily based

on syndromic presentation. For healthy individuals hospitalisation is infrequent and oral rehydration solutions should be used; for the immunocompromised large-volume intravenous fluid replacement is recommended. There are no currently licensed antiviral treatments for norovirus.[79]

1.3.3 Norovirus epidemiology

Norovirus is the most common gastrointestinal infection across the world, causing an estimated 684 million cases per annum (95% Uncertainty Interval 491 – 1,112 million).[31] In a recent systematic review the global prevalence of norovirus in patients with acute gastroenteritis was 18% (95% Confidence Interval 17 – 20%). The prevalence was higher in community settings (24%, 95% Confidence Interval 18 – 30%) than hospitalised patients (17%, 95% Confidence Interval 15 – 19%).[80]

In a data synthesis of foodborne illnesses across the world, norovirus was responsible for the most deaths (212,489 per year) and the most Disability Adjusted Life Years (DALYs) (15 million per year).[31] Factors associated with death included greater age, being male, living in care homes and underlying illnesses such as chronic respiratory diseases.[81] Norovirus cases may seek treatment from primary care and hospital services. In the US norovirus is estimated to contribute to approximately 1.7 million general practice visits and 400,000 emergency department visits each year, leading to $284 million of healthcare costs.[82] Globally, a recent study modelled that norovirus resulted in total annual direct health system costs of $4.2 billion (95% uncertainty interval $3.2–5.7 billion) and annual societal costs of $60.3 billion (95% uncertainty interval $44.4–83.4 billion).[83]

In the UK, a study based on re-testing stool samples from the mid-1990s using RT-PCR estimated the community incidence of norovirus disease to be 45 cases per 1,000 person-years; equating to 2 million episodes each year.[84] This estimate was updated by an analysis of the IID2 study data collected in 2008-2009, which estimated the community incidence of norovirus infection to be higher, at 59 cases per 1,000 person-years. This newer estimate equates to 3.7 million norovirus infections annually in the UK.[85]

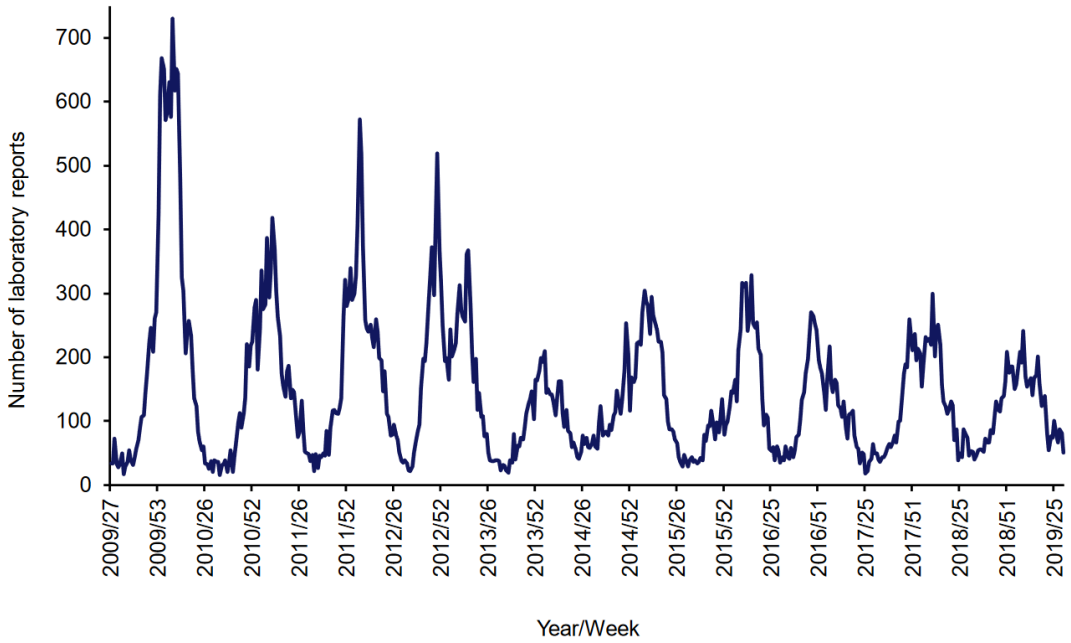
Based on the data from 2008-2009, the estimated cost to patients and the health service for norovirus was £81 million (95% Confidence Interval £63m – £106m), with each case having costs of approximately £30.[86] A more recent study based on data from 2013-2016

estimated that in England norovirus costs the National Health Service £108 million each year. The authors estimated that total annual economic burden in England was £298 million, with the loss of 6,300 quality-adjusted life years (QALYs).[87]

Rates of norovirus are highest in young children. Up to 90% of children experience at least one norovirus infection and up to 70% experienced norovirus-associated diarrhoea in the first two years of life.[88] In the UK, the age group with the highest incidence of norovirus in the community was under 5 years (143 cases per 1,000 person-years), with incidence rates decreasing with increasing age. Based on data from norovirus outbreaks, the incidence in women is significantly higher than it is for men,[61] although this is likely to be due to an ascertainment bias.

Norovirus infection shows a strong seasonality. The relationship between norovirus disease and winter may have been first recognised by Zahorsky in 1929, who used the alias “winter vomiting disease”.[50] A recent systematic review found that in most locations norovirus exhibited a clear seasonality, with a peak of incidence in winter months. The authors found that 79% of norovirus cases and 71% of norovirus outbreaks occurred in cooler months.[89] This seasonality can be seen in Figure 1.3. Data from England and Wales show that this seasonality may be due to the significant relationship between decreased temperature and increased norovirus incidence.[90]

Figure 1.3: Number of norovirus laboratory reports by week, England and Wales, 2009-2019



Published on 08 August 2019 by Public Health England[91]

Long term secular trends in the incidence of norovirus disease must be interpreted with care due to the adoption of RT-PCR testing in the late 1990s, which substantially improved testing sensitivity compared with electron microscopy.[54] Increases in the incidence of norovirus appear to follow from the periodic emergence of variant norovirus strains. The increase in norovirus outbreaks in the years following 2002 was linked to the emergence of a new variants in genogroup II: GII.4.[92] These pandemic variants include New Orleans 2009 and Sydney 2012.[93, 94]

1.3.4 Norovirus in care homes

Although norovirus can cause sporadic infections and outbreaks in all age groups, care home residents have been found to be at greater risk of norovirus infection,[95] and older people are at higher risk of hospitalization and death from norovirus.[96] Furthermore, care home residents have a significantly higher risk of gastroenteritis if they are physically debilitated.[97]

Reviews of the transmission of norovirus in healthcare settings found that norovirus outbreaks in such healthcare settings were associated with genogroup II strains [98] and lower attack rates than foodborne outbreaks.[99] Good hand hygiene practices during care

home outbreaks are essential. When testing hand samples of staff and residents during 12 norovirus outbreaks in 12 care homes, norovirus was detected in 43% of samples.[100] Good hygiene measures are particularly important as almost half (47%) of norovirus cases in care home outbreaks shed virus for more than 21 days after onset of symptoms.[101] A systematic review of infection control measures for norovirus in semi-enclosed settings found that although proper infection control measures are key to controlling norovirus outbreaks, the body of the published literature at the time of review did not provide an evidence-base for the value of specific procedures.[102]

In 2015, Petrignani *et al.* published a systematic review and meta-analysis of norovirus introduction routes into care homes and risk factors for spread.[103] This review included 38 outbreak reports and 23 observational studies. The evidence synthesised from this review suggests that norovirus introduction into a care home through people (residents, staff or visitors) is most frequent, but it was not possible with the available data to evaluate whether introductions were linked to symptomatic or asymptomatic people. In their meta-analysis, when considering both cohort and case-control studies, there was no compelling evidence that risk factors such as level of contact intensity, level of dependency and method of feeding were associated with attack rate. There was some evidence that exposure to vomit was associated with increased attack rate in residents [104] and staff.[97] However, despite the rigorous methods used in this review and even though they included nearly 1,000 outbreaks, this still represents only a small fraction of the total global number of care home norovirus outbreaks.

Regarding the burden of norovirus in care homes, there is very little published data on the incidence of sporadic norovirus cases in this setting. Most information on the burden of norovirus therefore comes from the analysis of outbreaks. A number of studies calculate the percentage of infectious disease outbreaks in care homes which are attributed as being caused by norovirus. Surveillance studies in Australia[46] and France[45] found the percentage caused by norovirus to be 40% and 36%, respectively. Other studies in south west England,[44] Oregon[42] and the Netherlands[43] found the percentage to be higher, at 74%, 77% and 78%, respectively. However, there are no comprehensive and recent data for England, with the south west England data being collected between 2002 and 2003. Furthermore, none of these studies calculated an incidence rate of norovirus outbreaks or estimated the total number of norovirus outbreaks per year.

From this section the two key gaps in the literature that I have identified are: (a) the lack of recent data from England on the proportion of care home outbreaks caused by norovirus (b) the absence of information on the total burden of norovirus outbreaks in care homes.

1.4 Surveillance of infectious gastroenteritis

1.4.1 Understanding the surveillance pyramid

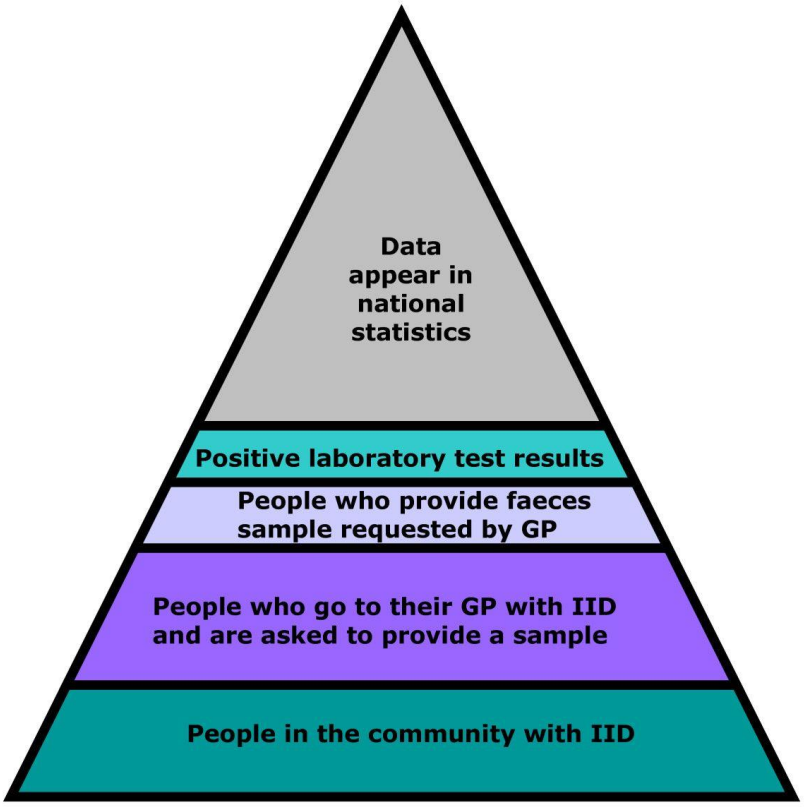
Surveillance is a vital component of infectious disease epidemiology. It is defined in the J.M. Last Dictionary of Epidemiology as:

> *"Systematic ongoing collection, collation, and analysis of data and the timely dissemination of information to those who need to know so that action can be taken."*

Surveillance should be continuous and ongoing; this distinguishes it from monitoring which is more intermittent or episodic, however usage of these two terms can vary depending on the context. The underlying importance of surveillance to infectious disease epidemiology comes from the way that surveillance generates information which can then be used for public health action, primarily the prevention and control of disease. The effectiveness of public health surveillance systems can be evaluated by criteria such as data quality, sensitivity and timeliness.[105]

For surveillance of infectious gastroenteritis in the community, data sources typically include reports of cases from general practice, laboratory diagnoses and reporting of outbreaks. These data should be collected and analysed in a timely fashion to allow any intervention. However, data on infectious gastroenteritis in the community must be interpreted in light of the "surveillance pyramid". This term is used to capture the degree of under-diagnosis and under-reporting which may occur at each stage in the process between a person becoming ill with infectious gastroenteritis and a report of this episode being captured in a national surveillance system. A pictorial representation of this surveillance pyramid is presented in Figure 1.4.

Figure 1.4: Diagram illustrating the surveillance pyramid for infectious intestinal disease (IID)



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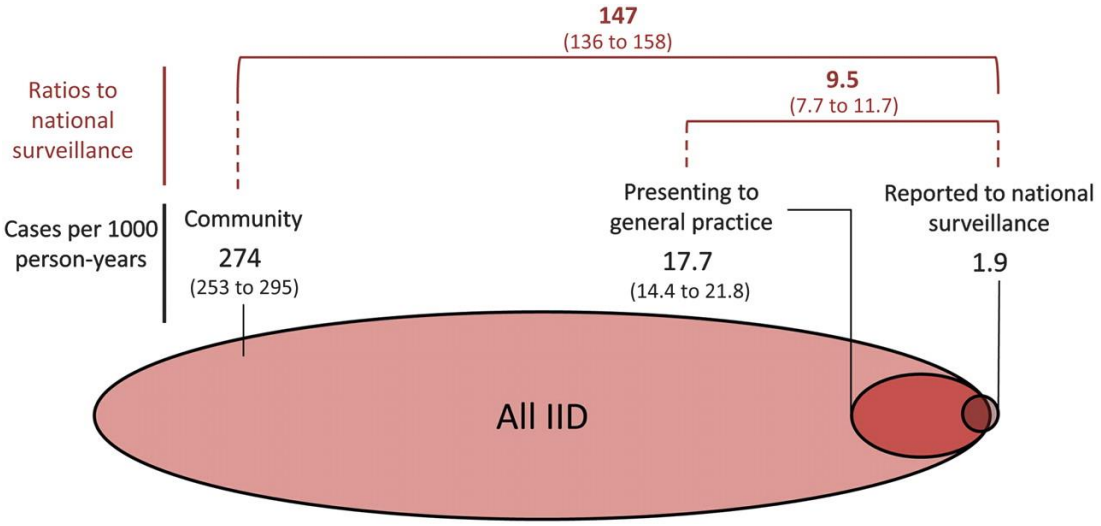
The degree of under-reporting at key stages of the surveillance pyramid was enumerated in the IID2 study in the UK in 2008-2009. The extent of under-reporting was shown to be substantial in this study, with the rate of community infectious gastroenteritis (274 per 1,000 person-years) estimated to be 147 times greater than the rate reported to national surveillance. Furthermore, the rate of IID reported in general practice was 9.5 times higher than that reported to national surveillance.[26] These results are illustrated in Figure 1.5. This surveillance pyramid effect is not confined to the UK. A study based in six other European countries found that under-reporting for gastrointestinal pathogens also occurred in these settings. There were wide variations in the under-reporting by country and pathogen, mainly caused by differences in healthcare usage and laboratory practice.[107]

Figure 1.5: Incidence rates of intestinal infectious disease from the IID2 study, UK



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This under-reporting encapsulated by the surveillance pyramid is a factor that needs to be considered and (if possible) adjusted for when estimating the burden of disease in a population.

1.4.2 Case definitions for individual cases and outbreaks in care homes

A central component of a successful surveillance system is the use of appropriate case definitions to classify correctly the health events under surveillance. Case definitions should be sufficiently sensitive to include all events of interest, whilst being suitably specific to capture only the events of interest.

For the surveillance of infectious gastroenteritis in care homes, the most relevant case definitions are those for individual cases and for outbreaks. For individual cases of infectious gastroenteritis, there is some variation in the definition used. For example, the WHO defines diarrhoeal disease as "the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)", whereas in the IID2 study, cases were defined as "persons with loose stools or clinically significant vomiting lasting less than two weeks, in the absence of a known non-infectious cause."[106]

For the surveillance of individual norovirus cases in care homes, the suggestion provided in 2012 by Stone *et al.* for the Society for Healthcare Epidemiology Long-Term Care Special Interest Group was that norovirus gastroenteritis be defined as illness meeting both of the following criteria:[108]

1) At least 1 of the following GI subcriteria
    a) Diarrhoea: 3 or more liquid or watery stools above what is normal for the resident within a 24-h period
    b) Vomiting: 2 or more episodes of in a 24-h period
2) A stool specimen for which norovirus is positively detected by electron microscopy, enzyme immunoassay, or molecular diagnostic testing such as polymerase chain reaction (PCR)

Regarding the definitions used for an outbreak of infectious gastroenteritis in care homes, these have changed over time and vary in different countries. In 1975, the US Centers for Disease Control and Prevention (CDC) produced a definition of gastroenteritis, which included either acute onset of diarrhoea (which they defined as liquid stools for more than 12 hours) and a likely non-infectious cause, or two or more recognised symptoms with a positive pathogen test.[109] This was built upon by McGeer *et al.* who published their definition of infectious gastroenteritis in care homes in 1992.[110] This stated that *one* of the following criteria should be met:

1) Two or more loose or watery stools *above what is normal* for the resident within a 24-hour period.
2) Two or more episodes of vomiting in a 24-hour period.
3) Both of the following: (a) a stool culture positive for a pathogen (*Salmonella*, *Shigella*, *E. coli* O157:H7, *Campylobacter*) or a toxin assay positive for *C. difficile* toxin and (b) at least one symptom or sign compatible with gastrointestinal tract infection.

These guidelines were reviewed and revised by Stone *et al.* in 2012 to incorporate developments, particularly regarding diagnostics, that had occurred over the previous 20 years.[108] This advisory group defined a norovirus outbreak as:

> *"In the absence of laboratory confirmation, an outbreak (2 or more cases occurring in a long-term care facility [LTCF]) of acute gastroenteritis due to norovirus infection may be assumed to be present if all of the following criteria are present ("Kaplan Criteria"): (a) vomiting in more than half of affected persons; (b) a mean (or median) incubation period of 24–48 h; (c) a mean (or median) duration of illness of 12–60 h; and (d) no bacterial pathogen is identified in stool culture."*

In the UK, the most recent published guidance for managing norovirus outbreaks in acute and community health and social care settings outlines the importance of defining an outbreak, but leaves the actual definition to the health protection and epidemiological surveillance organizations that collect and analyse the data.[111] This working group did however reject the use of the Kaplan criteria, on the basis that this expert group felt this criteria could only reasonably be applied retrospectively.

1.4.3 Surveillance in care homes

Routine surveillance of infectious gastroenteritis in care homes can either capture individual episodes of illness or outbreaks of infectious gastroenteritis. Regarding individual cases, there are currently no published examples of routine surveillance systems which are dedicated to recording these cases in care homes. In England, such cases may possibly be captured in syndromic surveillance,[112] as a notification of infectious disease (NOIDs) or as part of laboratory surveillance (Second Generation Surveillance System – SGSS) if a diagnostic specimen was submitted. However, these surveillance systems do not reliably include markers to link cases to care homes, so these systems cannot reliably be queried to report individual case data.

Surveillance for outbreaks of infectious disease in care homes primarily takes place in developed countries. National surveillance systems dedicated to the surveillance of infectious gastroenteritis outbreaks in care homes are uncommon; France and Australia are the only published examples of systems which operate in this way.[45, 46] Other countries such as the US,[113] Norway,[114] New Zealand,[115] and the Netherlands[43] have national-level gastroenteritis outbreak surveillance which includes outbreaks in care homes, but this setting is not the main focus. In England, care home gastroenteritis outbreaks have been captured as part of general outbreak surveillance since 1992.[41] Since 2010, care homes in England have been required by the CQC to report infectious gastroenteritis outbreaks to Public Health England (PHE).[116] However, there is presently no unified national surveillance system to collect this information. In most parts of England these outbreaks are recorded locally by PHE teams using a health protection case management tool rather than a surveillance system.[117]

In order to provide a more detailed background on the surveillance of norovirus in community settings such as care homes, I decided to undertake a systematic review which I

present as the next chapter. In this systematic review I assess published literature to understand the nature, scope and scale of community-based surveillance systems which capture information on norovirus disease.

1.5 Aims and research questions

In this thesis I will explore the epidemiology of infectious gastroenteritis in care homes and aim to build on the current evidence base. I aim to collect relevant data and conduct appropriate analyses to generate evidence. The following are the research questions which I intend to address gaps that I have identified in the knowledge base:

1. What is the incidence of infectious gastroenteritis in care home residents?
2. What is the incidence of care home gastroenteritis outbreaks?
3. What are the epidemiological characteristics of care home gastroenteritis outbreaks?
4. What proportion of care home gastroenteritis outbreaks are caused by norovirus?

1.6 Thesis outline

This thesis contains seven further chapters in which the context of the research is described, each of the four research questions are addressed and the results of the work is discussed. Apart from the last chapter, each chapter is based on a research paper. The thesis contains six peer-reviewed and published papers: Chapter 2, Chapter 3, Chapter 4, Chapter 5, Chapter 6 and Chapter 7. In accordance with the University of Liverpool Postgraduate Research Code of Practice, each chapter containing a published paper also has additional introductory text to explain the way it fits with surrounding chapters. This thesis is structured in the following way to address the questions outlined in the previous section:

Chapter 2 provides a systematic review of the surveillance methods used for norovirus disease in community settings and a geographical comparison of different surveillance systems. Additionally, this review collected community incidence data for all gastroenteritis and norovirus disease, providing context for the burden of acute gastroenteritis in non-hospital settings.

Chapter 3 presents the protocol used for a prospective cohort study I conducted to answer all four research questions and therefore understand the burden and transmission of acute gastroenteritis in care homes. In addition to the published protocol, this also includes more detailed information from the Research Ethics Committee (REC) approved study protocol. Finally, this chapter also provides an overview of the datasets used for analyses presented in the following chapters.

In Chapter 4, I present the main epidemiological results of the care home prospective cohort study. This provides evidence of the incidence of infectious gastroenteritis at an individual-level in care home residents. In this chapter I also present the results of two of the study components which provided preliminary information.

Chapter 5 describes the results of the study of care home outbreaks using a detailed dataset from Cheshire and Merseyside. This study addresses two research questions by providing an estimate of the incidence of care home outbreaks and exploring the epidemiological characteristics of such outbreaks, particularly aspects of transmission such as the effect of timely closure on outbreak duration.

In Chapter 6, I use care home outbreak surveillance data from an area of England (North East) which has high levels of stool sampling and all samples are tested for a wide range of pathogens. Using these data, I provide evidence to answer the research question regarding the proportion of care home gastroenteritis outbreaks caused by norovirus.

In Chapter 7, I address the question of the incidence of care home gastroenteritis outbreaks in England. I use a generalised linear mixed effects regression model to estimate the total burden of care home gastroenteritis outbreaks in England, adjusted for under-reporting.

In Chapter 8, I conclude the thesis by summarising and discussing of the findings from my research, consider the key limitations and challenges of this work, and make recommendations for action by public bodies and further research to build on the findings presented in this thesis.

Chapter 2 – Systematic Review

Community-based surveillance of norovirus disease: a systematic review

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How this publication fits into my thesis

In this chapter I build on the background provided in the introductory chapter and provide a more detailed background on the surveillance of norovirus in community settings such as care homes. I decided to conduct this systematic review to assess the published literature in a methodical way to understand the nature, scope and scale of community-based surveillance systems which capture information on norovirus disease.

The systematic review in this chapter describes the surveillance methods used for norovirus disease in community settings and makes a geographical comparison of different surveillance systems. By collecting and presenting community incidence data for all gastroenteritis and norovirus disease, this chapter provides data on the burden of acute gastroenteritis in non-hospital settings, which provides context for the following results chapters.

My contribution

I designed the study protocol then undertook the search, selection and analysis with JH, and drafted the manuscript.

2.1 Abstract

Background

Norovirus is a common cause of infectious gastrointestinal disease. Despite the increased ability to detect norovirus in affected people, the number of reported cases and outbreaks in the community is still substantially underestimated. We undertook a systematic review to determine the nature, scope and scale of community-based surveillance systems which capture information on norovirus disease.

Methods

We searched MEDLINE, EMBASE and Scopus for studies published between 01 January 1995 and 31 December 2015, using terms relating to norovirus and surveillance. Publications were screened independently by two reviewers using exclusion criteria. Data extraction from included papers was performed using a standardized data extraction form. Outcomes were descriptions of the methods reported in included papers, and any estimates of incidence rate of norovirus disease in each community, stratified by age.

Results

After exclusions, we reviewed 45 papers of which 23 described surveillance studies and 19 included estimates of incidence. The estimates of incidence varied by outcome measure, type of laboratory test and study population. There were two estimates of norovirus hospitalisation; 0.72 and 1.04 per 1000 person-years. Estimates of norovirus disease ranged between 0.024 cases per 1000 person-years and 60 cases per 1000 person-years and estimates of all gastroenteritis varied between 49 and 1100 cases per 1000 person-years.

Conclusions

Our systematic review found few papers describing community-based surveillance for norovirus disease. Standardised age-specific estimates of norovirus incidence would be valuable for calculating the true global burden of norovirus disease; robust community surveillance systems would be able to produce this information.

PROSPERO 2016:CRD42016048659

2.2 Background

Norovirus infection is the most common cause of infectious gastrointestinal disease in the United Kingdom (UK) and many other countries.[53, 118] Globally, it is estimated to be associated with 18% of all cases of acute gastroenteritis.[80] Norovirus is a common cause of gastroenteritis outbreaks in healthcare settings.[119] Outbreaks are difficult to control in enclosed settings and the evidence for the effectiveness of infection control methods remains inconclusive.[102, 120] The infection is typically mild and self-limiting and people who are infected rarely have contact with medical services; further detail on the clinical manifestations of norovirus has been described elsewhere.[53] Some groups, particularly the elderly, can have longer episodes of illness,[121] and are at risk of more serious outcomes.[122]

Surveillance of norovirus disease is essential for providing information for norovirus prevention and control.[123] Different types of surveillance system are used and have been described elsewhere.[120] Norovirus surveillance is largely based on laboratory diagnosis and the ability to detect norovirus in affected people has increased with the adoption of more sensitive molecular methods.[124] There is evidence that the number of reported cases and outbreaks in the community is substantially underestimated; and that this underestimation is greater in the community than hospital settings,[26, 120, 125] but there is little evidence of the type and variety of community-based norovirus surveillance systems. We were prompted to undertake this research to address this gap.

The aim of this research is to determine the nature, scope and scale of community-based surveillance systems which capture information on norovirus disease. To do this, we undertook a systematic review according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[126] In order to determine the nature, scope and scale of community-based surveillance of norovirus disease, we described the methods reported in papers included in the review, as a primary objective. A secondary objective was to capture the incidence rate of norovirus disease in each setting.

2.3 Methods

Protocol and registration

The review was registered on the PROSPERO International prospective register of systematic reviews on 03 October 2016 (PROSPERO 2016:CRD42016048659).[127] The review protocol followed the PRISMA checklist.

Eligibility criteria

Studies published between 01 January 1995 and 31 December 2015. No explicit geographical restrictions were applied. Only studies published in English were eligible. We excluded the following types of publication: studies of illness in persons residing in primary care settings, reports or reviews of outbreak investigations, review papers, editorials, conference abstracts or proceedings, randomized clinical trials or case reports, environmental surveillance, economic analyses, studies based on asymptomatic infections, surveys of molecular epidemiology or seroprevalence surveys.

Information sources

We searched the following electronic databases: MEDLINE, EMBASE and Scopus. The last date searched was 16 August 2016.

Search

We used the following search terms: (norovirus.ab,ti. OR (norwalk-like adj1 virus).ab,ti. OR (norwalk-like adj1 disease*).ab,ti. OR norwalk.ab,ti. OR small round structured virus.ab,ti. OR winter vomiting disease.ab,ti.) AND surveillance.ab,ti. The search terms were piloted prior to selection and are comprised of specific norovirus terms. The search terms for MEDLINE were developed initially. Terms were combined using Boolean operators. The same terms were used to search Scopus. When the searches were run in MEDLINE, each term was searched for within the title and abstract of the documents contained in each database; in Scopus, terms were searched within the title, abstract and keywords.

Study selection

All references identified by the search strategy were imported into the reference management programme EndNote X7 (Clarivate Analytics, USA). Using this software, publications from the different databases were combined and deduplicated. These publications were then screened applying the exclusion criteria. This screening was conducted independently by two reviewers (TI and JPH) to ensure the criteria were applied consistently. Differences between reviewers on first screening were reconciled by

discussion between the two reviewers. Full texts of all studies meeting the title and abstract screening criteria were examined independently by the two reviewers (TI and JPH) using a standardised eligibility form. Final agreement on study inclusion was determined through consensus between the two reviewers (TI and JPH).

In order to maximise the proportion of eligible studies included in the review, the reference lists of studies that met the inclusion criteria were searched to identify potentially relevant articles not included be the database searches. When potentially relevant articles were identified in this way, the two reviewers (TI and JPH) searched for abstracts and then screened in the same fashion as those identified by the database search. The full text of any abstract that met the eligibility criteria was assessed using the standardised eligibility form; final agreement was determined through consensus between the two reviewers.

Data collection process and data items

Data extraction from included papers was performed using a standardized data extraction form. The following data were extracted (where available): year published, predominant study type, surveillance type (active or passive), study setting, time period, study duration, geography (country, region), case definition, laboratory testing methods, proportion of norovirus detections, use of further typing methods, population age range, study population, person-time of study population, number of cases and incidence rate with 95% Confidence Interval. We defined the surveillance type as active if the person-time at risk was actively enumerated.

Summary measures

Outcomes were descriptions of the methods reported in included papers, and any estimates of incidence rate of norovirus disease in each community, stratified by age. Estimates of incidence rates were not pooled between studies.

Synthesis of results

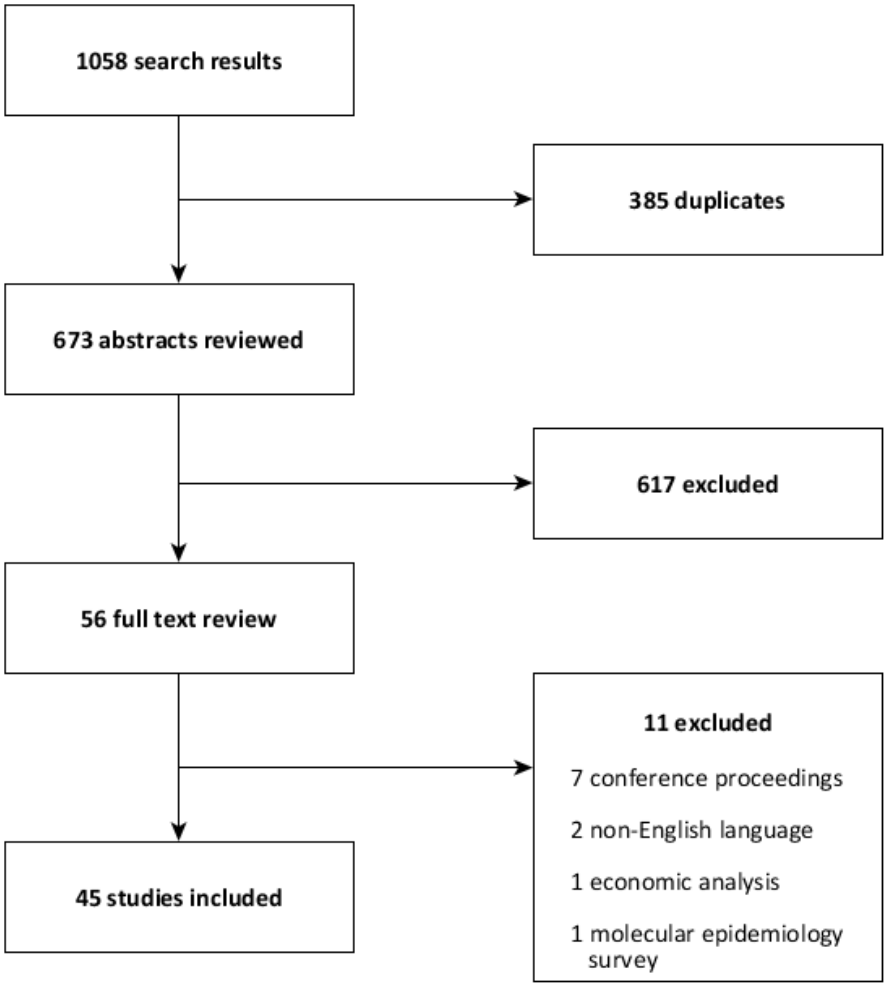
We compared methods used in included papers. We described the study design and methods used, the population under surveillance, the date of publication, the location of study and compared incidence rates in various studies, stratified by age where available.

2.4 Results

Study selection

The first searches identified 1058 papers; following deduplication this was reduced to 673 publications. After review of the title and abstract, 56 publications were included and 617 excluded. Of the 56 publications subject to full text review, 11 were excluded and 45 included in this systematic review (Figure 2.1). Of the 11 papers excluded after full text review, seven were conference proceedings, two were non-English language, one was an economic analysis and one was a survey of molecular epidemiology.

Figure 2.1: Study selection, systematic review of community-based surveillance of norovirus disease (n=1058)



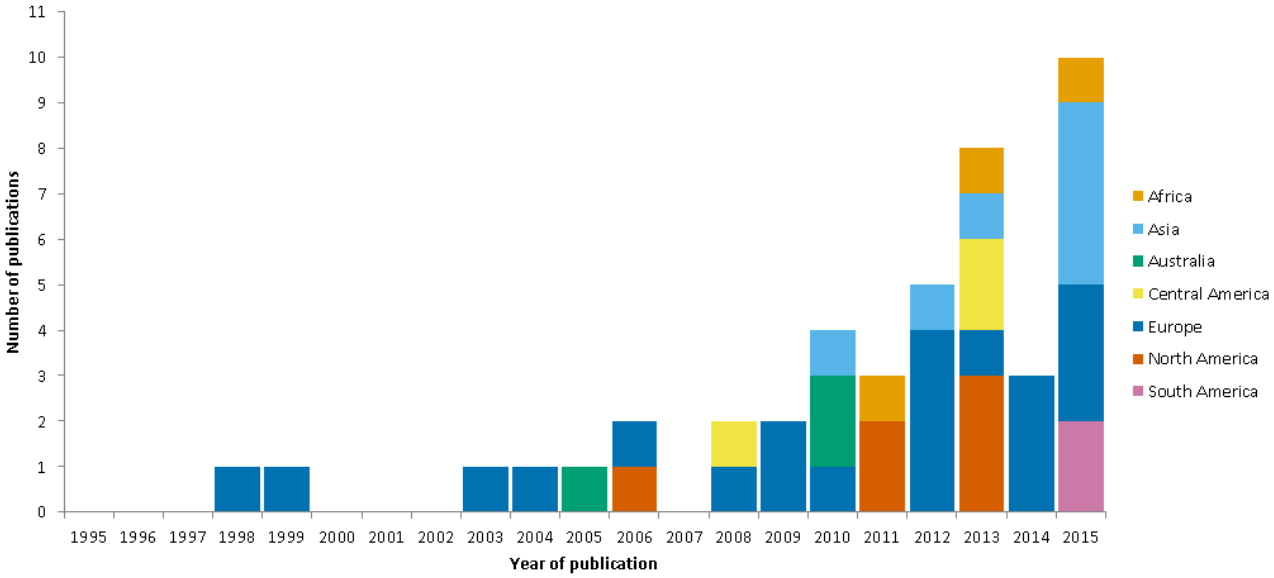
Characteristics of included studies

The number of publications regarding the community-based surveillance of norovirus disease increased over the 20 year period included in this review; two thirds of papers

(n=30) were published since 2010. Papers based in community settings in Europe (n=20) were most frequent, the majority of these being from the United Kingdom (n=7) and France (n=4). Other countries with multiple published studies include the United States of America (n=6), Australia (n=3) and China (n=3). Figure 2.2 shows the distribution of publications over time and by geography of study location.

Figure 2.2: Reviewed studies; shown by year of publication and geography of study location (n=44*)

**One study published in 2015 was based in several sites across the world*



A total of 23 publications described surveillance studies; 18 of these described surveillance of individuals, five described surveillance of norovirus outbreaks in the community. Other community-based publications included cohort studies (n=14), cross-sectional surveys (n=7) and one case-control study in a community setting. A breakdown of included publications by study type is shown in Table 2.

Table 2: Reviewed publications, by study type and outcome (n=45)

First Author	Year Published	Study Type	Surveillance Type	Incidence outcome measure	Study country	Study Duration (Years)
Dedman[128]	1998	Surveillance	Passive	Norovirus disease	UK	5
Wheeler[22]	1999	Cohort	Active	All gastroenteritis / Norovirus	UK	3
Lopman[129]	2003	Surveillance	Passive	-	UK	7
Froggatt[130]	2004	Surveillance	Passive	-	UK	0.5
Sinclair[131]	2005	Cohort	Active	-	Australia	1.5
Medici[132]	2006	Cohort	Passive	-	Italy	1
Vernacchio[133]	2006	Cohort	Active	All gastroenteritis	USA	1.5
Bucardo[134]	2008	Cohort	Passive	-	Nicaragua	1
Gomara[135]	2008	Cohort	Active	-	UK	1.25
Huhulescu[136]	2009	Cohort	Active	All gastroenteritis	Austria	1
Iturriza-Gomara[137]	2009	Cohort	Active	All gastroenteritis	UK	1.66
Gauci[138]	2010	Cross-sectional	Active	All gastroenteritis	Malta	1.66
Kirk[46]	2010	Outbreak	Passive	-	Australia	6
Kirk[139]	2010	Cohort	Active	-	Australia	1
Liu[140]	2010	Surveillance	Passive	-	China	1
Moyo[141]	2011	Cross-sectional	Passive	-	Tanzania	0.25
Scallan[142]	2011	Surveillance	Passive	-	USA	8
Vega[143]	2011	Outbreak surveillance	Passive	-	USA	1
Baumann-Popczyk[144]	2012	Cross-sectional	Active	All gastroenteritis	Poland	1
Oldak[145]	2012	Surveillance	Passive	All gastroenteritis	Poland	1
Ouyang[146]	2012	Surveillance	Passive	-	China	1
Tam[26]	2012	Cohort	Active	All gastroenteritis / Norovirus	UK	1.33
Thouillot[147]	2012	Outbreak surveillance	Passive	-	France	0.33
Ahmed[148]	2013	Cross-sectional	Active	All gastroenteritis	Dominica	1.5
Gould[149]	2013	Outbreak surveillance	Passive	-	USA	10
Ingram[150]	2013	Cross-sectional	Active	All gastroenteritis	Barbados	1

First Author	Year Published	Study Type	Surveillance Type	Incidence outcome measure	Study country	Study Duration (Years)
Nahar[151]	2013	Surveillance	Passive	-	Bangladesh	1
Payne[152]	2013	Surveillance	Active	Norovirus hospitalisation	USA	2
Saupe[153]	2013	Surveillance	Passive	-	USA	1.25
Trainor[154]	2013	Surveillance	Passive	-	Malawi	10
Verhoef[155]	2013	Cross-sectional	Passive	Norovirus disease	Netherlands	1
Arena[156]	2014	Surveillance	Passive	All gastroenteritis	France	2
Barret[45]	2014	Outbreak surveillance	Passive	-	France	1.5
Bernard[157]	2014	Surveillance	Passive	Norovirus disease	Germany	8
Anders[158]	2015	Cohort	Active	All gastroenteritis	Vietnam	4
Ballard[159]	2015	Cohort	Active	All gastroenteritis / Norovirus	Peru	9
Enserink[160]	2015	Cohort	Active	All gastroenteritis	Netherlands	3
Fernandez[161]	2015	Case-control	Passive	-	Colombia	not stated
Gaspard[162]	2015	Outbreak surveillance	Active	-	France	6
Lekana-Douki[163]	2015	Cohort	Passive	-	Gabon	1.25
Leshem[164]	2015	Surveillance	Active	Norovirus hospitalisation	Isreal	7
Platts-Mills[165]	2015	Cohort	Active	-	multi-site	3
Sakon[166]	2015	Surveillance	Passive	-	Japan	10
Thongprachum[167]	2015	Surveillance	Passive	-	Japan	4
Xue[168]	2015	Cross-sectional	Active	-	China	2

Description of methods reported in community-based norovirus surveillance

Reports of community-based surveillance of laboratory reports of norovirus infection were published from England and Wales,[128–130] Germany[157] and the United States of America (USA).[142] Surveillance using sentinel general practitioners (family doctors) was reported from France.[156] Surveillance of norovirus using a foodborne illness complaint system in the USA state of Minnesota.[153] Reports of the surveillance of norovirus outbreaks in the community were published from the USA.[143, 149] Norovirus outbreak surveillance in care homes was reported from France [45, 147, 162] and Australia.[46]

A number of papers described the surveillance of cases of norovirus acquired in the community, through the surveillance of cases admitted to hospital from the community. Sentinel networks or small groups of hospitals published their findings from Japan,[166, 167] Israel,[164] USA[152] and Bangladesh.[151] Four publications reported surveillance at individual hospitals in China,[140, 146] Poland[145] and Malawi[154]. Children under five years old were included in one case-control study in Colombia.[161] A total of 20 papers were classed as active surveillance and 25 were classed as passive surveillance.

Cohort studies captured surveillance data on norovirus disease in children in general practice,[133, 135, 137] in day care[160] and in hospital.[132, 134, 163] Two birth cohort studies, one in Vietnam[158] and one across eight sites in South America, Africa and Asia.[165] Four cohort studies captured surveillance data on norovirus disease in all of those attending general practice;[22, 26, 131, 136] one cohort study was based in 16 care homes[139] and one a cohort study of military personnel.[159] A number of cross-sectional studies from different countries collected information on the general population.[138, 144, 148, 150, 155] One study was of hospitalised children[141] and another included hospital outpatients.[168]

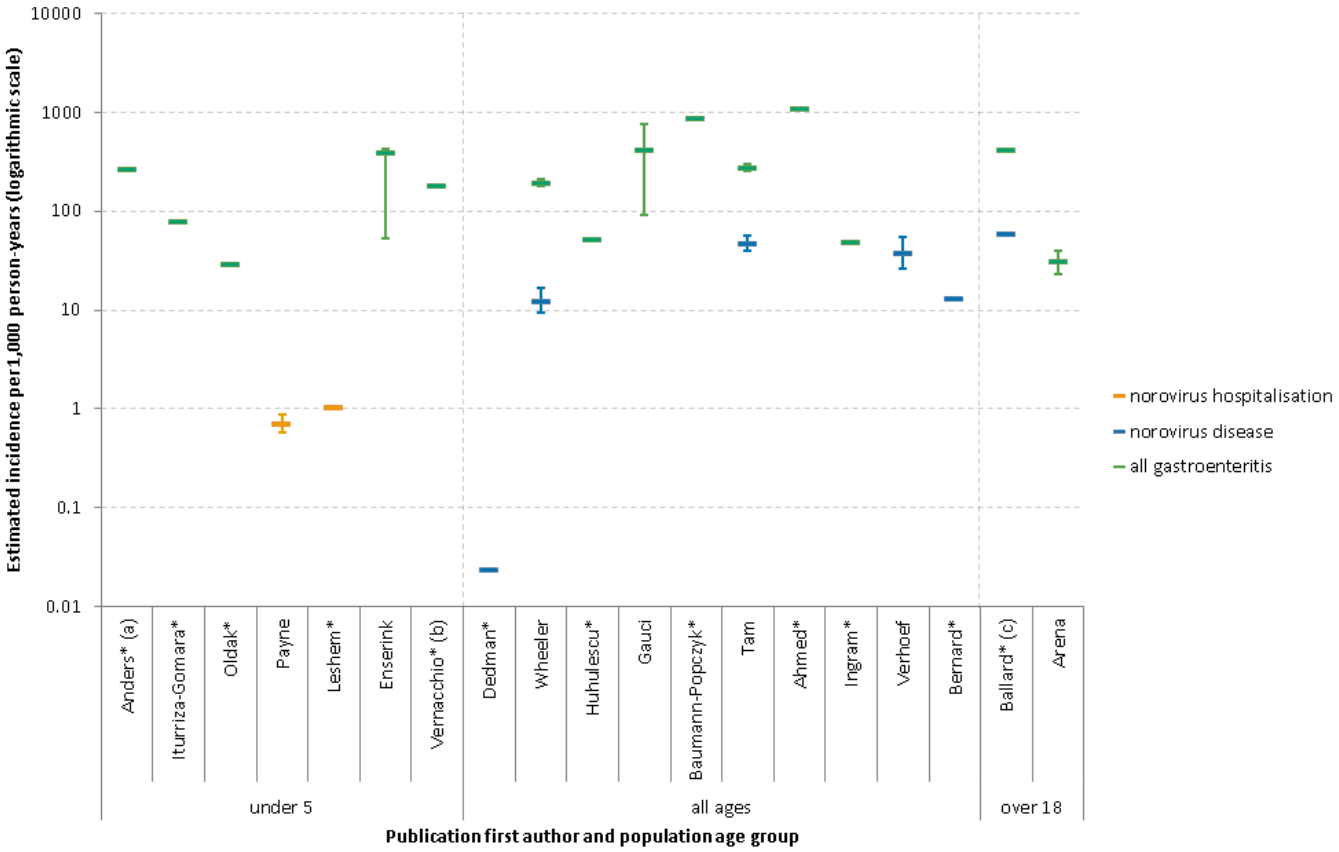
Of the 39 papers which covered the surveillance of individual cases, all but one used a laboratory test to confirm the presence of norovirus. Polymerase chain reaction (PCR) was used either alone or in combination with other methods by 29 of the reports; enzyme immunoassay (EIA) was used as the only method in two studies and electron microscopy (EM) as the only method in one study. The laboratory methods were either absent or unclearly defined in five studies. The case definition was based on the WHO definition of diarrhoea in 22 of the 39 studies; another symptomatic definition was used in 13 of the

studies, one study used a virological case definition and the case definition was unclear in the remaining three studies. Regarding the surveillance of norovirus outbreaks, three of the six used the Centres for Disease Control and Prevention (CDC) outbreak definition.[46, 143, 149] Comparable definitions were used by the other three studies.[45, 147, 162] All norovirus outbreak surveillance systems used some form of laboratory confirmation; PCR was used alone or in combination for five studies, the lab method wasn't specified in the other study.

Estimates of the incidence rate of norovirus disease in each community

Publications included in this review measured outcomes that can be classified into three groups; norovirus hospitalisation, norovirus disease and all gastroenteritis. A total of 19 papers included estimates of incidence, of which seven also published Confidence Intervals. Figure 2.3 depicts the estimated incidence rates by outcome and study age group. Of the 19 papers, 14 were classed as active surveillance and clearly enumerated the person-time at risk.

Figure 2.3: Studies with estimates of community incidence, shown by measured outcome and population age group (n=19)



**No published Confidence Interval estimate; (a) population under 1; (b)6 months to 3 years old; (c) males aged 18 to 34*

Two papers used norovirus hospitalisation as an outcome, both were based in those aged under five and reported similar estimates; 0.72[152] and 1.04[164] hospitalisations per 1000 person-years. Six papers provided estimates of norovirus disease incidence. Estimates of norovirus disease ranged between 0.024 cases per 1000 person-years and 60 cases per 1000 person-years.[22, 26, 128, 155, 157, 159]

Incidence rates of all gastroenteritis were estimated by 14 papers. Estimates in children under five ranged between 29.5 and 389 cases per 1000 person-years.[133, 137, 145, 158, 160] Estimates in all ages ranged between 49 and 1100 cases per 1000 person-years.[22, 26, 136, 138, 144, 148, 150] One paper estimated the incidence rate of all gastroenteritis in long-term care facility (LTCF) resident as 0.64 cases per 1000 bed-days.[139] Another estimated the incidence rate of gastroenteritis outbreaks in LTCFs as 16.8 per 100 LTCFs per year.[46]

2.5 Discussion

Our systematic review has found few papers describing community-based surveillance for norovirus disease. We found surveillance based on individual laboratory reports were reported from four countries; England and Wales, Germany, France and the USA. Surveillance of outbreaks in care homes was reported from France and Australia. We found a number of hospital-based surveillance reports capturing illness acquired in the community; these tended to be based in a single or small number of hospitals and many were cross-sectional or cohort studies in a fixed time period. Several papers from the USA reported on the surveillance of outbreaks associated with food.

The small number of national surveillance systems reporting norovirus disease is likely to be related to the knowledge that most people do not access health care for a diagnosis.[26] One explanation could be the lack of statutory basis for norovirus reporting. The European Surveillance System (TESSy) is a system used by European Union (EU) Member States and European Economic Area (EEA) countries for the collection, analysis and dissemination of data on communicable diseases. Norovirus disease is not one of the 52 communicable diseases covered by this surveillance system.[169] Another reason could be the low priority of testing for norovirus with limited healthcare or laboratory resources. Due to the usually mild self-limiting nature of the disease, testing for norovirus may not be prioritised by healthcare providers. This is an issue in high-resource countries, but is particularly relevant in low-resource settings. This under-representation of developing countries may be partially addressed by plans for the inclusion of norovirus in the World Health Organisation (WHO) global rotavirus surveillance network,[170] which includes a number of developing countries. The change in the number of papers published, whereby we observed that the majority have been published since 2010, is likely to be related to the change in testing from electron microscopy to more rapid and more sensitive techniques such as real-time polymerase chain reaction (RT-PCR) and EIA.[171]

We found that estimates of the incidence rate of community-based norovirus disease had three outcome measures; norovirus hospitalisation, norovirus disease and all gastroenteritis. The two estimates of norovirus hospitalisation in children were both similar, around one case per 1000 person-years. Of the estimates of norovirus disease, one estimate was far lower (0.024 cases per 1000 person-years) than the others.[128] This

much lower estimate is possibly due to the different diagnostic methods used; this is the earliest published study included in the review and at that time diagnosis of norovirus was by electron microscopy which is far less sensitive for detecting norovirus. This may also reflect changes in the criteria for testing for norovirus; as cheaper PCR tests have become more widespread, this may have led laboratories to widen the criteria for testing stool specimens for norovirus. The wide range of other estimates for norovirus disease (12.5 – 60 cases per 1000 person-years) and all gastroenteritis (29.5 – 1100 cases per 1000 person-years) probably reflects the different populations and age groups included. Unfortunately 12 of the publications included a point estimate, but did not include any estimate interval. Therefore, caution must be used when drawing conclusions from the differing estimates.

Subsequent to the period of this literature search, a report has been published on an enhanced surveillance system for norovirus in an area of China.[172] The rate of norovirus-associated diarrhoea that they observed was 89 cases per 1000 person-years (95% CI 82–97); this is higher than any of the estimates captured in this review, the next highest being 60 cases per 1000 person-years from a study in South America.[159] This higher rate in China may represent an increased incidence in this population, or could be a product of the extrapolations used to produce the estimate from the surveillance data.

In this review we were only able to include papers written in English due to resource limitations. As a consequence of not including those publications not in English, it is likely that we have under-represented the findings of countries where English is not widely spoken. In addition, some reports or descriptions of surveillance systems may be published on institute websites rather than indexed journals. This type of “grey literature” is difficult to search and capture in a systematic way, so is therefore excluded from this review, possibly affecting the representativeness of our findings. We were not able to undertake a meta-analysis of the norovirus incidence rates due to the extensive heterogeneity in study designs, laboratory methods, outcome measures and study populations. A meta-analysis to estimate the prevalence of norovirus in persons with acute gastroenteritis has previously been conducted.[80]

Of the 45 publications included in this review, incidence estimates were only available for 19. Excluding those publications reporting on the surveillance of outbreaks, 20 publications did not include an estimate of incidence. Of the 19 papers reporting incidence estimates,

14 were classed as active surveillance as they clearly enumerated the person-time at risk in the population. The five papers classed as passive surveillance used population denominators which assume that all persons would have been captured in the surveillance system had they become a case. It has been shown that a large proportion of norovirus cases are not captured in national surveillance systems,[26] so estimates from these passive systems have to be interpreted in this light. A number of the surveillance publications, particularly those based in hospitals, did not report or estimate a denominator population. Without a population denominator, it is not possible to calculate incidence rates. We would recommend that future publications of this kind include an estimate of the population denominator as good epidemiological practice, and to facilitate further research of this kind.

Conclusions

In this systematic review, we found that despite norovirus being an important cause of acute gastroenteritis, in terms of number of cases that occur, few papers describe community-based surveillance for it, and a small number report any measure of norovirus incidence. Standardised age-specific estimates of norovirus incidence would be valuable for calculating the true global burden of norovirus disease; robust community surveillance systems would be able to produce this information.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Chapter 3 – Study methods and data sources

Prospective cohort study to investigate the burden and transmission of acute gastroenteritis in care homes: a study protocol

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The study was sponsored by the University of Liverpool and approved the North West – Greater Manchester South Research ethics committee on 10 October 2016 (Appendix A).

How this publication fits into my thesis

Following the description of data on the burden of acute gastroenteritis in community settings presented in the previous chapter, this chapter presents the protocol used for a prospective cohort study that I conducted to understand the burden and transmission of acute gastroenteritis in my chosen community setting: care homes. In addition to the published protocol, this also includes more detailed information from the Research Ethics Committee (REC) approved study protocol. This chapter also provides a brief description of key datasets used for analyses presented in subsequent results chapters.

My contribution

I designed the study with co-authors, oversaw the study co-ordination, data collection and analysis, and wrote the manuscript.

3.1 Abstract

Introduction

Noroviruses are the leading cause of acute gastroenteritis in all age groups, but illness is more severe and causes excess mortality in the elderly, particularly those in long term care. The total burden of norovirus disease in the elderly in the UK is poorly defined; no current surveillance programmes systematically or accurately quantify norovirus infection in those living in care homes. The aim of this study is to evaluate an enhanced surveillance system for acute gastroenteritis among the elderly in care homes.

Methods and analysis

We will conduct this prospective cohort study in care homes in North West England; residents and staff at study care homes will be asked to participate. We will prospectively enrol a cohort of participants in an enhanced surveillance system to capture the incidence of acute gastroenteritis and use multiplex PCR to detect pathogens. We will sample symptomatic and non-symptomatic participants to understand characteristics of norovirus disease and susceptibility to infection. We will generate novel data on transmission dynamics by collecting data on the pattern of interactions within care homes using electronic proximity sensors. Comparisons of outbreak and non-outbreak periods will be used to quantify the impact of norovirus outbreaks on care homes.

Ethics and dissemination

The study has been approved by the North West – Greater Manchester South NHS Research Ethics Committee (REC Reference: 16/NW/0541). Study outputs will be disseminated through scientific conferences and peer-reviewed publications. This study will provide detailed insight on the burden and aetiology of acute gastroenteritis in care homes, in addition to generating novel data on transmission dynamics and risks. The study will identify areas for improving infection control practice, and allow more accurate modelling of the introduction of interventions such as vaccination.

3.2 Introduction

Noroviruses are endemic in the human population and are recognised as the leading cause of infectious intestinal disease across all ages.[26, 82, 173] In healthy populations norovirus gastroenteritis is generally mild and self–limiting, but there is increasing evidence that it may lead to long term sequelae [174, 175] and contribute to excess mortality in the elderly and the immunocompromised.[122, 176–182] The elderly, particularly those in long term care suffer a longer duration of illness with more severe symptoms, contributing to excess mortality.[122, 176]

The factors that facilitate sustained transmission in health and social care settings are likely to be the result of a combination of the environment, behaviour patterns associated with patients, visitors and staff, the characteristics of the norovirus strains, and/or host related factors that influence susceptibility to disease.[183, 184] At present the main approaches to preventing and controlling norovirus outbreaks, common across several national guidelines include promotion of hand hygiene, patient isolation (separation of symptomatic patients) and cohorting (grouping of patients based on symptoms), staff exclusion from work, visitor restrictions, enhanced environmental cleaning and disinfection, and closures of units.[111, 185–188]

The total burden of norovirus disease in the elderly population in the UK is poorly defined, despite the widespread acknowledgment that the elderly, and in particular, those in long term care are worst affected by norovirus illness. There are currently no surveillance programmes that can systematically or accurately quantify the levels of any cause of norovirus specific gastroenteritis among the growing aging population living in care homes. The ageing population in the UK means that those over 65 years old are the fastest growing sector of the population, which will result in increasing pressure and demand for health care and long term residential care in the future.[189] Norovirus infections are known to be more severe in this sector of the population, contributing to excess hospitalization and mortality.[65, 122, 157, 190, 191]

The relative importance of different drivers of transmission and factors that impact on susceptibility to disease and more severe illness among this population are poorly understood. Norovirus infections of the elderly are associated with prolonged shedding and

longer duration of symptoms,[192, 193] and it has been proposed that the elderly may contribute to the emergence of new epidemic strains that spread across the population.[194]

3.3 Aims and Objectives

The aim of this study is to evaluate an enhanced surveillance system for acute gastroenteritis among the elderly in care homes. This will provide data that can then be extrapolated and used in mathematical models to calculate the burden of norovirus infections in the elderly in long-term residential care in the UK, and the potential impact of a norovirus vaccine specifically targeted to this population.

Study objectives:

1) To study the feasibility of using an enhanced acute gastroenteritis surveillance system in care homes to generate novel descriptive data regarding norovirus infection in this population
2) To quantitatively assess the impact of norovirus illness on residential care institutions
3) To generate novel data on transmission dynamics and risks, by collecting both data on the pattern of interactions within care homes and data on virus characterisation
4) To understand characteristics of norovirus disease and susceptibility to infection (viral load, shedding duration, norovirus-specific IgA antibodies, blood group and microbiota composition [diversity index]) and use this to inform transmission dynamics studies, by sampling symptomatic and non-symptomatic participants
5) To understand the risk factors associated with acquiring norovirus infection in residential care settings during a norovirus outbreak

3.4 Methods and Analysis

Study setting and location

The study will take place in care homes in North West England. Care homes are defined as places offering accommodation and personal care for people who may not be able to live independently. This includes nursing homes that offer the same type of care but with the addition of 24-hour medical care from a qualified nurse.

The North West of England has a population of over 7 million people. Within the region there is a mixture of affluent and deprived areas, urban and rural. The study sites will be in the metropolitan boroughs of Liverpool and Sefton. The combined population of these two boroughs is 746,604, of which, 130,458 (17.47%) are aged 65 or older.[195] Within the two boroughs, there are 133 care homes registered with the Care Quality Commission.[196]

Sampling frame and strategy

The sampling frame is the total number of residential care homes for the elderly in the metropolitan boroughs of Liverpool and Sefton, registered with the Care Quality Commission. The sampling strategy is a convenience sample of sites that are approached and agree to participate. We will aim to recruit four study sites prospectively.

Study overview and study design

The study will be based on a prospective cohort of participants in the enhanced surveillance system (Component A). The other six study components are outlined in Table 3 and include different epidemiological, microbiological and quantitative elements.

Table 3: Summary of CHANGe study components

Study component	Study component description
A	Enhanced surveillance system
B	Pathogen testing
C	Individual norovirus risk factor study
D	Microbiota as a risk factor for norovirus infection and/or disease.
E	Transmission dynamics study
F	Norovirus outbreak risk factors
G	Quantitative assessment of the impact of norovirus outbreaks

Study site inclusion process

Potential study sites will be recruited in two ways. Study sites will be recruited prospectively to be included in all study components. These sites will be approached through the Liverpool Community Health Trust (LCHT). We will approach care homes after discussion with LCHT so that those approached are representative of the care homes in the sampling frame (e.g. in size and complexity). Study sites will also be recruited reactively. Potential study sites within the sampling frame will report to the Public Health England

Health Protection Team that they are experiencing an outbreak of gastroenteritis (as required by The Health and Social Care Act 2008). If this reported outbreak meets the study definition, PHE will inform the study team who will contact the study site to ask them to participate. Two members of the study team are substantive employees of PHE; their job roles entail surveillance of infectious disease outbreaks and they will therefore be informed of relevant outbreaks. Potential study sites that are reactively recruited will be asked to participate in the study components B, D, F and G. Studies recruited both prospectively and reactively will have background information collected on the type of residents, structure, capacity and staffing at the care home.

Study sample size

Data from Public Health England surveillance of gastrointestinal illness in care homes in Cheshire and Merseyside indicate that the median number of residents is 32 and the median number of staff is 35. Based on these estimates, it would be expected that there are an average of 67 participants per study site. The study will aim to recruit four study sites prospectively. It is therefore expected that approximately 268 participants will be included in all components of the study.

Enhanced surveillance system (Component A)

The study population will be residents and staff at study sites who have provided informed consent. Cases are defined as persons in the study population with the following:

a) Vomiting -Two or more episodes of vomiting in a 24 hour period OR
b) Diarrhoea -Three or more loose stools in a 24-hour period OR
c) Vomiting AND Diarrhoea – one or more episodes of BOTH symptoms in a 24-hour period

Confirmed cases will be defined as:
d) Cases with a positive laboratory diagnosis of an infectious cause

Causes of diarrhoea and vomiting should be believed to be infectious. Non-infectious causes, which are not to be counted, would include: long standing diarrhoea associated with disability or incontinence, ingestion of laxative drugs.

Current numbers of residents and staffing levels at each care home will be collected using a questionnaire, filled in by a member of staff in conjunction with a research nurse on the first Monday of each month. Faecal samples will be obtained for each case to determine whether the illness is caused by norovirus or another gastrointestinal pathogen; this sample will be collected as soon as possible after onset of illness. For each case, information including onset date, medical history, duration of symptoms, complications, hospitalisation, outcome (e.g. death) will be collected using a questionnaire. This questionnaire will be filled in by a member of staff on the same day as the faecal sample is collected, then checked and collected by a research nurse on the first Monday of each month.

We will describe the characteristics of the surveillance system and the epidemiology of cases it captures. Non-cases will contribute to the person-time at risk. We will calculate incidence rates for person-time at risk in each study site and for the study in total. We will compare the burden of norovirus, viral gastroenteritis of another cause and gastroenteritis of an unknown cause. We will describe the duration and severity of illness.

Pathogen testing (Component B)

Stool samples will be collected for cases as described for the enhanced surveillance system. The specimen request form will be completed and the sample and request form will be submitted to a laboratory to be tested for gastrointestinal pathogens. Samples will be posted using approved containers for the transport of diagnostic specimens. Samples will be sent to Liverpool Clinical Laboratories, based in The Royal Liverpool University Hospital.

Diagnostic tests will be done in real time, and results reported to the study team. Samples will be tested for 15 pathogens using Luminex xTAG® Gastrointestinal Pathogen Panel. Positive results will be reported to the study team and copied to the patient's general practitioner (GP). The operation of this study will not interfere with public health actions. A portion of each virus positive sample will be sent for genotyping and further characterisation. This work will not be conducted in real-time and will not lead to public health action.

We will describe the proportion positive for norovirus and for other infectious causes of acute gastroenteritis. We will describe the sequencing results of norovirus positive samples over time, by study site and in relation to the results of the enhanced surveillance system.

Individual norovirus risk factor study (Component C)

For each case with a norovirus positive laboratory result, where feasible, sequential stool samples will be taken at three time points (from onset): day 0-3, day 6-8 and day 12-15. For each sample, viral load will be measured by qRT-PCR.

For the purpose of testing for blood group, all participants enrolled prospectively in the enhanced surveillance system will be asked to provide a sample of saliva. Samples will be taken by research nurses within a month of consent being obtained. Laboratory analysis will use one enzyme immunoassay (EIA) for the detection of blood group antigens in saliva and another EIA for the detection of norovirus-specific IgA and IgG in saliva. Results will be standardised measuring total IgA.

We will compare proportion and level of cases with viral shedding over time. We will categorise study participants by blood group category and compare case incidence rates (based on person-time at risk) by pathogen.

Microbiota as a risk factor for norovirus infection and/or disease (Component D)

All participants enrolled prospectively in the enhanced surveillance system will be asked to provide a stool sample at the beginning of the study. Samples will be taken by research nurses within a month of consent being obtained. If study participants test positive for norovirus and provide a sequential stool sample, as detailed in study component C, this sample will also be used for microbiota investigations, in addition to the baseline sample.

Stool samples arriving for microbiota analysis will have norovirus viral load measured by qRT-PCR. Samples for microbiota analysis will be stored frozen for a maximum of 2 weeks prior to DNA extraction. Samples will be treated by bead beating and lysozyme prior to DNA extraction using a commercially available extraction kit. We will store two aliquots of each stool samples at -80°C, adding nucleic acid stabilising buffer to one of them. Stool DNA extraction will be conducted from the aliquots in stabilising buffer, in batches, once or twice a month.

DNA samples will undergo metataxonomic analysis with 16S rDNA in the first instance. An aliquot of DNA will be stored for further metagenomic analysis, subject to obtaining additional funding. The 16S rDNA PCR strategy will use a nested dual index protocol to amplify and barcode the variable V3 - V4 region (319f - 5' ACTCCTACGGGAGGCAGCAG 3' & 806r - 5' GGACTACHVGGGTWTCTAAT 3') resulting in ~469 bp PCR product.[197] Then barcoded 16s PCR products will be multiplexed and run in batches of up to 96 on the MiSeq to produce 2 x 300 bp reads.

Sequences generated on MiSeq will undergo a validated error correction protocol. We will trim the start and end of the reads based on quality scores using a tool such as Sickle (*https://github.com/najoshi/sickle*), error correction with BayesHammer[198] followed by overlapping reads with PANDAseq[199] with a minimum overlap of 10 bp for V3/V4 reads. These corrected and overlapped reads will then be analysed with QIIME.[200] USEARCH will be run using de novo and open reference operational taxonomic unit (OTU) clustering methods, and de novo chimera detection conducted with software such as UCHIME. Taxonomy will be assigned to OTUs using the naïve Bayesian RDP Classifier using both the SILVA and GREENGENES taxonomic databases.

Estimates of within-sample species richness (number of OTUs) and diversity (Shannon index) at multiple rarefaction depths will be compared between cases and controls, and between samples obtained from cases during the acute and convalescent phases, using Student's t-test.

Weighted and unweighted Unifrac will be used to measure distances in microbiota composition between these groups. These results will be visualised using principal coordinates analyses and statistically significant clusters identified using adonis. Random Forest regression will be used to identify OTUs that distinguish norovirus cases and diarrhoeal or asymptomatic controls and between samples obtained from cases during the acute and convalescent phases.

Transmission dynamics study (Component E)

We will quantify potential transmission paths into and within care homes using a survey instrument (an individually-worn electronic proximity sensor) that has previously proved

successful in characterizing interaction patterns in a study of influenza in an American school and in other settings.[201–203]

The study population will be participants at care homes enrolled in the enhanced surveillance system and visitors to those homes on the days of data collection. Visitors on the days in question will be consented using a specific consent form. Four 24 hour study periods will be chosen for the transmission dynamics study. The 24 hour periods selected will be a convenience sample based on study team availability and study site access. Interactions between individuals will be quantified using electronic proximity sensors, called motes, which are worn by or located next to participants and detect and record the nearby presence of other motes. The age, gender and role of individuals in the care home will be collected. A member of the study team will be present at the study site of the days of data collection to consent visitors and distribute the motes.

We will measure continuous, uninterrupted interactions between participants. We will sum the total durations of interactions over each 24 hour period and create participant contact networks with edge weights proportional to the total number of mutual interactions. We will use social network analysis and transmission models to relate infection attack rates and dynamics to measured interaction patterns.

Norovirus outbreak risk factors (Component F)

One of the objectives of this study is to understand the risk factors associated with acquiring norovirus infection in care homes during a norovirus outbreak. An outbreak will be defined as two or more cases (as defined in Component A) occurring in an institution, with onset of illness within 5 days. An outbreak will be considered finished if no new cases are ascertained for seven days. An outbreak-free period will be defined as a period of time ending three weeks before an outbreak is declared and beginning three weeks after an outbreak is considered over in an institution.

Participants enrolled at a study site where an outbreak has occurred will form a cohort in which we will investigate risk factors associated with infection. A member of the study team will administer a questionnaire to participants; the questionnaire covers demographic, illness and medication information, along with food and drink history and information on time spent in different areas of the study site.

We will compare patient characteristics and exposure histories between cases and non-cases, with the null hypothesis that risk factors have a similar distribution in cases and non-cases. We will investigate differences using univariable and multivariable analyses.

Quantitative assessment of the impact of norovirus outbreaks (Component G)

A case-crossover approach will be used to compare resource usage and operational efficiency in residential institutions during outbreak periods and outbreak-free periods (as defined in Component F). Data collected will include the symptoms of ill staff, the days of work lost, the need for additional staff (bank or agency) and additional cleaning. Operational impact data collected will include isolation of residents, transfers to health care facilities, blocking/delays on places to new residents. These data will be collected by a member of the study team from a member of the affected care home.

Data will be collected for the whole period when an outbreak is occurring. The increased resource usage during outbreaks will be measured by comparing periods when outbreaks are occurring with periods when there is not an outbreak occurring. Measurement in outbreak free periods will take place three weeks after the end of outbreaks so that activity will resettle to normal levels. We will test the null hypothesis will be that norovirus outbreaks do not have an impact on the resource usage of care homes.

3.5 Ethics and Dissemination

Consent

Informed consent will be obtained for each participant with capacity to consent. For those persons without capacity to consent, a nominated person that meets the criteria described in Section 32 of the Mental Capacity Act 2005 will be asked to provide consent.

Ethical approval

The study has been approved by the North West – Greater Manchester South NHS Research Ethics Committee (REC Reference: 16/NW/0541). The study is sponsored by the University of Liverpool.

Timeline

Administrative and logistical arrangements have been made to start the study in February 2017 and collect data for a two year period.

Dissemination of findings

Study results will be presented and discussed at appropriate scientific meetings, and published in open access peer reviewed journals. Appropriate metadata will be published with the research data to enable other researchers to identify whether the data could be suitable for their own research.

Funding statement

The research is funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Gastrointestinal Infections at University of Liverpool in partnership with Public Health England (PHE), in collaboration with University of East Anglia, University of Oxford and the Institute of Food Research. Thomas Inns is based at the University of Liverpool. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

Competing interests

The authors declare no competing interests.

3.6 Supplementary detail of CHANGe study methods

The full CHANGe study protocol was approved by the North West – Greater Manchester South NHS Research Ethics Committee (REC Reference: 16/NW/0541) on 10 October 2016. It was not possible to include the entire contents of protocol within the study protocol published in the BMJ. Therefore, in this section I have reproduced key sections from the REC-approved protocol which are supplementary to the published paper.

Consent

The procedure for informed consent will be as follows. The registered manager at each study site will be provided with training so that they are able to comply with the Mental Capacity Act 2005. The registered manager at each study site will be asked to indicate which potential participants have capacity to consent. Those with capacity to consent will be given the participant information leaflet and the participant letter of invitation by the study site staff. For those without the capacity to consent, the study site staff will identify the nominated person who makes decision on behalf of the person without capacity to consent. The study site staff will consult with the study team to ensure that these nominated persons fit the criteria described in Section 32 of the Mental Capacity Act 2005. The nominated person will be sent the appropriate participant information leaflet, the nominated person assent form and the nominated person letter of information. These materials will be handed out or posted by the study site, in pre-paid envelopes which will also include a stamped and addressed envelope for nominated persons to post completed forms back to the study site.

Information describing the study aims, procedures, potential risks and benefits will be contained in the appropriate participant information leaflets. For those participants at study sites which will be enrolled in Section 3.2.1., a question and answer session will be held at the study site by one of the study team. Both parts of this informed consent process (written and verbal information) will be delivered in English.

Questions from potential participants and nominated persons will be encouraged and answered fully by research nurses. Efforts will be taken, within the physical limitations of the study sites, to ensure the consent process is undertaken in an appropriately private environment. For all participants and nominated persons, the date and time that

information is provided will be noted. The absolute minimum time given to potential participants and nominated persons to consider participation will be 24 hours.

Potential participants and nominated persons who agree to participate will sign a form which will make clear the entirely voluntary nature of participation, stating specifically that they can refuse, that they can withdraw from the study at any time, and that non-participation or withdrawal will not impact on any part of the participant's healthcare. For potential participants with capacity to consent, this will be the study consent form. For nominated persons acting on behalf of potential participant without capacity, this will be the study assent form. Research nurses will also sign the consent and assent forms, to confirm the study has been fully explained. The consent/assent forms will be duplicate carbonless-copy paper: a copy will be retained by the study team. A copy of the study information sheet and the consent/assent form will be retained by the participant or nominated person. Once informed consent is received, the participant's GP will be sent a letter notifying them of the fact and explaining the nature of the study.

Obtaining consent from participants joining after study site recruitment

Potential participants who join a study site after the site is first recruited will be offered the opportunity to join the study. The site will have copies of the participant information leaflet, the participant letter of invitation, the participant consent form and the nominated person assent form. The study site will be asked to give these materials to new potential participants, or to the nominated person who makes decision on behalf of a person without capacity to consent. Each study site will be visited each week by a member of the study team, to ask whether any new participants have joined the study site and to countersign and collect consent/assent forms.

Identifying participants who are no longer permanently associated with the study site

A study team member will visit the study site each week. During this visit, they will record those participants who are no longer permanently associated with the study site. The date at which they left the study site will be recorded.

Reviewing consent status

Should the consent status of any person at a participant need to be reviewed, a member of the study team can be reached using contact details given in the participant information leaflets.

Study management

The study will be managed by the study team with clear responsibilities for the implementation and delivery of the different aspects. Study protocols, including forms and databases for data collection and storage, laboratory standard operating procedures, including quality control and quality assurance programmes, and analytical plans will be jointly drafted and approved by all collaborators before implementation. A common training programme will be developed for research nurses and staff of study sites. The team of investigators will communicate regularly by monthly group teleconferences and quarterly project steering group meetings to be held in Liverpool. Study progress and any potential issues or deviations from protocols will be monitored in monthly meetings.

Pseudonymisation of data

Each participant will be assigned a unique participant ID. This ID will be randomly generated and assigned at the point that consent/assent is received. This will link data across the study (questionnaire datasets to laboratory datasets). We will not retain names or dates of birth except for reporting laboratory results, as would be done as part of routine clinical practice.

Managing, storing and curating data

Study data will be kept centrally within the university office on password-protected computers and access will be limited to key project staff. Data will be backed-up regularly at University of Liverpool (UoL). The UoL SOPs related to data entry and management, and data safety and privacy guidelines, will be followed.

Data and documentation at the UoL is managed, stored and curated in keeping with the University's Information Security policy, which defines the preservation of confidentiality, integrity and availability and is informed by the principles set out in IS0 27001. All UoL computer-based information assets are stored on server systems operated by the

Computing Services Department at UoL. The data storage of these systems is resilient to failures; it is backed up on a daily basis to systems also held in secure locations.

The participant ID will be used to link study datasets; a database containing non-pseudonymised participant information will be held in a separate password-protected database. Physical copies of forms containing non-pseudonymised participant information will be held in a securely locked cupboard in a UoL office. Physical copies of forms containing pseudonymised data will be stored at the same address in a separate locked cupboard.

Data produced by the project will contain clinical and laboratory information, which will be handled according to UoL institutional policies outlined above and in line with MRC data management principles. All electronic files will submit to local file naming conventions and metadata will be associated where appropriate. The research team will hold the database linking participant identifiers and participant IDs on a password protected database at a secure location at the University of Liverpool. Study data will be held on password protected databases using a variety of formats including Access and SQL. For most data types, standard file formats will be used (e.g. text, Excel, Word, Access files) and data storage requirements will be managed through centralized file servers.

Study resources

This study will be funded with a total of £79,345 from the NIHR Health Protection Research Unit in Gastrointestinal Infections. In addition to this funding, 1.5 WTE research nurses will be available to work on this study.

Data from Public Health England surveillance of gastrointestinal illness in care homes in Cheshire and Merseyside indicate that the median number of residents is 32 and the median number of staff is 35. Using this information, we can expect that there will be 67 participants per study site. We will aim to recruit four study sites prospectively. We therefore estimate that there will be 268 participants at sites enrolled prospectively.

The rate of UK-acquired IID, standardized to the age and sex distribution of the UK population, was 274 cases per 1000 person-years (88). Given that we estimate 268 participants will be followed up for approximately 2 years, this would be 536 person-years

and we may therefore expect 147 episodes which will meet the case definition and require pathogen testing of a stool sample.

Although final costings for the Luminex pathogen testing are not currently available, the study funding will be sufficient for all material and service costs for sample testing outlined in this study protocol.

In recognition of the extra work that sample collection will add to staff time and to encourage sample collection, we will provide a £5 voucher for each stool sample that fits the study criteria. This voucher will be given to the person collecting the sample.

3.7 Additional data sources used in this thesis

In addition to data from the prospective cohort study outlined in this chapter, for the research in this thesis I also used data from other sources. For the most important of these sources, I have outlined a summary of what they are and why I used them. Further details of how they were used are given in the methods sections of the relevant chapters.

Second Generation Surveillance System (SGSS)

In England, under the Health Protection (Notification) Regulations (2010) diagnostic laboratories are mandated to notify PHE of positive results for a range of causative agents. However under previous and existing arrangements, most laboratories already voluntarily report a much wider and more comprehensive list of organisms. SGSS (https://sgss.phe.org.uk/) is a system which collects and stores these laboratory data. It includes patient demographic data, along with the positive laboratory result.

I used this data sources in Chapters 5 and 7 to capture positive pathogen results from care home gastroenteritis outbreaks. I did so because SGSS forms the only routine surveillance dataset which records these data. However, as discussed later in this thesis, few care home residents with infectious gastroenteritis submit stool samples for testing.

HPZone

Public Health England has a health protection function to (broadly) prevent the transmission of infectious diseases and manage incidents and outbreaks which may

threaten public health. A number of geographically-based Health Protection Teams (HPTs) fulfil this function. Reports of cases, incidents and outbreaks are received by HPTs. Since 2010, HPTs have used HPZone, a web-based case management system, to record this information and file risk assessments, correspondence and related enquiries.[117]

I used HPZone data in Chapters 6 and 7 to include reports of care home gastroenteritis outbreaks routinely received by HPTs. In most areas of England, this is the only system used to routinely collect these data. However, it was designed as case management software rather than for surveillance purposes, so key data are inconsistently collected in different areas. I discuss this issue further in the remaining chapters.

Care Quality Commission (CQC)

In Chapter 1, I introduced the CQC. Briefly, in England it is mandatory for care homes to apply for registration with the CQC. Once registered, care homes are monitored and inspected by the CQC for compliance with their standards. After inspection, a report is written by the CQC and each care homes is given a rating. This rating is one of four categories: “Outstanding”, “Good”, “Requires Improvement” and “Inadequate”. The CQC maintains an online database of currently registered care homes which is updated on a monthly basis and can be downloaded as an Excel file.[196]

I used CQC data in Chapters 5, 6 and 7 to give an accurate denominator of the number of care homes in each geographical area. Due to new care homes registering and some closing, this denominator does change slightly over time.

Chapter 4 – Care home individual disease and outbreak incidence

Prospective cohort study to investigate the burden and transmission of acute gastroenteritis in care homes: epidemiological results

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How this publication fits into my thesis

In this chapter I present the key epidemiological results of the prospective care home cohort study. This addresses the first key knowledge gap detailed in the introduction by providing evidence of the incidence of infectious gastroenteritis at an individual level in care homes. Some data on the incidence of care home gastroenteritis outbreaks is presented, but this is not the main focus. This then leads to the study which forms the next chapter, where outbreak incidence and epidemiological characteristics are analysed. Additional to the publication, in this chapter I also present the results of two of the study components which provided preliminary information.

My contribution

I conceived and designed the study with APC, JPH, RV, NJB, MIG and SOB. I co-ordinated data collection with APC. I undertook the analysis, wrote the first draft and revised the manuscript.

4.1 Abstract

Objective

To estimate the incidence of gastroenteritis in individuals in care homes.

Design

Prospective cohort study.

Setting

Five participating care homes in North West England, United Kingdom.

Participants

Residents and staff present at the five study care homes between 15 August 2017 and 30 May 2019 (n = 268).

Outcome measures

We calculated incidence rates for all gastroenteritis cases per 1000 person-years at risk and per 1000 bed-days at risk. We also calculated the incidence rate of gastroenteritis outbreaks per 100 care homes per year.

Results

In total 45 cases were reported during the surveillance period, equating to 133.7 cases per 1000 person-years at risk. In residents the incidence rate was 0.62 cases per 1000 bed-days. We observed 7 outbreaks in all care homes included in surveillance, a rate of 76.4 outbreaks per 100 care homes per year. 15 stool samples were tested; three were positive for norovirus, no other pathogens were detected.

Conclusions

We found that surveillance of infectious gastroenteritis disease in care homes based on outbreaks, the current general approach, detected a majority of cases of gastroenteritis. However, if policymakers are to estimate the burden of infectious gastroenteritis in this setting using only routine outbreak surveillance data and not accounting for non-outbreak cases, this study implies that the total burden will be underestimated.

4.2 Introduction

Gastrointestinal infections are an important issue in care homes for the elderly (also known as long-term care facilities). Care home residents are more susceptible to infectious gastroenteritis and the environment is ideal for transmission of gastroenteritis.[95] Because infection control measures are challenging to implement, further infections and outbreaks frequently occur based on a single index case.[103] In this population, gastrointestinal infections can cause more severe morbidity, hospitalisation, and are associated with greater mortality.[122, 176]

Surveillance of infectious gastroenteritis in care homes varies in presence and scope in different countries, and where it exists it is focussed on the detection of outbreaks. These outbreak surveillance systems exist in countries such as France, Australia and England.[45, 46, 204] Using these surveillance data, it is possible to estimate the burden of care home gastroenteritis outbreaks.[205] However, this does not account for any sporadic (non-outbreak-related) disease.

The incidence of gastroenteritis in care homes is poorly researched, with few studies published over the last 40 years, the majority originating in the United States.[34, 42, 113, 206] The objective of this study was to estimate the incidence of gastroenteritis in individuals in care homes in north west England; therefore, addressing this gap in the evidence base, and providing data to understand the burden of infectious gastroenteritis in this setting.

4.3 Methods

The study protocol has been published and the methods are fully described there and presented in Chapter 3.[207] Briefly, we conducted a prospective cohort study in residents of five care homes in North West England. The study took place from 15 August 2017 to 30 May 2019.

Study population

The sampling frame was the total number of residential care homes for the elderly in the local authorities of Liverpool and Sefton, registered with the Care Quality Commission. The five care homes selected were a convenience sample of care homes in this sampling frame that were approached and agreed to participate. The locations of the study care homes are

shown in Figure 4.1. All study care homes were recruited prospectively at the same time; no other care homes were invited to participate and declined. All residents and staff members who were present at study care homes during the study period were eligible to participate. Eligible participants with capacity to consent were consented by study research nurses; for those without capacity to consent a nominated person who met the criteria described in Section 32 of the Mental Capacity Act 2005 was asked to provide consent.

Figure 4.1: Location of study sites, England, 2017-2019

Surveillance system

The number of residents and staffing levels at each care home were collected at the start of the study period using a questionnaire, administered to each care home manager. Data including: age, sex, general practitioner, date of arrival at the home and position in the home were collected in person by trained research nurses. Participants were recruited between 15 August 2017 and 08 November 2018. Participants were recruited from the start of the study period, with new residents and staff being recruited when entering the care home. No participants were ill with gastroenteritis at the point of recruitment or recruited as a result of such illness. Study research nurses employed active surveillance by visiting each study care home on a weekly basis to ascertain new participants, episodes of illness meeting the case definition and details about participants withdrawing from the study. During these visits, study research nurses met with key leadership staff to understand any changes at the home in the preceding week. For each case, information

including onset date, medical history, duration of symptoms, complications and hospitalisation were collected using a questionnaire. Case report questionnaires were completed by a study research nurse.

Case definitions

The primary outcome was a case of gastroenteritis. Gastroenteritis cases were defined as persons in the study population with vomiting (two or more episodes of vomiting in a 24-hour period) OR diarrhoea (three or more loose stools in a 24-hour period), OR vomiting AND diarrhoea (one or more episodes of both symptoms in a 24-hour period). Confirmed cases were defined as cases with a positive laboratory diagnosis of an infectious cause. Non-infectious causes such as long-standing diarrhoea associated with disability or incontinence and ingestion of laxative drugs were excluded from the study case definition based on the clinical judgement of a study research nurse. Outbreaks were defined as two or more cases occurring in an institution, with onset of illness being within 5 days.

Study size

As described in the CHANGe study protocol, the target study sample size was for 268 participants to be included.[207]

Microbiological analysis

For each case, participants were asked to provide a faecal sample to determine the cause of symptoms; these samples were collected as soon as possible after onset of illness. Samples were sent to Liverpool Clinical Laboratories, based in the Royal Liverpool University Hospital. Diagnostic tests were conducted in real time and results reported to the study team. Samples were tested for 16 pathogens using Luminex xTAG Gastrointestinal Pathogen Panel (Luminex Molecular Diagnostics, Austin, Texas, USA). Results were reported to the study team and copied to the participant's general practitioner. The operation of this study was designed so that it did not interfere with public health action.

Statistical methods

We characterised the demographics of study participants and described differences between residents and staff. We described the distribution of gastroenteritis case onset date over time, along with the number and incidence rate of outbreaks (with binomial 95%

Confidence Interval). We calculated incidence rates for all gastroenteritis cases. Participants could contribute multiple illness episodes. The denominator was the person-time at risk (PTAR) in study participants; incidence rates are expressed per 1000 person-years at risk for all groups and per 1000 bed-days for residents. Bed-days were defined as days that the resident was present in the care home; participant PTAR was censored if they left the care home. PTAR was calculated in the same way for residents and staff and commenced when participants were recruited into the study and was censored when they left the study care home; otherwise it was censored when the surveillance period ended on 30 May 2019.

Ethical approval

The study was approved by the North West–Greater Manchester South NHS Research Ethics Committee (REC Reference: 16/NW/0541).

Patient and Public Involvement

Patients, carers, or members of the public were not actively involved in the design of this research.

4.4 Results

In total 268 participants (159 residents and 109 staff) were recruited into the study from five care homes. Seventy nine participants (59 residents and 20 staff) withdrew from the study before the end of the surveillance period. None of these withdrawals were due to serious adverse events. Fifty five (93%) of resident withdrawals were due to death from an unrelated cause, with four residents leaving the care home to return to live independently. All 20 staff withdrawals were due to the participant leaving employment at the study care home. The participants contributed a total of 122,898 days PTAR (66,489 days PTAR for residents; 56,409 days PTAR for staff). The median contribution of PTAR was 504 days (range 2 – 837 days). A summary of participant demographics is shown in Table 4. The median age of participants was 71 years (range 19-99); the median age of residents was 82 and the median age of staff was 44. In total, 190 participants were female (70.9%); 62.9% of residents and 82.6% of staff were female. It was not possible to calculate the participation rate as the denominator of staff and residents in each home was not available.

Table 4: Demographics of study participants, by care home and role in the home

Care home	*Total*			*Residents*			*Staff*		
	N	Median age	% Female	N	Median age	% Female	N	Median age	% Female
1	88	79	59	69	82	58	19	37	63
2	45	79	62	34	85	62	11	55	64
3	80	55	83	33	78	70	47	44	92
4	29	59	79	13	86	69	16	43	88
5	26	59	81	10	88	70	16	49	88
Total	268	70	71	159	82	63	109	44	83

In total 45 cases of gastroenteritis were reported during the surveillance period, equating to 133.7 cases per 1000 person-years at risk. The incidence rate of illness in residents was 225.2 cases per 1000 person-years at risk and the incidence rate of illness in staff was 25.9 cases per 1000 person-years at risk (Table 5). For residents, the incidence rate was 0.62 cases per 1000 bed-days. Two participants became a case twice during the study. No cases were excluded based on a non-infectious cause of diarrhoea.

Table 5: Case incidence rates, by care home and role in the home

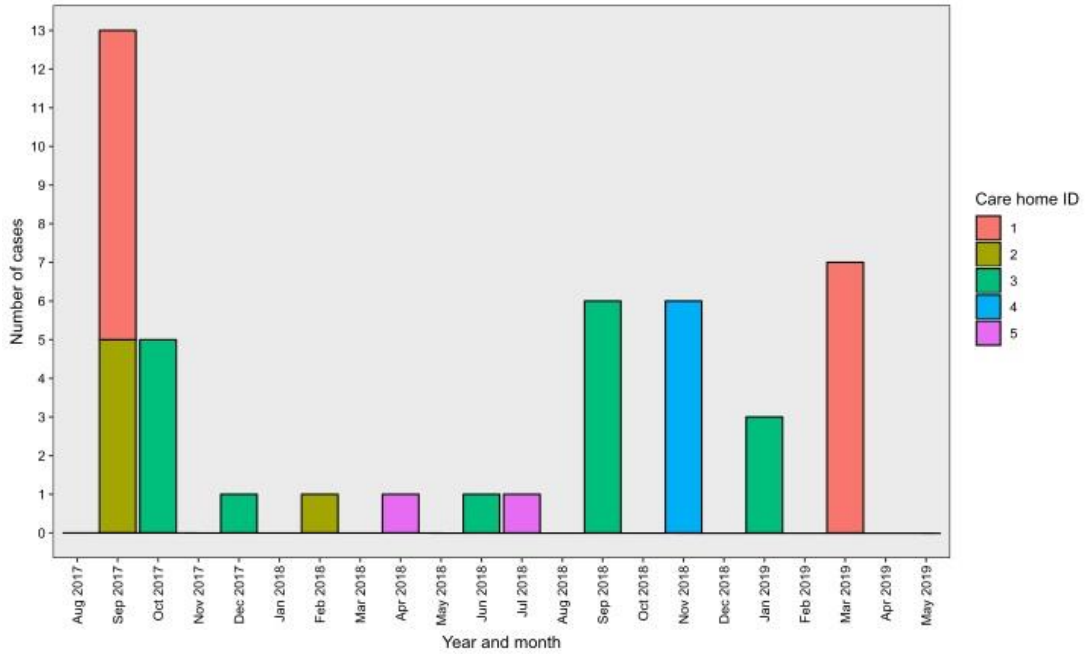
Care home	*Total*			*Residents*			*Staff*		
	PTAR (years)	Cases	Incidence rate[a]	PTAR (years)	Cases	Incidence rate[a]	PTAR (years)	Cases	Incidence rate[a]
1	110.2	15	136.1	80.8	15	185.6	29.4	0	0
2	55.9	6	107.3	37.7	6	159.3	18.3	0	0
3	108.3	16	147.8	38.7	13	335.5	69.5	3	43.1
4	35.9	6	167.1	14.8	5	337.4	21.1	1	47.4
5	26.2	2	76.5	10.0	2	200.3	16.2	0	0
Total	336.5	45	133.7	182.0	41	225.2	154.4	4	25.9

[a] *per 1000 person-years*

The distribution of case onset dates is shown in Figure 4.2. A majority of cases were reported in September and October during both winters. We observed seven outbreaks in study participants in these care homes, an incidence rate of 76.4 outbreaks per 100 care homes per year (95% Confidence Interval: 44.2 – 92.9 outbreaks per 100 care homes per year). Three outbreaks were observed in care home 3 (5, 6 and 3 cases, respectively), two

outbreaks were observed in care home 1 (8 cases and 7 cases) and one outbreak was observed in both care homes 2 (5 cases) and 4 (6 cases). No outbreaks occurred in care home 5 during the study. In total, 40 (89%) cases were defined as part of an outbreak. The most frequently reported symptoms were: diarrhoea (62%), vomiting (47%), nausea (22%) and abdominal pain (6%). No cases reported bloody stool, fever or headache. Seven cases (16%) reported both diarrhoea and vomiting. Duration of illness for cases was not available.

Figure 4.2: Epidemic curve showing distribution of cases by month and study care home



At least one faecal sample was collected for 15 cases (33.3%) of the 45 reported cases. No samples were collected for any of the four cases in staff. The 15 samples were tested for multiple pathogens. Norovirus was detected in three samples. No pathogen was detected in 12 samples.

For the 15 stool specimens which were received, the median time delay between onset of symptoms and the sample being taken was 3 days (range 0 – 18 days). The median delay for samples positive for norovirus was 0 days (range 0-1 days). This was significantly shorter (Wilcoxon rank sum test, p-value = 0.016) than the delay for samples which were negative (median 4 days, range 1-18 days).

4.5 Discussion

Main findings

In this active surveillance study using a prospective cohort design we recorded gastroenteritis cases in care homes over a 22 month period and observed 7 outbreaks in study participants, a rate of 76.4 outbreaks per 100 care homes per year. Both this point estimate and the lower bound of the 95% Confidence Interval are greater than the incidence rate of 37.1 outbreaks per 100 care homes per year reported during routine, passive surveillance in the same geographical area between 2012 and 2016.[204] This difference may reflect increased reporting of illness due to regular contact with the care homes as part of the study, which is likely to have improved ascertainment of outbreaks.

We found that the incident rate of illness in participants was 133.7 per 1000 person-years at risk, and that the rate was far higher in residents (225.2 per 1000 person-years) than in staff (25.9 per 1000 person-years). This difference could be caused by a number of factors: it may reflect trends in the wider community where norovirus incidence is higher in older people than those of working age,[208] good hygiene and infection control practices by staff, reduced exposure in staff who go home when not on shift, the increased susceptibility of elderly residents who are physically debilitated,[97] and illness not being reported by staff, some of whom do not receive sick pay. The incidence rate of illness in residents can also be expressed as 0.62 cases per 1000 bed-days; this study is the first time this metric has been estimated for care homes in the UK and as such will provide data to inform any modelling of the economic burden of gastroenteritis in this setting.

In this study, we observed that 89% of cases were defined as part of an outbreak. This comparatively low level of individual cases may be due to factors such as; the susceptible nature of residents, the high degree of potential contacts and the difficulty of maintaining hygiene. These factors could explain why people in a care home who acquire a gastrointestinal infection are likely to infect another and therefore gastrointestinal illness in these settings frequently causes outbreaks. This finding therefore supports the continued surveillance of gastrointestinal disease in care homes being focussed on outbreaks as this constitutes the majority of disease burden.

The study protocol was for a stool sample to be submitted for each case; in practice this only occurred for 33% cases. Of the 15 samples tested, norovirus was the only pathogen identified, being found in 3 cases. Despite being tested for, no other pathogens were

identified, which may have been associated with delay between symptom onset and stool submission Due to the small number of stool samples in this study, caution should be exercised if these results are to be used to infer the proportion of gastroenteritis in care homes caused by norovirus.

Strengths

One of the key strengths of this study was its active surveillance design, whereby a research nurse visited each study site each week to check on the status of study participants. During the 22-month duration of the study, this was a resource-intensive approach and meant that care homes involved in the study were constantly aware of the need to report illness in study participants. This active surveillance design meant that our study is likely to have recorded a higher proportion of cases than an alternative passive surveillance design, an assertion supported by the incidence rate being higher than that reported from the same area during routine surveillance.

This is the first active surveillance study to follow up individuals in a care home setting for gastrointestinal illness. The advantage of this study design is that the individual level of participation and surveillance allowed the calculation of person-time at risk and the recording of sporadic cases of illness, in addition to outbreaks. This is a valuable addition to the literature as the description of individual cases, including sporadic illness, is not covered in other studies that mainly focus on the burden of gastroenteritis outbreaks. These findings are key to understanding the burden of sporadic gastroenteritis in care homes, which is important when calculating the total burden of illness in this setting.

An additional strength of this study was the capacity to test each of the cases for a wide variety of pathogens. In contrast to other studies which focus on testing for norovirus or other viral pathogens in care home settings, we used a multiplex PCR test which was capable of detecting 15 pathogens. By using the Luminex GPP, we were confident that we had coverage for the most likely known pathogens and would be able to detect them in any cases that arose during the study.

Limitations

A key limitation of this study was that it included a small convenience sample of care homes in one area of England. Due to the nature of the study, it was only possible to

include those care homes which were approached and agreed to participate. It may have been that the five care homes included in the study varied systematically from the others in the sampling frame in aspects such as: the level of care provided, the vulnerability of residents to infection, the socio-economic status of residents and infection prevention and control practices. However, it was not possible to obtain such information on all homes in the sampling frame and therefore it is not possible to make a formal comparison. Due to the resource-intensive active surveillance design it was only possible to include a maximum of five sites in this study. It may be that the small number of geographically clustered care homes in this study limits the generalisability of these findings to other areas of the country and internationally. The inferences that can be made from this study may also be affected by the duration of the surveillance period; although the 22 months of the study include two winters, it may have been that the circulating viruses during these seasons was atypical.

Another potential limitation may have been that the participants in our study care homes who consented to take part were systematically different from those in the care homes who did not take part. The consenting process to enrol participants in this study was agreed with the relevant ethics committee and meant that the study team did not have access to the personal information of staff or residents at the home who did not consent to take part. Therefore, it was not possible to compare the characteristics of those who took part to those who did not. Furthermore, by following the agreed consenting process, because we could not record departures and arrivals of persons at the home who were not participants, although we knew the capacity of each home, we could not calculate the participation rate in each home. Although it was not possible to formally calculate the participation rate, it is possible to note that participation could have been higher. One reason for this was the consenting process for those (mainly elderly) residents without capacity to consent. Safeguarding the rights of such people is very important, but the process we were asked to follow made it very difficult to identify and contact the correct person to represent the interests of that person. Therefore, fewer residents without capacity were enrolled in the study than would have otherwise been the case.

One issue that has previously been identified when studying gastroenteritis illness in care homes is the difficulty in obtaining stool samples for pathogen testing.[204] Even with weekly visits to the care homes, we only obtained stool samples from 33% of the cases. For the samples we received, we found that frequently these were taken several days after the

onset of symptoms and this may account for the 80% of samples where no pathogen was identified. During the study we acknowledged this difficulty in obtaining stool samples and implemented a £5 voucher scheme on 28 June 2018 to incentivise stool collection. Unfortunately, this was not particularly effective as 30% of cases submitted a stool sample before this point, compared to 36% afterwards. This low proportion of stool samples shows one of the challenges of operating the study in very busy care home environments with staff working at a level where they do not have much excess capacity.

Results in the context of the international literature

In this study, the incidence rate of infectious gastroenteritis in care home residents was estimated to be 0.62 cases per 1000 bed-days. This finding is substantially higher than the mean global incidence estimate in a systematic review of published surveillance; the pooled estimate of incidence from this meta-analysis was 0.40 (95% Confidence Interval 0.27 – 0.56) episodes per 1000 bed-days. 9 However there was considerable heterogeneity between the 15 studies, with the highest incidence (1.9 episodes per 1000 bed-days) being reported from a German study using electronic health records.[35] The authors of this systematic review were surprised with the low rate of gastroenteritis in the meta-analysis and the results of our study support this observation, being a substantially higher incidence. This higher incidence is likely to reflect enhanced case-finding in our study due to the active surveillance design. However, the incidence rate from our study was still lower than that reported in persons aged over 65 years living in the community.[191]

4.6 Conclusion

The key implication for policymakers to be drawn from this study is that we found that surveillance of infectious gastroenteritis disease based on outbreaks in care homes, the current general approach, detected a majority of cases of gastroenteritis. However, if policymakers are to estimate the burden of infectious gastroenteritis in this setting using only routine outbreak surveillance data and not accounting for non-outbreak cases, this study implies that the total burden will be underestimated. Combining findings from this study with data on the distribution of outbreaks in care homes would be a way for future research to fully estimate the burden of infectious gastroenteritis in this setting.

Acknowledgements

The authors would like to acknowledge the hard work and dedication of the research nurses from Royal Liverpool and Broadgreen University Hospitals NHS Trust and North West Coast Clinical Research Network who worked on this study. We would like to thank the management and staff at each of the study care homes for their engagement in participate in this study. The authors would also like to thank Jonathan M Read and David J Allen for their contribution to the study protocol.

4.7 Transmission dynamics study

Background

Chapter 3 outlined the methods for the transmission dynamics study, one of the components of the CHANGe study. The aim was to quantify potential transmission pathways into and within care homes; in particular by characterizing interaction networks, weighted by duration, between residents, staff and visitors. The intention was for data collection to take place in study care homes, during four 24 hour periods, with the 24 hour periods selected being a convenience sample based on study team availability and study site access.

In order to capture data on potential contacts between participants in each care home, I intended to use a survey instrument which has previously used in characterizing interaction patterns in a US school study of influenza and other settings.[201–203] The instrument is known as a proximity detecting "mote", shown in Figure 4.3.

Figure 4.3: A proximity detecting "mote"

These motes are small electronic data-logging devices which use weak radio signals to detect when they are within range of another mote, and log these instances. The motes transmit a signal every 20 seconds and listen for other motes' signals. Whenever a mote detects another mote, it records its unique mote ID, the current time, and the radio signal strength to approximate the distance to the other mote. Participants were intended to be asked to keep these motes in close proximity during a 24 hour period. Depending on the level of mobility of each participant, they can either be worn around the neck on a lanyard

enclosed in a pouch if the participant is walking, or fixed to a chair if the participant is in a stationary or mobile chair or placed on a bed-side table if the participant is confined in bed.

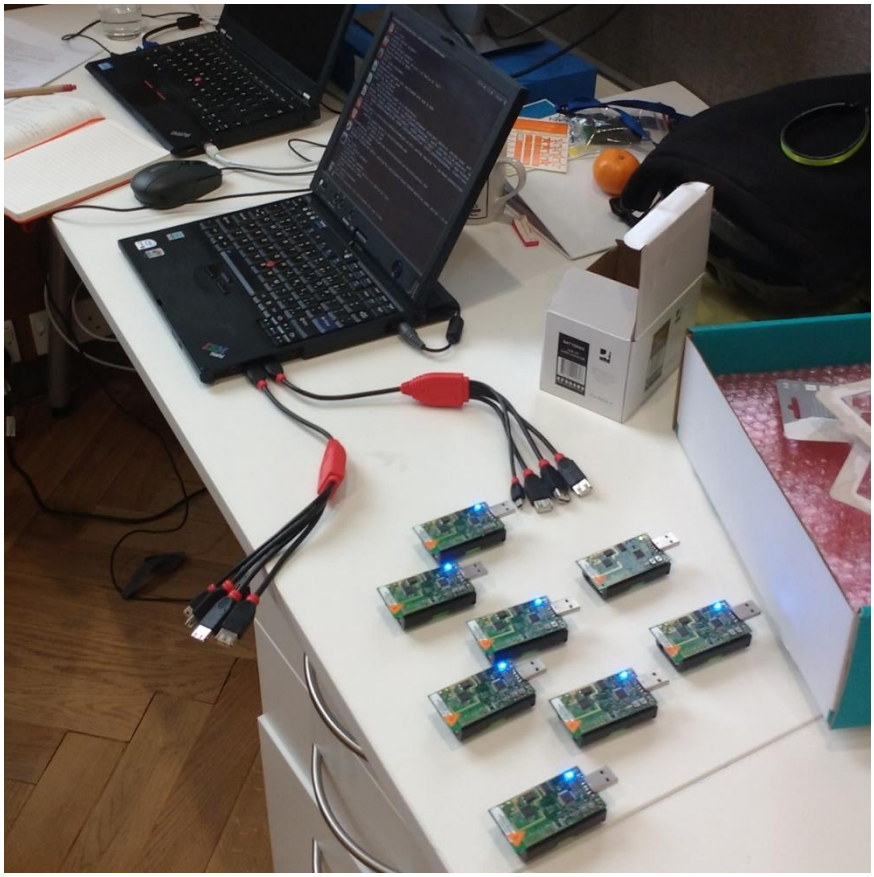
The objective was to measure continuous, uninterrupted interactions between participants, sum the total durations of interactions over each 24 hour period and create participant contact networks with weights proportional to the total number of mutual interactions. Following this the intention was to use simulation modelling, point process models and network analysis to relate infection attack rates and dynamics to measured interaction patterns. The hypothesis was that the risk of infection is associated linearly with interaction rates and that the proximity of cases was associated with infection risk. I also planned to explore how spatio-temporal proximity relates to infection risk using a range of plausible statistical models and suitable penalising criteria (Akaike Information Criterion).

Testing methods

Prior to commencing the transmission dynamics component of the CHANGe study, the motes were tested. The motes had not previously been used for this purpose in the UK and I undertook this testing to learn how to use them and to provide data (such as signal strength and proximity) to calibrate my analysis. I hoped to use these test data to understand the format and type of outputs from the motes and the optimum way of analysing the raw data.

The code that I used to operate and test these motes was originally written in C and Python by David D. Galloway (University of Pittsburgh) and Marcel Salathé (Pennsylvania State University) for their study in a US school setting.[201] This code requires a machine with a Linux operating system for operation. Motes are connected to the machine via USB; a programme is then run to wipe the device and install the correct mote software. There are three types of mote: control, timer and standard. Each batch of motes that are programmed must have a control mote, this provides a signal to activate the other motes. Timer motes provide a signal to synchronise contacts between motes. Standard motes emit radio frequency signals at intervals of 20 seconds plus a random offset of between -0.5 and 0.5 seconds. A picture showing motes being programmed during a test is shown in Figure 4.4.

Figure 4.4: An example of mote programming in progress during a test



Together with Dr Anne Jones (Mathematics Department, University of Liverpool) I conducted a series of 11 tests using the motes. Details of these tests including the dates and number of motes used are shown in Table 6. The tests took place between 17 October 2017 and 30 January 2018 on the campus of the University of Liverpool.

Table 6: Details of the preparatory mote tests

Experiment	Date of test	Date data collected	Number of motes
1	2017-10-17	2017-10-17	**16**
2	2017-11-14	2017-11-14	**31**
3	2017-11-30	2017-11-30	**31**
4	2017-11-30	2017-11-30	**31**
5	2017-11-30	2017-11-30	**31**
6	2017-12-14	2017-12-19	**24**
7	2017-12-14	2017-12-14	**10**
8	2017-12-19	2017-12-19	**20**
9	2017-12-19	2017-12-19	**20**
10	2017-12-21	2017-12-21	**6**
11	2018-01-30	2018-01-30	**30**

During these tests I programmed the motes, attempted to ensure their correct activation, ran the motes for a period of time and then downloaded data from them. I processed and analysed raw data from the motes using R 3.5.0.[209]

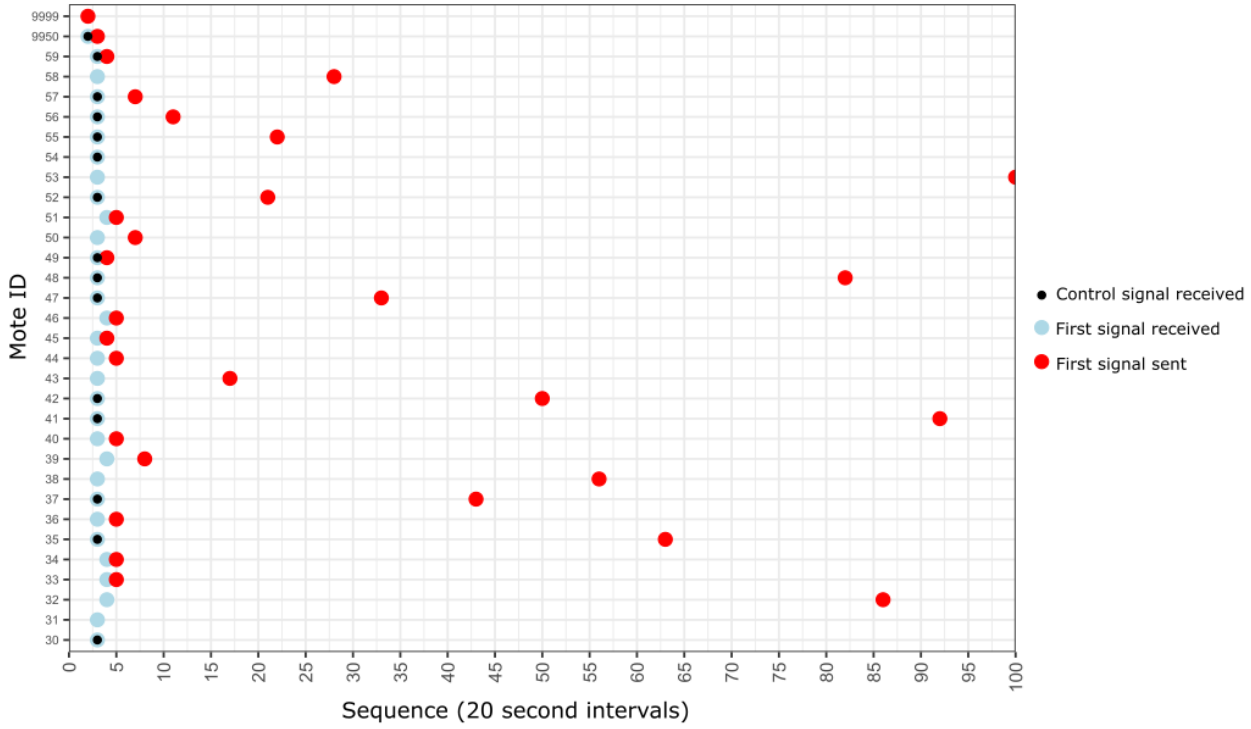
Testing results

During the series of tests, two key issues were apparent that affected the operation of the motes and their suitability for the transmission dynamics study:

1) Problems with activation

The mote programming process has previously been outlined above in testing methods. As described, the standard motes require activation to start recording signals received, and to send signals to other motes. During all 11 tests, despite standardising positions and orientations of standard motes around the control mote, the time it took standard motes to activate was variable and unpredictable. Furthermore, after variation in the time to activate, across the 11 tests, 22 of the 261 motes (8.4%) did not send a signal out to other motes. Repeated testing established that it was not the same faulty motes consistently failing to send, but rather motes that successfully sent signals would not work in a subsequent test. For example, in test 4 (Figure 4.5) one can observe that there is substantial variation in the time taken to activate the motes to send a signal. Given that the x axis is a sequence of 20 second intervals, it can be seen that some motes took 28 minutes to start sending a signal. In this test, three motes (30, 31 and 54) failed to send any signals to other motes.

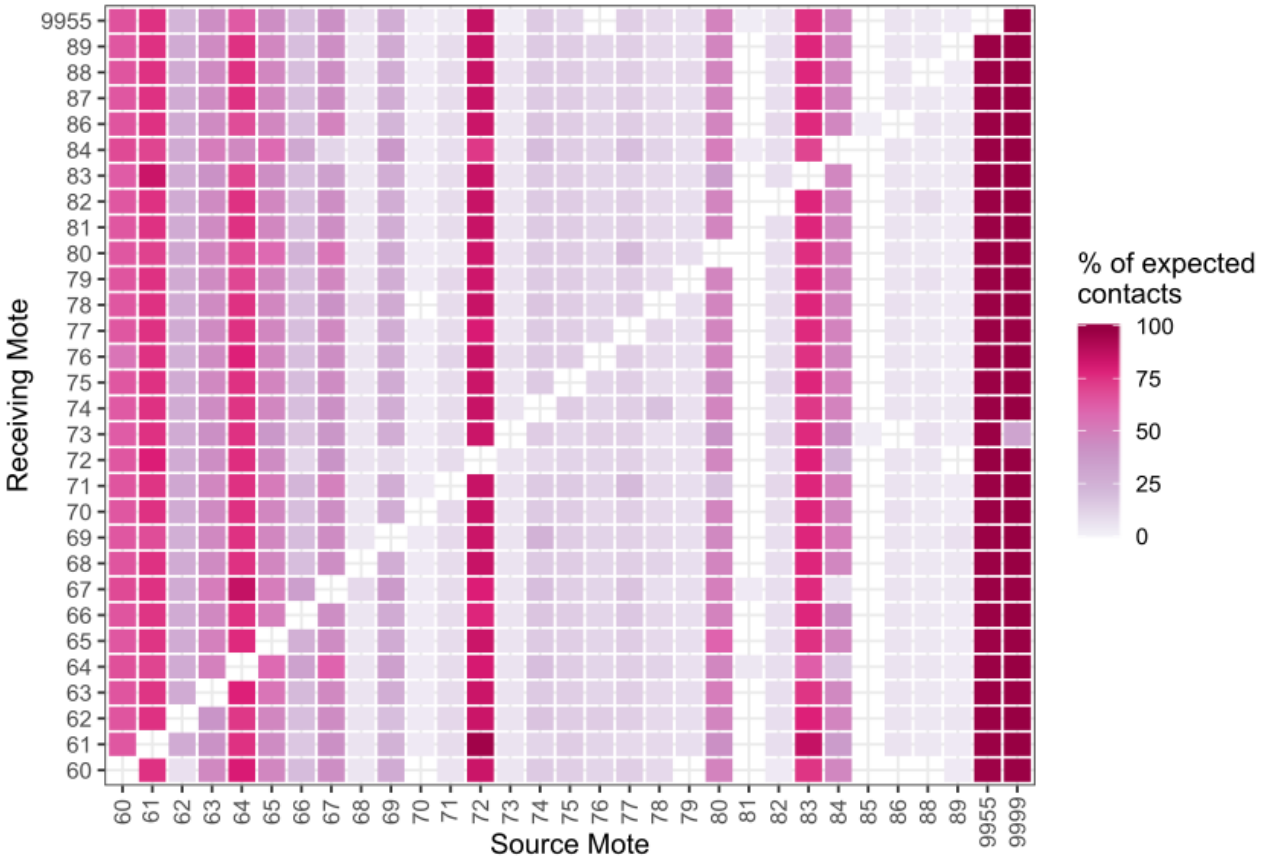
Figure 4.5: A summary of activation times for each of the motes during test 4



2) Consistency and reliability of recording contacts

Once activated, the motes should send and receive signals every 20 seconds and record the signals of motes within a 2-3 metre range. The motes were tested in two ways - firstly, in a room with standardised distances and orientations to understand discrepancies between motes, and secondly, in office situations with dispersed motes to simulate their use in care homes. In addition to the delay in activation of sending a signal, it was apparent that certain motes did not appear to send sufficiently strong signals that could be picked up by other motes, even in standardised, evenly space testing conditions. As with the delayed activation, repeated testing showed that this behaviour was consistent to particular motes, but it did not appear in this series of tests to be completely random. As an illustration, results from test 11 are shown below in Figure 4.6. This shows a matrix of contacts, with the source mote on the x axis and the receiving mote on the y axis. Squares with a deeper red colour indicate that of the expected signals, a higher proportion were actually observed.

Figure 4.6: A plot showing a matrix of contacts registered between motes during test 11



In this test, motes were evenly spaced and all within 3 meters of each other. If the motes had functioned as expected, the outcome of this plot would show a uniform dark red colour. As can be seen in Figure 4, two motes (81 and 85) did send signals, but these signals were received very weakly by only 4 and 2 receiving motes, respectively. Several other motes (70, 73, 79, 82, 86, 88, 89) had signals received by a majority of the other motes, but less than 25% of expected contacts.

Discussion

I found that the mote devices showed substantial variation in their activation and recording of contacts between them. In controlled environments I did not find that it was possible to replicate contact networks between motes positioned with known position and orientation. The differences in recording contacts between motes did not appear to be device-specific, as the same motes worked well in subsequent tests, but nor did these missed contacts seem to be random, in which case post-hoc imputation would have been a possible approach to infer missing contacts.

Based on the limitations experienced when using these motes during testing, it would have been unrealistic to have used these motes in CHANGe study care homes and expect them to reliably collect data to meet the key aim of the transmission dynamics study. Conducting this component of the study in care homes would have required significant resources from the study team, and placed a burden on the care home in terms of disruption to usual activity.

Quantifying potential transmission pathways into and within care homes is an important task and information produced from such a study would be valuable, both to better devise interventions to reduce norovirus transmission, and to model strategies for vaccination now that potential norovirus vaccine candidates are in development. If other researchers were to undertake work with comparable objectives, there are other technologies such as WiFi, Bluetooth, Radio-frequency identification (RFID) and Global Positioning Signals (GPS) which could be used to create wearable positioning tools. Should researchers want to construct their own, doing so using the open-source Arduino platform would enable reliable replication by other researchers.[210] There are packed solutions such as Pozyx, that use ultra-wideband radio technology to provide centimetre-level accuracy,[211] but using these at the scale of a care home would require a significant level of resource.

Conclusion

The results of the mote testing indicate that with the devices in question, running the programme that was available, it would not be feasible or proportionate to conduct the CHANGe transmission dynamics study in care homes.

4.8 Quantitative assessment of the impact of norovirus outbreaks

Background

Chapter 3 outlined the methods for this quantitative assessment of the impact of norovirus outbreaks, one of the components of the CHANGe study. The aim was to quantify the wider operational impact of these outbreaks on care homes; in particular, by characterizing the associated costs. I decided to use a case-crossover approach (the protocol of which is in Chapter 3) to compare resource usage and operational efficiency in residential institutions during outbreak periods and outbreak-free periods.

Methods

The intended study period was for all outbreaks in care homes in these local authorities which started between 15/03/2018 and 15/09/2018 to be included. Information on the characteristics of the outbreak, associated costs, hospitalisations and delayed admissions, was collected using a questionnaire, administered by community infection control nurses in Sefton and Liverpool local authorities and analysed using Microsoft Excel.

Results

In the study period, 38 outbreaks were reported in these two local authorities. A total of 8 questionnaires were completed (21% of outbreaks) and returned between 21/03/2018 and 24/05/2018. No further questionnaires were returned after this.

The attack rate in residents ranged from 16% to 59%; staff reported illness in four of the eight outbreaks, with the attack rate ranging from 5% to 28%. The duration of these outbreaks was between three and 14 days (median 8 days).

Staff took additional days off in three outbreaks; a total of 30 days off. Additional care staff costs were only given for one outbreak, totalling £95. Three outbreaks were associated with additional cleaning staff costs, reporting a total extra cost of £706. Three residents were hospitalised in total, from two outbreaks. In addition, two admissions from hospital were delayed, these were for different care homes.

Discussion

One of my key findings from this study was the difficulty in obtaining this information from care homes. Community infection control nurses work closely with care homes during outbreaks and were the most appropriate group to collect this information. When approached to participate in this study, they were keen to be involved and happy to collect the data. However, the community infection control nurses have a very large workload and are frequently understaffed. Despite repeated intervention from myself, it was not possible to increase engagement and response. The high workload of community infection control nurses, combined with reluctance of care homes to engage with work outside their core responsibilities, is the most likely reason for the low response to this study.

Due to the low response rate (21%) and the study data mainly being collected outside of the main winter illness season, I did not believe that the data collected in this study represented a sufficiently large and representative sample which allowed an estimate to be calculated with confidence. I therefore conducted a descriptive analysis of the available data, presented above. Despite the lack of response there is some evidence from this study that outbreaks contribute to increased operational costs. Had I obtained a more comprehensive dataset, I would have used these findings and combined them with other modelled results to estimate the economic burden of care home outbreaks on the care home system itself.

Conclusion

The results of this study demonstrate the difficulty in obtaining this information in this setting, using community infection control nurses. Gaining data on the operational impact of care home gastroenteritis outbreaks is important to properly quantify the burden of this illness in the population. For further research, I suggest investigators consider the resources available to them and how best to make such a study feasible given the workload of staff involved. Involving care home management directly to obtain operational costs data may be a more feasible approach.

Chapter 5 – Care home outbreak surveillance and lessons for prevention

How timely closure can reduce outbreak duration: gastroenteritis in care homes in North West England, 2012–2016

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How this publication fits into my thesis

Following the results in the previous chapter which mainly related to individual gastroenteritis cases in care homes, this chapter focuses on care home outbreaks. I analysed a detailed surveillance dataset from Cheshire and Merseyside to address two research questions: providing an estimate of the incidence of care home outbreaks and exploring the epidemiological characteristics of such outbreaks, particularly aspects of transmission such as the effect of timely closure on outbreak duration.

My contribution

I designed the study with co-authors. I cleaned and then analysed the data. I drafted the manuscript and revised it in line with reviewer comments.

5.1 Abstract

Objectives

Data on outbreaks of infectious gastroenteritis in care homes have been collected using an internet-based surveillance system in North West England since 2012. We analysed the burden and characteristics of care home outbreaks to inform future public health decision-making.

Methods

We described characteristics of care homes and summary measures of the outbreaks such as attack rate, duration and pathogen identified. The primary analysis outcome was duration of closure following an outbreak. We used negative binomial regression to estimate Incidence Rate Ratios (IRR) and Confidence Intervals (CI) for each explanatory variable.

Results

We recorded 795 outbreaks from 379 care homes (37.1 outbreaks per 100 care homes per year). In total 11,568 cases, 75 hospitalisations and 29 deaths were reported. Closure within three days of the first case (IRR=0.442, 95%CI 0.366-0.534) was significantly associated with reduced duration of closure. The total size of the home (IRR=1.426, 95%CI=1.275- 1.595) and the total attack rate (IRR=1.434, 95%CI=1.257-1.595) were significantly associated with increased duration of closure.

Conclusions

Care homes that closed promptly had outbreaks of shorter duration. Care home providers, and those advising them on infection control, should aim to close homes quickly to prevent lengthy disruption to services.

5.2 Background

Infectious gastroenteritis is a common cause of illness in care homes, which provide an environment well suited for the spread of infectious disease.[7] In a systematic review of published surveillance, the mean global incidence of infectious gastroenteritis in care home residents was estimated to be 0.40 (95% Confidence Interval 0.27 – 0.56) episodes per 1000 bed-days.[34] Norovirus is the most common cause of gastroenteritis outbreaks in care homes [95] and is associated with excess mortality in the elderly.[122, 176, 190] The majority of norovirus infections are transmitted person-to-person.[37] It is difficult to prevent transmission of norovirus because of its low infectious dose, lack of long term immunity to reinfection, and the fact that infected people can shed norovirus asymptomatically at high levels for at least 3 weeks.[101]

Few surveillance systems capture the incidence of gastroenteritis in care homes.[34] Most contemporary surveillance data for infectious gastroenteritis outbreaks in care homes come from France or Australia. There is a national surveillance system in France which has published data from a two year period.[45] Care homes in one region of France are part of an enhanced surveillance system, which has been studied to better understand the aetiology and burden of infectious gastroenteritis outbreaks in that population.[147, 162] Similar surveillance is undertaken in Australia at national level, detailed epidemiological descriptions of outbreaks in this population are available.[46]

In England, the Care Quality Commission (CQC) requires that care homes report significant outbreaks of infectious gastroenteritis to Public Health England (PHE).[116] Information on general outbreaks of infectious gastroenteritis has been collected since 1992.[41] However there is no dedicated national surveillance system for care home outbreaks.

In December 2012 a secure internet-based surveillance system was established in Cheshire & Merseyside in the North West of England to collect reports of care home outbreaks with agreement from the Cheshire & Merseyside Health Protection Team (CMHPT) and the relevant Infection Prevention and Control Teams. We analysed these surveillance data to provide insight into the burden and characteristics of care home gastroenteritis outbreaks and to inform future public health action.

5.3 Methods

Setting

This study took place in Cheshire & Merseyside, North West England. The area comprises nine Local Authorities and a total population of just under 2.5 million; 19% of the population are aged 65 and over.[212] The region had 535 care homes registered with the CQC as of 08 December 2016.[213] Care homes in England must register with the CQC in accordance with Schedule 1 of The Health and Social Care Act 2008 (Regulated Activities) Regulations 2014.

Definitions

A care home was defined as a residential long-term care facility, with or without nursing care. An outbreak of gastroenteritis was defined as two or more individuals with diarrhoea and/or vomiting within a care home, where symptoms were of a suspected infectious nature (not associated with prescribed drugs or treatments and not associated with an underlying medical condition or illness). Outbreaks of a bacterial aetiology or suspected food poisoning were excluded.

Surveillance system

The local Community Infection Prevention & Control Team (CIPCT) is informed by the care home of an outbreak; the CIPCT team records this information using an internet-based questionnaire with the database stored on a secure server. The questionnaire collects information on the characteristics of the care home, details of the cases in residents and staff, and any microbiological testing. The database is accessed by CMHPT who produce routine surveillance reports for local public health stakeholders. The reports are followed up with the CIPCT teams to confirm details before final publication. Stool samples were tested at local laboratories; bacteriology using routine culture, parasitology using Enzyme-linked Immunosorbent Assays (EIA), *Clostridium difficile* using two stage testing as per national guidance which includes EIA,[214] and virology using Polymerase Chain Reaction (PCR) tests. Positive stool sample results were extracted from SGSS (https://sgss.phe.org.uk/) and matched to outbreak using the outbreak ID.

Analysis

This analysis includes outbreaks between 01 December 2012 and 31 November 2016, a four year period. We matched study surveillance data to CQC care home registration data extracted on 08 December 2016;[213] data were matched using care home postcode and

name. CQC data contains a four-stage rating of the care home based on inspection reports. This dataset covers currently registered care homes and has been updated monthly at a national level since September 2015.

We described characteristics of care homes reported to the surveillance system and summary measures of the outbreaks. We calculated attack rates using the total number of cases reported divided by the total number of residents and staff at the care home. The number of days that the care home was closed to new admissions or visitors was used as the outcome measure in multivariable analysis. We examined the association between this outcome and the following variables; total number of persons at the home, total attack rate, winter season, CQC overall rating, presence of residents with dementia, ratio of residents to staff and days between first case and closure. We categorised total number of persons at the home into quartiles, and total attack rate into three groups (under 20%, 20 to 39.9% and 40% and over). We used negative binomial regression to estimate Incidence Rate Ratios (IRR) and Confidence Intervals (CI) for each variable, using random-effects to account for clustering due to multiple outbreaks from the same care home. Descriptive analysis was conducted using R [209] and regression analysis was undertaken using Stata 13.1 (StataCorp, College Station, Texas).

5.4 Results

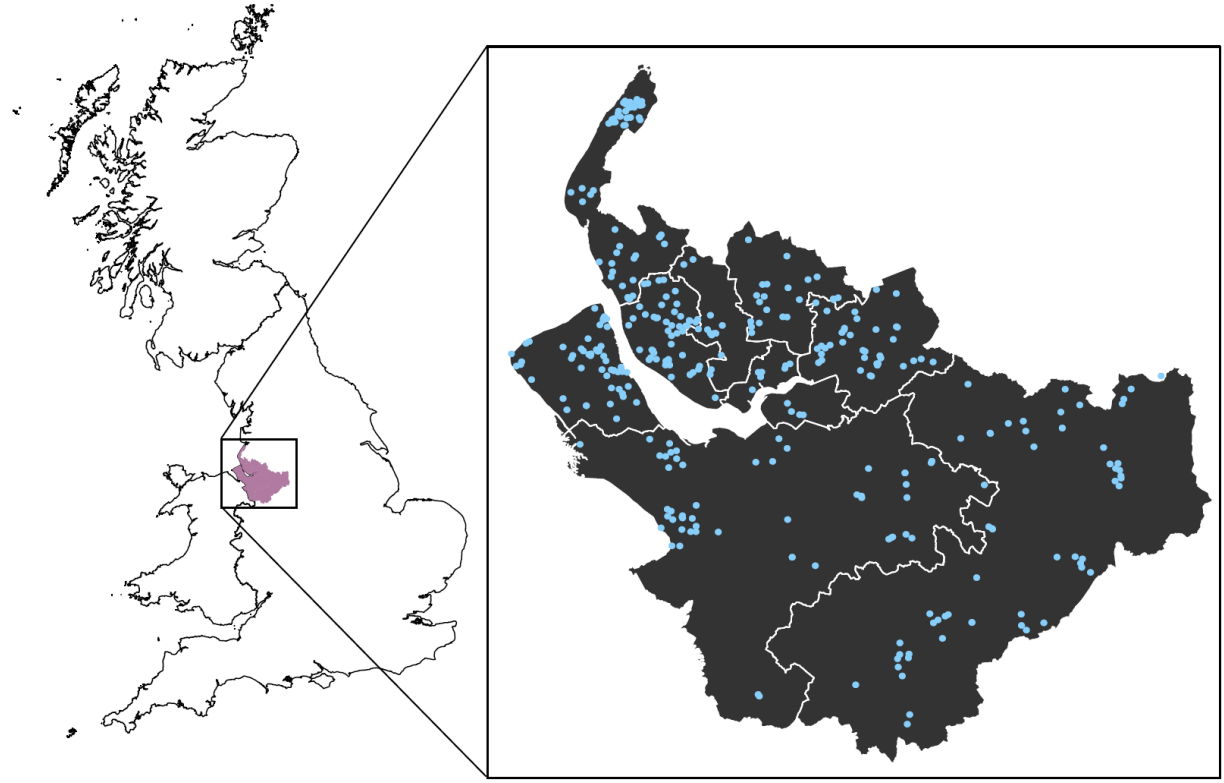
From 1 December 2012 to 31 November 2016, 795 outbreaks were recorded from 379 care homes. Over the four year study period this equates to a rate of 37.1 outbreaks per 100 care homes per year. More than one outbreak was reported by 47.7% (181/379) of care homes; the highest number of outbreaks reported by one home in this period was 19. The number and rate of outbreaks in all nine Local Authorities in the Cheshire & Merseyside area are shown in Table 7. The greatest number of outbreaks was reported in Local Authority E (160), but the greatest rate of outbreaks was reported from Local Authority H (60 outbreaks per 100 care homes per year). The geographical distribution of care home outbreaks is shown in Figure 5.1.

Table 7: Number and rate of outbreaks by local authority, November 2012 to December 2016

Local Authority	Number of outbreaks	Registered care homes	Rate per 100 care homes per year
A	131	79	41.46
B	126	75	42.00
C	31	23	33.70
D	20	27	18.52
E	160	74	54.05
F	115	116	24.78
G	36	34	26.47
H	84	35	60.00
I	92	111	20.72

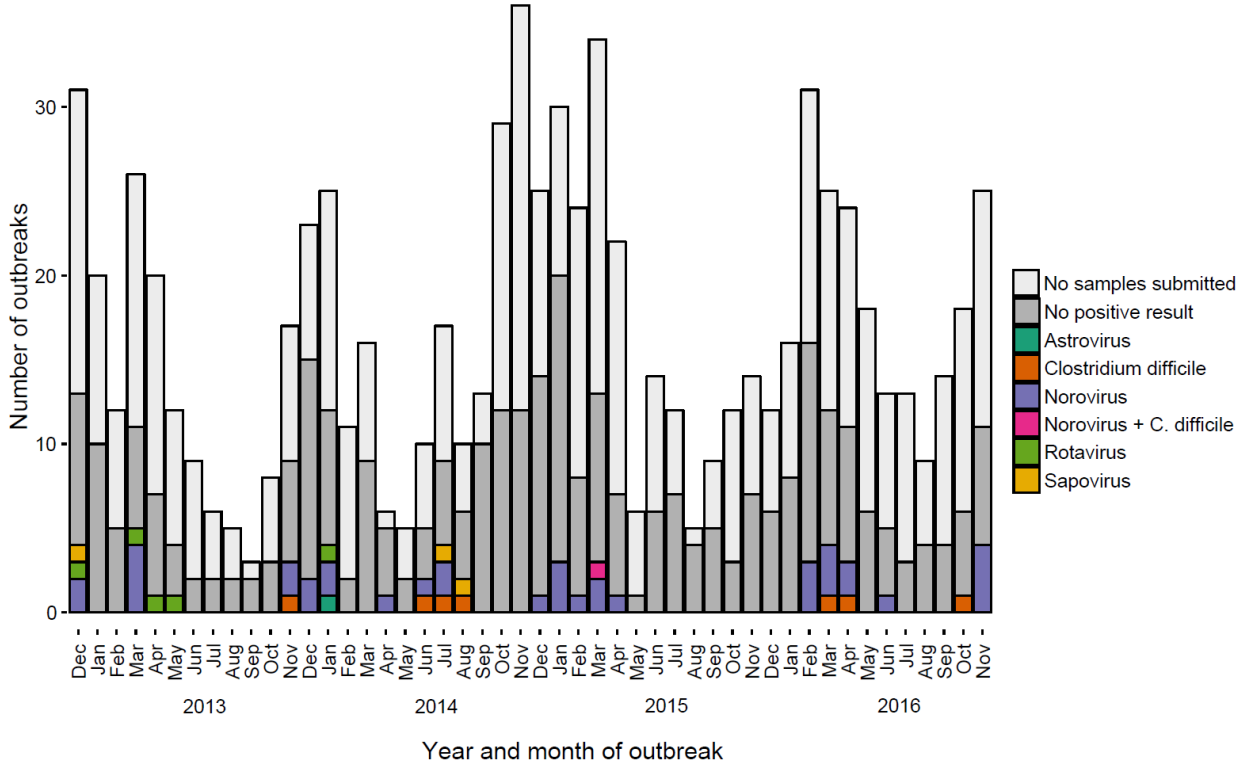
The median number of residents was 34 (range 7 - 112) and the median number of staff was 36 (range 7 - 160). The surveillance data could not be linked to CQC data for 113 (29.8%) care homes. Of the 266 care homes with CQC information, all were in operation in December 2016 and the following overall ratings were given; inadequate (11), requires improvement (103), good (150) and outstanding (2).

Figure 5.1: Geographical area covered by surveillance and location of care homes reported outbreaks (n=379), November 2012 - December 2016



Reported outbreaks exhibited a winter seasonal distribution; outbreaks were most commonly reported in November (92), December (91), January (91), February (78) and March (101). The distribution of outbreaks by month is shown in Figure 5.2. This figure also shows the outbreaks for which a sample was submitted for microbiological analysis; at least 1 sample was submitted for 356 (44.7%) outbreaks. The following pathogens were detected; norovirus (37), *Clostridium difficile* (7), rotavirus (5), sapovirus (3), astrovirus (1), mixed pathogens (norovirus and *C. difficile*) (1). Although included in the testing program, no *E. coli* O157 or Salmonella was detected. No positive result was recorded for 302 (85%) of outbreaks where a sample was submitted.

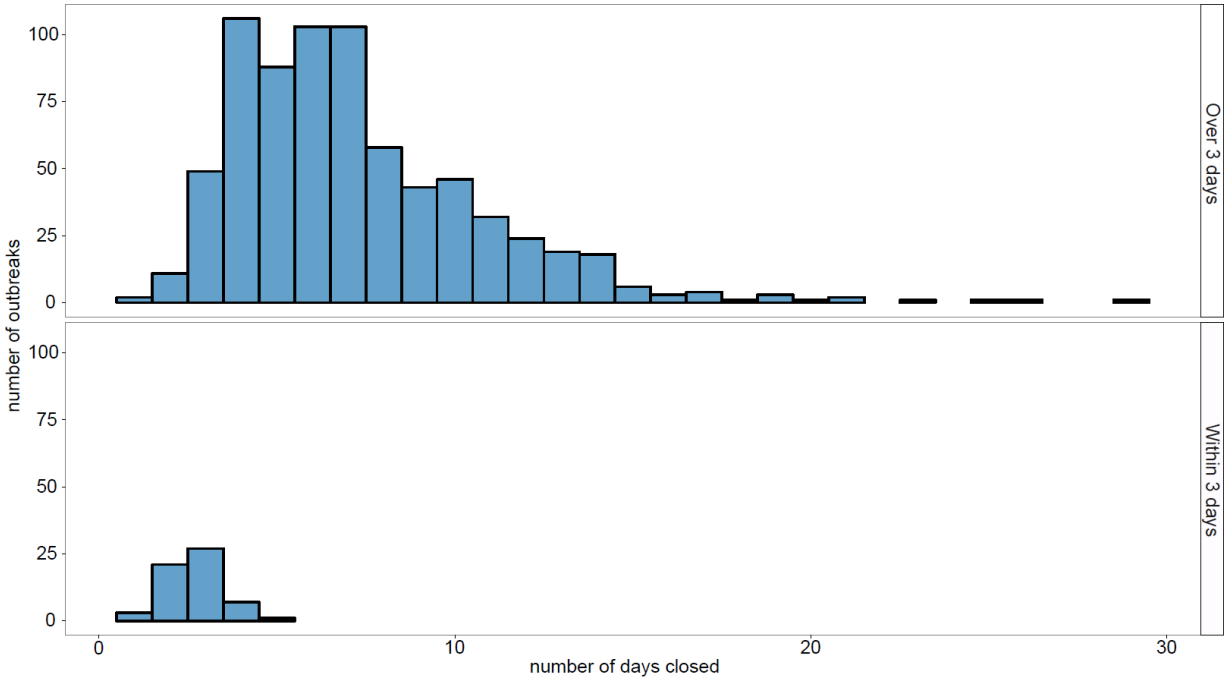
Figure 5.2: Number of care home outbreaks, showing those with samples submitted and the result, November 2012 - December 2016



In total 11,568 cases (8,539 residents and 3,029 staff) were reported as part of the 795 outbreaks. Of these, 75 cases were hospitalised (69 residents and 6 staff) and 29 residents were reported to have died. The median attack rate was 6% in staff and 30% in residents. The median attack rate was 17.6% of all persons per home (range 1.2% - 100%); the attack rate was under 20% in 448 outbreaks, between 20% and 39.9% in 286 outbreaks and over 40% in 64 outbreaks. The median ratio of residents to staff was 0.89 (range 0.17 to 5.86).

Care homes were closed for a median of 6 days during an outbreak (range 1-29 days). The distribution of length of closure is shown in Figure 5.3. The median time between the first case and the care home closure was 8 days (range 2-29 days); 59 homes closed within 3 days of the first case, compared to 657 which closed more than 3 days after the first case. The homes which closed within 3 days of the first case remained closed for a median of 3 days (range 1-5) compared to a median of 7 days (range 1-29) for homes that closed more than 3 days after the first case.

Figure 5.3: Duration of closure for each outbreak recorded in the surveillance system (n = 795), stratified by whether the closure was within 3 days of the first case, November 2012 - December 2016



Results of the negative binomial regression analysis are shown in Table 8. In univariable analysis, the duration of closure was significantly associated with: the total size of the home (IRR = 1.374, 95% CI = 1.244-1.517 in the largest quartile); total attack rate (IRR = 1.370, 95% CI = 1.213-1.547 for outbreaks with an attack rate over 40%); presence of residents with dementia (IRR = 1.106, 95% CI = 1.033-1.184); ratio of residents to staff (IRR = 0.914, 95% CI = 0.846-0.986); and closure of the home within 3 days of the first case (IRR = 0.371, 95% 0.311-0.441).

Table 8: Negative binomial regression analysis showing factors associated with increased duration of care home closure, November 2012 to December 2016

Variable		*Univariable*				*Multivariable*			
		IRR	**95% Confidence Interval**		**P**	**IRR**	**95% Confidence Interval**		**P**
			Lower	Upper			Lower	Upper	
Total size of home (quartile)	1st (smallest)		*ref*				*ref*		
	2nd	1.189	1.075	1.315	<0.001	1.154	1.038	1.283	0.008
	3rd	1.339	1.213	1.479	<0.001	1.282	1.150	1.430	<0.001
	4th (largest)	1.374	1.244	1.517	<0.001	1.426	1.275	1.595	<0.001
Total attack rate	Under 20%		*ref*				*ref*		
	20 to 39.9%	1.464	1.366	1.570	<0.001	1.391	1.290	1.500	<0.001
	40% and over	1.370	1.213	1.547	<0.001	1.434	1.257	1.636	<0.001
Winter outbreak		1.032	0.965	1.104	0.362	1.008	0.940	1.080	0.822
CQC overall rating		1.053	0.991	1.119	0.092	1.031	0.964	1.102	0.376
Residents with dementia		1.106	1.033	1.184	0.004	1.050	0.974	1.133	0.200
Ratio of residents to staff		0.914	0.846	0.986	0.023	0.977	0.895	1.068	0.613
Closure within 3 days		0.371	0.311	0.441	<0.001	0.442	0.366	0.534	<0.001

When adjusted simultaneously for other variables, the variable most strongly associated with decreased overall duration of closure was closure within 3 days of the first case (IRR = 0.442, 95%CI = 0.366-0.534). When adjusted for other variables, the presence of residents with dementia (IRR = 1.050, 95% CI = 0.974-1.133) and the ratio of residents to staff (IRR = 0.977, 95% CI = 0.895-1.068) were no longer significantly associated with increased duration of closure. The total size of the home remained associated with increased duration of closure (IRR = 1.426, 95% CI = 1.275- 1.595 in the largest quartile), as did the total attack rate (IRR = 1.434, 95% CI = 1.257-1.595 for outbreaks with an attack rate over 40%). There was little evidence that outbreaks occurring in winter (IRR = 1.008, 95% CI = 0.940-1.080) or that the overall CQC rating of a home (IRR = 1.031, 95% CI = 0.964-1.102) were significantly associated with duration of closure.

5.5 Discussion

In the surveillance system 795 outbreaks from 379 care homes were recorded. The attack rate of 37.1 outbreaks per 100 care homes per year is substantially higher than that observed in France (4.6 to 5.5 outbreaks per 100 facilities per year)[45] and Australia (16.8 outbreaks per 100 facilities per year).[46] The difference in reported outbreak rates may be due to different resident populations, different structural or organisational arrangements, or lower levels of circulating pathogens at the time of surveillance. This finding could, however, represent more complete ascertainment by community health staff in frequent contact with local care homes. Ascertainment could have also been improved by the use of an internet-based reporting system, the use of which has been shown to increase the level of reporting of hospital-based norovirus outbreaks.[125]

We found that care homes that closed promptly had outbreaks of shorter duration. This supports similar findings in care homes in other European countries[45, 215] and is consistent with comparable work looking at norovirus outbreaks in hospital which also found that prompt closure led to a shorter duration of outbreaks.[44, 216] We based these findings on the date of closure and the onset date of the first case. The date on which the outbreak was identified was not collected in this surveillance system, and thus we used time to closure after the first case as a proxy for outbreak identification.

We also found that increased duration of closure was significantly associated with increased size of the home and increased attack rate; both findings are epidemiologically plausible and have been observed in other studies.[103] The lack of significant association with CQC rating could be related to the scoring criteria used in this metric. Only a very minor part of the CQC rating covers topics such as infection prevention policies which have been shown to be important in preventing transmission in this setting.[217] This lack of significant association with CQC rating could also reflect the timing of the rating information; CQC data was extracted in December 2016 and therefore the ratings of a care home included in this analysis may not correspond to the rating of the care home at the point when the outbreak occurred.

Duration of closure is an important outcome as it may have a direct impact on a care home in terms of delayed admissions, and a wider impact on hospitals that are prevented from discharging patients to the affected care home. Duration of closure could be influenced by many factors. These may be organizational issues within the care home such as the time required to complete cleaning prior to re-opening and occupancy levels. As we did not capture resident capacity and therefore occupation rate, we were not able to adjust for this in our analysis. Evidence has shown that infection control measures are most effective when implemented in care homes within three days.[215] It is possible that good infection control measures slow down transmission but do not stop it, prolonging the outbreak and duration. However, information on the timing of infection control implementation, infection control policies, leadership or decontamination resources was not collected, so it was not possible to examine this. Some care homes may have taken longer to reopen as they did not have sufficient staff to undertake a deep clean promptly. This is less plausible, as the ratio of residents to staff was adjusted for in the analysis, and the significant relationship with other variables remained. In addition, it is possible that outbreaks with a high attack rate initially were more likely to be reported as they could be easier to recognize. It is plausible that the duration of these outbreaks may have been shorter due to the early onset of most cases, though it was not possible to test this, as onset dates for individual cases were not collected.

Over the four year surveillance period there were 11,568 cases, 75 hospitalisations and 29 deaths in this population; if this were extrapolated over the whole of England, this would represent a substantial burden of illness across the country. Although not directly

comparable, this rate of hospitalization and mortality appears to be lower than that observed in similar settings;[190] the difference could be due to underreporting, a different population or different treatment practices. Unfortunately it was not possible to calculate incidence or morbidity measures per bed-day with the information collected in this system. Such information would be useful in order to model individual risks to residents.

We saw marked seasonality in the outbreaks, with more outbreaks occurring during the winter months (November to March). However, outbreaks were reported year round, highlighting the continuing need for good infection prevention and control practice. The winter increase we observed is in line with individual case data in hospitals [218] and the general population.[90] This seasonality in care home outbreaks may reflect the increased levels of infection circulating in the community, which increases the risk that staff, visitors or admitted residents will introduce the infection into the home. Introductions of norovirus into care homes by people are far more frequent than through food.[103]

The most commonly detected pathogen was norovirus, which is consistent with studies in similar settings in other countries.[45, 46] Other viral pathogens such as rotavirus, sapovirus and astrovirus were less commonly detected. These viruses are less frequently detected in the general UK population [26] but have previously been associated with gastroenteritis outbreaks in care homes.[219–221] One of the key limitations when interpreting these findings is the large proportion (85%) of outbreaks in which samples were taken but no result was recorded. This may have been due to samples not being sent to the laboratory, not being tested at the laboratory due to procedural issues, or not being tested for viruses. Another explanation is that the database was frequently not updated with positive results from laboratory testing due to these results being reported after the surveillance report was completed. Unfortunately it was not feasible with the information stored in the surveillance database to cross-reference these results with laboratories in the area.

The primary aim of the surveillance system was to capture outbreaks of viral gastroenteritis; outbreaks of bacterial aetiology or food poisoning should have been captured on a separate incident management system and therefore not be included in this system. However, due to the syndromic nature of the case and outbreak definitions used in

this surveillance system, and the small proportion of outbreaks where a sample was taken and the result recorded, some such outbreaks may have been included in this system.

One of the strengths of this analysis is that the dataset covers a large population and a wide geographical area including urban, rural and urban/rural mixed areas. It also covers a 4 year period thereby avoiding periods of unusually high or low rates of illness. One of the main limitations of this work is the difficulty of formally ascertaining the completeness of these surveillance data, both over the study period and in the different geographical areas. It might have been that ascertainment improved in the winter, leading to the observed winter increases in recorded outbreaks. Due to the close collaboration between CMHPT and CIPCTs, the data completeness is perceived to be good. Without an external dataset to validate these findings it is difficult to formally assess the completeness of these data. Nevertheless, our findings from this surveillance system are broadly consistent with other studies. Another limitation of these data is that by the nature of the surveillance system, they only include cases which are part of outbreaks. Without collecting similar information on sporadic cases of gastroenteritis, it is impossible to estimate the full burden and cause of gastroenteritis in care homes.

5.6 Conclusions

In this study we present detailed gastroenteritis outbreak surveillance data from care homes in one area of England. This information is key to our understanding of the magnitude, cause and transmission dynamics of gastrointestinal illness in this vulnerable population. Further research is needed to understand the dynamics of and the pathogens causing gastroenteritis outbreaks in care homes, and the total associated burden of outbreak and non-outbreak infectious gastroenteritis in this population. The main finding is that closure within three days of the first case reduced significantly the duration of care home closure. This is important and has implications for care home providers and those advising on infection control practice.

Declarations

Ethics approval and consent to participate

No ethical approval was required as these data were collected for public health surveillance under The Health Protection Legislation (England) Guidance 2010.[222]

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

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Acknowledgments

We would like to particularly thank the Community Infection Prevention & Control Teams for their participation in this surveillance work, along with those staff reporting outbreaks from care homes. We also acknowledge the Care and Quality Commission for the use of their care home rating data.

Chapter 6 – Pathogens in care home outbreaks

What proportion of care home outbreaks are caused by norovirus? An analysis of viral causes of gastroenteritis outbreaks in care homes, North East England, 2016-2018

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How this publication fits into my thesis

In the previous chapter I provided a comprehensive analysis of the incidence and epidemiological characteristics of care home gastroenteritis outbreaks. However, the data on pathogens responsible for such outbreaks was not readily available from this dataset and therefore I decided that a further study was necessary to address the fourth research question: what proportion of care home gastroenteritis outbreaks are caused by norovirus? To do this, I use care home outbreak surveillance data from an area of England (North East) which has high levels of stool sampling and all samples are tested for a wide range of pathogens.

My contribution

I conceived and designed the study with co-authors. I undertook the data collection and analysis, wrote the first draft and revised the manuscript.

6.1 Abstract

Background

Outbreaks of infectious gastroenteritis are common in care homes for the elderly. Norovirus can cause these outbreaks, but diagnosis is frequently based solely on clinical characteristics. Our objective in this study was to describe the epidemiology of norovirus and other gastrointestinal pathogens in these settings.

Methods

We analysed surveillance data from gastroenteritis outbreaks reported in North East England between 04 July 2016 and 01 July 2018. Stool samples taken during these outbreaks were tested for a range of viral and bacterial pathogens. We described the epidemiology of these outbreaks and explored the characteristics of norovirus outbreaks versus from other viral causes using multivariable logistic regression.

Results

From the 566 care home gastroenteritis outbreaks in this study, we found that norovirus was the pathogen most frequently isolated. Norovirus was detected in 64% of outbreaks with a pathogen identified. Sapovirus was found in 13%; rotavirus in 11%. We found that norovirus outbreaks were associated with higher attack rates (aOR 1.03, 95% CI 1.01-1.05) and fewer cases sampled (aOR 0.74, 95% CI 0.60-0.91), compared to outbreaks caused by other viral pathogens.

Conclusions

These results are important as they quantify the contribution of norovirus to gastroenteritis outbreaks in care homes. Given this evidence, we emphasize the importance of non-specific outbreak interventions that can affect the impact of all such outbreaks. We further recommend that these findings are used to inform the implementation strategies of any norovirus-specific interventions such as a norovirus vaccine.

Keywords: norovirus, gastroenteritis, outbreaks, surveillance

6.2 Background

Acute infectious gastroenteritis is a common cause of morbidity in the general population.[223] Residential care homes for the elderly (also known as long-term care facilities), including those offering nursing care, provide an environment suited to the acquisition and spread of infectious agents causing gastroenteritis.[7] Because of this, outbreaks of acute gastroenteritis in semi-enclosed settings such as care homes are difficult to prevent and challenging to control.[102] This is a public health concern because the morbidity and mortality associated with gastroenteritis outbreaks is higher amongst the elderly residents of care homes.[176, 190]

Norovirus has been reported as the most frequent cause of care home gastroenteritis outbreaks.[95] Norovirus outbreaks are particularly difficult to prevent in care homes due to its low infectious dose, the lack of long term immunity to reinfection, its persistence in the environment and the possibility of infected persons shedding virus asymptomatically.[101] There are other viral pathogens such as sapovirus, astrovirus, rotavirus and adenovirus which have been reported to have caused outbreaks of gastroenteritis in care homes.[43, 47] However, there is limited evidence-base to understand the relative contribution of these viral pathogens, and bacterial pathogens such as Salmonella and Campylobacter, to the total burden of care home gastroenteritis outbreaks in England. Despite this lack of evidence, outbreaks of diarrhoea and vomiting in care homes are commonly classed as being caused by norovirus, on clinical and epidemiological characteristics alone, which may lead to a substantial overestimate of the burden of norovirus outbreaks.[224]

The aim of this study was to describe the epidemiology of gastroenteritis outbreaks in care homes in North East England, with particular reference to norovirus.

6.3 Methods

Setting

In England, all care homes (residential facilities providing social and nursing care to the elderly) are required to be registered with and inspected by the Care Quality Commission (CQC) in accordance with Schedule 1 of The Health and Social Care Act 2008 (Regulated Activities) Regulations 2014. Care homes are advised by the CQC to report outbreaks to

Public Health England (PHE) but this is not mandatory.[225] In North East England, there are 12 local authority areas with a total population of 2.645 million in 2017, and 742 CQC registered care homes. PHE North East operates a surveillance system for gastroenteritis outbreaks in care homes. The study population comprised all North East CQC registered care homes. The study included all gastroenteritis outbreaks reported from 04 July 2016 to 01 July 2018.

Outbreak definition

An outbreak was defined as two or more cases of diarrhoea and/or vomiting occurring in staff and/or residents in the same home within a short time period.[226] No standardised definitions were used for "diarrhoea" or "a short period of time". The start of an outbreak was defined as the date of onset in the index case; the end of an outbreak was defined as 72 hours after the resolution of symptoms in the last case. Outbreak reports were received by PHE and entered on to an electronic case management system (HPZone).[117]

Pathogen detection

All study care homes were asked to submit stool samples from at least six cases during outbreaks of infectious gastroenteritis. All these stool samples were processed in one laboratory in Newcastle-upon-Tyne, tested for the following pathogens; *Campylobacter* sp., *Salmonella* sp., *E. coli* O157, *Shigella* sp. (all using culture), norovirus, sapovirus, rotavirus, astrovirus, adenovirus (all using multiplex PCR), *C. difficile* (three stage testing following national guidance)[14] and *Cryptosporidium* spp.(Phenol-auramine staining and fluorescence microscopy). Stools samples were only tested for *C. perfringens* and *B. cereus* if this was requested based on clinical and epidemiological assessment of the outbreak. All pathogen testing was conducted using agreed laboratory standards.[227] Laboratory results were recorded daily on a Structured Query Language (SQL) database.

Data collection

Epidemiological data captured in the surveillance system included variables such as: number of residents and staff at the home, the number of cases in residents and staff, date of outbreak onset and outbreak duration. Laboratory data included number of stool samples, number of cases tested and pathogen testing results. Data were extracted from HPZone, with data checked against paper outbreak records. Laboratory data were

extracted from the relevant SQL database and joined with the epidemiological data using a unique outbreak identifier.

Data analysis

We calculated the incidence rate of care home gastroenteritis outbreaks per 100 care homes per year for each local authority and the percentage of outbreaks with stool samples submitted. We calculated resident attack rates as number of cases divided by number of residents. The number of residents and duration of outbreak were included as continuous variables. We calculated the ratio of staff to residents and used this as a continuous variable. Outbreaks with an onset date after week 42 and before week 16 (based on ISO 8601) were classed as occurring during winter and analysed as a binary variable. We described the number of outbreaks by month of onset. We used loess regression to fit smooth curves to show the change in the percentage of outbreaks with a sample submitted over time and the change in the percentage of outbreaks norovirus positive over time. Where only one pathogen was isolated from an outbreak, this was assigned as the cause. We also described outbreaks where more than one pathogen was identified.

We used those outbreaks with a single viral pathogen identified for a multivariable analysis. The outcome was detection of norovirus. Outbreaks with no pathogen or multiple pathogens identified were excluded from the multivariable analysis. We used a mixed-effects logistic regression model to explore the characteristics of norovirus infection versus other viral causes, simultaneously adjusted for all other explanatory variables. Random care home-level intercepts were used to account for within-home correlation. The explanatory variables included *a priori* as we believed them to be associated with norovirus outbreaks were: resident attack rate, care home population, outbreak duration and number of cases sampled. The other three variables (number of virus-positive samples, ratio of staff to residents and winter) were regarded as potential confounders so added to the model and retained if they improved model fit, as measured using the Akaike information criterion (AIC).[228] Interaction terms between parameters were added and tested for significance using a likelihood-ratio test from the lmtest package and then assessed using AIC for improved model fit if significant.[229] All analyses were conducted using R 3.5.0.[209]

6.4 Results

During the study period we recorded a total of 566 outbreaks from 339 care homes. This equates to an incidence rate of 38.14 outbreaks per 100 homes per year. Of the 339 care homes reporting outbreaks, 194 (57.2%) reported only one outbreak during the study period, with the maximum being 7 outbreaks reported by one care home. Of the 566 outbreaks, at least one stool sample was submitted for laboratory testing for 362 (64.0%) outbreaks.

A breakdown of the number of care homes, number and incidence rate of outbreaks, and number and percentage of outbreaks with a faecal sample submitted for pathogen testing is shown in Table 9. The area with the lowest incidence rate of outbreaks was Redcar and Cleveland (25.5 outbreaks per 100 care homes per year) and the highest was North Tyneside (64.1 outbreaks per 100 care homes per year). The area with the highest percentage of outbreaks with a stool sample submitted was County Durham (72%), which was substantially higher than the percentage from Newcastle upon Tyne (51.3%), the lowest of the 12 areas.

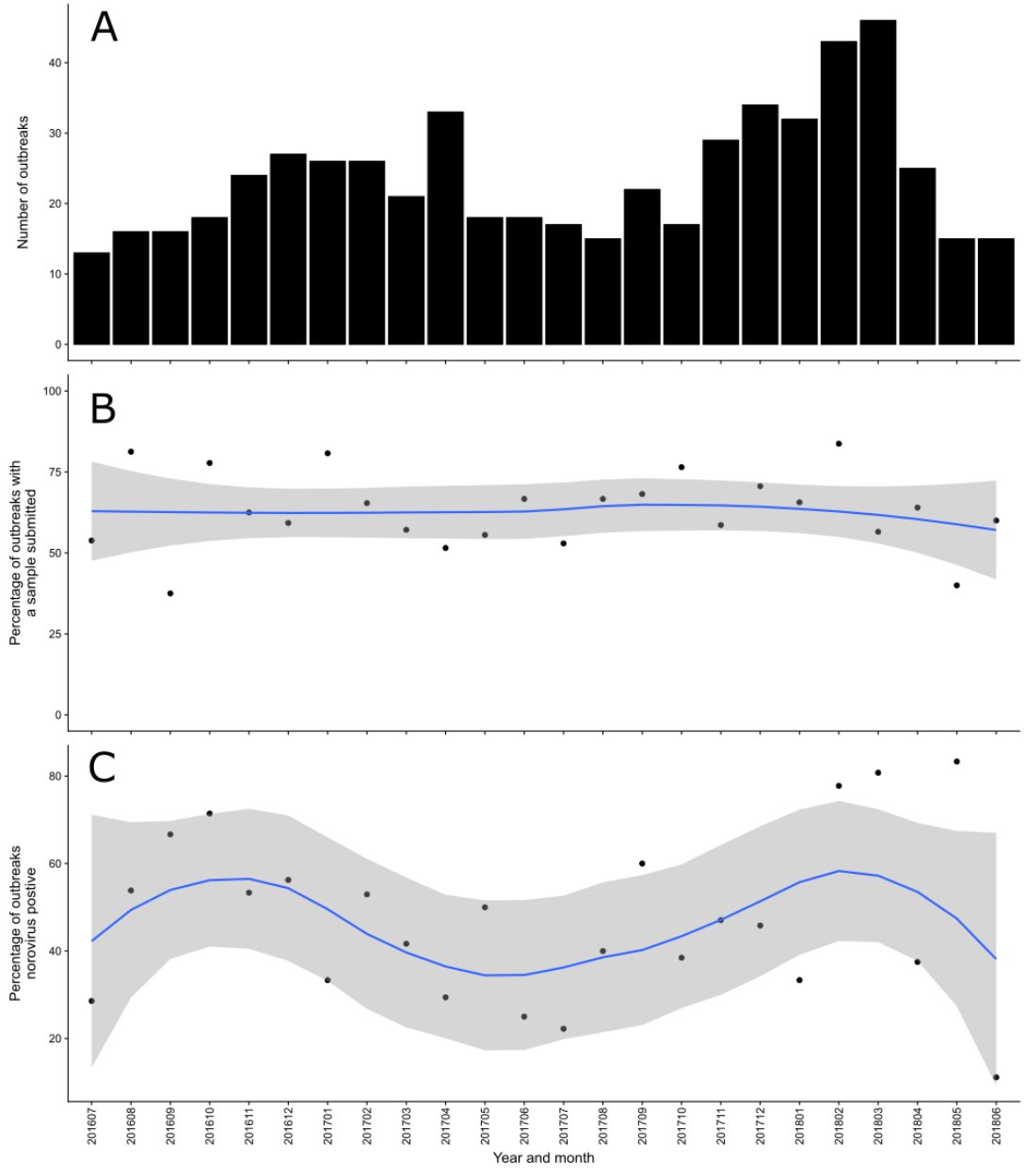
Table 9: Care homes gastroenteritis outbreaks by local authority area (n=566), North East England, 2016-2018

Local Authority	Total registered care homes	Home reporting an outbreak	Percentage of homes with outbreak	Outbreaks	Outbreaks per 100 care homes per year	Outbreaks with samples submitted	Percentage with samples submitted
County Durham	144	66	45.8	107	37.2	79	72.0
Darlington	33	18	54.5	32	48.5	21	65.6
Gateshead	66	30	45.5	55	41.7	35	60.0
Hartlepool	23	15	65.2	20	43.5	11	55.0
Middlesbrough	43	17	39.5	27	31.4	19	70.4
Newcastle upon Tyne	62	28	45.2	39	31.5	20	51.3
North Tyneside	46	30	65.2	59	64.1	33	54.2
Northumberland	98	45	45.9	75	38.3	49	64.0
Redcar and Cleveland	53	15	28.3	27	25.5	19	66.7
South Tyneside	32	18	56.2	29	45.3	20	65.5
Stockton-on-Tees	53	22	41.5	36	34.0	21	58.3
Sunderland	89	35	39.3	60	33.7	35	58.3
Total	**742**	**339**	**45.7**	**566**	**38.1**	**362**	**64.0**

The temporal distribution of outbreaks is shown in Figure 6.1A. In the 2016/17 season the month with the largest number of outbreaks was April 2017 (n = 33). During the 2017/18

season there were more outbreaks than the previous season, with the number of outbreaks peaking in March 2018 (n = 46). The percentage of outbreaks with a sample submitted is shown over time in Figure 6.1B. There was variation in the percentage submitted by month, with the lowest in September 2016 (37.5%) and highest in February 2018 (83.7%), however there was no notable trend or periodicity.

Figure 6.1: Care home gastroenteritis outbreaks by month and year, North East England, 2016-2018 A) Total number of outbreaks B) Percentage of outbreaks with a faecal sample submitted, with loess regression smoothed line (blue line) and 95% Confidence Interval (grey) C) Percentage of outbreaks with a positive norovirus sample, with loess regression smoothed line (blue line) and 95% Confidence Interval (grey)

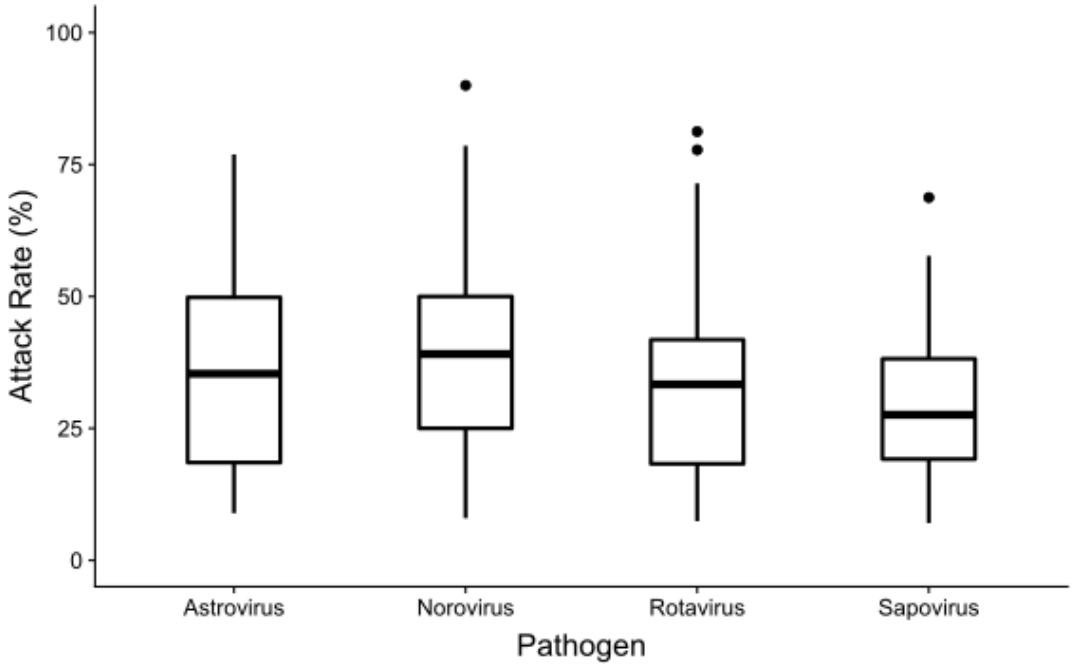


From the 362 laboratory-tested outbreaks, a pathogen was detected in 284 (78.5%) outbreaks; of these 263 (92.6%) had a viral pathogen identified, 257 (90.4%) with a single viral cause. Six viruses were detected, in order of frequency: 181 norovirus (64%), 37 sapovirus (13%), 32 rotavirus (11%), six astrovirus (2%) and one adenovirus (0.4%). Norovirus and sapovirus were detected together in 2 outbreaks; norovirus and rotavirus were also detected together in 2 outbreaks. *Clostridium difficile* was detected in 4 outbreaks and *Campylobacter* in 2 outbreaks. Norovirus and *C. difficile* were detected together in 2 outbreaks. There were only 38 outbreaks for which samples were tested for *C. perfringens* and *B. cereus*. *C. perfringens* was identified in 15 (39%) of these outbreaks, but the toxin gene was only detected in three outbreaks. *B. cereus* was not identified in any outbreaks.

Overall, 50% of the 362 outbreaks with a sample submitted had a positive norovirus result and no other pathogen detected. The percentage of outbreaks with a sample submitted that was positive for norovirus is shown by month in Figure 6.1C. Norovirus was detected in every month, with the lowest proportion of outbreaks being caused by norovirus in June 2018 (11%). There was a seasonal change in this relationship, with a higher percentage of samples positive for norovirus during the winter months in both seasons.

The median population (residents and staff) of care homes in this dataset was 96 people (Interquartile range (IQR) 70 - 121); the median number of residents was 44 (IQR 34 – 57). The median ratio of staff to residents was 1.16:1 (IQR 0.99:1 – 1.38:1). Of the 284 outbreaks where a stool sample was submitted, the median number of cases tested was 3 (IQR 2 – 4). The median attack rate in residents was 27.3% (IQR 15.7% - 41.7%). For those 256 outbreaks of astrovirus, norovirus, rotavirus and sapovirus the distribution of resident attack rates is shown by pathogen in Figure 6.2: this excludes the one adenovirus outbreak. The attack rate was highest in norovirus outbreaks (39.1%), followed by astrovirus outbreaks (35.4%), rotavirus outbreaks (33.3%) and sapovirus outbreaks (27.6%). However, these differences in AR are not statistically significant (Figure 6.2).

Figure 6.2: Boxplot showing the distribution of attack rates in residents during care home gastroenteritis outbreaks of a confirmed viral cause (n = 256*), North East England, 2016-2018



** excluding one adenovirus outbreak*

For the 257 outbreaks of a single viral cause, the association between various outbreak characteristics and norovirus detection is shown in Table 10. These are compared with outbreaks where sapovirus, rotavirus, astrovirus or adenovirus were identified. In the univariable analysis norovirus outbreaks had a significantly higher attack rate: Odds Ratio (OR) 1.02 (95% CI 1.01 – 1.05). None of the other outbreak characteristics such as care home population size, outbreak duration, number of cases tested, number of virus-positive samples, outbreak during winter or the staff to resident ratio were significantly associated with norovirus in the univariable analysis. In the multivariable analysis, when simultaneously adjusted for other variables, higher attack rates in residents were significantly associated with norovirus (aOR 1.03, 95%CI 1.01 – 1.05). Norovirus was also significantly associated with fewer cases being sampled (aOR 0.74, 95% CI 0.60 – 0.91). No other variables were significantly associated with norovirus outbreaks in the multivariable model. No interaction terms were statistically significant.

Table 10: Association between outbreak characteristics and norovirus detection, care home gastroenteritis outbreaks of a confirmed viral cause (n=257), North East England, 2016-2018

Variable	Other viruses (n = 76)		Norovirus (n = 181)		OR	p value	aOR	95% Confidence Interval		p value
	Mean	SD	Mean	SD						
Resident attack rate	33.04	*19.27*	38.30	*17.74*	1.02	0.038	1.03	1.01	1.05	0.004
Number of residents	44.75	*19.58*	45.73	*16.41*	1.00	0.679	1.02	0.99	1.04	0.077
Outbreak duration	20.84	*10.41*	18.87	*10.60*	0.98	0.174	0.98	0.95	1.01	0.130
Number of cases sampled	3.66	*2.33*	3.17	*1.83*	0.89	0.080	0.74	0.60	0.91	0.005
Number of virus-positive samples	2.46	*1.71*	2.53	*1.55*	1.03	0.749	1.25	0.97	1.62	0.091
Outbreak in winter? (number and percentage	48	*63.20*	129	*71.30*	1.45	0.201	.	.	.	.
Ratio of staff to residents	1.21	*0.38*	1.21	*0.40*	1.02	0.965	1.17	0.53	2.57	0.701

6.5 Discussion

In this study, we found that norovirus was the pathogen most frequently isolated during care home gastroenteritis outbreaks. Norovirus was the single pathogen identified for 64% of outbreaks where a pathogen was identified; from this we infer that norovirus was the primary cause of gastroenteritis outbreaks in care homes. The percentage of norovirus outbreaks was broadly consistent during the year, but there was some evidence that norovirus accounted for a greater percentage of outbreaks during winter months. We found norovirus outbreaks to be associated with higher attack rates and fewer cases being sampled. Regarding the association between norovirus and higher attack rates, a recent systematic review found that attack rates were influenced by resident mobility and dependency, staff–resident contact intensity, exposure to vomit, and route of feeding.[103] However it was not possible to assess these relationships in this study as these data were not collected.

In this setting the proportion of stool samples submitted for pathogen testing (64%) was slightly higher than the rate of stool testing during care home gastroenteritis outbreaks in other settings in England [204] and France.[45] Given the high proportion of outbreaks tested for a range of pathogens, we have greater assurance in our findings regarding the relative importance of different pathogens in care home gastroenteritis outbreaks. However, the median number of cases sampled was three, which is lower than the recommended guideline of at least six cases, reducing the likelihood of pathogen detection. There remains a possibility that outbreaks where a sample had been submitted were systematically different from those where no sample was submitted, leading to some bias within these results.

In this study, we found that 92.6% of outbreaks with a pathogen detected had a viral pathogen identified. This proportion of outbreaks with a viral cause is substantially higher than a previous study in England and Wales between 1992 and 1994 which attributed 57% of outbreaks in residential facilities where a sample was submitted to viral causes and 29% to bacterial causes, but this may be due to improvements in *Salmonella* Enteritidis control in United Kingdom (UK) eggs and in viral detection methodologies.[41] A similar picture was seen in systematic review of such outbreaks published between January 1997 to June 2007, which assigned 69% to viral causes and 31% to bacterial causes.[37] Our finding that a greater proportion of outbreaks had a viral cause may reflect changes in: the

completeness of reporting, the food hygiene arrangements, the probability of bias introduced by voluntary sampling, infection control practices and inter-annual changes in viral circulation.

One of the strengths of this study was that all outbreak samples were tested for a wide range of viral and bacterial causes, giving us confidence in the pathogen results produced. After norovirus, the next most frequently identified pathogen in this study was sapovirus, attributed as causing 13% of outbreaks. Sapovirus was the second most common viral pathogen identified in a large community study in the UK [26] and has previously been identified in 66% of norovirus-negative care home outbreak samples in one study in the US.[47] However, sapovirus was not detected in one study of care home outbreaks in The Netherlands [43] and was not tested for during several other studies in similar populations.[44, 46] Similarly, rotavirus was detected in 11% of our study outbreaks. This is consistent with findings from other studies that it can cause gastroenteritis outbreaks in this population [43, 46] and a study in France which found that norovirus and rotavirus together accounted for 95% of gastroenteritis outbreaks in care homes.[45] Our finding that rotavirus was the third most frequently observed pathogen demonstrated the continued circulation of this virus in the elderly, despite the introduction of rotavirus vaccine for infants in the UK in 2013, and the corresponding decrease in the total number of cases, primarily in infants and toddlers.[230]

The results of this study were obtained from one comparatively small area of England over a two-year period. We recognise that as such, there is a question as to whether these findings are representative of the situation over time and in other areas of England. However, in 2016/17 and 2017/18 the number of norovirus laboratory reports in England and Wales were comparable to those seen in the previous 3 years,[231] indicating that the national burden of norovirus was similar to previous years and therefore comparable. Although the study took place in one contiguous geographical area, a recent analysis of care home gastroenteritis outbreaks in England show that the rates in this area were equivalent to other areas in England.[205] Given this, we believe that it would be reasonable to generalise these study results to other seasons and other areas of England. As to generalisation to other countries, the appropriateness of this would depend on factors such as: the levels of pathogens circulating at the time of surveillance, different

residential populations, different organisational or structural settings, and different infection control practices.

In this study one of the possible limitations was the definition used for attributing a causal pathogen to an outbreak, where we assigned a pathogen as causal if only that pathogen was identified in that outbreak. This is a point of difference from other studies in similar settings [46] which have used previous Centers for Disease Control and Prevention (CDC) definitions that require two or more stool samples with an aetiological agent to assign it as a cause.[232] One effect of using our study definition may be that it is less specific and incorrectly allocates outbreaks not caused by that pathogen. However, we believe our approach is justified as it is consistent with the more recent surveillance definition for norovirus gastroenteritis used by CDC for long-term care facilities.[108] Another possible limitation was that we did not include staff in the care home population size or attack rate. We made this decision due to our concern of under- or over-reporting illness in care home staff. This could have biased our findings relating to attack rates, as the attack rate may have been reduced/inflated for those homes with a higher proportion of staff. We did however include staffing levels with our analysis by including the ratio of residents to staff in the home.

Comparing these results in the context of international literature is difficult due to the different methods of surveillance for outbreaks, varying sampling regimes and the range of different pathogens tested for using a range of methodologies. However, our findings were broadly consistent with other studies which found similar percentage of norovirus outbreaks in other settings such as: Oregon (77%),[42] the Netherlands (78%) [43] and south west England (74%).[44] Comprehensive surveillance of such outbreaks in Australia (40%) [46] and France (36%),[45] found lower percentages attributed to norovirus, although a direct comparison is difficult as Kirk *et al.* defined an outbreak as being caused by norovirus only if at least two samples were positive. The percentage of care home outbreaks attributed to norovirus in our study is substantially higher than the estimated prevalence of norovirus found in sporadic cases of acute gastroenteritis in the community in a worldwide meta-analysis (24%).[80] This may reflect the increased susceptibility of care home residents,[95] the opportunities for transmission [7] and the difficulty of implementing effective infection control measures in such a setting.[37]

6.6 Conclusions

In this study, we quantified the percentage of care home gastroenteritis outbreaks attributed to norovirus and other pathogens. We found that norovirus caused 64% of outbreaks where a pathogen was identified and that further 27% of care home outbreaks were caused by a different viral pathogen. Given this evidence, we emphasize the importance of non-specific outbreak interventions such as good hygiene, prompt reporting and strong infection control procedures that can affect the impact of all such outbreaks. However, norovirus-specific interventions (such as a norovirus vaccine) could prevent up to two thirds of outbreaks that are associated with the highest attack rates.

Ethics approval and consent to participate

Ethical approval was not required as these data were collected for public health surveillance under The Health Protection Legislation (England) Guidance 2010. No administrative permissions were required to access the raw data used in this study.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analysed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Thomas Inns is affiliated to the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Gastrointestinal Infections at University of Liverpool in partnership with Public Health England (PHE), in collaboration with University of East Anglia, University of Oxford and the Quadram Institute. Thomas Inns is based at University of Liverpool. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

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Chapter 7 – How many care home outbreaks are there?

Estimating the burden of care home gastroenteritis outbreaks in England, 2014-2016

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How this publication fits into my thesis

In Chapters 4, 5 and 6 I have provided results regarding the incidence of care home gastroenteritis outbreaks, my second research question. However, these studies are all in comparatively small, geographically defined areas in England, respectively Merseyside, Cheshire and Merseyside and North East England. One motivation for studying these areas was that anecdotally their surveillance is understood to be effective. In order therefore to understand the situation in England as a whole, I conducted the following study to account for less effective reporting in other areas. I did this using a generalised linear mixed effects regression model which adjusted for under-reporting.

My contribution

I conceived and designed this study with JH, RV, NA and SOB. I undertook the analysis with HEC and JH. I wrote the first draft, revised and approved the manuscript.

7.1 Abstract

Background

Outbreaks of infectious gastroenteritis in care homes are common, with norovirus a frequent cause. In England there is no co-ordinated national surveillance system. We aimed to estimate the burden of these outbreaks.

Methods

Using a generalised linear mixed effects regression model we described the relationship between the observed number of care home outbreaks and covariates. Estimated model parameters were used to infer uplift in the number of outbreaks expected if all areas were subjected to enhanced surveillance. From this we then estimated the total burden of care home gastroenteritis outbreaks in this period.

Results

We estimated a total of 14,146 care home gastroenteritis outbreaks in England during 2014-2016; this is 47% higher than the reported total and a rate of 32.4 outbreaks per 100 care homes per year. The median number of outbreaks from the model estimates was 31 (IQR 20 – 46) compared to 19 (IQR 12 – 34) reported from routine surveillance.

Conclusions

This estimated care home gastroenteritis burden in England indicates that current surveillance substantially underestimates the number of outbreaks, by almost half. Improving this surveillance could provide better epidemiological knowledge of the burden of norovirus to inform public health policy, particularly with the advent of norovirus vaccines.

7.2 Background

Residential care homes for the elderly provide an ideal environment for acquisition and spread of infection.[7] Outbreaks of infectious gastroenteritis in care homes are common, with 16.8 outbreaks per 100 care homes per year being reported from a study in Australia.[46] Norovirus is the pathogen which has been reported as being the most frequent cause of care home infectious gastroenteritis outbreaks.[95] Norovirus is estimated to be responsible for 10-20% of gastroenteritis hospitalisations in older adults [96] and has been associated with excess mortality in the elderly.[122] There are few surveillance systems to detect norovirus disease in community settings.[127] There are surveillance systems which capture information on infectious gastroenteritis outbreaks in care homes in France [45] and Australia.[34]

In England, information on general outbreaks of infectious gastroenteritis in care homes has been collected since 1992.[41] Since 2010, the Care Quality Commission (CQC) has required care homes in England to report outbreaks of infectious gastroenteritis to Public Health England (PHE).[116] Despite this, there is no co-ordinated national surveillance system to collect this information; in most of England, this information is captured locally by PHE using a health protection case management tool.[117] However, in certain areas of England there are enhanced surveillance systems that capture more detailed information on care home gastroenteritis outbreaks.[204, 217]

Given the lack of a dedicated surveillance system, there is no routine way of calculating the burden of care home gastroenteritis outbreaks. Estimating the magnitude of this burden is important as it quantifies the direct impact upon the facilities and can also be used to infer indirect impacts on hospitals, given that patients are often transferred between care homes and hospitals. In this research we used a modelling approach to estimate the total burden of care home gastroenteritis outbreaks in England, adjusted for under-reporting. Comparable approaches have previously been used to estimate the under-reporting of norovirus illness in the community.[233]

7.3 Methods

Study design

In this analysis we used an ecological study design with the local authority in England as the unit of analysis. Data were aggregated at local authority level, for the period 1 January 2014 to 31 December 2016 (the study period). The number of care home gastroenteritis outbreaks in each area in the study time period was the primary outcome. From this we calculated the reported rate of care home gastroenteritis outbreaks per 100 care homes per year.

Study definitions

We defined a care home as a facility providing long-term residential care, with or without nursing care. An outbreak was defined as either "two or more cases of gastrointestinal infection occurring around the same time, in residents or their carers" or "an increase in the number of cases above the number normally observed".[234] Routine surveillance is defined as a system that captures basic information on an outbreak (care home name, date of outbreak, number of cases). Enhanced surveillance is defined as a system that captures more detailed information than routine surveillance (eg. outbreak duration, population denominator, pathogen isolated). Both enhanced and routine surveillance are passive surveillance systems.

Data sources

In England care homes have a legal requirement to register with, and be inspected by, the CQC in accordance with Schedule 1 of The Health and Social Care Act 2008 (Regulated Activities) Regulations 2014. The CQC database of registered care homes [213] was queried to obtain the number of care homes by local authority. The relevant PHE surveillance systems were queried to obtain the number of care home outbreaks in each local authority reported during the study period.

The Office for National Statistics provides population data for England. For each local authority, the following data were obtained: the total population, the proportion of the population under the age of 5 years and the proportion of the population over 65 years old.[235] We included the proportion of the population under 5 in our analysis as rates of norovirus infection are significantly higher in this group compared to those in other age groups.[208] All public hospital laboratories in England report data to the Second

Generation Surveillance System (SGSS).[236] From SGSS we obtained the number of laboratory confirmed norovirus cases in the study period by local authority. In England, the Department for Education maintain a database of all schools. From this, we obtained the number of primary schools (for children aged 4-11) in each local authority.[237] We included primary schools as an explanatory variable in our model because schools are the community institution most affected by norovirus outbreaks besides care homes.[238]

Statistical methods

We described the data by calculating the rate of reported care home gastroenteritis outbreaks per 100 care homes per year for each local authority. We calculated this rate for the whole of England, along with the total number of reported outbreaks. We used hexagonal cartograms of local authorities in England to represent graphically the spatial variation in reported outbreak rate.[239] We used t-tests to compare the values of each explanatory variable for local authorities with routine surveillance to those with enhanced surveillance.

We used a generalised linear mixed model to describe the relationship between the number of outbreaks per local authority and a range of explanatory variables. The outcome variable for local authority *i* was the number of outbreaks in local authority *i*. The negative binomial family was chosen over the Poisson family to account for the fact that there was more variation in the count data than could be explained by the simpler Poisson distribution-based GLM. Random region-level intercepts were included to accommodate geographical variation and intrinsic but unmeasured differences between PHE regions.[240] In this analysis we assumed that ascertainment of outbreaks was more complete in areas with enhanced surveillance (which collect more detailed information).

The explanatory variables selected a priori were: number of care homes, area population, proportion of the population under the age of 5 years, proportion of the population over the age of 65 years, number of laboratory confirmed norovirus cases, number of primary schools in the local authority. These were analysed as continuous variables. A binary variable was used to indicate whether a region was subject to enhanced surveillance or not. Where necessary, explanatory variables were rescaled to ensure model convergence. We then used the model together with a simulation-based approach to estimate what the number of outbreaks in each local authority might be if all local authorities in England had

an enhanced surveillance system. We conducted these analyses using R,[209] using the lme4 package for the regression model.[241] We undertook a sensitivity analysis to assess the effect of influential observations.

Our chosen model estimated the association between each explanatory variable and the number of gastroenteritis outbreaks. For area *i* the predicted count was simulated as a random realisation from a negative binomial distribution with shape parameter λ and mean μ set as the fitted value for area *i* which has been obtained directly using estimated parameters from the model based upon the original data but recoding all areas as if they were enhanced (enhanced = 1). Since sampling variation causes this number to vary each time it is simulated the whole process was repeated 10,000 times and these values were used to estimate the true number of outbreaks across England with an empirical 95% Confidence Interval. Model estimates were combined with recent study data on the characteristics of acute gastroenteritis outbreaks in care homes [204] to quantify the number of cases linked to these outbreaks. The statistical specification of this model is shown as supplementary material in Appendix C.

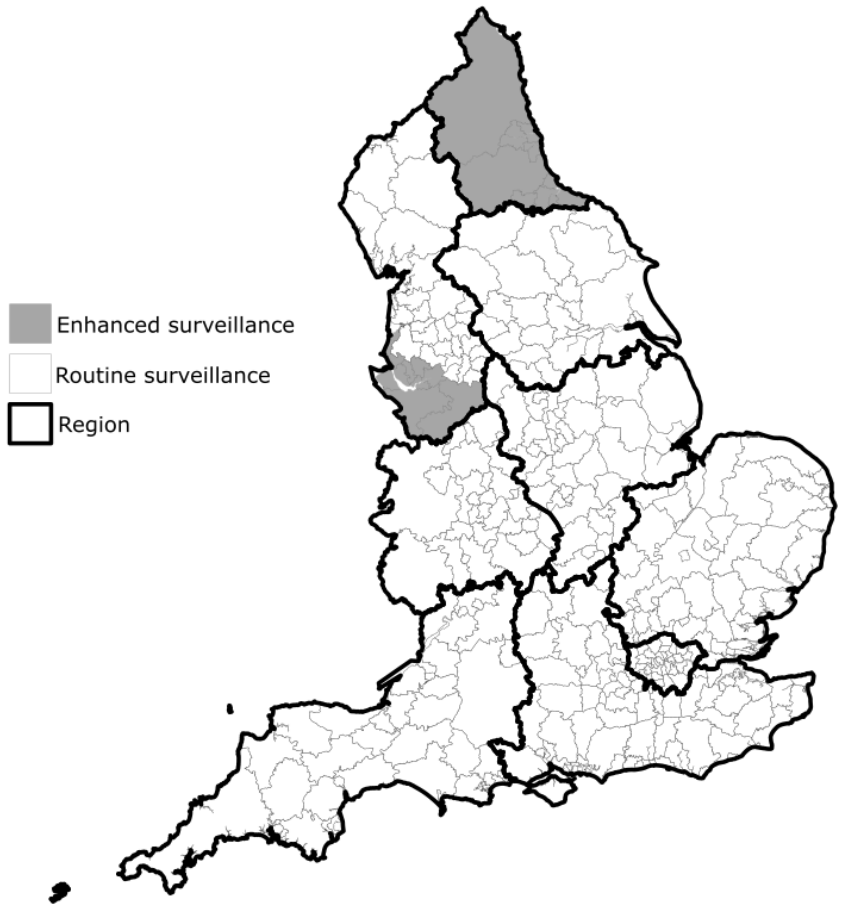
7.4 Results

There are 326 local authorities in England of which, twenty one reported to an enhanced surveillance system. The geographical location of the local authorities with routine and enhanced surveillance is shown in Figure 7.1. During the study period, there were 9594 gastroenteritis outbreaks in 14229 care homes. A summary for each of the study variables, comparing routine and enhanced areas, is provided in Table 11 below.

Table 11: Summary characteristics for study variables, by surveillance type, for all local authorities (n=326), England, 2014-2016

	Routine (n = 305)			Enhanced (n = 21)			
Variable	**Median**	**25p**	**75p**	**Median**	**25p**	**75p**	***p* value**
Number of outbreaks	19	12	31	69	42	93	<0.0001
Number of care homes	36	25	54	58	35	80	0.0037
Number of lab confirmed norovirus cases	31	13	64	28	15	48	0.6246
Total population (000s)	128.5	97.0	197.7	203.3	147.9	316.0	0.0030
Proportion under 5	0.06	0.05	0.07	0.06	0.06	0.06	0.5390
Proportion over 65	0.18	0.15	0.22	0.18	0.16	0.20	0.8626
Number of primary schools	54	40	73	75	54	106	0.0014

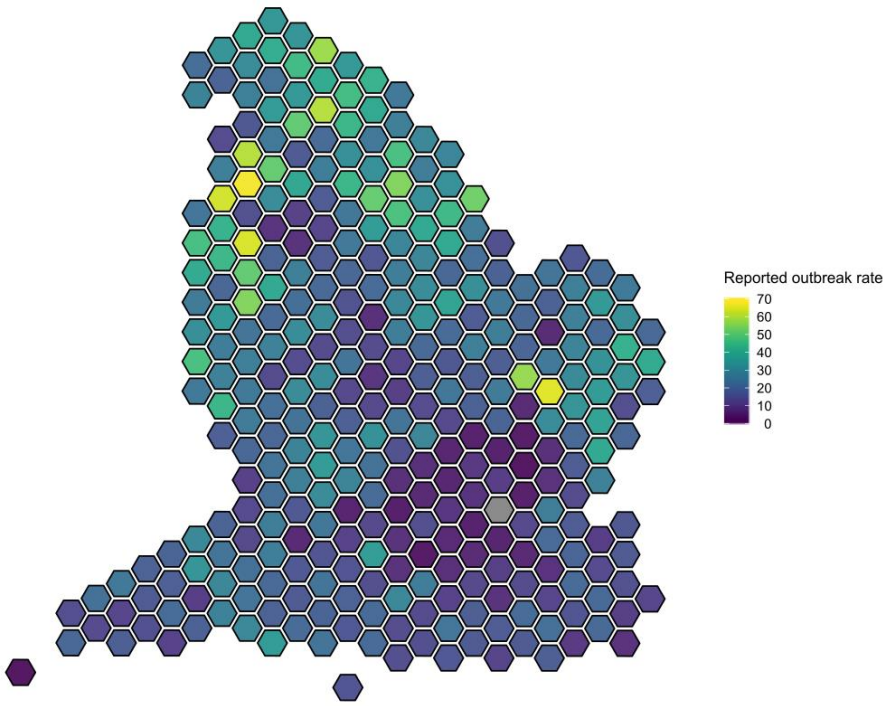
Figure 7.1: Map showing care home gastroenteritis surveillance system and PHE region, for each local authority (n = 326), England, 2014-2016



The number of laboratory confirmed norovirus cases (p = 0.6246), proportion of the population under 5 (p = 0.5390) and proportion of the population over 65 (p = 0.8626) were not significantly different between local authorities with routine and enhanced surveillance. Local authorities with enhanced surveillance had a significantly higher total population (p = 0.0030), greater number of reported outbreaks (p < 0.0001), greater number of care homes (p = 0.0037) and greater number of primary schools (p = 0.0014).

Over the three year study period, 22.48 outbreaks per 100 care homes per year were reported. The median rate was 20.37 outbreaks per 100 care homes per year (Interquartile range (IQR) 12.79 – 29.29 outbreaks per 100 care homes per year). The mean rate in the enhanced area was 39.67 (IQR 33.33-45.83), significantly higher than the mean rate of 21.40 (IQR 12.39-27.53) observed in the local authorities with routine surveillance (p < 0.0001). There is substantial geographical variation in the reported rate of gastroenteritis outbreaks in care homes (Figure 7.2).

Figure 7.2: Hexagonal cartogram showing reported outbreak rate per 100 care homes per year, for each local authority (n = 326), England, 2014-2016



The results of the negative binomial regression model with random effects are shown in Table 12. Simultaneously adjusting for all variables in the model, the variable most strongly

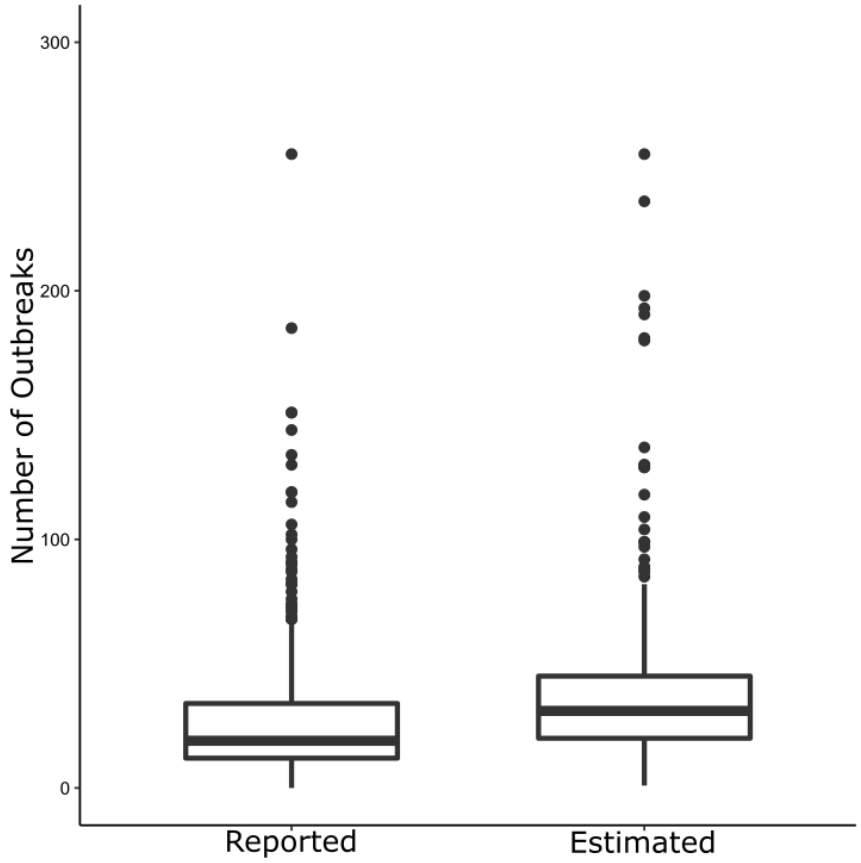
associated with the outcome was the number of care homes (coefficient = 1.96, p = <0.001). The other variables significantly associated with the outcome were the number of laboratory confirmed norovirus cases (coefficient = 1.08, p = 0.012) and the number of primary schools (coefficient = 1.15, p = 0.035). There are nine regions, these were included in the model as a random effect; intercepts varied from the lowest in London (-1.217) to the highest in Yorkshire and Humber (0.578). In the sensitivity analysis without influential observations there were no changes to the direction, magnitude or significance of variable estimates from the negative binomial regression model with random effects.

Table 12: Results of negative binomial regression model with random effects (n=326)

Variable	Coefficient	95% CI	*p*
Fixed effects			
Enhanced surveillance	1.54	1.16-2.03	0.003
Number of care homes	1.96	1.74-2.21	<0.001
Number of laboratory confirmed norovirus cases	1.08	1.02-1.14	0.012
Total population	0.97	0.82-1.14	0.668
Proportion under 5	0.97	0.89-1.06	0.530
Proportion over 65	1.01	0.91-1.11	0.874
Number of primary schools	1.15	1.01-1.31	0.035
Random part (Region)	*Intercept*		
East Midlands	-0.021		
East of England	0.109		
London	-1.217		
North East	0.289		
North West	0.281		
South East	-0.181		
South West	-0.117		
West Midlands	0.285		
Yorkshire and Humber	0.578		

From this model, we estimate that there were a total of 14,146 (95% Confidence Interval 13,372 – 14,975) care home gastroenteritis outbreaks in England from 2014 to 2016. This is 4552 (47%) greater than the reported number and equates to a rate of 32.4 outbreaks per 100 care homes per year. The distribution of reported outbreaks is compared to the estimated numbers in Figure 7.3 below. The median number of reported outbreaks was 19 (IQR 12 – 34), compared to 31 (IQR 20 – 46) from the estimated data.

Figure 7.3: Box plot showing the distribution of care homes outbreaks for local authorities (n = 326), comparing reported count to the estimated count, England, 2014-2016



A recent study [204] reported that; the median number of residents in a care home was 34, the median number of staff was 36; and that the median acute gastroenteritis attack rate was 30% in residents and 6% in staff. Based on these data, we hypothesise that in the region of 174,845 cases (144,289 residents and 30,556 staff) might have been affected in total.

7.5 Discussion

From our analysis, we estimate that there was a total of 14,146 care home gastroenteritis outbreaks in England during this period, a 47% increase on the reported total of 9,594 outbreaks. This is the first estimate of the total care home gastroenteritis burden of infection in England and translates to a rate of 32.4 outbreaks per 100 care homes per year in England. This is important as acute gastroenteritis, particularly norovirus gastroenteritis, is a common cause of morbidity, especially in the elderly.[122] Care home gastroenteritis outbreaks should largely be preventable with good infection prevention and control.[242] This study provides evidence to show that we are currently underestimating this burden

which not only has direct impacts on residents and staff at the facilities, but also wider impacts on hospitals though delayed discharges and importation of cases which can cause outbreaks and subsequent bed closures.[243]

For international comparison, this estimated rate of 32.4 outbreaks per 100 care homes per year in England is higher than the reported rates from Australia (16.8 [95% Confidence Interval, 12.4 – 22.7] outbreaks per 100 care homes per year),[46] and far higher than the reported rate from France (4.6 – 5.5 outbreaks per 100 care homes per year).[45] These comparison data have not been adjusted for under-reporting in the way we have used in this paper; were this to happen, it could be that the estimated rates in these countries would be closer to that estimated from our model for England. Other factors which could have been associated with differences in reported outbreak rates include: different populations at risk, different structural, organisational or infection control arrangements, or different levels or types of circulating pathogens during the study period.

In this study our definition of gastroenteritis was not pathogen-specific. Norovirus is a common cause of acute gastroenteritis in care homes, with numerous introduction routes and risk factors for spread.[103] Norovirus incidence has a bimodal distribution and after children under 5, the elderly are the next most affected group;[208] in this group norovirus has been associated with mortality [122] and between 2014 and 2016 there were between 20 and 31 deaths directly attributed to norovirus infection those aged over 60 years which represents between 86% and 97% of norovirus-attributed deaths annually.[244] Data from the United States reported the number of norovirus outbreaks in care homes,[245] but without robust denominator data on the number of facilities, it is not possible to compare outbreak rates. Norovirus has been estimated to cause between 48%[41] and 73%[45] of care home gastroenteritis outbreaks, but there are no suitable contemporary data from England which could be used to estimate the proportion of this outbreak burden which is caused by norovirus. If this were available, it would be a logical extension of this work to apply that to this estimate, and use this in conjunction with other work,[85] to estimate the burden of norovirus gastroenteritis in the community. Considering the potential of norovirus vaccines currently in development, these data on the burden of norovirus in the community could be combined with estimates of the hospital burden of norovirus disease [87] to provide a baseline to assist vaccine policy-makers.

Gastrointestinal disease data collected in surveillance systems are frequently an underestimation of the underlying burden of illness.[26] The use of multiplication factors to adjust for under-reporting is a common approach, but there is a need for them to be well calibrated to each context.[246] In this analysis, we estimated that the burden was approximately 50% higher than the reported data. This indicates that there is substantial capacity to improve the surveillance configuration in England to effectively capture these outbreaks. It is also likely that even enhanced surveillance systems missed outbreaks because they were not reported by the care homes despite the legislation. A previous study [204] suggested that higher attack rates were associated with late reporting. Given the possibility that even enhanced systems missed some outbreaks, it is likely that our estimate of the outbreak burden is a conservative one.

In our model we observed a significant positive association between the number of primary schools in a local authority and the number of care home outbreaks. This would be expected as rates of norovirus infection are significantly higher in children compared to those in other age groups [208] and schools are commonly affected by norovirus outbreaks.[238] Therefore, an area with care home gastroenteritis outbreaks would also be expected to have school gastroenteritis due to pathogens circulating in the community. There is no comprehensive or reliable dataset of school gastroenteritis outbreaks in England, so the number of primary schools was included as a proxy for this information. This relationship between primary school and care homes, and its relevance to transmission of norovirus, should be considered when formulating potential vaccination strategies as and when a vaccine is available.

In this study we used a binary classification (routine/enhanced) of surveillance system which is likely to have been a crude measure of the effectiveness of these systems. In each area, a number of factors will affect the effectiveness of surveillance; the care home management, the engagement of community infection control staff and practices of local PHE staff amongst many reasons. For example, in the East of England during this period there was a surveillance system in place, but this system did not meet our definition of an enhanced system as this system did not collect additional information. This binary classification is therefore a limitation, but makes the analysis feasible given the available data. Additionally, this analysis was predicated on the assumption that outbreak ascertainment was greater in those areas with enhanced systems. The results of this study

provide evidence to support this assumption, but further work is needed to understand the precise characteristics of enhanced systems that increase outbreak ascertainment, so that these can be adopted more widely.

Ideally we would like to have enhanced surveillance spread more evenly across regions as this represents a potential source of sampling bias. However the nature of surveillance systems means that areas which are and are not enhanced is beyond our control and is predetermined by external factors such as local structures, funding and research interests. Due to the retrospective observational nature of this study randomising the nature of surveillance systems was not possible and we have instead sought to control for biases and confounders using an appropriate generalised linear model-based methodology. We thus interpret estimates provided by our approaches fairly cautiously and acknowledge the inherent uncertainties.

Another potential limitation of the study is the ecological design which means that any inference from this analysis is restricted to the level of the local authority and therefore it is not possible to make any conclusions at the level of the individual care home. In our model we used random effects to provide information on PHE regions. This was intended to account for differential practice between PHE teams; these showed that accounting for other explanatory variables, some areas such as London had lower counts of care home gastroenteritis outbreaks than other regions such as Yorkshire and Humber.

7.6 Conclusions

Our results indicate the current mixed surveillance approach to gastroenteritis outbreak surveillance in care homes in England is considerably underestimating the burden of infection. This translates to a substantial burden of infection on staff and residents on these institutions, along with indirect impacts on the wider healthcare system. To reduce this underestimation, we recommend that Public Health England work towards implementing a surveillance system to standardise the collection of these outbreak data. Linked to this work on the surveillance system, Public Health England should liaise with the CQC, community infection control staff and care home managers to communicate the importance of this form of surveillance. Comprehensive and timely surveillance of care home gastroenteritis outbreaks could improve public health practice by highlighting areas

of effective infection control and providing an early warning of an intensive norovirus season which could inform hospital bed management.

Chapter 8 - Discussion

8.1 Description of chapter contents

In this chapter I summarise my research and discuss the findings from this work. Each results chapter has a discussion section within it, but in this chapter I take themes from each of these chapters and place the findings within the context of other work, both historically and internationally. I follow this by detailing some of the most relevant challenges which arose from this research, so that others can better understand its limitations and approach similar research questions in the light of my experience. Finally, I synthesise the findings from this work together with results from other research and the challenges I faced to inform recommendations on the direction of future research of infectious gastroenteritis in care homes.

8.2 Overview of research results

I conducted a systematic literature review (Chapter 2) which described surveillance for norovirus disease in community settings. This review added to the evidence base by showing that there were few papers describing this type of surveillance and there is scope for robust community surveillance systems to provide estimates of norovirus incidence. I developed and ran such surveillance for infectious gastroenteritis in care homes, a type of community setting. This was the first active surveillance study of infectious gastroenteritis in this setting in the UK. The original protocol for this surveillance study is included in Chapter 3. I presented the results from this research in Chapter 4; these provided evidence for the incidence rate of infectious gastroenteritis in this setting, along with data on the incidence rate of outbreaks and pathogens isolated. In Chapter 5, I moved from individual illness to a study of outbreaks. In this chapter I provided a detailed analysis of the dynamics of gastroenteritis outbreaks in care homes, using data from an enhanced surveillance system in an area of England. I built on this in Chapter 6 by presenting evidence of the relative importance of norovirus in care home gastroenteritis outbreaks, compared to other pathogens, evidence that has not been published in England since 2004. This used existing surveillance data from another area of England. In Chapter 7, I looked at another aspect of gastroenteritis outbreaks in care homes; I used surveillance data for the whole of England to produce a novel estimate the total number of outbreaks, adjusted for under-reporting. This estimated number of outbreaks is an aspect of the burden of disease in this population.

8.3 Themes from this thesis

8.3.1 Surveillance in care homes

In the introduction to this thesis, I highlighted the importance of surveillance for the timely and accurate collection of public health data. The use of such surveillance data to answer the questions posed in my introduction runs though the course of this work: I have reviewed the surveillance of norovirus in the community (Chapter 2), implemented a surveillance study for infectious gastroenteritis in care homes (Chapters 3 and 4) and analysed care home surveillance data from various sources (Chapters 5, 6 and 7).

The aim of my systematic review in Chapter 2 was to determine the nature, scope and scale of community-based surveillance systems for norovirus disease. From this, I found that there were few papers describing such surveillance. The papers which had been published on such surveillance were predominantly from Western Europe, USA and Australia. However, the focus solely on norovirus in this chapter is slightly divergent to the content of the other chapters, which have a wider emphasis on all infectious gastroenteritis. This arises from the complex relationship between infectious gastroenteritis surveillance and norovirus disease. Most infectious gastroenteritis reported in care home settings are perceived as being caused by norovirus, often without epidemiological or microbiological evidence. Through the research presented in Chapter 6, I showed that this perception is justified, hence the relevance of focussing the systematic review on norovirus in community settings.

When contextualising the results from the research I present in this thesis, how do these fit with what is known about surveillance for infectious gastroenteritis in care homes? As I noted in Chapter 7, there is no co-ordinated national surveillance system for infectious gastroenteritis in care homes in England, either for individual cases or for outbreaks. From the systematic review in Chapter 2 and other literature searches I have not found any evidence of routine surveillance for individual cases in care homes in England or from other countries. Therefore, the results of the prospective active surveillance study presented in Chapter 4, the first such study to be conducted in England, are valuable in providing estimates of the incidence of non-outbreak illness that have not previously been available.

Regarding surveillance of infectious gastroenteritis outbreaks in care homes, there are examples of routine surveillance systems which collect this information from countries such as France, Australia, Norway and parts of the USA.[45–47, 247] The results I present in Chapters 4, 5 and 6 provide comparable data from different areas of England which can be contrasted with data from other countries. In each of these chapters I have compared the results from this care home surveillance within the context of these international comparisons and previous historical data from England [22, 129] to answer the study questions listed in Chapter 1.

When interpreting my findings from surveillance data, it is useful to contextualise these by reflecting on the effectiveness of the surveillance systems underlying these data. In Chapter 5 I studied the Cheshire and Merseyside system, the North East system was my focus in Chapter 6 and in Chapter 7 I used data from the rest of England which does not have a dedicated surveillance system for outbreaks in care homes. Guidelines exist for formally evaluating surveillance systems,[105] however such evaluation is a substantial undertaking, outside the scope of this thesis. My experience was that the systems in chapters 5 and 6 were generally effective, being simple, sensitive, representative and timely, all characteristics of an effective surveillance system.[105] However, I did feel that the data quality of both systems could be improved; in Chapter 5 I noted the low proportion of outbreaks with positive pathogen results, and in Chapter 6 my data collection required extensive cross-checking between electronic and paper records. In contrast, I would not characterise the system in the rest of England as an effective surveillance system for care home outbreaks. I showed in Chapter 7 that there is poor sensitivity, with an estimated 47% under-reporting. I also found the quality of data that can be systematically collected in the case management tool used by PHE (HPZone) to be insufficient for surveillance purposes. This experience of the challenges of using HPZone data for the surveillance of care home outbreaks leads to one of my recommendations in Section 8.5.

8.3.2 Incidence of disease

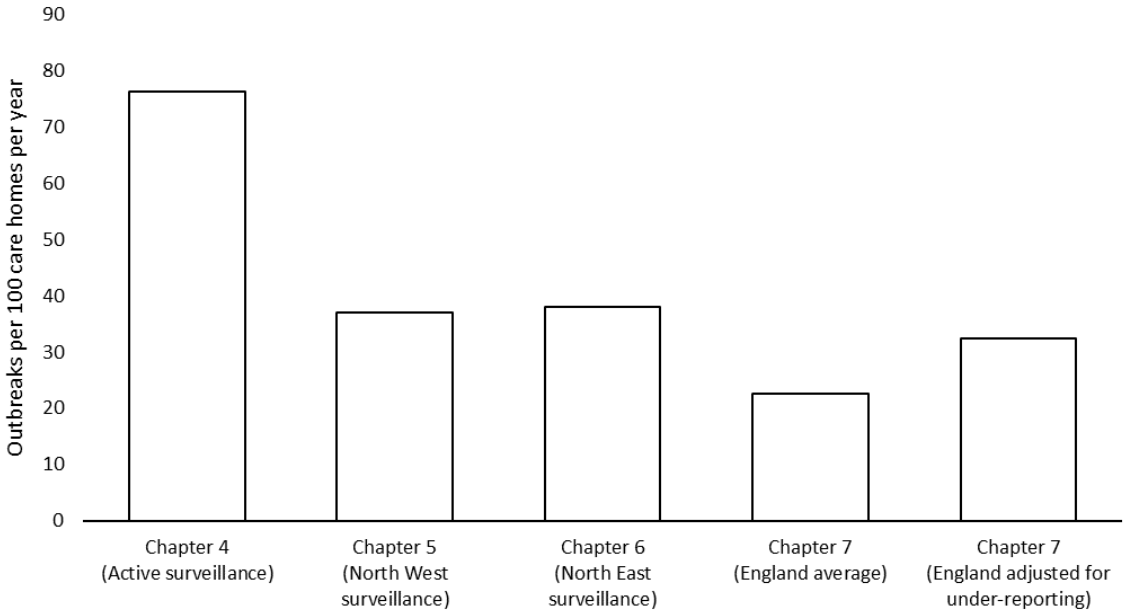
Providing information on the incidence of infectious gastroenteritis in care homes was part of the main aim of my research. During the course of this research I did this in three ways: firstly, by providing an estimate of the incidence of individual cases in care homes (Chapter 4), secondly, by producing estimates of the incidence of outbreaks in care homes from

different geographical areas (Chapters 4, 5, 6 and 7) and thirdly, by producing an estimate of the total annual number of outbreaks in England, adjusted for under-reporting (Chapter 7).

In Chapter 4, I presented estimates of incidence for cases of infectious gastroenteritis for all persons in care homes (133.7 cases per 1000 person-years at risk), residents only (252.5 cases per 1000 person-years at risk) and as a bed-day comparison (0.62 cases per 1000 bed-days). As mentioned in the previous section, because there are no routine surveillance systems which capture these data in England, this is novel information. This is higher than a pooled estimate of incidence from a systematic review of published studies (0.40 episodes per 1000 bed-days, 95% Confidence Interval 0.27 – 0.56), however there was considerable heterogeneity between studies in this meta-analysis.[139] One of the other important findings from this Chapter was that 89% of cases in this setting were defined as being part of an outbreak. This observation can be used when interpreting the data on the incidence of outbreaks to infer the total burden of infectious gastroenteritis illness in care homes in any future modelling study.

In the course of this research I calculated the incidence rate of infectious gastroenteritis outbreaks in four settings. In Chapter 4, from an active surveillance study between 2017 and 2019 it was 76.4 outbreaks per 100 care homes per year. In Chapter 5, from a routine surveillance system in approximately the same geographical area between 2012 and 2016 it was 37.1 outbreaks per 100 care homes per year. In Chapter 6, from a routine surveillance system in North East England between 2016 and 2018 it was 38.1 outbreaks per 100 care homes per year. In Chapter 7, from various routine surveillance systems in England between 2014 and 2016 it was 22.5 outbreaks per 100 care homes per year. The incidence rates of outbreaks presented here thus vary from 22.5 per 100 care homes per year across the whole of England, to 76.4 outbreaks per 100 care homes per year from a small active surveillance study in one area of England. The incidence rate I report for England is consistent with that reported from national surveillance in Australia (16.8 per 100 care homes per year)[46] and higher than that reported from France (4.6 to 5.5 outbreaks per 100 care homes per year).[45] In the discussion section of Chapter 5, I provide potential explanations for these observed differences in this measure of the burden of disease.

Figure 8.1: Bar chart showing the distribution of incidence rates for care home infectious gastroenteritis outbreaks presented in each chapter



One explanation for differences in reported incidence rates of outbreaks of infectious gastroenteritis in care homes is the possibility of differential ascertainment in different areas. In particular, the issue of under-reporting leading to lower outbreak incidence rates and therefore lower estimates of disease burden. In Chapter 7, I used a modelling approach to estimate that, once adjusted for potential under-reporting, the number of outbreaks was 47% higher than reported. I estimated that in this three year period there were 14,146 outbreaks (95% Confidence Interval 13,372 – 14,975), a direct quantification of the burden of disease.

One aspect which was more challenging to capture was severe disease such as hospitalisation and death. It was possible to extract these data from the surveillance system I analysed in Chapter 5 and I found that from the reported outbreaks, for cases in care home residents, 0.81% were hospitalised and 0.34% were reported to have died. These findings are consistent with results from a recent Norwegian study which estimated that for infectious gastroenteritis outbreaks in care homes, 0.91% of cases were admitted to hospital and 0.67% were reported to have died due to norovirus infection.[247]

8.3.3 Dynamics of outbreaks

As I noted in Chapter 1, I intended to address the broad issue of transmission of infectious gastroenteritis in care homes by understanding the spatio-temporal dynamics of

interactions between residents, providing data on the natural history of outbreaks and by providing evidence on the pathogens responsible for illness. Unfortunately it was not possible to conduct the spatio-temporal dynamics work. A fuller explanation of the challenges I encountered in this is given in section 8.4.2. The findings related to the dynamics of outbreaks are discussed here, with the discussion regarding the pathogens responsible in the following section.

Chapter 5 contains the most detailed information on the dynamics of outbreaks, although Chapter 4 does contain some of this information in a more limited form. Regarding the temporality of outbreaks, one of the key observations from both chapters is that although there is temporal variation in the incidence of these outbreaks, and the incidence is highest in the winter months, infectious gastroenteritis outbreaks do occur throughout the year. This persistent risk justifies the tireless use of proper infection control processes to prevent such outbreaks. Looking at the duration of care home closure, I found that the median duration of closure was six days (range 1 – 29 days), and that closing the home within three days of the first case was significantly associated with shorter outbreak duration. This supports similar findings in care homes in other countries,[45, 215] and is consistent with similar work focussed on norovirus outbreaks in hospital settings.[44, 216] In Chapters 5 and 6, I presented the attack rates in residents for these outbreaks. From the study in Cheshire and Merseyside I estimated that the median attack rate in residents was 30%, which was similar to the median attack rate from the North East data (27.3%) in Chapter 6. Regarding the spatial distribution of outbreaks, it was not possible within the scope of this research to look formally at differences between geographical areas in England. In contrast, one of the assumptions of my work in Chapter 7 to assess under-reporting was that the number of outbreaks in each English local authority are drawn from the same population.

8.3.4 Pathogens

One of the main questions when considering and interpreting the data on the burden and transmission of infectious gastroenteritis in care homes presented here is the question of which pathogens are responsible, and to what degree? As I noted in Chapter 1, answering this question, particularly regarding the contribution of norovirus in comparison with other pathogens, was one of the main aims of this thesis. In Chapter 4, I found that norovirus was the only pathogen identified (in 3 of 15 samples). Although the samples were tested for a range of pathogens, due to the small number of samples it was not possible to infer the

proportion of gastroenteritis in care homes caused by norovirus from these results. This was the only part of the thesis in which I obtained data on pathogens causing individual cases of illness rather than outbreaks and so it is unfortunate that there were so few samples submitted despite the repeated reminders and attempts to incentivise sample collection. I discuss this further in section 8.4.2.

Data regarding the proportion of outbreaks caused by norovirus are more widely available than for individual cases. In Chapter 5, I found that from a surveillance system in the North West of England, norovirus was the most frequently detected organism. However, stool samples were received from only 45% of outbreaks and no pathogen was recorded from 85% of outbreaks. In Chapter 6, I used surveillance data from an area of North East England that had more comprehensive testing of outbreaks, with 60% of outbreaks being sampled and all samples being tested for a wide range of pathogens. In this system a pathogen was detected in 78.5% of outbreaks and the most frequently detected pathogens were: norovirus (64%), sapovirus (13%), rotavirus (11%) and astrovirus (2%). This percentage of care home outbreaks being caused by norovirus is consistent with previous findings from England and Wales (57%) published in 1997 [41] and South West England (74%) published in 2004.[129] As noted in the discussion section in Chapter 6, the surveillance data from Australia [46] and France [45] found a lower percentage of norovirus, which may reflect differences in the criteria (such as number of positive specimens) used to assign norovirus as the causative agent.

In addition to norovirus, the finding that 92.6% of outbreaks with a pathogen detected were due to viruses is important for the understanding of the transmission of infectious gastroenteritis in care homes. From this, we can infer that the majority of transmission in this setting is through typical viral gastroenteritis mechanisms, rather than food-borne mechanisms more commonly associated with bacterial pathogens. Given this evidence, with the variety of viral pathogens, this highlights the importance of prompt intervention and non-pathogen-specific hygiene and infection control measures to minimise the attack rate.

8.4 Key challenges

8.4.1 Observational epidemiological studies in care homes

During the initiation and operation of the observational epidemiological studies presented in this thesis, I found that there were several complex issues which affected the feasibility of research in care home settings. These particularly impacted the active surveillance study which is presented in Chapters 3 and 4. In chronological order, the first challenge was in finding care homes that were willing to participate. In this study I found that although the direct resource implications for care home participation were minimal, there was a general reluctance to participate from care home registered managers. Their concerns were primarily that they could not spare the comparatively small amount of staff time needed to understand and engage with the study process. As noted in the discussion in Chapter 4, this reluctance to participate may have led to the care homes taking part being unrepresentative of other care homes in the area. However it was not possible to quantify this potential bias.

Secondly, the consenting process for the recruitment of participants in study care homes was resource-intensive for the study team and it took a substantial amount of time to recruit individuals into the study. As noted in the discussion of Chapter 4, this led to fewer of the most vulnerable residents being included in the study and made it impossible for the percentage participation to be calculated. It is extremely important for research to be proportionate and safeguard the rights of those individuals without capacity to consent; to this end I worked with the Research Ethics Committee to ensure that our study complied with Section 32 of the Mental Capacity Act 2005. However, the agreed process for those without capacity to consent made it very difficult to identify and contact the correct person representing the interests of the potential participant. This had to be done by the care homes themselves and due to the low frequency of visitors to residents in homes, most of these were posted out to relatives; of these, few were returned. This led to a lower number of residents without capacity being enrolled in the study than would have otherwise been the case. Using an opt-out rather than an opt-in recruitment approach may improve participation and reduce the resource burden required of the care home staff. However this would be challenging to reconcile with the stipulations of the Mental Capacity Act 2005.

Thirdly, the operation of a prospective cohort study in a care home setting was highly resource-intensive for the study team, relative to other possible approaches to obtain similar data. It was a stipulation of the Research Ethics Committee that study staff recruiting participants should be clinically trained and in this study I was fortunate to have the resources available to use research nurse time. The study ran for 22 months and each of the five homes should have been visited each week, approximating 440 research nurse visits. This required a substantial resource commitment that could not easily be scaled up for larger studies or may not be available to other researchers. Furthermore, working in the social care sector rather than a clinical setting required a change of approach and emphasis that some research nurses struggled with. This meant that some research nurses required additional training and support, leading to further resources being needed.

8.4.2 Stool sample collection in care homes

When examining the burden and transmission of infectious gastroenteritis in care homes, one of the key issues is to determine which pathogens are responsible for disease. Differences in symptoms displayed by cases are insufficient to determine the responsible pathogen; this necessitates using a microbiological test of a stool sample from one of the residents of the care home. In the research I undertook for this thesis, two of the biggest challenges were the low proportion of cases with a stool sample tested, and the low proportion of stool samples where a pathogen was detected. This first challenge was highlighted by my findings in both Chapters 4 and 5. In Chapter 4, the study protocol required a stool sample to be submitted for all cases, however this only happened for 33% of cases despite reminders from research nurses during weekly visits. I believe that one of the issues behind this difficulty in obtaining samples was care home staff reluctance to do additional work outside of their normal duties; although in addition to cleaning and changing a resident with a soiled pad, picking a sample and putting it in the packaging provided would only take an additional two minutes. To try to provide an extra incentive to staff, on 28 June 2018 I implemented a £5 gift voucher for taking stool samples from cases. However as described in Chapter 4 this only increased sample rates from 30% to 36%.

These results showed the difficulties of obtaining stool samples for individual cases from care homes; in Chapter 5, I observed a similar challenge for outbreaks. I found that from the surveillance system in Cheshire and Merseyside, at least one stool sample was submitted for only 45% of outbreaks, although it was not possible to calculate the

percentage of individual cases for which a sample was submitted. In comparison, I analysed data from North East England in Chapter 6, where the sampling of care home gastroenteritis outbreaks was more complete. Even in this setting, stool samples were submitted for only 64% of outbreaks. The situation for outbreaks is slightly different from individual cases, as stool samples may not be required (or requested) for all cases, but it remains important to identify a causative pathogen if this affects the implementation of infection control measures. The difficulties in obtaining stool samples that I encountered during this research, even from active and enhanced surveillance, appears to be a structural issue related to care homes and implies that another approach may be required for future work to gain a more complete insight into the pathogens causing infectious gastroenteritis in care homes. Alternatives approaches such as faecal or rectal swabs may be more acceptable to care home staff and could be trialled for future studies in this setting.

Turning to the challenge of identifying pathogens in stool samples for cases of infectious gastroenteritis in care homes, the results of Chapters 4, 5 and 6 are pertinent for this point. In the, admittedly limited, number of samples submitted in the study I presented in Chapter 4, no pathogen was detected in 80% of them. In Chapters 5 and 6, I presented the results from outbreak surveillance studies; in Chapter 5 there was no positive pathogen result recorded for 85% of outbreaks for which a sample was submitted, whereas in Chapter 6 this was the case for only 21.5% of outbreaks. This may have been due to differences between the two studies in the time elapsing between symptom onset, sample collection and testing. Alternatively, it could have been an artefact of the difficulties linking outbreak surveillance data to laboratory surveillance system (e.g. SGSS) data used in Chapter 5.

8.4.3 Issues with the transmission dynamics study

One of the objectives of the active surveillance study detailed in Chapters 3 and 4 was to obtain data to better understand the spatio-temporal dynamics of the movement of persons within care homes. I then intended to combine this with other data relating to the transmissibility of norovirus and other viral pathogens to create an accurate model of infectious gastroenteritis transmission in care homes. Unfortunately, as shown by the results presented in the second section of Chapter 4, the equipment available to record this data (the “motes”) did not function as intended and it was not possible to complete this

component of the study. Wearable equipment which can record spatial position and interactions with similar devices is available, and more modern devices are potentially less intrusive to wear, but would require a substantial resource investment to acquire the volume of devices needed to cover all individuals in a care home setting. Unfortunately I did not have the resources available to obtain this alternative technology, however this approach may be suitable for other researchers with appropriate funding. Even with modern wearable devices, researchers would still have to consider the issue of consent in vulnerable residents.

Another possibility would be to eschew wearable devices and instead use video recording in each room to classify inter-personal interactions which may constitute potential transmission events. This method has the advantage of potentially being more specific in identifying interactions which could be potential transmission routes (e.g. hand-to-hand contact) and excluding those which most probably would not be (e.g. walking past each other in a corridor). However, if this method were to be used, this would create a substantial infringement of each participant's privacy and this would need to be balanced against the scientific benefit of such research. It would also be challenging to deal with persons in the care home who did not consent, but may be included in any footage taken at the home. Given the difficulties previously described in obtaining informed consent in this study population, the feasibility of using video recording to answer this question is doubtful.

8.4.4 Limitations of current surveillance

As aforementioned in section 8.3.1, there is no dedicated surveillance system for infectious gastroenteritis in care homes in England, either for individual cases or for outbreaks. In most parts of England, some information is collected in Public Health England's case management system (HPZone) when care home managers or community infection control nurses report. The CQC recommends that care home registered managers report outbreaks of infectious disease to Public Health England, although this is not legally mandated and adherence to this recommendation is not examined as one of the criteria against which care homes are formally assessed. It is likely that because this reporting is voluntary, there is substantial under-reporting. I attempted to quantify this under-reporting through my work in Chapter 7; I estimated that the number of outbreaks is 47% higher than the number reported to PHE and recorded in HPZone. However, this modelling approach may

not have accounted for care homes which did not inform Public Health England at all. One option would be for researchers to audit care homes to quantify directly the completeness of reporting and conduct qualitative work to identify any barriers to reporting. However, additional work regarding the adherence of care homes to CQC guidance was outside the scope of the work I undertook for this PhD.

The case management system currently used by PHE (HPZone) records information on outbreaks such as the date, initial number of cases and suspected pathogen. During, and at the end of an outbreak, this may be updated with total case numbers, duration of illness and laboratory confirmation of a pathogen result. However, because this is a case management system rather than a surveillance system, updating the record with this information is not required, and there are no dedicated fields with which to do so. This meant that many records on HPZone contained incomplete data, and a substantial proportion of data was entered as free text, making it very challenging to extract. I was therefore only able to research the dynamics of outbreaks in care homes for areas of the country such as Cheshire and Merseyside and the North East, which have enhanced measures for the collection of these data.

8.4.5 Generalisability of this work

Because of this aforementioned absence of a dedicated surveillance system for care home gastroenteritis outbreaks in England, I decided to focus my research in this thesis on these geographical areas with enhanced surveillance (north east England and Cheshire and Merseyside) and the area where I conducted my prospective cohort study (Merseyside). One potential challenge from this is that these areas have comparatively small populations; 2.65 million, 2.47 million and 1.42 million, respectively. Due to their population sizes, location in the north of England and possibly more socio-economically deprived populations, it is possible that the findings from these chapters have limited generalisability to other parts of the United Kingdom and countries with similar social care arrangements. One of the main challenges during research for this thesis was balancing the desirability of having results from large generalizable populations with the practicalities of having limited resources and few areas which routinely captured appropriate information. I have tried to expand beyond the localised scope of work by estimating the burden of disease in the England (Chapter 7) and conducting the systematic review covering surveillance systems for norovirus in the community across the world. Thus, although ensuring the

generalisability of this research is a challenge, I believe that the scope of my work, from local to national and international, has generated knowledge which can be used in other settings.

8.4.6 Personal reflection on the challenges in this research

The challenges I discuss in this chapter can be classified into two broad categories: structural and local. Structural challenges include issues such as surveillance systems, requirements from ethical committees and demands on staff working in care homes. These issues did impact significantly on my work, but there is little I could do to influence them if I were to do a similar study in future.

One of the key local issues which impacted on my research was the difficulties some of the research nurses had with working in a care home setting (Section 8.4.1). Managing research nurse performance took up a greater proportion of my time than I was expecting and did make it more difficult to recruit participants and obtain stool samples than it otherwise might have been. Reflecting on this, I think that in future for similar research I would make it a priority to have oversight of research nurse recruitment, and invest time in appointing suitable candidates. Another of the local issues which affected my work was the failure of the instruments for the transmission dynamics study (Section 8.4.3). This equipment was available to me at the start of my study, but the person with expertise at using them had recently left the university. Because my primary objective was to obtain ethical approval to start data collection, I included this component of the study without testing the equipment. In retrospect, I probably should have tested the motes to ensure they functioned properly before including them in the protocol, rather than assuming that they worked. However, I am realistic that due to time pressure it's not always possible to have all equipment standardised prior to the start of a study.

8.5 Recommendations for further work

In this chapter I have drawn out the main results from the research presented in this thesis and described the key challenges that I faced in the course of this work. Based on this knowledge, I make the following recommendations for action by public bodies and further research to build on my findings.

1. Reporting of infectious gastroenteritis outbreaks in care homes

Throughout this chapter I have noted that quantifying the number of outbreaks is an important component of understanding the burden of infectious gastroenteritis in care homes. In section 8.4.4, I stated that although reporting outbreaks to Public Health England is recommended by the CQC, there is no legislation to enforce this, nor is adherence to this recommendation formally assessed by the CQC during regular inspections of care homes. Legislating to make reporting mandatory by care homes is likely to be unnecessary as the same effect, of increasing the completeness of report, could be achieved by the CQC making it part of their ratings. In order to rate care homes, CQC monitor metrics under five headings: Are they safe? Are they effective? Are they caring? Are they responsive to people's needs? Are they well-led? These are further broken down into a number of questions called "key lines of enquiry". I suggest that evidence of adhering to the recommendation to report outbreaks to PHE should be included in the key lines of enquiry used to rate whether care homes are well-led. I believe this would have the effect of improving the completeness of gastroenteritis outbreak reporting by care homes as failure to do this would materially affect their rating.

Recommendation: For the CQC to include outbreak reporting to PHE in their criteria used to rate care homes.

2. Appropriate surveillance system to capture infectious gastroenteritis outbreaks in care homes

In Chapter 4, I found that outbreak surveillance captured 89% of infectious gastroenteritis cases in care homes. Given this and the resource intensive nature of individual level surveillance, I would recommend outbreak-level surveillance as the most appropriate for this setting. One of the key challenges I identified in this thesis is that when outbreaks of infectious gastroenteritis in care homes are reported to Public Health England, this information is not consistently captured. The case management system currently used by PHE (HPZone) was not designed as a surveillance system and is an inadequate tool for capturing relevant data and updating it during the course of an outbreak. PHE is in the process of designing and implementing a system to replace HPZone and this presents an opportunity to influence the design of the successor system. PHE should ensure that the

new system has specific fields which capture key outbreak metrics in the correct format, prompts to ensure all information is entered by the close of the outbreak and is easy to query using well-recognised languages such as SQL. These changes would ensure that the new case management system could also function as an effective surveillance system for care home gastroenteritis outbreaks.

Recommendation: For PHE to ensure that the successor system to HPZone is designed appropriately for the surveillance of care home gastroenteritis outbreaks.

3. Estimate the economic burden of norovirus disease in care home settings

The research I present here has provided detailed and timely epidemiological knowledge of the burden of norovirus morbidity in care home settings. This could be used to inform public health policy, particularly decisions regarding the introduction of a norovirus vaccine, should one become available. However, as highlighted earlier in the chapter, it was not within the scope of this thesis to provide evidence on the economic burden caused by norovirus disease in care homes. Such further work could build on the data I present in these chapters by combining these with cost estimates to individuals, the care homes themselves and tertiary care. In Chapter 7, I estimated the number of care home gastroenteritis outbreaks in England; this could be combined in a future study with data from Chapter 6 to estimate the total number of care home outbreaks caused by norovirus in England. This could then be combined along with data such the incidence rate of gastroenteritis per bed-day, the number of Quality-Adjusted Life-Years (QALYs) lost by cases of norovirus in care homes, the extra staffing and cleaning costs to homes from outbreaks, and the cost to hospitals from delayed discharges to homes closed to admissions during an outbreak. Together, these data could be used to produce a comprehensive model of the economic burden of norovirus disease in care homes. This could then be used by policy-makers as part of their decision making process when producing a policy to implement a norovirus vaccine in the future.

Recommendation: For further research to estimate the number of care home outbreaks caused by norovirus, and to include this in a model of the total economic burden of norovirus disease in care homes.

4. Use electronic health records to study the individual burden of gastroenteritis morbidity in care homes

In this chapter, three of the key challenges that I described related to: the difficulties in conducting observational epidemiological studies in care homes, difficulties in collecting stool specimens for pathogen testing, and limitations with the current surveillance. In each of these passages, I have described my experiences and detailed the aspects in which future researchers working in this area might experience issues. However, there are two possible approaches using electronic health records to answer similar research questions which it may be fruitful for future researchers to explore. Firstly, there are several systems which capture general practice consultation data and can be queried in a pseudo-anonymous way. These systems capture data such as patient demographics, the diagnosis, microbiological testing result and some have an indicator that the patient was resident in a care home. Any future researcher could, with the appropriate ethical approval, use such a system to estimate the burden of gastroenteritis in individuals in care homes. This would have the advantage of estimating from a much larger population than would be possible with a direct observational approach. Secondly, many of the large care home chains in England collect their own data on illness in residents of their care homes, including syndromic presentation, treatment and presence of outbreaks. Researchers have previously worked with these care home chains to answer questions regarding antibiotic usage. It may be possible for future researchers to collaborate in a similar way. This may be a method to address the question of care home outbreak reporting completeness to PHE, as such a record could be cross-referenced against any surveillance system.

Recommendation: for future research aiming to estimate the burden of infectious gastroenteritis in care homes to explore the possibility of using electronic health records.

8.6 Conclusion

In the course of this thesis I have aimed to investigate the burden and transmission of infectious gastroenteritis in care homes. The four questions that I endeavoured to answer in the course of this research were: 1) What is the incidence in care home residents? 2) What is the incidence of outbreaks in care homes? 3) What are the characteristics of care home outbreaks? 4) Which pathogens are responsible, and to what degree?

In this chapter I have outlined the ways in which I have added to the evidence base in the course of answering these questions. I have produced data to estimate the incidence rate of infectious gastroenteritis in Chapter 4, calculated multiple incidence rates for outbreaks in Chapters 5, 6 and 7, analysed the characteristics of care home outbreaks in Chapters 4 and 5, and provided a detailed analysis of pathogens responsible for care home outbreaks in Chapter 6. Based on the research in these chapters, I identified the key challenges which I encountered; issues such as working in a care home environment, collecting stool samples, using “motes”, limitations of current surveillance and the generalisability of this work. Finally, I combined the evidence I created during this work and in consideration of the challenges I faced, I recommend changes in the way that public bodies operate and avenues for future research. Suggested changes for CQC to improve the reporting of care home outbreaks and for PHE to ensure that they have a system capable of collecting this information flow directly from my experiences and should be proportionate and feasible actions. My recommendation for future research in this area to explore using electronic health records stems directly from the challenges I faced in obtaining data. Finally, my hope is that these results can be built upon further in future research to estimate the number of care home outbreaks caused by norovirus, and to then use this to model the total economic burden of norovirus disease in care homes. This will be important baseline data against which to assess the likely impact of a norovirus vaccine in the future.

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Appendix A: Research Ethics Committee Approval for CHANGe study

Revised 17 October 2016

NHS
Health Research Authority

North West - Greater Manchester South Research Ethics Committee
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8002

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

10 October 2016

Professor Sarah O'Brien
The Farr Institute@HeRC
Waterhouse Building (2nd Floor, Block F)
1-5 Brownlow Street
L69 3GL

Dear Professor O'Brien

Study title:	**Study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside**
REC reference:	**16/NW/0541**
Protocol number:	**UoL001224**
IRAS project ID:	**208468**

Thank you for your letter of 26 September 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Mrs Lesley Thornton.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Kieran Hall, nrescommittee.northwest-gmsouth@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the

Appendix B: CHANGe study materials

This section includes a sample of the key CHANGE study materials. This appendix includes:

- Participant demographic information questionnaire
- Individual case report
- Stool sample collection guidance
- Study consent form
- Study letter of invitation
- Study participant information sheet

Participant demographic information questionnaire

1) Care home ID: | | | |

2) Name of person completing the report:…….

3) Date of report: ……../……../……. (dd/mm/yyyy)

Details of the participant:

4) Participant ID: | | | | | | | | (Assigned by study team)

5) Surname:……. 6) Forename (s):……

7) Date of birth: ……../……../……. (dd/mm/yyyy) 8) Gender: ……..

9) Name and address of registered GP practice:……..

……

……

……

10) Name of participant's GP: ……

If the participant is a resident:

11) Date of arrival at the home: ……../……../……. (dd/mm/yyyy)

12) Room number:……. 13) Which floor is the room on? …….

Questionnaire continues on the next page

If the participant is a member of staff:

14) Date which you started working at the home: ……../……/……. (dd/mm/yyyy)

15) Hours worked per week (average):…….

16) Job title:……

Individual case report

1) Care home ID: | | | |

2) Name of person completing the report:…….

3) Date of report: ……../……../……. (dd/mm/yyyy)

Details of the person who is ill:

4) Participant ID: | | | | | | | |

5) Date of first symptom: ……../……../……. (dd/mm/yyyy)

6) Does the person have the following symptoms?

Diarrhoea	Y	/	N
Vomiting	Y	/	N
Nausea	Y	/	N
Blood in stools	Y	/	N
Abdominal pain	Y	/	N
Fever	Y	/	N
Headache	Y	/	N

7) Has a stool specimen been taken? Y / N

8) Has the person been admitted to hospital? Y / N

9) Is the person taking any antibiotic medication? Y / N

If yes, please list……..

10) Is the person taking any statins? Y / N

(e.g. Lipitor, Lescol, Lipostat, Crestor, Zocor)

How to collect a stool sample for laboratory tests

In your envelope you will find:

- The sample pot (blue top), this has a small plastic spoon fitted to the underside of the lid
- A plastic bag
- Plastic gloves
- A stool sample collection device (Fe-Col®)
- A sample form

Information to be provided with the sample:

Label on sample pot:

Fill in details on the label on the sample pot (blue top), to include: participant's full name and date of birth.

Laboratory Request Form

Fill in the details on the Laboratory Request Form

Instructions about how to collect a mobile adult's stool sample

- Use a clean toilet which has been well flushed
- Wash your hands thoroughly, using soap and running water, then dry well**.**
- If you want to use the gloves provided, put them on.

Open the stool sample collection device and place the biodegradable paper loop over the toilet seat. Sit over the loop to pass stool, and when you have finished, collect a sample with the spoon provided in the blue screw cap tube.

Try to scoop enough of the stool from a soiled pad to fill the sample pot to the 5 ml marker. However, if this is not possible, obtain as much of the stool as you can.

Place blue top with spoon over the collection tube and screw it tightly.

Tear the paper loop and drop it into the toilet bowl. Flush the toilet normally.

Instructions about how to collect an immobile adult's stool sample.

Use the plastic spoon fitted to the sample pot lid to scoop enough of the stool from a soiled pad to fill the sample pot to the 5 ml marker. However, if this is not possible, obtain as much of the stool as you can.

Please note:

Try not to spill the stool on the outside of the sample pot. If this happens please clean the outside of the sample pot with soap and warm water, wash your hands thoroughly, then dry the sample pot and your hands well.

When you have finished collecting the sample

Put anything you have used to collect the sample, eg, plastic gloves, soiled pad, in a plastic bag, tie up the bag and put it in the bin.

Wash your hands thoroughly, using soap and running water, then dry well**.**

Place the sample pot in the plastic bag.

Keep the package in a cool place (but not your fridge)

It is important that stool samples reach the laboratory as "fresh" as possible (within 12 hr of collection) as longer storage time can affect the test results.

In order to arrange collection please call the following number: XXXXXXXXXXX

Thank you for your co-operation

Appendix 3.1 - Study Consent Form

Study name: Study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

Name of researcher: Mr Thomas Inns / Prof Sarah O'Brien

	Please **place your initials next to the statements below that you agree with**:	Initial
1	I have read/been read the information sheet for the study. I have had the chance to ask questions and am happy with the answers.	
2	I agree to be asked about my health for this study.	
3	I agree that stool samples can be taken from me and stored for the purpose of this study.	
4	I agree that saliva samples can be taken from me and stored for the purpose of this study.	
5	I agree that my samples can be stored and used for future ethically approved research studies.	
6	I agree that my proximity to other people may be recorded using a low-power radio-frequency device for the purpose of this study	
7	I agree that approved study staff will have access to my medical records	
8	I understand that only approved study staff will have access to information that could identify me.	
9	I understand that information collected in this study that cannot be used to identify me may be shared with other researchers conducting studies to benefit others.	
10	I understand that taking part in this study is voluntary and that I can withdraw at any time, without giving a reason and without this affecting my medical care.	
11	I understand that if I lose the capacity to consent during the study, I will be withdrawn and any identifiable data or samples will be retained and used in the study	

Print Name of participant: _____

Signature of participant: _____Date_____

Name of person obtaining consent:_____

Signature of study staff _____Date_____

Consent form version 1.1 30/08/2016

Local Principal Investigator: Thomas Inns

Chief Investigator: Prof. Sarah O'Brien

Study name: CHANGe – a study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

Dear Sir/Madam,

We would like to invite you to take part in this research study. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what will happen if you agree to take part.

We are trying to reduce the number of people that fall ill with diarrhoea and vomiting. In the UK, the most common cause of diarrhoea and vomiting in adults is an infection called norovirus.

The purpose of this research is to understand how many people in care homes get diarrhoea and vomiting, find out what causes it and how it is spread.

Please take time to read this information sheet carefully and to ask any questions you might have. It is important to understand that you do not have to accept this invitation and should only agree to take part if you want to.

Yours sincerely,

SARAH O'BRIEN SIGNATURE

Prof Sarah O'Brien MB BS, FRCP, FFPHM, DTM&H
Professor of Infection Epidemiology and Zoonoses
Epidemiology and Population Health
University of Liverpool

What happens if I decide to take part in the study?
All you have to do is complete the consent form, which tells us that you are happy to take part in the study. We will inform your GP that you are taking part in the study.

What happens if I leave the study?
You can stop taking part in the study at any time. You do not need to explain why. We will ask your permission to use any information or results we have obtained up until the point you stop taking part. If you do not give us permission to do this, we will remove all files and data relating to you.

Who has checked the study?
This study has been checked by the North West - Greater Manchester South Research Ethics Committee of the National Health Service.

Will my information be secure?
Yes. We will adhere to the Data Protection Act (1998), which tells us how to keep your data secure.
The information that we collect will be stored on a secure network, and will only be accessed by authorised members of the study team using special passwords. We will not give your details to anyone else. Your name or any information that might be used to identify you will be kept anonymous.

What will happen at the end of the study?
The results of the study will be published in scientific journals with open access and presented at various scientific conferences. We will not use your name or any information that might be used to identify you.

Who is organising and paying for this study?
The University of Liverpool is organising this study. This study is funded by the National Institute for Health Research: Health Protection Research Unit in Gastrointestinal Infections.

Where can I get further information?
If you have any questions about taking part in the study, please contact: Thomas Inns by email at thomas.inns@liverpool.ac.uk or by telephone on 0151 794 9871.

If you are unhappy about any aspect of this study and want to make a complaint you can do this through the NHS Complaints Procedure.

·CHANGe·

Care Home Acute Norovirus Gastroenteritis study

Study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside

A research study by the University of Liverpool.

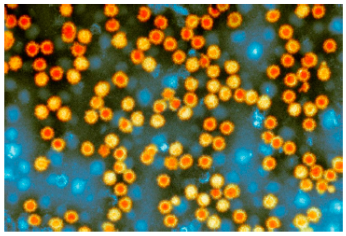
UNIVERSITY OF LIVERPOOL

Participant information sheet
resident
Version 1.2. 30-08-2016

Why we need your help
We are trying to reduce the number of people that fall ill with diarrhoea and vomiting. In the UK, the most common cause of diarrhoea and vomiting in adults is an infection called norovirus.

The purpose of this research is to understand how many people in care homes get diarrhoea and vomiting, find out what causes it and how it is spread.

Why me?
You have been asked to take part in the study because you live in a care home that is participating in the study. However, it is up to you whether you take part or not. If you decide that you do not want to take part, this will not affect your care in any way.



What sort of study is this?
This is an observational research study that is taking place in care homes in Liverpool and Sefton.

What will I be asked to do?
If you agree to take part in the study, we will do the following:

1. Collect a sample of your stool if you are ill with diarrhoea and vomiting; we will test this to find out what is making you ill.

2. Collect a sample of your saliva; to confirm what blood type you are and whether this affects your chances of becoming ill.

3. Collect a sample of your stool on an occasion when you are not ill; we will test this to find out what types of bacteria you have in your gut and whether this affects your chances of becoming ill.

4. We may ask you to keep a small low-power radio frequency device ("mote") close-by for a 24 hour period; to work out how diseases that cause diarrhoea and vomiting are spread in care homes.

What is a "mote"?
A mote is a small (2.5cm x 7.5 cm x 2 cm) electronic device powered by two AA batteries. A mote sends out a weak radio signal, similar to a cordless phone, every 20 seconds, and records the signals of any other motes.

Are there any risks to taking part in the study?
The risks of participating in the study are very low. There is no risk or any discomfort from taking stool or saliva samples.

What are the benefits of taking part in the study?
There is no direct benefit to participants. You will be helping us to improve our knowledge of how diseases that cause diarrhoea and vomiting spread in care homes and how to avoid it.

Appendix C: Supplementary material for Chapter 7

The negative binomial mixed effects model is a model for count data which extends the Poisson mixed effects model. It is useful when data are over-dispersed in that it relaxes the Poisson model constraint that the conditional mean and variance within the model are the same (model dispersion parameter fixed at 1), and allows the variance to be greater than the mean, which is commonly what is required for over-dispersed data. Technically, the negative binomial model arises by first specifying a Poisson model for the observed data Y_{ij} and then allowing the rate parameter μ within that model to follow a gamma distribution. A region-level random effect, U_j such that $U_j \sim N(0, \tau^2)$ was incorporated in the model to reflect the fact that observations from the same region *j* may be more similar than those from different regions.

Let Y_{ij} , *i* = 1,…, *n* be the count for individual (local authority) i in region *j*. Then conditional on random effects $U_j \sim N(0, \tau^2)$, the Y_{ij} are independent negative binomial random variables

$$Y_{ij} \sim NegBin(\alpha, \mu_{ij})$$

such that

$$\mu_{ij} = E(Y_{ij}|U_j) = exp[x_{ij}'\boldsymbol{\beta} + U_j]$$

and for *p* independent explanatory variables, β is an unknown *p* x 1 vector of regression coefficients.