The Second Study of Infectious Intestinal Disease in the Community (IID2 Study)

Final report

Department of Health

iid2 The Second Infectious Intestinal Disease Study

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The Second Study of Infectious Intestinal Disease in the Community (IID2 Study)

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Final Report

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LIST OF ABBREVIATIONS

ACMSF	Advisory Committee on the Microbiological Safety of Food
BMS	Biomedical Scientist
CDSC NI	Communicable Disease Surveillance Centre, Northern Ireland (Northern Ireland Public Health Agency from October 2009)
CfI	Centre for Infections
CI	Confidence Intervals
CT value	Cycle threshold value
CV	Coefficient of variation
EIA	Enzyme Immunoassay
EMIS	Egton Medical Information Systems
FSA	Food Standards Agency
GCP	Good Clinical Practice in Research
GP	General Practice
HPA	Health Protection Agency
HPS	Health Protection Scotland
IID	Infectious Intestinal Disease
IID1	The First Study of Infectious Intestinal Disease in the Community
IID2	The Second Study of Infectious Intestinal Disease in the Community (this study)
IMD	Index of Multiple Deprivation
IQA	Internal Quality Assurance
IQC	Internal Quality Control
LGP	Laboratory of Gastrointestinal Pathogens
LSHTM	London School of Hygiene and Tropical Medicine
MLA	Medical Laboratory Assistant
MRC GPRF	Medical Research Council General Practice Research Framework
NS-SEC	National Statistics Socioeconomic Classification
ONS	Office of National Statistics
PCR	Polymerase chain reaction
RCGP WRS	Royal College of General Practitioners' Weekly Returns Service
RR	Rate Ratio
RTN	Regional Training Nurse
RT PCR	Reverse Transcription Polymerase Chain Reaction
SOP	Standard operating procedure
SSL	Secure Socket Layer
UEA	University of East Anglia
UoM	University of Manchester
VTEC	Vero cytotoxin-producing E. coli
WHO	World Health Organisation

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CHAPTER 1

EXECUTIVE SUMMARY

1.1 INTRODUCTION

This report describes the Second Study of Infectious Intestinal Disease in the community (IID2 study). The main aim of the IID2 study was to determine if the incidence of infectious intestinal disease (IID) had changed since the mid-1990s. A secondary aim was to re-calibrate national surveillance data. It comprised seven separate but linked studies:- a retrospective Telephone Survey of self-reported illness, a Prospective, Population-Based Cohort Study, a General Practice (GP) Presentation Study, a GP Validation Study, a GP Enumeration Study, a Microbiology Study and a National Reporting Study. All elements except the National Reporting Study were piloted between 3rd September 2007 and 1st December 2007. The main studies took place between 28th April 2008 and 31st August 2009 (except the Telephone Survey which ran from 1st February 2008 to 31st August 2009).

1.2 OBJECTIVES

The objectives of the IID2 study were to:-

1. Estimate prospectively the number and aetiology of cases of IID in the population, contacting NHS Direct (and the equivalent NHS24 in Scotland), presenting to General Practitioners and having stool specimens sent routinely for laboratory examination in the UK.
2. Compare these numbers and the aetiologies with those captured by the UK laboratory reporting surveillance systems and with calls to NHS Direct in England and Wales and NHS24 in Scotland.
3. Determine the proportion of cases of IID likely to have been acquired abroad.
4. Compare the surveillance patterns from the first and second studies of infectious intestinal disease for England using reporting ellipses.
5. Compare the aetiology of IID in the first and second IID studies for England.
6. Estimate the number of cases of IID in the population of each UK nation, based on recall, via a national Telephone Survey of self-reported diarrhoea, conducted over two time periods: a week, and a month.
7. Compare the burden of self-reported illness through the national Telephone Survey with the burden of self-reported illness captured through NHS Direct in England and NHS24 in Scotland.
8. Compare the prospective and self-reporting methods for estimating IID incidence in the UK, over two time periods: a week and a month.

Additional objectives were to:-

9. Compare molecular methods with traditional microbiological techniques for IID diagnosis.
10. Determine the contribution of *Clostridium difficile* to the aetiology of infectious intestinal disease in the community.
11. Assess retrospective and prospective methods for determining IID burden.

1.3 METHODS

The IID2 study was composed of seven separate, but related, studies.

1.3.1 Study 1: National Telephone Survey

In Study 1, we asked a sample of people (n=14,726), via a Telephone Survey, if they had recently experienced symptoms of diarrhoea or vomiting. We asked one group (n=12,381) about symptoms during the previous seven days and another group (n=2,345) about symptoms during the previous 28 days to compare estimates of community incidence of IID obtained using the two different time periods. We compared this with the incidence estimate from Study 2 (Prospective Population-Based Cohort Study). We also compared incidence rates in the four UK countries.

1.3.2 Study 2: Prospective Population-Based Cohort Study

In Study 2, we recruited 7,033 people at random from 88 General Practices across the UK and followed them up at weekly intervals for up to one year to find out how many developed new symptoms of IID. People who developed IID completed a symptom questionnaire about their illness and their contact with health services, e.g. NHS Direct/NHS24, and provided a stool sample. We compared the community incidence of IID with corresponding estimates from the Telephone Survey. We also compared the incidence of IID in England in 2008-9 with the incidence in 1993-6, at the time of IID1. We randomly assigned the practices in Study 2 into two groups – those taking part in Studies 3 and 4, or those taking part in Study 5.

1.3.3 Study 3: General Practice (GP) Presentation Study

In Study 3 (37 practices completed) Study Nurses invited everyone who consulted their GP for a new episode of IID to complete a symptom questionnaire and provide a stool sample. We used this information to estimate the incidence and aetiology of IID in people presenting to primary care.

1.3.4 Study 4: General Practice (GP) Validation Study

In Study 4 we audited recruitment to the GP Presentation Study (Study 3). Study Nurses searched practice records for anyone presenting with a new episode of IID to the practices taking part in Study 3 during the study period. They generated a list of all the patients that should have been included in Study 3 using Read diagnostic codes and compared this with the actual recruitment list. We used this information to determine under-ascertainment in Study 3.

1.3.5 Study 5: General Practice (GP) Enumeration Study

In Study 5 (40 practices completed) Study Nurses searched practice records for anyone presenting with a new episode of IID. They recorded the patient's age, sex, postcode, place of consultation, admission to hospital and whether or not a stool sample was requested. If a sample was requested they recorded the result. We then compared proportion of cases of IID in the GP Presentation Study (Study 3) with the incidence of laboratory-confirmed infection documented in the GP Enumeration Study (Study 5).

1.3.6 Study 6: Microbiology Study

In Study 6, all stool samples from Studies 2 and 3 were examined first at the HPA Manchester Laboratory using conventional microbiological techniques and then at the HPA CfI at Colindale using molecular methods.

1.3.7 Study 7: National Reporting Study

In Study 7, we used the results from studies 1 to 6 to estimate under-ascertainment of community IID in national surveillance data by comparing the incidence estimates from Studies 1 to 6 with those generated from national surveillance data.

1.4 RESULTS AND INTERPRETATION

We estimated that around 25% of people in the United Kingdom suffer from an episode of IID in a year. We estimated that for every case of IID in the UK reported to national surveillance systems

there were 147 in the community. The most commonly identified pathogens were, in order of frequency, norovirus, sapovirus, *Campylobacter* **spp. and rotavirus.**

There were 1,201 definite cases of IID and a total of 4,658 person-years of follow-up (86% of the maximum achievable follow-up time) in the community cohort (N = 6,836; participation rate ≈ 9%). The age-sex standardised rate of IID in the community in the UK was 274 per 1,000 person-years (around 1 in 4 members of the population). We estimated that for every case of IID in the UK reported to national surveillance systems there were 147 in the community.

Sixty-five percent of the 1,201 definite cases of IID in the cohort submitted a stool sample for laboratory examination so we used multiple imputation methods to account for missing data. Using the full panel of tests, 40% of samples tested contained one or more pathogens, the most commonly identified being norovirus (16.5% of samples), sapovirus (9.2%), *Campylobacter* spp. (4.6%) and rotavirus (4.1%). The IID2 Study coincided with the introduction of a new genotype of sapovirus into the UK population.

Clostridium perfringens, *Salmonella* spp., and *Escherichia coli* O157 were each found in less than 1% of samples and *Listeria monocytogenes* was not found at all.

We estimated that less than 2% of people in the UK consulted their GP for an episode of IID and that for every case of IID reported to national surveillance there were 10 presenting to General Practice in the UK. The most commonly identified pathogens were, in order of frequency, *Campylobacter* **spp., norovirus, sapovirus and rotavirus.**

In total 1,254 people with IID were recruited into the GP Presentation Study. Following adjustment for under-ascertainment and practice list inflation there were an estimated 5,546 definite cases of IID presenting to General Practice and 312,232 person-years of follow-up. Thus, the estimated incidence of IID presenting to General Practice was 18 cases per 1,000 person-years. We estimated that for every case of IID in the UK reported to national surveillance systems there were 10 that presented to General Practice.

Eighty-eight percent of cases in the GP Presentation Study submitted a stool sample and 51% were positive for one or more pathogens. Using the full panel of tests, the most frequently identified pathogens in samples from cases of IID presenting to general practice in the UK were *Campylobacter* spp. (13% of samples), norovirus (12.4%) sapovirus (8.8%) and rotavirus (7.3%). *Salmonella* spp. were detected in only 0.8% of cases. This was less than cases with *C. perfringens* (2.2%), Enteroaggregative *E. coli* (1.4%), *Cryptosporidium* (1.4%) or *Giardia* (1.0%). Two or more pathogens were found in stool samples from 4.6% of cases in the GP Presentation Study.

We found only one case of *C. difficile*-associated diarrhoea in the Prospective Cohort Study and 10 cases in the GP Presentation Study.

This suggests that in unselected community samples, i.e. samples from people who have not necessarily had recent or frequent contact with health or social care, the incidence of *C. difficile*-associated diarrhoea is very low.

We found that around 8% of people in the Prospective Cohort Study and 12% of people in the GP Presentation Study reported having travelled outside the UK in the 10 days prior to illness onset.

There were differences in the rate of IID estimated from the Prospective Cohort Study and the Telephone Survey.

From the Telephone Survey we estimated that the rate of IID in the community in the UK was 1,530 cases per 1,000 person-years (i.e. five times higher than the rate in the Prospective Cohort Study) using 7-day recall and 533 cases per 1,000 person-years using 28-day recall i.e. twice as high as in

the Prospective Cohort Study). To attempt to understand this variation in community rates in the two types of study we triangulated rates around presentation to General Practice. The rates from the Prospective, Population-Based Cohort Study, the GP Presentation Study, the GP Enumeration Study and an external data source (the Royal College of General Practitioners' Weekly Returns Service) were all of a similar order of magnitude and substantially less than in the Telephone Survey. These findings suggest that the cohort approach might provide more reliable estimates, at least for episodes of IID that involve health care contact.

There was variation in the IID rate estimates by country in the Telephone Survey but the confidence intervals were wide and all overlapped so that there was insufficient evidence to indicate that differences between countries were important.

The estimated rate of IID in the community in England was 43% higher in 2008-9 (IID2) than in 1993-6 (IID1) whilst the estimated rate of IID presenting to General Practice in England in IID2 was 50% lower than in IID1. Approximately 50% of people with an episode of IID in both studies reported absence from work or school because of their symptoms.

The burden of IID in the community that is hidden from national surveillance systems was greater in IID2 than in IID1. The main reason for this hidden burden was the smaller proportion of cases presenting to general practice.

In England, the ratio between cases reported to national surveillance and those occurring in the community had changed.

Using molecular methods in the IID2 Study meant that we could test low volume samples for the complete range of pathogens. Taking into account the changes in target organisms and diagnostics (and re-calculating ratios from IID1 where necessary) we found that the ratio of cases reported to national surveillance in England to cases in the community had changed from ≈ 1:85 in IID1 to ≈ 1:150 in IID2. For norovirus the changes was from ≈ 1:1,000 in IID1 to ≈ 1:300 in IID2. The ratios for *Campylobacter* spp., *Salmonella* spp. and rotavirus were similar in both studies.

Although the hidden burden of IID had increased between the two study periods the ratio of cases reported to national surveillance to cases presenting to general practice had improved for all IID and for all the pathogens that we considered i.e. national surveillance data capture had improved between IID1 and IID2 for cases who presented to General Practice.

A small proportion of people with IID (<2%) contacted NHS Direct or NHS24.

Decreases in GP presentation were unlikely to be explained by the introduction of these telephone information and advice services.

1.5 CONCLUSION

The burden of IID in the United Kingdom is substantial. In England the estimated incidence of IID in the community increased by 43% between 1993-6 and 2008-9 and cases presenting to general practice decreased by around 50% so that the hidden burden of IID is greater now than it was 12 years ago. Approximately 50% of people with IID reported absence from work or school because of their symptoms. The pathogens most frequently associated with IID in the community and presenting to primary care were norovirus, sapovirus, rotavirus and *Campylobacter* spp. *Clostridium difficile*-associated diarrhoea was rare.

CHAPTER 2

BACKGROUND AND OBJECTIVES

2.1 INFECTIOUS INTESTINAL DISEASE

Infectious intestinal disease (IID) is an important public health problem worldwide. In developed countries IID-related mortality is low but morbidity remains high. In the mid-1990s it was estimated that around 1 in 5 people in England suffered from IID each year and the annual cost to the nation was around £750 million (Food Standards Agency (FSA, 2000; Wheeler *et al*., 1999; Roberts *et al*., 2003). Recent estimates from the Food Standards Agency suggest that the annual cost of foodborne illness (a proportion of all IID) in England and Wales is high at around £1.5 billion (Table 2.1).

Table 2.1: Estimated costs attributable to foodborne illness (England and Wales)

	Costs, £m (2008 Q1 Prices)*			
Year	**NHS**	**Lost earnings and other expenses**	**Pain and Suffering**	**Total Cost of IFD (England and Wales)**
2003	27	115	1,316	1,458
2004	33	130	1,605	1,768
2005	28	115	1,359	1,503
2006	30	130	1,425	1,586
2007	29	125	1,361	1,515
2008	29	125	1,321	1,475

* To compensate for inflation, costs are based on 2008 quarter 1 prices, to allow for comparison to be made between years.

2.1.1 What is IID?

IID commonly presents as an acute episode of diarrhoea and vomiting in otherwise healthy people. There may also be systemic upset with fever, but usually the illness is short-lived and resolves completely. Defining IID more precisely is difficult and confusion arises from the variety of different terms used to describe gastro-intestinal and foodborne disease. Figure 2.1 gives a schematic illustration of the inter-relationship between the use of the four terms gastro-intestinal infection, IID, gastroenteritis, and food poisoning.

IID is a subset of both gastro-intestinal infection and gastroenteritis since it is always characterised by gastro-intestinal symptoms. The term gastroenteritis refers to inflammation of the stomach and intestines and includes non-infectious causes such as alcohol, food intolerance, Crohn's disease, and ulcerative colitis (Table 2.2). There are several gastro-intestinal infections that do not necessarily give rise to symptoms of gastroenteritis such as botulism, *Helicobacter pylori* infection, listeriosis, and poliomyelitis, and some that are caused by non-infectious agents such as mycotoxins or mercury.

Figure 2.1: The inter-relationships between terms used to describe gastrointestinal and foodborne disease

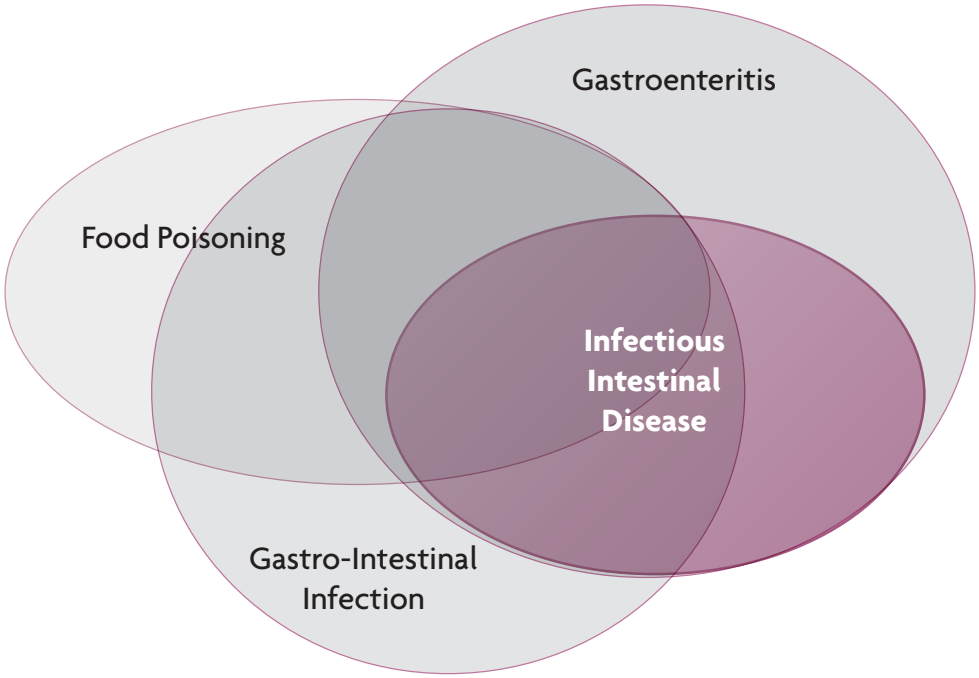


Table 2.2: Conditions causing food poisoning, gastroenteritis or gastrointestinal infection but not IID

Food poisoning but not IID
Chemicals e.g. histamine, dioxin
Heavy metals e.g. mercury
Mycotoxins
Botulism
Gastroenteritis but not IID
Irritable bowel syndrome
Inflammatory bowel disease e.g. Crohn's disease
Food intolerance
Alcohol
Gastrointestinal infection but not IID
Helicobacter pylori
Botulism

2.1.2 Pathogens that commonly cause IID

IID is caused by a range of bacteria, viruses, and protozoa (Adak *et al*., 2002; Musher, 2004) (see Appendix 1). The disease may be spread from person to person, arise from a common food or environmental source, or result from exposure to animals. Food and water can be primary sources or become contaminated from an infected person or animal. Pathogens that can be food- or water-borne include *Salmonella*, campylobacters, norovirus, and *Cryptosporidium*, whereas others such as *Shigella sonnei* and rotavirus are usually spread from person to person. Conversely, several important food- or water-borne pathogens such as *Listeria monocytogenes*, *Salmonella* Typhi and *S.* Paratyphi, *Clostridium botulinum*, and hepatitis A and E cause systemic infection but little intestinal disease.

2.2 NATIONAL SURVEILLANCE SYSTEMS FOR IID

There are three main sources of routinely collected data on IID in the UK (Wall *et al*., 1996):

- Statutory notifications from clinicians of cases of food poisoning.
- Voluntary reports from diagnostic laboratories of laboratory confirmed infections.
- Standard report forms submitted by health protection units on general outbreaks of IID.

In addition, there are several voluntary, primary care and community surveillance schemes that provide information on consultation rates for IID.

2.2.1 Statutory notification

Food poisoning is a statutorily notifiable disease, as are several other IID including: cholera, dysentery (amoebic or bacillary), paratyphoid fever and typhoid fever (McCormick, 1993) (Table 2.3). From 6th April 2010, infectious bloody diarrhoea became notifiable in England under the new Health Protection (Notification) Regulations 2010. In Scotland, food poisoning ceased to be notifiable on 1st January 2010.

Table 2.3: Notifiable IID and Food Poisoning in the United Kingdom

Notifiable In Notifiable IID	England and Wales[1]	Scotland[2]	Northern Ireland[3]
Cholera	Yes	Yes	Yes
Clinical syndrome due to *E. coli* O157 infection	No	Yes	No
Dysentery	No	No	Yes
Enteric fever (typhoid or paratyphoid)	Yes	Yes	Yes
Food poisoning	Yes	No	Yes
Gastroenteritis (persons under 2)	No	No	Yes
Haemolytic uraemic syndrome	Yes	Yes	No
Infectious bloody diarrhoea	Yes	No	No

Notes: 1 = Health Protection (Notification) Regulations 2010 and The Health Protection (Notification) (Wales) Regulations 2010; 2 = Part 2 (Notifiable Diseases, Organisms and Health Risk States) of The Public Health etc. (Scotland) Act 2008; 3 = Public Health Act (Northern Ireland) 1967 (amended 1990)

The term 'food poisoning' is not defined in legislation, but a definition, previously adopted by the World Health Organisation (WHO), was circulated to all UK doctors by the Chief Medical Officers in 1992 (CMO, 1992). This defines food poisoning as:

'any disease of an infectious or toxic nature caused by or thought to be caused by the consumption of food or water'.

In addition to formal notification, local authorities also record cases ascertained by other means. These are mostly cases identified during the course of routine follow-up of sporadic cases or during outbreak investigations, with a small number arising from complaints made by members of the public.

2.2.2 Voluntary reports from diagnostic laboratories

Laboratory reporting underpins the national surveillance system for IID. All Health Protection Agency (HPA) regional laboratories and reference laboratories, most NHS laboratories, and a small number of private laboratories throughout England and Wales report weekly via electronic links to the HPA Centre for Infections (CfI), although some NHS laboratories still report on paper. Similar schemes exist in Scotland and Northern Ireland.

The National Standard Method for investigation of stool samples for bacterial pathogens briefly outlines the bacteria responsible for enteric infection and the methods used for their isolation (Health Protection Agency, 2008). It is recommended that primary laboratories routinely screen faeces for *Campylobacter*, *Salmonella*, *Shigella* and *Escherichia coli* O157 on all diarrhoeal (semi-formed or liquid) faeces. The investigation of faeces for *Clostridium perfringens* is normally only performed in food poisoning incidents. Laboratory confirmation requires either isolation of the same serotype from the faeces of affected individuals and from food, or detection of the enterotoxin in the faeces of affected individuals, or faecal spore counts of $>10^5$ organisms per gram. Faeces may also be screened for other bacteria as indicated by clinical details, for example in patients with prolonged diarrhoea or dysenteric syndromes for whom no cause can be found, or in association with outbreaks.

Stool samples are also tested for intestinal parasitic infections and routine diagnosis still depends mainly on examination of stool samples by microscopy for the identification of helminth eggs and protozoan trophozoites and cysts.

Stool samples are not routinely tested for viruses except in children less than 5 years of age, adults over 60 years, food-handlers and immunocompromised patients. Most laboratories test for norovirus and rotavirus all year round, but in a minority testing may be restricted to the winter gastroenteritis season (Atchison *et al*., 2009). Samples from outbreaks of gastroenteritis in semi-closed communities such as hospitals and nursing homes are tested for norovirus. Samples are tested for adenovirus, norovirus, and rotavirus by enzyme immuno-assay (EIA), polymerase chain reaction (PCR), or reverse transcription (RT)-PCR, although practice varies widely.

Most human isolates of *Salmonella* from England and Wales are forwarded for confirmation and further identification to the national *Salmonella* Reference Unit at the HPA Laboratory of Gastrointestinal Pathogens (LGP). *Salmonella* spp. and *E. coli* O157 from Northern Ireland are also routinely sent to LGP. Laboratories are also encouraged to send isolates of *E. coli* O157 to the Gastrointestinal Infections Reference Unit at LGP for further identification and definitive typing. Similar arrangements exist in Scotland which has its own *Salmonella* and Vero cytotoxin-producing *E. coli* reference laboratories. In England and Wales, isolates of *Bacillus cereus*, *C. perfringens*, and *Staphylococcus aureus* are submitted to the Foodborne Pathogens Reference Unit at LGP for typing and/or toxin testing. There is considerable overlap between notified cases of food poisoning and laboratory reports of IID. However, there is no linkage between the two systems at national level so it is not possible to eliminate duplication or to combine the datasets.

2.2.3 Surveillance scheme for general outbreaks of IID

This is a voluntary scheme run by CfI that collects data on general outbreaks of IID in England and Wales. Similar arrangements exist in Scotland and Northern Ireland. A general outbreak is defined as 'an outbreak affecting members of more than one private residence or residents of an institution'. The definition excludes outbreaks that are confined to a single household, e.g. a family outbreak, but includes geographically widespread outbreaks linked by organism, serotype or phage type.

When CfI becomes aware of a possible general outbreak, usually through the laboratory reporting scheme, a structured questionnaire is sent to the consultant in communicable disease control based in the appropriate local health protection unit for completion when the outbreak investigation is finished. There are several potential reporting biases which might affect the completeness or

representativeness of the data collected (O'Brien *et al*., 2002). For example, outbreaks at social functions affecting a defined cohort of people are more likely to be identified and investigated than those where cases are widely dispersed in the community. Bias can also be introduced by the person completing the form who is responsible for indicating the probable mode of transmission and the factors likely to have contributed to the outbreak.

2.2.4 Primary care and community surveillance

There are several primary care surveillance schemes in operation that collect information on consultations and episodes of illness diagnosed in General Practice, including IID. The longest established scheme is the Royal College of General Practitioners (RCGP) Weekly Returns Service, and the largest is the HPA/Q Surveillance National Surveillance Scheme. In 2000, the NHS Direct/HPA Syndromic Surveillance scheme was established based on calls to the information and advice service, NHS Direct. There is also a range of similar schemes operating in Scotland and Wales. However, no syndromic surveillance scheme for IID exists in Northern Ireland.

2.2.4.1 RCGP Weekly Returns Service (WRS)

The WRS is a network of about 100 General Practices located mainly in England (Fleming *et al*., 2002). The total population covered by the WRS averages approximately 900,000. Consultations for IID are determined according to Read diagnostic codes assigned by the practitioner (Chisholm, 1990). Read codes are the recommended national standard coding system in General Practice. However, a variety of different codes may be used for IID and there is no validation of diagnosis. Consultation rates for IID recorded by the WRS have fallen dramatically over the last 10 years. The mean weekly incidence of IID episodes was 17 per 100,000 in 2008 compared with 38 per 100,000 in 1999.

2.2.4.2 HPA/Q Surveillance National Surveillance Scheme

The HPA/Q Surveillance scheme is a collaborative project between the HPA and the University of Nottingham that monitors a variety of conditions that might indicate infectious diseases (Smith *et al*., 2007). It comprises a sample of around 4,000 General Practices from across the UK that use Egton Medical Information Systems (EMIS) clinical software. Although EMIS is the leading primary care information technology provider in the UK, only a minority of practices in Scotland and Northern Ireland use it. As in the WRS, consultations for IID are determined according to Read diagnostic codes assigned by the practitioner but there is no validation of diagnosis. Data are extracted electronically from a primary care-derived database (Q Surveillance) that contains information on clinical consultations, prescriptions, tests and results, and referrals for a population of approximately 20 million patients currently registered. Relevant indicators for IID include vomiting, diarrhoea, diarrhoea with hydration therapy, and gastroenteritis. Trend summaries for these indicators are fed back to public health practitioners in a weekly bulletin.

2.2.4.3 NHS Direct/HPA Syndromic Surveillance Scheme

NHS Direct is a nurse-led health advice and information service, which covers the whole of England and Wales. Algorithms are used to sort and categorise calls by a variety of symptoms/syndromes. There is no formal diagnostic coding, but calls are assessed for severity by nurse advisers to recommend priority for further care. Data on several symptoms/syndromes are received electronically from across the country and analysed by the HPA on a daily basis. The weekly NHS Direct/HPA Syndromic Surveillance Bulletin includes reports of major rises in symptoms and regularly updated national graphs showing age-group specific trends for individual symptoms/syndromes including diarrhoea and vomiting (Cooper *et al*., 2003). There is a similar scheme in Scotland based on the NHS24 telephone helpline, but there is no NHS helpline in Northern Ireland.

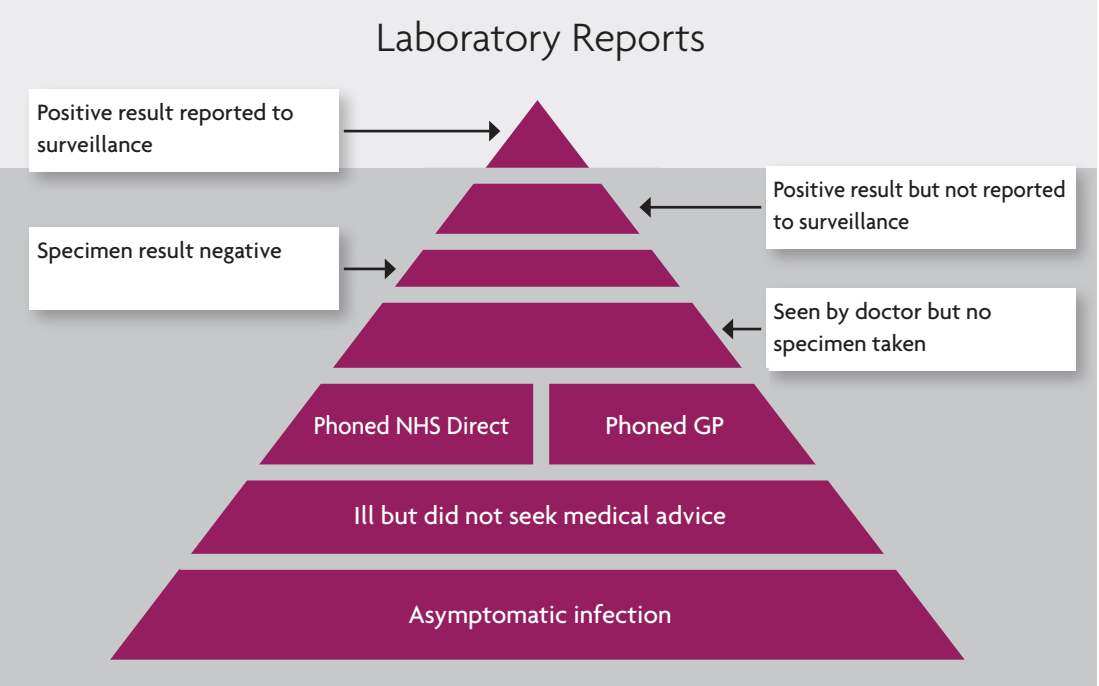
2.3 THE SURVEILLANCE PYRAMID

Although IID is very common in the community not all cases present to the healthcare system, and not all cases that present are reported to national surveillance. For example, reports of laboratory confirmed IID pathogens represent a fraction of the true incidence since many patients do not seek

medical attention. A sub-set of those that do will submit a stool sample for analysis. When a sample is submitted, a pathogen is not always identified, but where the sample is positive this result is not always reported to national surveillance.

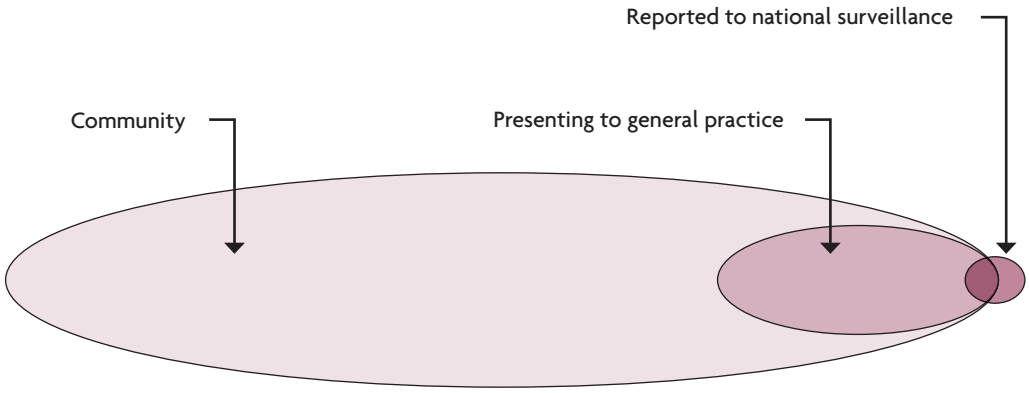
Since reporting of IID to national surveillance depends on patients seeking healthcare, laboratory reports are more likely to represent patients at the severe end of the IID spectrum (Food Standards Agency, 2000). As a result, many IID cases are not captured in routine data sources, and surveillance data in the UK thus underestimate the total IID burden. This pattern of under-ascertainment is commonly described schematically as a surveillance pyramid. In Figure 2.2 we have adapted the conventional representation of the surveillance pyramid to take account of healthcare systems currently operating in the UK. By calibrating the proportion of cases of IID that are undetected at each surveillance step it is possible to extrapolate from laboratory-confirmed cases (represented by the top of the pyramid) to estimate the overall burden of disease in the community (represented by the bottom of the pyramid) provided that the determinants of reporting/ratio of reported cases to cases in the community is stable over time.

Figure 2.2: The surveillance pyramid: laboratory reports represent only a fraction of the true prevalence of IID



There are, however, limitations in the depiction of the surveillance pyramid. First, it might be implied that each layer is simply a sub-set of the previous layer. This is misleading since, in fact, each layer represents a subset of the total disease burden. Secondly it fails to illustrate that not all cases of IID reported to national surveillance originate in the community, e.g. nosocomial cases acquired in hospital. In this study, therefore, we present reporting patterns as sets of intersecting ellipses (Figure 2.3). Each ellipse represents the frequency of IID in the community, presenting to general practice and reported to national surveillance respectively. The ellipse representing the general practice component is completely contained within the ellipse representing IID in the community to indicate that IID presenting to general practice originates from cases in the community who consult their GP. By contrast, the ellipse representing IID reported to national surveillance only partly intersects the community and general practice ellipses, to indicate that a fraction of reported IID cases originate from hospitals and other institutions, and are not captured by the methods used in the IID2 study.

Figure 2.3: The surveillance ellipse: the relationship between IID in the community, presenting to general practice, and reported to national surveillance



2.4 THE EPIDEMIOLOGY OF IID

Campylobacter spp. are the most commonly reported bacterial cause of IID in the UK (Table 2.4). Laboratory reporting of *Campylobacter* spp. fell by 24% between 2000 and 2004. However, this downward trend has since been reversed (Figure 2.4). In 2008 the national surveillance centres in the UK recorded 55,609 laboratory confirmed cases of infection – an 11% increase since 2004.

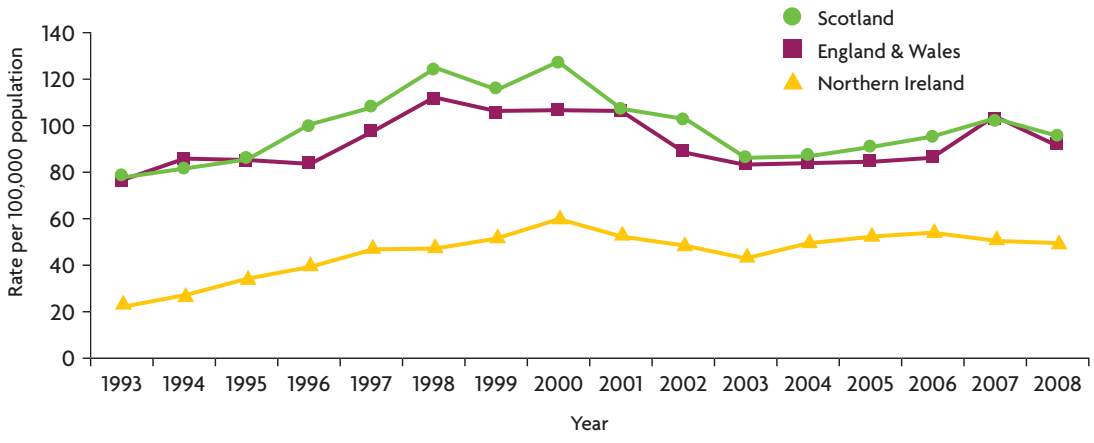
Table 2.4: Number of laboratory reports of selected gastro-intestinal pathogens in the United Kingdom, 2000-2008.

	Campylobacter	**Non-typhoidal Salmonellas**	**VTEC O157**	***Listeria monocytogenes*[a]**	**Rotavirus**
2000	65,720	16,607	1,142	115	19,129
2001	61,404	17,976	1,046	163	19,516
2002	54,075	15,830	852	157	16,564
2003	51,473	16,419	874	251	17,273
2004	49,750	14,476	926	232	16,823
2005	52,196	12,652	1,155	220	15,589
2006	52,662	12,822	1,216	208	15,561
2007	58,054	13,213	1,113	259	14,711
2008	55,609	12,091	1,237	206	16,440

[a] bloodstream infections

Source: Health Protection Agency, Health Protection Scotland, Public Health Agency for Northern Ireland.

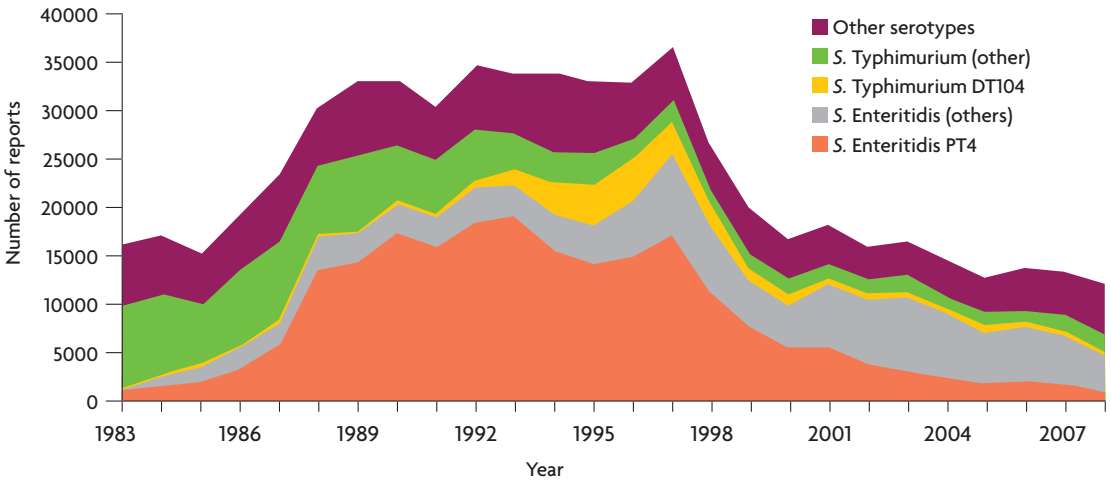
Figure 2.4: Laboratory reports of Campylobacter in the UK, 1993-2008



Source: Department for Environment, Food and Rural Affairs, Zoonoses Report 2008.

There has been a downward trend in the reporting of non-typhoidal salmonellas since 1997 following the introduction of vaccination of chicken breeder and layer flocks in Great Britain during the mid-1990s (Figure 2.5). In the period 2000-2008 laboratory reports fell by 27%. This is mainly attributable to a decline in illness due to *Salmonella* Enteritidis phage type 4.

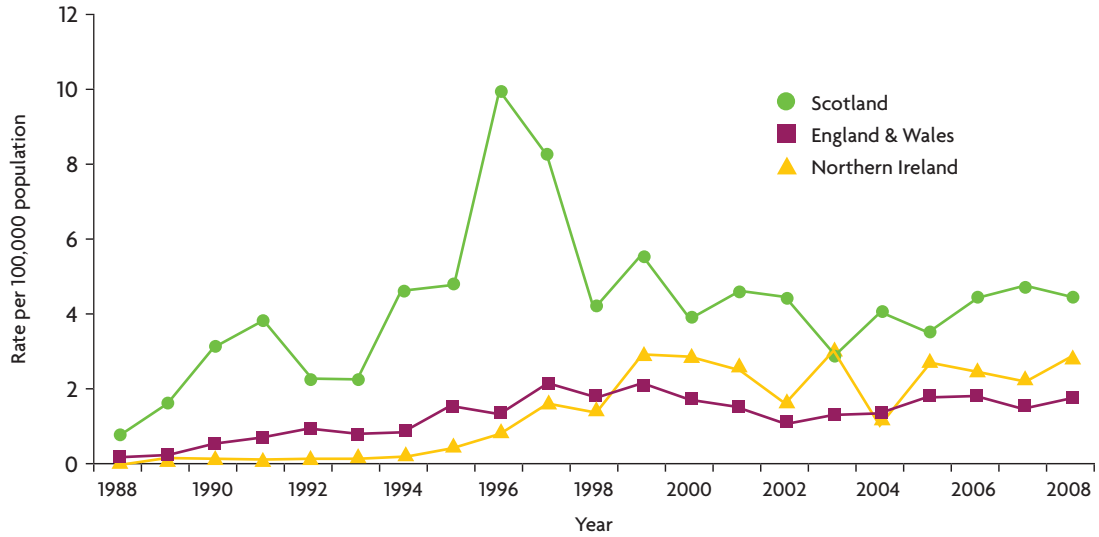
Figure 2.5: Laboratory reports of Salmonella by serotype in the UK, 1983-2008



Source: Department for Environment, Food and Rural Affairs, Zoonoses Report 2008.

Reporting of Vero cytotoxin-producing *E. coli* O157 (VTEC) has not shown any consistent trend in recent years (Figure 2.6). Variations from year to year in the number of cases reported tend to be linked to the occurrence of outbreaks of infection.

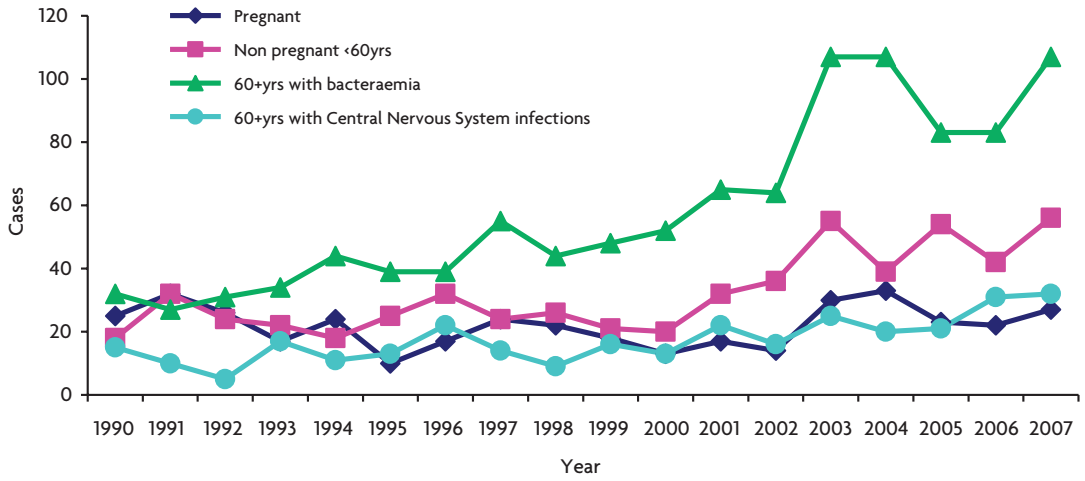
Figure 2.6: Laboratory reports of VTEC O157 in the UK, 1988-2008



Source: Department for Environment, Food and Rural Affairs, Zoonoses Report 2008.

Since 2000 there has been a marked rise in the incidence of disease due to *L. monocytogenes* in England and Wales (ACMSF, 2009; Gillespie *et al*., 2009). Analyses of the surveillance data show that these rises are driven by increases in bacteraemia in people over 60 years of age (Figure 2.7).

Figure 2.7: Trends in human listeriosis showing an increase in bacteraemia in people over 60 years of age, England and Wales 1990-2007



Source: Health Protection Agency

The number of norovirus infections has increased dramatically over the last 10 years with 7,677 reported in 2009. However, much of this increase has probably been influenced by the introduction of improved laboratory detection methods. In recent years, there has been a shift from the use of electron microscopy to the use of immunoassay and PCR-based methods. However, most laboratories continue to reserve testing for specimens collected during outbreak investigations. Specimens derived from sporadic cases of illness are not routinely tested for norovirus.

The reporting of rotavirus has tended to fluctuate from year to year within the range 15,000 to 20,000 laboratory reports per year (Table 2.4).

2.5 RATIONALE FOR THE CURRENT STUDY

2.5.1 The Food Standards Agency's foodborne illness reduction target

In 2001, the Food Standards Agency's strategic plan for 2000-2006 included a specific target to reduce foodborne illness by 20% in five years (Food Standards Agency, 2001). Progress against this target was measured using laboratory-report based surveillance data for five key pathogens: salmonellas, campylobacters, *C. perfringens*, *E. coli* O157 and *L. monocytogenes* (Food Standards Agency, 2002). Although only a minority of cases result in a positive laboratory report, it was considered that laboratory data provide a reliable indication of trends in *Salmonella*, *Campylobacter*, *L. monocytogenes* and *E. coli* O157. It was acknowledged, however, that the system was probably less reliable at detecting *C. perfringens*, except as an important cause of outbreaks.

To continue to monitor progress, there was a need to establish whether or not the relationship between disease burden in the community and official statistics had changed. In the last decade, several changes in the NHS and health protection services, described below, might have altered that relationship to a greater or lesser degree. It was important that the scientific community, the Food Standards Agency and, ultimately, the public had confidence in the measurement of the foodborne disease target. To achieve this, contemporary information on the relationships in the surveillance pyramids was required.

2.5.2 The First Study of Infectious Intestinal Disease (IID1)

The public health impact of IID was underlined by the publication of The Study of IID in England ((IID1) Food Standards Agency, 2000). The field work was undertaken between August 1993 and January 1996. The incidence of community IID in that study was estimated at 194 cases of IID per 1,000 person years, indicating that approximately 20% of the population has an episode of IID

each year (Wheeler *et al*., 1999). As well as defining disease burden, a major component of IID1 was the calibration of national surveillance systems, i.e. estimating the factor by which the number of cases of IID due to specific pathogens reported to national surveillance needed to be multiplied to estimate the actual number of infections in the community. By comparing rates of IID reported to national surveillance to IID rates in the community (the so-called indirect method of comparing rates), it was established that for every case of IID reported to national surveillance 88 cases had occurred in the community. For campylobacters the ratio of reports to national surveillance to disease in the community was 1:10, and for salmonellas was approximately 1:4. Accounting for improvements in diagnostics for viruses in the intervening years the ratio for norovirus in IID1 was recalculated to be around 1:1000 (Phillips *et al*., 2010).

2.5.3 Changes to Surveillance Systems since IID1

During the intervening years, rates of laboratory-confirmed infections associated with IID reported to UK national surveillance systems have fallen. However, this might not reflect a true decline in disease as there have been structural changes that could have affected national surveillance over the same time period. In primary care, people can now call NHS Direct (or NHS24) 24 hours a day to find out if they can treat their symptoms at home or if it is necessary to visit a GP or other healthcare provider. Clinical laboratories no longer report directly to the national centre in England but via regional units. The creation of the Health Protection Agency in 2003 reduced the number of lead laboratories directly under the control of the public health services from 48 to nine, with a possible reduction in the range of microbiological tests applied to each sample. However, during this time there have also been developments in electronic reporting of laboratory results to national centres replacing the earlier manual systems thereby improving completeness and timeliness of reporting.

2.5.4 Changes to diagnostic microbiology since IID1

There have been significant changes in microbiological methods used in diagnostic laboratories in the UK over the past decade with a greater use of automation and the introduction of molecular assays. However, these developments have mostly been applied to specimens other than faeces. In most laboratories the methods used for detection of enteric pathogens remain unchanged from the time of the IID1 study, with a few exceptions (Pawlowski *et al*., 2009). Although PCR tests have been described for all of the major enteric pathogens, and were used to improve the detection rate in archived faeces specimens from the IID1 study (Amar *et al*., 2007), the only commonly available diagnostic PCR tests are for enteric viruses, which are used in a small number of specialist virology centres. Immunoassays were in routine use in the 1990s for rotavirus and adenovirus and now many laboratories also use immunoassays for *C. difficile* toxin and norovirus detection. Some laboratories have replaced labour intensive microscopy for *Giardia* and *Cryptosporidium* with immunoassays, but the culture methods used for the major bacterial pathogens (*Campylobacter*, *Salmonella*, *Shigella* and *E. coli* O157) remain unchanged.[1]

2.5.5 Methods for Estimating the Population Burden of IID

Most studies for estimating community burden of IID in developed countries are either prospective cohort studies or retrospective cross-sectional surveys. The prospective cohort design consists of recruiting volunteers and asking them to record relevant symptoms, over a defined time period, often in some form of diary. The retrospective study involves contacting people, usually by telephone and asking about symptoms in the recent past. A major advantage of population-based, prospective cohort studies is the ability to request stool specimens from people who report illness so that the range of gastrointestinal pathogens causing symptoms can be determined. Retrospective studies do not provide information on the microbiological causes of illness; however, they are much quicker and cheaper to complete (Table 2.5).

[1] Available at http://www.hpa-standardmethods.org.uk/documents/bsop/pdf/bsop30.pdf - Date accessed 19th June 2010.

Table 2.5: Advantages and disadvantages of prospective and retrospective study methods for estimating the population burden of IID

Prospective cohort studies
Advantages
• Microbiological sampling is possible
Disadvantages
• Expensive, especially if a nationally distributed study is required
• Potential for drop-out (loss to follow-up) if follow-up period is long
• Generalisability limited if cohort participants are a highly selected group
• Sensitisation and reporting fatigue
• Takes longer to complete
Telephone surveys (retrospective)
Advantages
• Cheaper than a prospective study
• Results can be obtained more quickly
Disadvantages
• Sampling bias if based on landlines (misses mobile-only users, those without telephones and those out of the house at the time of the call e.g. younger and single people)
• Inaccurate recall including telescoping or forgetfulness
• Random selection of household members is difficult
• No possibility for assessing aetiology by microbiological sampling

Estimates of population burden of disease differ substantially between retrospective and prospective study designs even when using identical case definitions. This was highlighted in the IID1 Study, in which the incidence of IID estimated using a retrospective design was 0.55 episodes per person-year, compared with 0.19 per person-year in the prospective cohort component (FSA, 2000). There are several possible explanations for this discrepancy which need to be investigated more fully.

Prospective cohort studies are prone to several problems, including loss to follow-up, sensitisation and reporting fatigue. In IID1, 39% of the original cohort of 9,296 persons was lost to follow-up over six months, which could have resulted in inaccurate incidence estimates if those lost to follow-up had a very different risk of IID compared with those who remained in the study. Sensitisation occurs when respondents become more aware of issues related to their health because they are participating in a health-related study (Strickland *et al*., 2006), and as a result perceive more symptoms during early follow-up than before enrolment. For studies with long periods of follow-up, or frequent follow-ups, participants can also become fatigued with the follow-up process (Strickland *et al*., 2006). If participants tire of completing a health diary, or returning data via postcard or e-mail, they might be less likely to report symptoms over time (Strickland *et al*., 2006; Verbrugge, 1980). This might be a particular problem in studies in which participants are required to submit a stool specimen as some people might find this distasteful and be reluctant to do it. This pattern of sensitisation-fatigue, where illness reporting is highest during the early weeks of follow-up and subsequently decreases, is characteristic of much longitudinal data (Strickland *et al*., 2006; Gill *et al*., 1997; Marcus, 1982) and was seen in IID1 (Food Standards Agency, 2000).

Retrospective surveys are generally much cheaper than prospective cohort studies, mainly because each participant is only contacted once. Information can be collected in different ways, including face-to-face interviews, telephone interviews, postal questionnaires, or through the internet. Common problems in such retrospective surveys include sampling bias, response bias and poor

recall. Sampling bias can occur if the sampling frame used to identify participants excludes certain sections of the population that might have a different risk of illness. For example, telephone surveys based on calls to landlines will exclude households that do not have fixed line telephones. This could result in bias if, for example, having a landline is correlated with socioeconomic or other factors that are related to risk of illness. Response bias occurs when those who choose to respond to a survey differ in important ways from those who decline to take part. For example, in both telephone and postal surveys, respondents are often more likely to be older people and women, and may have a different risk of illness compared with the general population.

A major problem in retrospective studies is inaccurate recall. Surveys of IID commonly ask respondents to recall symptoms occurring in the previous month. Accurate reporting requires that respondents remember not only whether they experienced relevant symptoms, but also that they recall the date of onset, the duration, and the severity of symptoms. If respondents are less likely to remember illness that occurred some time previously, disease incidence will be underestimated. Conversely, respondents might recall illness episodes as having occurred more recently than they actually did, thereby inflating disease incidence. This latter phenomenon is known as "telescoping".

Finally, another major challenge of IID studies is standardisation in order to allow international comparisons of incidence rates. Case definitions used in different studies vary greatly, regardless of the study design. The case definition can influence the observed incidence of IID by as much as 1.5 to 2.1 times even within a given country (Majowicz *et al*., 2008). To overcome this, a standard, symptom-based definition has been developed that should allow international comparison in future (Majowicz *et al*., 2008).

Several comprehensive reviews of studies have recently been published and they cover estimated rates of gastrointestinal illness in developed countries (Roy *et al*., 2006), and the estimated burden and cost of foodborne disease (Flint *et al*., 2005; Buzby and Roberts, 2009).

2.6 THE SECOND STUDY OF INFECTIOUS INTESTINAL DISEASE (IID2)

2.6.1 Design innovations

IID1 was confined to England. However, the foodborne disease reduction target relates to the whole of the UK. IID2 therefore described surveillance patterns for England, and for the UK as a whole. The impact of the introduction of NHS Direct/NHS24 on surveillance data was estimated.

IID2 included a comparison of prospective and retrospective methods for estimating the community incidence and population burden of IID. In a Telephone Survey, the accuracy of effects of recall of self-reported IID was examined over two different time periods. If the degree of under-reporting or telescoping can be defined, and shown to be relatively stable, telephone surveys could provide a robust and cost-effective method for making future estimates of population burden of IID.

2.6.2 Changes to microbiological methods

Following a review of IID1, and discussion with the Food Standards Agency, samples were not examined for some micro-organisms that were considered of doubtful pathogenicity despite the fact that those tests were carried out in IID1. This meant re-calculating the proportion of positive samples overall and by pathogen in IID1 so that comparisons with IID2 were valid.

In addition, molecular methods were employed for pathogen detection and characterisation, alongside conventional methods (Amar *et al*., 2005; Amar *et al*., 2007; Iturriza *et al*., 2009). This allowed comparisons with IID1 and will also allow future comparisons since, in 10 years time, molecular methods are likely to be in routine use. Re-analysis of archived stool samples from IID1 increased the identification of an aetiological agent from 53% in cases using conventional methods to 75% using PCR (Amar *et al*., 2007). This study should therefore provide the bridge between data generated by "old" and "new" methods.

There were also some other changes to microbiological examination procedures. For example, the in-house *C. perfringens* enterotoxin assay used by the reference laboratory in IID1 was no longer available and so isolates were examined for enterotoxin using a commercial immunoassay.

A major change between IID1 and IID2 was the decision not to fund collection of samples for pathogen detection from a control group. This meant restricting the range of pathogens sought and had implications for defining positive samples using molecular methods (see Section 8.2.5.2). A summary and rationale for the changes to microbiological methods is presented in Table 2.6.

Table 2.6: Changes in microbiological methods between IID1 and IID2

Bacteria	**Change from IID1**	**Reason**
Aeromonas spp	Not tested	Of doubtful pathogenicity and significance.
Arcobacter spp	Not tested	Of doubtful pathogenicity significance.
Bacillus spp	Not tested	Very few cases in IID1. Difficult to confirm pathogenicity.
Campylobacter spp	Do not use filter method or Skirrow medium	Filter method primarily for *C. upsaliensis*. Very few positives in IID1.
Clostridium difficile cytotoxin	Immunoassay to detect toxins A&B	Commercial immunoassay to replace in-house cytotoxin test
Clostridium perfringens	Use immunoassay to screen for enterotoxin	A more specific and meaningful test than spore counts.
Escherichia coli O157	Use CT-SMAC	CR-SMAC used in previous study. CT-SMAC now in routine use.
Listeria spp.	Include as a new pathogen	*L. monocytogenes* is one of the FSA's target organisms.
Plesiomonas shigelloides	Not tested	Very low numbers in IID1.
Staphylococcus aureus	Not tested	Low numbers in IID1. Similar numbers in cases and controls
Vibrio spp	Not tested	Frequency in UK too low, but is included for cases with history of recent foreign travel.
Yersinia spp	Change of enrichment protocol	Adopt HPA standard method.
Protozoa		
Cryptosporidium parvum *Giardia intestinalis*	Testing of faeces by PCR will increase the yield and provide confirmation	Genotyping is of epidemiological importance
Viruses		
Adenovirus 40, 41 Astrovirus Rotavirus A and C Norovirus Sapovirus	PCR assays	Not available at the time of previous IID study. Archive results from previous IID study indicate this is important.

2.6.3 Objectives

The objectives of the IID2 study were to:-

1. Estimate prospectively the number and aetiology of cases of IID in the population, contacting NHS Direct/NHS24, presenting to GPs and having stool specimens sent routinely for laboratory examination in the UK.
2. Compare these numbers and the aetiologies with those captured by the UK laboratory reporting surveillance systems and with calls to NHS Direct in England and NHS24 in Scotland.
3. Determine the proportion of cases of IID likely to have been acquired abroad.
4. Compare the surveillance patterns from the first and second studies of infectious intestinal disease for England using reporting ellipses.
5. Compare the aetiology of IID in the first and second IID studies for England.
6. Estimate the number of cases of IID in the population of each UK nation, based on recall, via a national Telephone Survey of self-reported diarrhoea, conducted over two time periods: a week, and a month.
7. Compare the burden of self-reported illness through the national Telephone Survey with the burden of self-reported illness captured through NHS Direct in England and NHS24 in Scotland.
8. Compare the prospective and self-reporting methods for estimating IID incidence in the UK, over two time periods: a week and a month.

Additional objectives were to:-

9. Compare molecular methods with traditional microbiological techniques for IID diagnosis.
10. Determine the contribution of *Clostridium difficile* to the aetiology of infectious intestinal disease in the community.
11. Assess retrospective and prospective methods for determining IID burden.

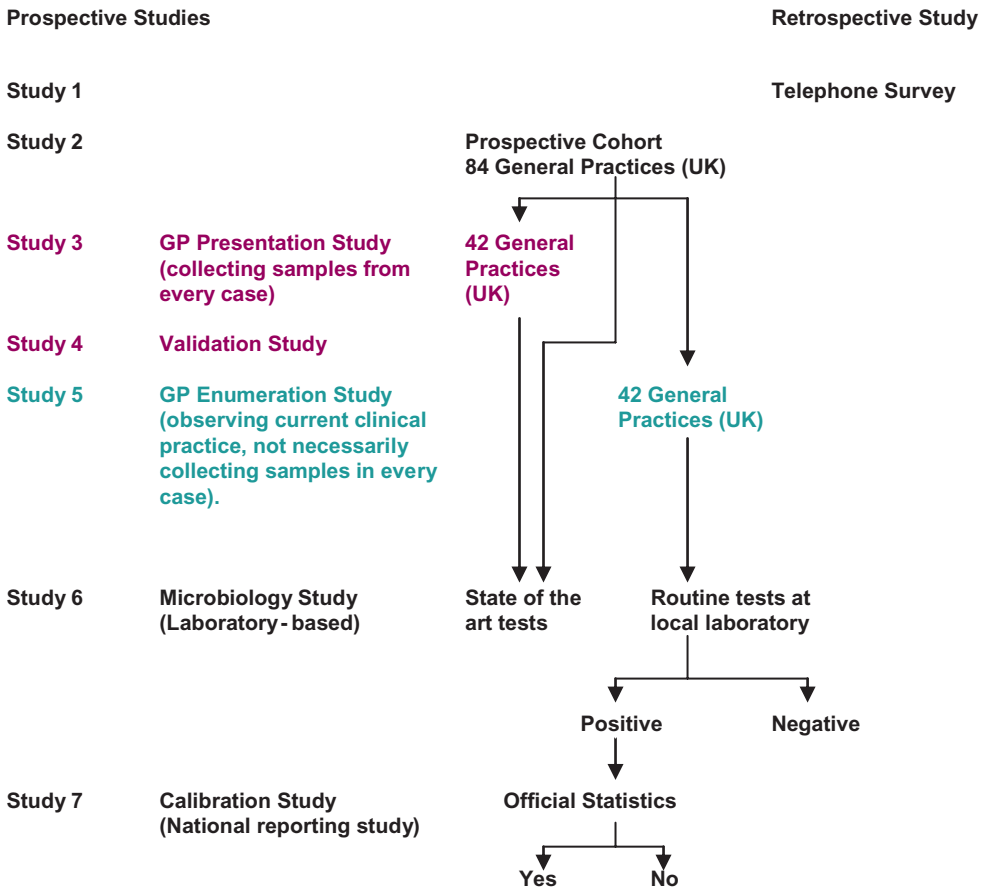
CHAPTER 3

METHODS

3.1 OVERVIEW OF STUDY DESIGN

The IID2 study was composed of seven separate, but linked studies (Figure 3.1) (O'Brien *et al*. 2010). We piloted the methods between 3rd September and 30th November 2007 and conducted the main studies concurrently between 28th April 2008 and 31st August 2009 (except for the Telephone Survey which ran from 1st February 2008 to 31st August 2009).

Figure 3.1: IID2 Study - Planned Design



3.1.1 Study 1: National Telephone Survey

In Study 1, we asked a sample of people, via a Telephone Survey, if they had recently experienced symptoms of diarrhoea or vomiting. We asked one group about symptoms during the previous seven days and another group about symptoms during the previous 28 days to compare estimates of community incidence of IID obtained using the two different time periods. We compared this with the incidence estimate from Study 2 (Prospective Population-Based Cohort Study). We also compared incidence rates in the four UK countries.

3.1.2 Study 2: Prospective Population-Based Cohort Study

In Study 2, we aimed to recruit 8,400 people at random and follow them up for a period of one year from 84 General Practices across the United Kingdom - the sample size required to detect a 20% reduction in the incidence of IID presenting to general practice since the mid-1990s. We followed

up participants weekly for one calendar year to find out how many developed new symptoms of IID. People who developed IID completed a symptom questionnaire about their illness and their contact with health services, e.g. NHS Direct/NHS24, and provided a stool sample. We compared the community incidence of IID with corresponding estimates from the Telephone Survey. We also compared the incidence of IID in England in 2008-9 with the incidence in 1993-6, at the time of IID1. We randomly assigned the practices in Study 2 into two groups – those taking part in Studies 3 and 4, or those taking part in Study 5 (see below).

3.1.3 Study 3: General Practice (GP) Presentation Study

In Study 3 (42 practices) Study Nurses invited everyone who consulted their GP for a new episode of IID to complete a symptom questionnaire and provide a stool sample. We used this information to estimate the incidence and aetiology of IID in people presenting to primary care.

3.1.4 Study 4: General Practice (GP) Validation Study

In Study 4 we audited recruitment to the GP Presentation Study (Study 3). Study Nurses searched practice records for anyone presenting with an episode of IID to the practices taking part in Study 3 during the study period. They generated a list of all the patients that should have been included in Study 3 using Read diagnostic codes (Chisholm, 1990) and compared this with the actual recruitment list. We used this information to adjust incidence estimates in Study 3 for under-ascertainment.

3.1.5 Study 5: General Practice (GP) Enumeration Study

In Study 5 we aimed to recruit the remaining 42 practices. Study Nurses searched practice records for anyone presenting with an episode of IID. They recorded the patient's age, sex, postcode, place of consultation, admission to hospital and whether or not a stool sample was requested. If a sample was requested they recorded the result. We used this information to estimate the proportion of IID-related consultations in routine practice that have laboratory-confirmed infection documented in the medical records.

3.1.6 Study 6: Microbiology Study

In Study 6, all stool samples from Studies 2 and 3 were examined first at the HPA Manchester Laboratory using conventional microbiological techniques and then at the HPA CfI at Colindale using molecular methods.

3.1.7 Study 7: National Reporting Study

In Study 7, we used the results from studies 1 to 6 to estimate under-ascertainment of community IID in national surveillance data by comparing the incidence estimates from Studies 1 to 6 with those generated from national surveillance.

3.2 SETTING

The setting for the study was the population of the United Kingdom (UK). The sampling frame for the prospective studies comprised the Medical Research Council General Practice Research Framework (MRC GPRF) and Primary Care Research Networks in England, Wales, Scotland and Northern Ireland. In the Telephone Survey we created a database of landline telephone numbers by taking a random selection of telephone numbers from GP surgeries across the UK and changing the last three digits.

3.3 CASE DEFINITIONS AND EXCLUSION CRITERIA

Cases of IID were defined as people with loose stools or clinically significant vomiting lasting less than two weeks, in the absence of a known non-infectious cause, preceded by a symptom-free period of three weeks. Vomiting was considered clinically significant if it occurred more than once in a 24-hour period and if it incapacitated the case or was accompanied by other symptoms such as cramps or fever.

The exclusion criteria were:-

- Patients with terminal illness.
- Patients whose first language was not English and for whom a suitable interpreter was not available.
- Patients with severe mental incapacity.
- Patients with non-infectious causes of diarrhoea or vomiting: Crohn's disease, ulcerative colitis, cystic fibrosis, coeliac disease, surgical obstruction, excess alcohol, morning sickness and, in infants, regurgitation.

These exclusions were employed because an infectious aetiology could not reliably be determined, and because it would have been difficult to determine date of onset for acute symptoms among patients with these conditions.

A case of *Clostridium difficile*-associated diarrhoea was defined as an individual with symptoms of diarrhoea not attributable to another cause (i.e. in the absence of other enteropathogens), occurring at the same time as a positive toxin assay.

3.4 ETHICS COMMITTEE FAVOURABLE OPINION AND CONSENT

We received a favourable ethical opinion from the North West Research Ethics Committee (07/MRE08/5) on 19th April 2007. In addition we sought NHS Research Management and Governance approval for each of the study sites. This amounted to 37 separate applications and approvals.

We obtained and recorded oral informed consent from participants in the Telephone Survey using the CopyCall Telephone Recorder. We obtained written informed consent from all adults in the prospective studies. We obtained written informed assent from children and written informed consent from their parent or guardian.

3.5 PILOT STUDIES

We undertook the pilot studies between 3rd September 2007 and 1st December 2007 and submitted a full report to the Food Standards Agency in December 2007. We have included an overview of the pilot studies to explain changes made to the original protocol.

3.5.1 Objectives

The objectives of the pilot studies were:-

3.5.1.1 National Telephone Survey: To assess the recruitment process, participant compliance and efficiency of data entry procedures.

3.5.1.2 Prospective Population-Based Cohort Study: To test the feasibility of the recruitment process and the efficiency of participant follow-up, both overall and by practice, and to assess the procedures for case ascertainment and the quality of data entered into a web-based system.

3.5.1.3 GP Presentation Study: To assess the level of case referral by GPs, evaluate procedures for work-up of IID cases and assess the quality of data entered into the web-based system.

3.5.1.4 GP Validation Study: To evaluate the search strategy for identifying patients with IID from practice records using Read codes in practices undertaking the GP Presentation Study.

3.5.1.5 GP Enumeration Study: To evaluate the search strategy for identifying patients with IID from practice records using Read codes in the remaining GP practices, where clinical practice was simply observed.

3.5.1.6 Microbiology Studies: To determine the number of stool samples available in sufficient quantity for testing, to obtain initial estimates of the frequency of organisms identified by microbiological examination (including enrichment and PCR), and to measure the time taken for data transfer between laboratories and GPs.

3.5.2 Methods

3.5.2.1 National Telephone Survey

The pilot study took place between 18th October 2007 and 1st December 2007. First, we generated a landline number bank by obtaining the full list of GP practices in each UK country, randomly selecting 100 of these practices, and then replacing the last three digits of the surgery telephone number with 150 randomly generated numbers between 000 and 999. Telephonists selected numbers at random from the number bank and dialled. For valid numbers they made up to four attempts to contact the household on various days and at different times.

For valid telephone numbers, the telephonists asked the person who answered the telephone if they wished to take part in the survey. If they agreed they were then asked to choose the household member (present at the time of the call) whose birthday occurred next. Telephonists sometimes interviewed respondents aged ≥12 years directly, but they interviewed a parent or guardian about participants aged <12 years. Telephonists obtained verbal informed consent from all participants and parents of children aged <16 years. They recorded all calls using CopyCall Telephone Recorder software. Telephonists asked respondents whether they had experienced diarrhoea and/or vomiting and basic demographic characteristics. If respondents reported diarrhoea and/or vomiting, telephonists asked more detailed questions about symptoms and timing, use of healthcare service, diagnostic methods, treatment practices and the effect of their illness on work and daily activities.

3.5.2.2 Prospective Population-Based Cohort Study

The pilot studies in primary care began on 3rd September 2007. Six volunteer general practices were recruited to take part in the pilot study – five from England and one from Scotland. Study Nurses generated a random sample of people from the practice age-sex register. They sent study information to eligible subjects with a reply slip and stamped, addressed envelope. They followed up non-responders with a second letter and then a telephone call. Study Nurses invited people who were interested (up to a maximum of 30 participants) to attend a baseline recruitment interview. If they agreed to participate the Study Nurses asked if they would prefer to be followed-up via replying to a weekly automated e-mail or by returning weekly postcards. Study Nurses obtained written consent from all participants (assent from children). They entered data onto a secure, bespoke web-based database. The Study Nurses stopped recruiting when they reached their target of 30 people enrolled.

3.5.2.3 GP Presentation Study

This took place between 17th September 2007 and 19th November 2007 in three practices selected randomly from the six practices undertaking the Cohort Study. People who fulfilled the case definition and consulted a GP or nurse in person or by telephone, or were seen by out-of-hours providers (excluding NHS Direct/NHS24) were invited to take part. If they were interested, the person conducting the consultation gave them a study information sheet and a specimen pot and informed them that the Study Nurse would contact them. The GP completed a referrals notepad and sent the referral to the Study Nurse.

3.5.2.4 GP Validation Study

The three practices conducting the GP Presentation Study also undertook the GP Validation Study during the same time period. The Study Nurses conducted a search of the practice records using a list of IID-related Read codes (Appendix 2) and produced a line list of all people who had presented to the practice with a new episode of IID between 17th September 2007 and 19th November 2007. Having collected the validation data the Study Nurses then checked the line list against the list of people recruited into the GP Presentation Study.

3.5.2.5 GP Enumeration Study

The GP Enumeration Study covered the period between 17th September 2007 and 19th November

2007 and took place in the three practices not taking part in the GP Presentation Study. Study Nurses conducted a search of the practice records using a list of IID-related Read codes (Appendix 2) and produced a line list of all cases of IID that had presented to the practice during the study period.

3.5.2.6 Microbiology Studies

Microbiological testing was performed at two sites. Diagnostic testing (traditional microbiology) was performed at the HPA Regional Laboratory at Manchester and molecular testing at CfI, Colindale, London.

3.5.3 Results and Discussion

3.5.3.1 Telephone Survey

In the six-week pilot period, a total of 5,608 telephone numbers (including invalid numbers, non-answered calls, ineligible numbers and refusals) was dialled. Of the 2,251 subjects with valid residential telephone numbers invited to take part in the survey, 887 (39.5%) completed an interview. Issues identified in the pilot study included the inefficiency of making three calls to valid numbers, difficulties with implementing the next birthday method of sampling within households and problems applying questions on socioeconomic classification.

3.5.3.2 Prospective Population-Based Cohort Study

In total, 2,213 eligible participants were invited of which 327 (14.8%) people responded positively and 169 (51.9%) of these joined the cohort during the time allotted for the pilot. Of those declining, 25% stated that they had insufficient time to participate, 35% were not interested in taking part, 16% said that they were often away and 24% gave other reasons. The most commonly cited "other reason" for not taking part was not having (or never having) had diarrhoea and/or vomiting (34%). We needed to amend the participant invitation letter and information sheets to clarify the fact that participants need not have (or ever have had) diarrhoea or vomiting in order to take part in the study.

Compliance with follow-up was good regardless of whether the participant chose e-mails or postcards and the quality of data on the web-based database was high.

The implication of the pilot study was that we needed to invite a larger number of people to achieve the required sample size than we had anticipated initially.

3.5.3.3 GP Presentation Study

In total 23 patients presenting to their GP were invited to take part, 16 responded positively (70%) and 13 (81%) were recruited. One patient had recovered before their interview and two patients did not attend their appointment.

3.5.3.4 GP Validation Study

Sixty-five eligible IID-related consultations were identified corresponding to an average of three consultations per practice per week. In total, 13 cases (20%) were recruited into the GP Presentation Study representing an average recruitment rate of 0.6 cases per week.

Anecdotal evidence from the Study Nurses suggested that General Practitioners were just becoming accustomed to introducing the IID2 study to symptomatic patients when the pilot study stopped.

3.5.3.5 GP Enumeration Study

One hundred and twenty-six consultations were identified in the three practices taking part in this study corresponding to an average of 4.7 IID-related presentations per practice per week. Apparent discrepancies between the Validation and Enumeration Study results related to practice

size, age/sex distribution of patients registered with the practices, the use of different GP clinical management software systems and inconsistencies in Read coding between practices.

3.5.3.6 Microbiology Studies

Twenty seven stool samples were submitted to the HPA Manchester Laboratory between 10th October 2007 and 30th November 2007. Three were insufficient for full examination resulting in 24 specimens (89%) being examined and sent to the HPA Centre for Infections for molecular testing. Of the 24 specimens examined in Manchester, a pathogen was detected in four (16.6%). *C. perfringens* enterotoxin was detected in three specimens (12.5%) and *Giardia* spp. in one specimen (4.2%). Of the 24 samples received at CfI a pathogen was detected in 11 (45.8%) samples. Norovirus was detected in seven (29.2%) samples and sapovirus, astrovirus and *Campylobacter jejuni* in one (4.2%) sample each. A mixed infection with rotavirus and *Giardia* spp. was detected in one (4.2%) sample.

3.5.4 Implications for the Main Studies

The major implications arising out of the pilot studies included:-

- Inefficiency of three or more telephone call for unanswered calls in the Telephone Survey.
- Difficulty operating the next birthday method of sampling in the Telephone Survey.
- Lower than anticipated participation in the Cohort Study.
- Lower than anticipated invitations from GPs to patients to take part in the GP Presentation Study.
- Difficulty applying census questions on socio-economic classification in the Telephone Survey and Cohort Study. This proved more of a problem in the Telephone Survey where some individuals became very suspicious of detailed questions about their occupation.

3.5.5 Changes to the Study Protocol and Study Material as a Result of the Pilot Studies

3.5.5.1 Dropping the Third Telephone Call

The third telephone call was abandoned unless this was by prior arrangement with a survey participant.

3.5.5.2 Replacing the Next Birthday Method of Random Sampling within Households

We replaced the next birthday method of random selection with a method that used seniority within the household. Household size was used to generate a random number reflecting age relative to other household members (i.e. 1st oldest, 2nd oldest ....nth oldest).

3.5.5.3 Improving Participation in the Prospective Population-Based Cohort Study

To improve Cohort Study participation we:-

- Redrafted invitation letters and participant information sheets to make it clear that participants did not need to have symptoms (or ever have had symptoms) in order to take part in the study.
- Doubled the size of the mail-shot to ensure that we achieved the required sample size.

3.5.5.4 Improving Invitations to the GP Presentation Study

To improve invitations by GPs into the GP Presentation Study we:-

- Used professionally designed posters to increase awareness of the study for those people in the waiting room, so that patients could ask the receptionist for an information leaflet, make another appointment with the Study Nurse or ask their GP about the study during the consultation.
- E-mailed each practice their observed referral rates against the expected referral rates and a short newsletter with anonymised charts comparing practice performance.
- Asked the Study Nurses to perform monthly validation searches with the top five Read codes to track recruitment by practice and then to target practices with lower invitation rates with site visits, or offers of extra support.

3.5.5.5 Streamlining questions on occupation

We included a question on job title in the Cohort Study and the Telephone Survey. In the Cohort Study we continued to ask the full set of Census questions in order to assign socioeconomic classification. In the Telephone Survey we planned to code occupation using Computer Assisted Structured Coding Tool (CASCOT) software[2] to compare the Telephone Survey group with the Cohort Study group based on job title.

A revised study protocol was submitted to, and approved by, the North West Multi-Centre Research Ethics Committee on 6th March 2008. The changes could not be implemented before NHS Research Management and Governance approval had been granted by each of the 37 NHS R&D Organisations. Completing this process took approximately four months.

3.6 MAIN STUDIES

The main studies took place from 28th April 2008 to 31st August 2009. The exceptions were that the Telephone Survey continued from 1st February 2008 and practices that took part in the pilot study carried on recruitment and weekly follow-up of pilot participants. However, changes to the protocol were not implemented at local level until Ethics and R&D approvals had been granted. This meant a staggered start to recruitment in the main study. The study methods are described in full below.

3.6.1 National Telephone Survey of Self-Reported Illness

We created an IID2 Study telephone numbers database by obtaining the full list of GP practices in each UK country, randomly selecting 100 of these practices, taking their contact number, and replacing the last three digits with 150 randomly generated numbers between 000 and 999. To compensate for potential over-sampling in urban areas, noted in the pilot study, we also included telephone number stems from primary school listings (21,750 schools across the UK) and deleted any duplicate numbers.

We selected households by random digit dialling of land lines from the IID2 Study telephone numbers database. We did not use mobile phone numbers. The risk of introducing bias by not using mobile phone numbers was offset by a number of considerations:-

- The use of mobile phone numbers is not yet standard and reliable sampling frames are not readily available.
- Many mobile phone users are children and it would have been unethical to contact them directly.
- It is not easy to localise mobile phones to a geographical area.

In general terms, people without landlines tend to be younger and of lower socio-economic status – groups who tend to respond poorly to surveys. It is, therefore, unclear whether use of mobile phone numbers would help to mitigate selection bias. However, to assess the potential for bias introduced by only using landlines, we asked people recruited into the Prospective Population-Based Cohort Study about their main method of telephony. Approximately 95% reported primarily using a landline.

A well-trained team of six to 10 part-time telephonists made calls between 5 pm and 9 pm on weekdays and between 10 am and 2 pm at weekends. Telephonists did not know the name of the respondent, or the property they were calling. As telephone number generation was completely random, the number sometimes belonged to a commercial property or a fax machine or had not been assigned. When this happened, or if a valid household refused to take part, the telephonists did not call the number again. For valid numbers telephonists made no more than three attempts to contact the household on different occasions, according to an agreed algorithm (Appendix 3).

[2] http://www2.warwick.ac.uk/fac/soc/ier/publications/software/cascot/details/ - Date accessed 19th July 2010

Telephonists randomly selected participants (present at the time of the call) in households with more than one person by asking to speak to the "Nth" oldest person in the household. "N" was a computer-generated random number based on the number of people at home at the time of the call. All participants gave oral consent to take part in the survey. If the person selected was a child under 12 years of age, the telephonists interviewed the parent or guardian. For participants aged between 12 and 16 years old the interview was conducted either with the parent or guardian or with the child, depending on parental preference.

The Telephone Survey incorporated questions on socio-demographic characteristics, recent history of foreign travel, details of any clinical symptoms of IID and healthcare seeking behaviour (if appropriate) (Appendix 4). To investigate whether the accuracy of symptom reporting varied according to recall period, we assigned participants randomly to questions about symptoms within the previous seven days (80% of interviews) or 28 days (20% of interviews). Calls were recorded using CopyCall Telephone Recorder or Retell 957 software. This call recording software started recording automatically when the telephone call began, and stopped and saved the call automatically when the call ended. All recordings were stored centrally and time-date stamped so that specific files could be accessed easily. Calls were recorded to allow double data entry for data validation, and to fulfil the ethical requirement for documented informed consent. The telephonists entered data directly onto a bespoke, secure, electronic database (Microsoft Access™) during the course of the interview and data were stored off-site as a safety measure.

3.6.2 Prospective Population-Based Cohort Study

We conducted the Prospective Population-Based Cohort Study in 88 practices. Fifty-seven practices were from the MRC GPRF, 29 from the Primary Care Research Network in England and two from the Scottish Primary Care Research Network.

3.6.2.1 Training

Staff at the MRC GPRF organised training for the Study Nurses taking part in the study to ensure they understood the protocol. Most of the training sessions were held in London and each lasted a day. The agenda covered the background, study design and procedures, specimen collection, record searches and electronic data capture (Appendix 5). We covered all relevant aspects of good clinical practice in research (GCP), including how to obtain informed consent (or assent) and collect, process and store data securely. The sessions were led by members of the IID2 study team including the Chief Investigator, Project Manager, Study Manager, Microbiologist, Senior Research Nurse, Senior Nurse Manager and Senior Clinical Scientist. We conducted 19 one-day training sessions in total and approximately 10-20 nurses attended each time. We trained Study Nurses from a further eight practices on site since they were unable to attend the training days in London.

We used standardised training materials to ensure consistency and trained Study Nurses from practices taking part in the GP Presentation and Validation Studies separately from those taking part in the Enumeration Study to avoid any potential confusion.

We covered electronic data capture during the training days and showed the Study Nurses how to use a bespoke, secure web-based data system developed by Egton Software Services (see section 3.9) via a training website. We ensured that they could log in to the training website after the training day to familiarise themselves with the system before they recruited their first participants. They received a comprehensive Study Nurse manual detailing all aspects of running the study in the practice including the recruitment processes, exclusion criteria, case definition and follow up procedures. To avoid any confusion, there were separate manuals for those conducting the GP Presentation/ Validation studies, and for those conducting the Enumeration Study. There was also a training manual for the web-based system, along with instructions on how to use the study registers, randomly select patients from their practice list, perform a mail merge, and collect specimens.

In addition, we gave Study Nurses the reporting algorithm from the laboratory, detailing the reporting process from the laboratory to the practice.

3.6.2.2 Participant recruitment

The aim was to recruit 100 randomly selected participants of all ages in each practice and to follow them up for a period of one calendar year from their recruitment date. Study Nurses generated a randomised list of 800 individuals from the practice age-sex register via practice software or by using Research Randomizer[3]. They carried out a brief record search. The GPs in the practice reviewed the lists prior to the invitations being sent to identify people who should not be approached because they met the exclusion criteria or those who it would be inappropriate to invite. Exclusions at this stage were logged on a study register.

Study Nurses posted study information (Appendix 6) to adults along with a reply slip and pre-paid envelope. For children they sent invitation letters and study information to the parent or guardian, along with a child information sheet (Appendix 6) and a pre-paid return envelope. Recipients indicated on the reply slip whether they were interested in learning more about the study or not. If they were not interested they were asked to state why. Non-responders received a second letter a fortnight after the original invitation (Appendix 6).

Individuals who expressed interest in the study were invited to attend a baseline recruitment interview. At this session the Study Nurse went through a Microsoft PowerPoint™ presentation about the study (Appendix 7). People who agreed to take part provided written, informed consent (Appendix 8), and baseline demographic and socioeconomic information (Appendix 9). Children were invited to the surgery with their parent or guardian. The child and parent or guardian was taken through the consent procedure using child study material. If the child was willing to participate, their parent or guardian provided consent. Baseline data were recorded on the secure web-based system. Study Nurses gave the participants a stool sample kit with written instructions on how to collect and send a stool sample to the HPA Regional Laboratory in Manchester if they developed symptoms of IID (Appendix 10). In addition participants received a short symptom questionnaire (Appendix 9) to be completed and returned to the Study Nurse in a pre-paid envelope if they experienced symptoms. The symptom questionnaire included questions on date of onset and duration of symptoms, symptom profile and severity, contact with healthcare services as a result of the illness (including contact with NHS Direct or NHS24, contact with or visits to a general practice clinic, walk-in centre or accident and emergency department, and visits to hospital including any overnight stays) and history of foreign travel in the 10 days before symptom onset (Appendix 9). Study Nurses provided replacement sample pots and questionnaires for participants who developed symptoms, in case they experienced multiple episodes during the study period. They sent out the replacement study materials three weeks after the illness episode to ensure that any further samples were from a new episode of illness. Participants received instructions for completing the weekly follow-ups, and could elect to be followed-up either by e-mail or by postcard, as described in the next two sections.

All the information on identification and recruitment of participants was recorded on a study register (Appendix 11). This register was created in Microsoft Excel™ format. Anonymised registers were transferred to the MRC GPRF Coordinating Centre by e-mail on a weekly basis for inclusion in a central database.

3.6.2.3 E-mail follow-up

To be eligible for the e-mail group, participants needed to access their e-mail account more than three times a week. They were asked to ensure that the e-mail would not enter the "Spam" folder.

[3] Available at www.randomizer.org - Date accessed 25th June 2010

They received an automated e-mail every Monday and were asked to click on the appropriate hyperlink within the body of the email to report whether or not they had experienced symptoms of diarrhoea and/or vomiting during the previous 7 days (Appendix 12). Responses were recorded automatically onto the web-based data system. A reminder e-mail was sent automatically if the participant did not respond after three days. The Study Nurses also ran a weekly report to identify non-responders, who were then contacted by telephone and asked to respond to the e-mail. If participants persistently failed to reply to their e-mails they were dropped from the study after four weeks of consecutive non-response. We also stopped sending e-mails to participants who chose to withdraw from the study.

3.6.2.4 Postcard follow-up

Participants who chose to be followed up by postcard were given 52 pre-dated, postage-paid postcards (Appendix 12). They were asked to return a postcard to the Study Nurse each week indicating whether they had experienced symptoms of diarrhoea and/or vomiting during the previous 7 days (as per e-mail follow-up). Study Nurses entered information from postcards onto the web-based data system. They ran weekly reports to identify missing postcards and telephoned non-responders reminding them to mail their postcard. If a participant did not return postcards on four consecutive weeks, they were dropped from the study.

3.6.2.5 Second phase of recruitment

During the first phase of recruitment to the Prospective Population-Based Cohort Study, certain groups (16-24 year-old males and 25-34 year olds) were particularly under-represented. These groups were targeted with revised study material aimed specifically at these age groups during a second phase of recruitment (Appendix 6).

A random list of 250 individuals aged between 16 and 34 years was generated from the patient register of each practice. Those who had been approached previously in the first phase of recruitment were excluded, and the remainder received a letter signed by their GP. This contained an invitation to take part in the study, an information sheet that explained the study and what would be involved if they agreed to participate, and a pre-paid envelope in which to return their response. People who were interested in the study were recruited using the procedures described above.

3.6.3 General Practice (GP) Presentation Study

General practices were assigned randomly to take part in the GP Presentation Study (and Validation Study) or the GP Enumeration Study (see section 3.6.5). The aim was to recruit all patients who fulfilled the case definition and consulted a healthcare practitioner (e.g. General Pracitioner or practice nurse) in person or by telephone, or were seen by an out-of-hours service provider. Telephone contact with NHS Direct/NHS24 was not included. Anyone registered with the practice who consulted their General Practitioner for an episode of IID was eligible unless they met the exclusion criteria (see section 3.3).

The Study Nurses introduced the GP Presentation Study to the General Pracitioners at practice meetings and other informal meetings. They provided each healthcare practitioner (normally the General Practitioner) with a laminated information sheet that included the case definition and a referral pad to provide minimal information for the Study Nurse (i.e. patient's name, date of birth and telephone number).

During the consultation all patients who fulfilled the case definition should have been invited to take part in the study. The healthcare practitioner gave them a study information sheet and a specimen pot and informed them that the Study Nurse would contact them. Children and their parent or guardian received a children's information sheet (Appendix 6).

The Study Nurses invited interested patients to attend a baseline recruitment interview. At this session the Study Nurse explained the study using a Microsoft PowerPoint™ presentation (Appendix

7). If the person agreed, they signed a consent form (Appendix 8) and completed a questionnaire containing baseline demographic and socioeconomic information, as well as clinical details regarding their illness and contact with healthcare services (Appendix 9). Children were invited to the surgery with their parent or guardian. The child and parent or guardian was taken through the consent procedure using child study material. For children willing to participate, their parent or guardian provided consent. If the participant brought a stool sample this was sent immediately to the HPA Manchester Laboratory. Otherwise the Study Nurse checked that the participant had a specimen pot and went through the instructions for collecting a sample (Appendix 10). Anonymised details of all patients referred to the Study Nurse were entered into an electronic study register (Appendix 11). Each Study Nurse sent an updated secure version of the study register to the MRC GPRF Coordinating Centre every week. This information was updated weekly on a central database.

3.6.4 General Practice (GP) Validation Study

The aim of the GP Validation Study was to determine the degree of under-ascertainment[4] of recorded IID in the GP Presentation Study. All practices participating in the GP Presentation Study took part in the Validation Study. Study Nurses in each practice searched the practice database once a month, throughout the duration of the GP Presentation Study, using a pre-determined set of Read codes (Appendix 2) to identify all IID-related presentations occurring during the same time period as the GP Presentation Study.

The Study Nurses recorded the following details, where available in the medical records, on a standard form:- the case's age, sex, symptoms, date of onset and information about the place of consultation, admission to hospital, recent travel outside the UK, time off work/school and whether or not a stool specimen had been requested (Appendix 9). If a stool sample was requested as part of the consultation and the results were recorded in the medical records, the Study Nurse recorded the result. Once the Study Nurses had completed this search, they checked to see if the case had been recruited into the GP Presentation Study. If so, they recorded the relevant GP Presentation Study number onto an electronic study register (Appendix 11), which contained anonymised data on all patients in the Validation Study (including age, sex and study ID). Hard copies of all anonymised forms were forwarded to the MRC GPRF for entry onto a dedicated Microsoft Access™ Validation database. The anonymised electronic study registers were also forwarded to MRC GPRF Coordinating Centre on a monthly basis.

3.6.5 General Practice (GP) Enumeration Study

The GP Enumeration Study was a survey of routine clinical practice for the management of IID cases and of IID organisms identified in routine laboratory practice. The aim was to compare the results of the GP Presentation and Enumeration Studies to determine the relationship between the total number of people who consulted their GP with IID, and the number of people who consulted with IID and had the cause of their infection laboratory confirmed in routine clinical practice. Using the same pre-determined set of Read codes as that used in the Validation Study (Appendix 2), the Study Nurses identified all patients from the practice database for whom the consultation coding was compatible with IID. Where available in the medical records, they recorded the following details directly on the web-based data system:- the case's age, sex, symptoms, date of onset, place of consultation, admission to hospital, recent travel outside the UK, time off work/school and whether or not a stool sample was requested. If a stool sample was requested as part of the consultation, and a result was recorded in the medical records, the Study Nurse recorded the result (Appendix 9).

3.6.6 NHS DIRECT/NHS24

The HPA Real-Time Syndromic Surveillance Team in Birmingham provided data on calls to NHS Direct and NHS24 during the two-year period 1st July 2007 to 30th June 2009. We excluded data for the last two months of the IID2 Study (1st July 2009 to 31st August 2009) to avoid artefacts in call rates resulting from the H1N1 influenza pandemic. The introduction of emergency telephone

[4] Under-ascertainment is used to assess the completeness of referral of eligible cases into the study.

assessment tools for colds and flu during this period led to a dramatic drop in the calls to these services that were categorised as diarrhoea and vomiting.

For NHS Direct we obtained anonymised individual records on all calls for which the main complaint was recorded as 'Diarrhoea', 'Vomiting' or 'Food poisoning'. Information was available on each call regarding date of the call, the age and sex of the patient, call type (based on the predominant complaint as assessed by the triage nurse) and call outcome (based on what the caller was advised to do).

For NHS24, only aggregated data were available. We obtained the number of calls received each day for which the main complaint was recorded as 'Diarrhoea' or 'Vomiting', aggregated by age group. Information on sex and call outcome was not available.

3.6.7 National Surveillance Study

Individual, anonymised records of positive identifications of IID-related pathogens reported to each of the national surveillance systems between 1st April 2008 and 31st August 2009 were downloaded from the respective databases. The laboratory reports requested covered the range of pathogens sought in the IID2 Study. To allow for reporting delays the data were extracted after 1st December 2009. The data fields extracted were:-

- Unique identifier
- Country
- Age in years
- Sex
- All available date variables (date of onset, date of specimen, date of receipt, date of report to GP, week number).
- All available pathogen information (genus, species and any other sub-classification and typing information).
- Information on foreign travel (if available).

Only reports of stool samples were included. If repeat specimens were available for an individual patient only the first specimen result for an illness episode was included. The following pathogen reports were excluded:-

Salmonella Typhi and *S.* Paratyphi, *Vibrio cholerae*, *C. difficile*, *Yersinia* spp. other than *Y. enterocolitica* and sapovirus. There is no national surveillance for sapovirus, and most laboratories do not look for it. *C. difficile* was excluded because most of the reports to national surveillance for this organism arise from heathcare settings rather than the community.

3.6.8 Sample Size Calculations

3.6.8.1 Telephone Survey

The sample size calculations for estimating the overall frequency of IID via self-report Telephone Survey for each UK nation are shown in Table 3.1

Table 3.1: Sample size calculations for estimating the overall frequency of IID via self-report - Telephone Survey

Duration of recall period	Incidence in IID1 recall questionnaire	Widest acceptable Confidence Interval (CI)	Number needed to survey in each UK nation
28 days	6%	4%	500
7 days	1.5%	1%	2,500

The sample size calculation was based on an expected frequency of IID of 6%, with a 95% confidence interval (CI) of 4% to 8%. Allowing for differentials in response rate the number needed to survey in each UK nation was increased by 20% i.e. to 600 for recall over 28 days and to 3,000 for recall over seven days.

3.6.8.2 Prospective Population-Based Cohort Study

Table 3.2 shows the sample size calculations for estimating a single UK-wide surveillance pyramid for the Prospective Population-Based Cohort. This was based on the ability to detect a 20% change in incidence of all IID compared with IID1 with 80% power and 95% precision. The table shows the required number of person-years and GP practices (recruiting 100 patients from each practice) by country, based on the relative populations of the four UK countries.

Table 3.2: Sample size required for Prospective Cohort Study in order to estimate a single UK-wide surveillance pyramid

Organism	England				Wales	
	Baseline incidence*	Reduction to be detected	Person years	GP practices	Person years	GP practices
All IID	19.20%	20%	2,000	20	200	2
Severe cases*	6.00%	20%	7,000	70	400	4
Campylobacter	0.87%	20%	500,000	5,000	2,400	24
Salmonella	0.22%	20%	500,000	5,000	9,500	95
Campylobacter+Salmonella	1.10%	20%	200,000	2,000	2,000	20
Campylobacter+Salmonella + C. perfringens	1.34%	20%	100,000	1,000	1,600	16

Organism	Scotland		Northern Ireland		UK	
	Person years	GP practices	Person years	GP practices	Person years	GP practices
All IID	200	2	65	1	2,465	25
Severe cases*	700	7	300	3	8,400	84
Campylobacter	4,200	42	1,400	14	508,000	508
Salmonella	16,400	164	5,500	55	531,400	532
Campylobacter+Salmonella	3,400	34	1,200	12	206,600	207
Campylobacter+Salmonella + C. perfringens	2,800	28	1,000	10	106,200	107

* Cases presenting to General Practice

3.6.8.3 GP Presentation Study

Table 3.3 shows the sample size estimates for the GP Presentation Study in order to estimate a single UK-wide surveillance pyramid. The calculations were based on the ability to detect at least a 20% change relative to IID1 in cases of IID presenting to general practice with 90% power and 95% precision. The table shows the required number of person-years and GP practices (assuming an average GP practice size of 6,000 patients) by country, based on the relative populations of the four countries.

Table 3.3: Sample size required for the GP Presentation Study in order to estimate a single UK-wide surveillance pyramid

Organism	England				Wales	
	Baseline incidence*	Reduction to be detected	Person years	GP practices	Person years	GP practices
Campylobacter	4.10%	20%	115,000	20	7,000	2
Salmonella	0.16%	50%	41,000	7	3,000	1
Salmonella	0.16%	40%	67,000	12	4,000	1
Salmonella	0.16%	30%	127,000	22	8,000	2
Salmonella	0.16%	20%	302,000	51	18,000	3
C. perfringens	0.13%	20%	364,000	61	22,000	4
Organism	**Scotland**		**Northern Ireland**		**UK**	
	Person years	**GP practices**	**Person years**	**GP practices**	**Person years**	**GP practices**
Campylobacter	12,000	2	4,000	1	138,000	25
Salmonella	5,000	1	2,000	1	51,000	10
Salmonella	7,000	2	3,500	1	81,500	16
Salmonella	13,000	3	4,500	1	152,500	28
Salmonella	31,000	6	10,500	2	361,500	62
C. perfringens	38,000	7	13,000	3	434,500	75

* Incidence of GP presentation in IID1 study

3.6.9 Microbiology Studies

3.6.9.1 Stool Sample Collection

The stool sample collection kit (Figures 3.2 and 3.3) comprised a plastic universal container with a screw top and integral plastic spoon, a specimen pot label, absorbent wadding, a rigid plastic container into which the universal container was inserted, a strong cardboard box that complied with Post Office regulations for posting pathological specimens and a strong plastic postage-paid envelope addressed to the HPA Regional Laboratory in Manchester. The kit also contained an instruction sheet describing how to obtain a sample (Appendix 10). The universal container was marked at 10 ml indicating the quantity of sample required to enable the full range of tests to be performed. A laboratory request form to be returned with the sample was also included in the kit. This contained the following details:- name and address of the GP, name, age, address, date of birth and study number of the participant, clinical details, time and date of illness onset, date of specimen collection and history of foreign travel (Appendix 10).

Figure 3.2: Sample Collection Kit

Figure 3.3: Sample Container Packaging

3.6.9.2 Processing of Samples at HPA Regional Laboratory in Manchester

All stool samples from the Prospective Population-Based Cohort Study and the GP Presentation Study were examined first at the Manchester laboratory. On receipt in the laboratory, the weight of stool sample was estimated by assessing the volume of faeces and recording this in grams. Participant and GP details were transferred from the laboratory request form onto the laboratory computer database (Telepath™). Table 3.4 shows the range of tests performed at the HPA Regional Laboratory in Manchester. All samples were tested on the day of receipt. An initial 10% suspension of the stool sample was made in 0.1% peptone water and used to inoculate the various selective plating media and enrichment broths.

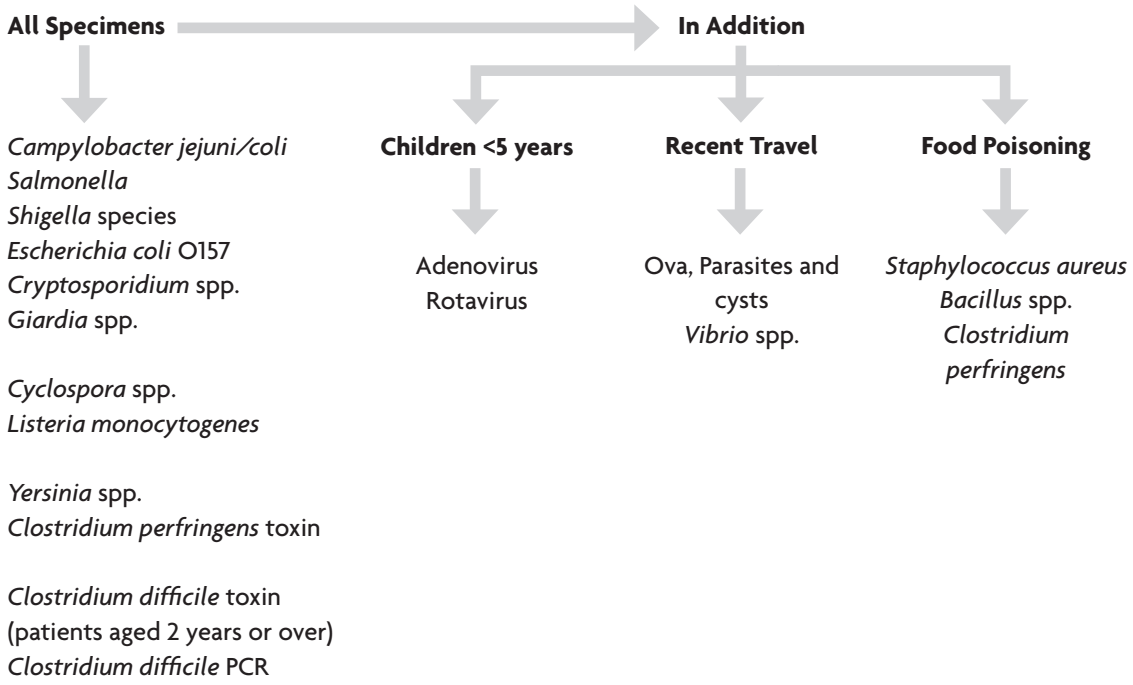
Figure 3.4 shows the flow diagram for sample processing at the HPA Laboratory in Manchester. At this stage the specimens were cultured for *Campylobacter jejuni/coli*, *E. coli* O157, *L. monocytogenes*, *Salmonella* spp., *Shigella* spp. and *Yersinia* spp. They were also examined by enzyme-linked immunoassay (EIA) for *C. perfringens* enterotoxin, *Cryptosporidium* and *Giardia* and by light microscopy examination of a stained smear for *Cyclospora* and *Cryptosporidium*.

Table 3.4: Target Organisms: Primary Diagnostic Methods

Bacteria	**Methods**
*Campylobacter jejuni/coli**	Direct plating - modified cefeoperazone, charcoal deoxycholate (CCD) agar. Enrichment culture – Preston broth.
Clostridium perfringens (enterotoxin)	Techlab™ (Blacksburg, USA) enzyme linked immunosorbent assay (ELISA), all positives to be cultured and isolates sent to the reference laboratory.
Clostridium difficile cytotoxin	Premier™ (Meridian Bioscience Inc., Cincinnati, OH) toxins A and B enzyme immunoassay (EIA)
Escherichia coli O157*	Direct plating on Cefixime Tellurite Sorbitol MacConkey agar. Enrichment in Modified Tryptone Soya Broth with Novobiocin.
Listeria spp *(monocytogenes)**	Direct plating – polymyxin acriflavine lithium chloride ceftazidime asculin mannitol (PALCAM) agar**
Salmonella spp*	Direct plating – Xylose Lysine Dextrose (XLD) Agar and Desoxycholate Citrate Agar (DCA). Enrichment culture – Selenite F broth and Rappaport Vasilliades Salmonella enrichment broth.
Shigella spp*	Direct plating – XLD and DCA.
Yersinia spp*	Direct plating - Cefsulodin Irgasin Novobiocin (CIN) selective agar. Enrichment culture – Tris Buffer Yersinia enrichment broth.
Protozoa	
Cryptosporidium parvum	Techlab™ Giardia/Cryptosporidium check, r-biopharm™ RIDA™ Quick Cryptosporidium; Modified Ziehl-Neelsen (ZN) stain
Giardia intestinalis	Techlab™ Giardia/Cryptosporidium check, r-biopharm™ RIDA™ Quick Giardia
Cyclospora	Modified ZN stain
Viruses	
Rotavirus	Premier™ Rotaclone
Adenovirus	Premier™ Adenoclone

* All positive isolates were sent to the relevant reference laboratory.
** PALCAM agar was used in previous studies (Jensen, 1993; Grif *et al*., 2003)

Figure 3.4: Flow Diagram illustrating the Microbiological Examination of Specimens at Manchester



As part of the routine diagnostic algorithm, samples from patients with a history of foreign travel were also tested for *Vibrio* spp. and for ova, cysts and microscopic parasites using National Standard Methods (BSOP30 and BSOP31[5]). If the patient was considered by the GP to be part of a potential food poisoning outbreak the samples were cultured for *C. perfringens*, *Staphylococcus aureus* and *Bacillus* spp. using National Standard Methods (BSOP30). All isolates of the major enteric bacteriological pathogens were submitted to the HPA CfI for specialist confirmatory tests and strain characterisation.

Two approaches were used for the detection of *C. difficile* positive stools. Samples from all patients aged 2 years or over were examined by EIA for *C. difficile* toxins A and B. All samples were tested using a commercial PCR kit (Cepheid™) and positive results determined according to the manufacturer's instructions.

Samples that were immunoassay positive for *C. difficile* toxin or PCR-positive were cultured using National Standard Method BSOP10[6] and all isolates recovered were typed using an established ribotyping technique (Brazier *et al*., 2008)

Two approaches for detecting viruses were used. Samples from children under 5 years of age were examined for rotavirus and adenovirus 40, 41 by immunoassay. This is routine clinical practice, which supported clinical management of the participants. Samples were batched and sent from Manchester to the HPA CfI via courier twice per week.

If the sample supplied was insufficient to allow the whole range of tests to be performed the laboratory staff asked the Study Nurses to encourage the case to submit another stool sample. If the stool sample was still too small, or the case did not provide another sample the criteria shown in Table 3.5 were applied. All samples were subsequently examined at the CfI for the five major viral pathogens by quantitative PCR.

[5] Available at http://www.hpa-standardmethods.org.uk/national_sops.asp - Date accessed 19th June 2010
[6] Available at http://www.hpa-standardmethods.org.uk/national_sops.asp - Date accessed 19th June 2010

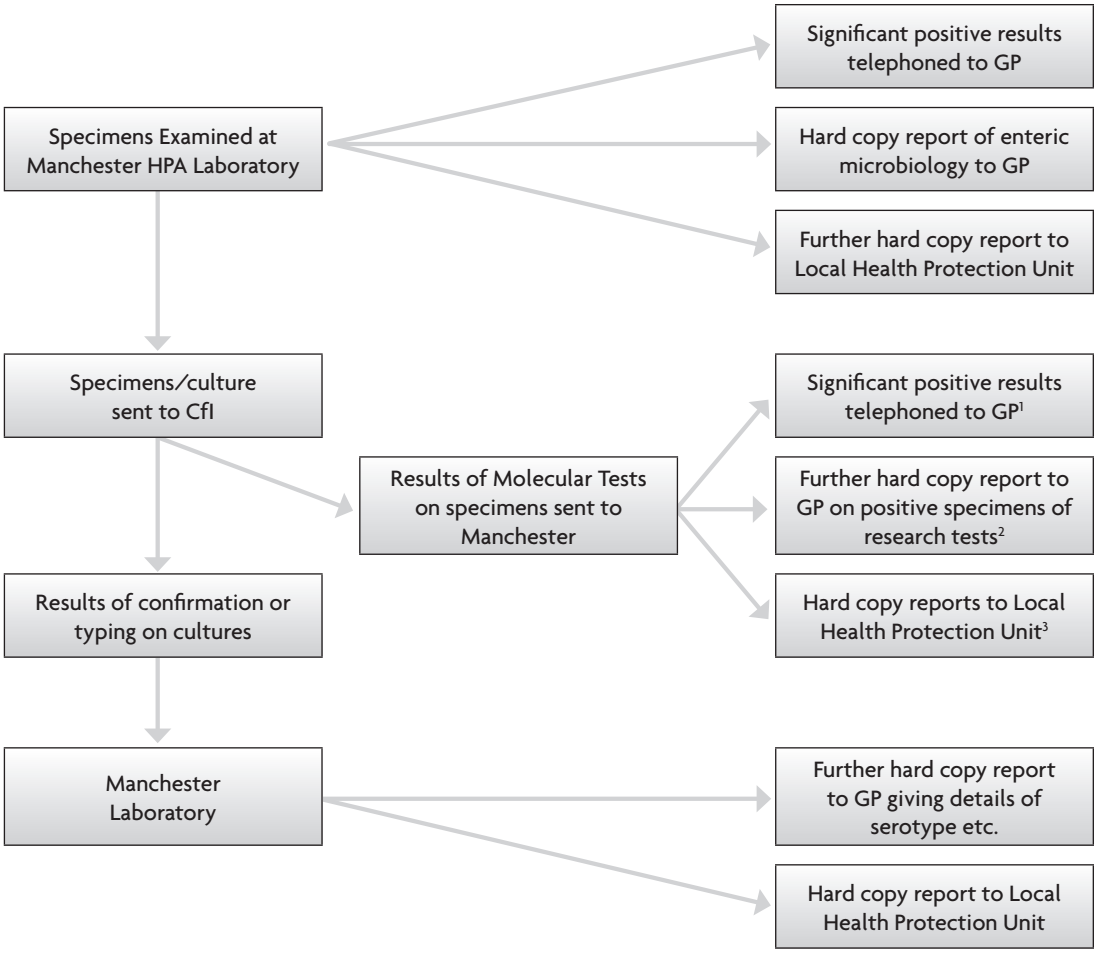
All primary diagnostic test results were reported to the originating GP practice using the Manchester laboratory computer system (Telepath™). Experienced clinical microbiologists reported by telephone to the Study Nurse or GP all positive findings deemed clinically significant. To assist with interpretation of results we developed a set of microbiology factsheets that we placed on our public-facing study website (www.gutfeelings.org.uk) (Appendix 13). Positive results were also notified to the local health protection unit. Any additional positive results from the PCR tests performed at CfI were also reported by the Manchester Laboratory. Details are shown in the reporting algorithm in Figure 3.5. All test results were entered onto the web-based data system.

Table 3.5: IID2 priority list for testing insufficient specimens

Priority	Core Study Tests	Additional under 5 years	Additional Foreign Travel	Additional Food Poisoning
1	*Campylobacter jejuni/coli* *Escherichia coli* O157 *Salmonella/Shigella*			
2		Rotavirus Adenovirus		
3	*Cryptosporidium* *Giardia*			
4			*Vibrio*	
5				*C. perfringens* enterotoxin *Staphylococcus aureus* *Bacillus* spp (culture)
6	*C. perfringens* enterotoxin *Listeria monocytogenes* *Yersinia* *Cyclospora* *Clostridium difficile* (toxin)			
7	PCR viruses (CfI)			
8			Ova & Cysts of Parasites*	
9	Archive			

* If insufficient second sample requested as symptoms will persist

Figure 3.5: Reporting Algorithm for Microbiological Diagnostic Results



Notes:-

[1] These include specimens positive by molecular methods for the established enteric pathogens e.g. *Salmonella*, *Campylobacter*, *E. coli* O157, *Cryptosporidium*, *Giardia* and Norovirus.

[2] Hard copy reports sent to GPs of all positive specimens by molecular tests, including enteric viruses and non-O157 VTEC. These reports had the following comments included:

Additional report on research tests:

"Pathogen name"

Comments: Please refer to the information sheet on IID2 Website (http://www.gutfeelings.org.uk/) that gives specific details of the pathogen isolated or detected.

[3] Hard copy reports of all significant pathogen tests (see 1 above) but not other enteric viruses or *Listeria* spp. Specimens positive for non-O157 VTEC were reported but had a covering letter attached explaining the possible significance of the result.

3.6.9.3 Molecular Methods used at HPA Centre for Infections

Figure 3.6 shows the flow diagram for sample processing at the CfI. Two nucleic acid extracts were prepared from each stool sample by a modification of the method of Boom and colleagues (1990). For one sample of DNA mechanical disruption using zirconia beads was included (McLauchlin *et al*., 1999) and in the second sample RNA was immediately converted to cDNA through random primed reverse transcription (Green *et al*., 1993). The reverse transcriptase reactions using random hexamer priming have been described elsewhere (Amar *et al*., 2003; Amar *et al*., 2004; Amar *et al*., 2005). Each extract was examined by real-time PCR for a range of potential pathogens (Table 3.6). These were C. *jejuni*, *C. coli*, *C. difficile*, *L. monocytogenes*, *Salmonella* species, rotavirus, norovirus, sapovirus, adenovirus, astrovirus, *Cryptosporidium*, *Giardia* and *E. coli* (Enteroaggregative and Vero cytotoxin-producing (genes encoding VT1 and VT2)).

Nucleic acid extraction and reverse transcription were monitored through the inclusion of DNA (fragment of Phocine herpes virus 1 gB gene) and RNA (fragment of the mouse mengo virus genome) controls. Positive and negative microbe-specific controls were included in each assay run in order to monitor the target-specific reagents. Extraction controls were quantitative, allowing the use of Westgard rules (Westgard *et al*., 1997)[7] to determine whether the assays were within +3 standard deviations (SD) of the expected value and to determine the co-efficient of variation (CV). Suitable criteria for assigning positive results based on cycle threshold values were determined for the viral pathogens (Phillips *et al*., 2009a; Phillips *et al*., 2009b).

Two samples of 1-2ml each of a 10% faecal suspension, the remaining faecal material, 5x 10µl of a DNA extract and 5x 10µl of cDNA extract were archived for future study. Participants in the study gave their explicit consent for this.

Positive laboratory findings were reported to HPA Regional Laboratory in Manchester when detected and negative findings on completion of testing.

All results were entered onto the web-based data system. If necessary a follow-up computer-generated clinical report containing the results of the molecular (research) tests was issued by the HPA Regional Laboratory in Manchester and posted to the General Practitioner.

[7] Available at www.westgard.com – Date accessed 25th June 2010

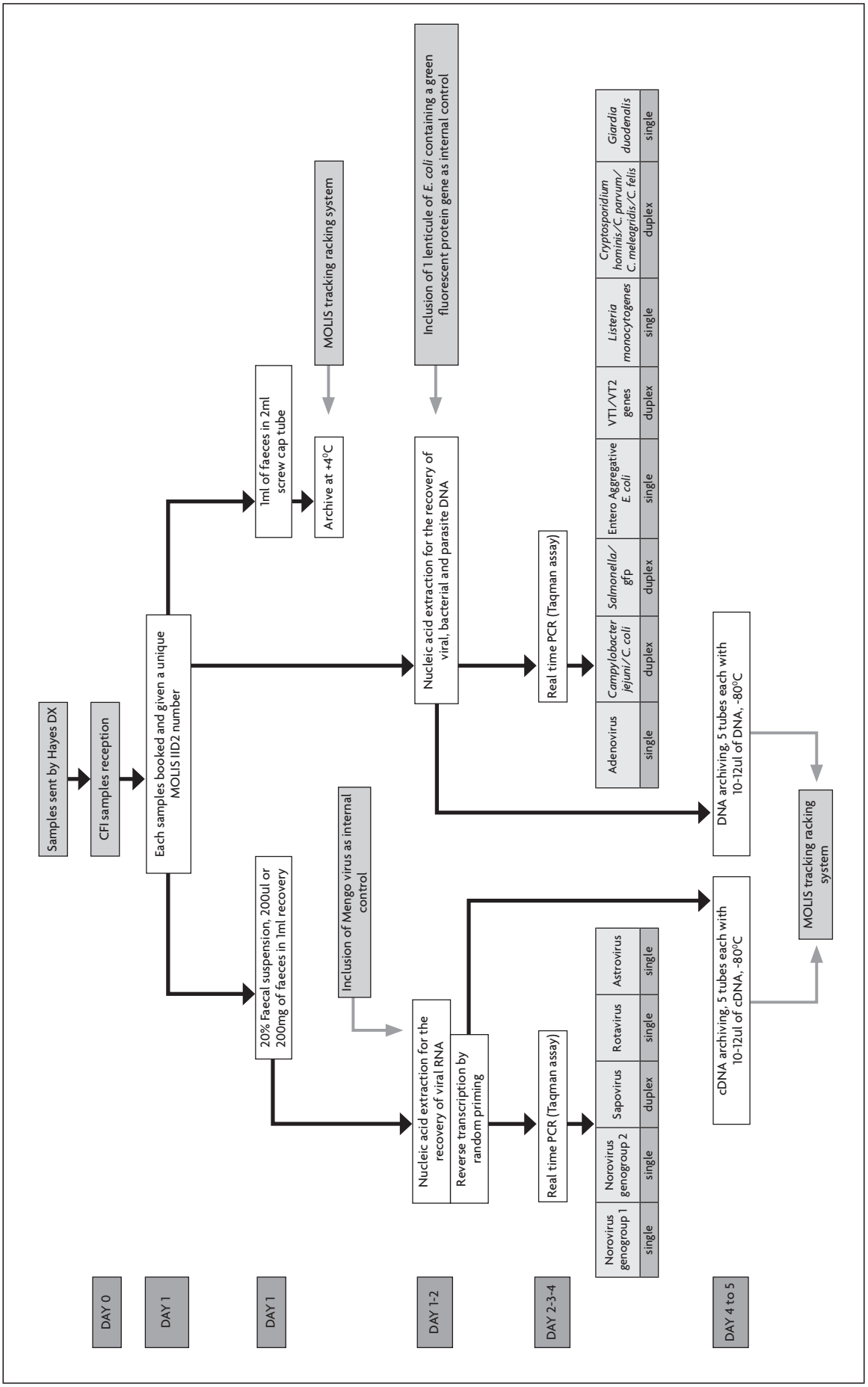


Figure 3.6 Flow diagram describing sample processing at CfI

Table 3.6: Table showing genomic targets for the detection of a range of bacterial, viral and parasitic pathogens by molecular methods

PCR (SOP)	Assay – chemistry	Target Organism	Gene Encoding Proteins	References
NOR1	SINGLE-5'exonuclease	Norovirus genogroup 1	RNA dependent RNA polyermerase/capsid	Kageyama *et al*. 2003
NOR2	DUPLEX-5'exonuclease	Norovirus genogroup 2	RNA dependent RNA polyermerase/capsid	Iturriza *et al*. 2002
		Mengo virus mutant vaccine strain MC (internal RNA control)	Not known	Comite Europeen de Normalisation (CEN)
ROTA	SINGLE-5'exonuclease	Rotavirus Group A	Viral Protein 6	Iturriza *et al*. 2002 Iturriza *et al*. 2008
SAPO	DUPLEX-5'exonuclease	Sapovirus	Polymerase-capsid junction (2 probes)	Oka *et al*. 2006
ASTR	SINGLE-SYBR Green	Astrovirus	Capsid	Noel *et al*. 1997
ADEN	SINGLE-5'exonuclease	Adenovirus type 40 and 41	Long fibre protein	Tiemessen and Nell 1996
CAMP	DUPLEX-5'exonuclease	*C. jejuni*	Membrane associated protein	Best *et al*. 2003 Fox, A (2009) Pers. Comm.
		C. coli	Lipoprotein of iron binding protein	
SALM	DUPLEX-5'exonuclease	*Salmonella enterica*	Glycotransferase	Murphy *et al*. 2007
		Green Fluorescent Protein gene (gfp) inserted into a *E. coli*	GFP Protein	
EAGG	DUPLEX 5'exonuclease	EnteroAggregative *E. coli*	Anti aggregation transporter	Amar *et al*. 2005 Frahm and Obst 2003
		Phocine herpesvirus 1 (Internal DNA control)	Glycoprotein B	Use of PHV-1 as an internal control for DNA extraction from clinical material – Barts and the London NHS Trust in-house method"; Duncan Clark, Gavin Wall, Zoie Aikin, Khidir Hawrami – Unpublished data
LIST	SINGLE-5'exonuclease	*Listeria monocytogenes*	Haemolysin A	Amar *et al*. 2007
VT1-VT2	DUPLEX-5'exonuclease	Verocytotoxin 1 Verocytotoxin 2	Verocytotoxin 1 Verocytotoxin 2	Moller and Anderson 2003
GIAR	SINGLE-5'exonuclease	*Giardia* spp.	Elongation Factor 1 alpha	Amar *et al*. 2007
CRYP	DUPLEX-5'exonuclease	*C. hominis, C. parvum, C. meleagridis, C. felis*	*Cryptosporidium* oocyst wall protein	Amar *et al*. 2007
CDIF	MULTIPLEX-5'exonuclease	Toxin-producing *C. difficile*	Toxin B gene (*tcdB*), binary toxin (*cdt*), and *tcdC* gene single-base deletion at nucleotide 117 (*tcdB*)	Huang *et al*. 2009 Novak-Weekly *et al*. 2010 Swindells *et al*. 2010

3.6.9.4 Definition of positive quantitative PCR results based on molecular methods used at the CfI

Table 3.7 summarises the tests performed at the CfI. The cut-off points for positive results, based on the cycle threshold (CT) values, are shown in the table.

For all organisms tested by quantitative PCR, a CT value <40 was considered positive. For norovirus and rotavirus, however, Amar *et al*. (2007) demonstrated that a considerable fraction of asymptomatic individuals test positive for these two organisms, based on data on archived specimens from both IID cases and controls in the first IID study that were re-tested using PCR. Moreover, Phillips *et al*. (Phillips *et al*., 2009a; Phillips *et al*., 2009b) showed that a fraction of IID cases with evidence of norovirus or rotavirus infection had CT values indicative of low viral loads comparable with those seen in asymptomatically infected individuals. This suggests that in a fraction of norovirus and rotavirus IID cases with low viral loads, disease is unlikely to be caused by these organisms and infection is likely to be coincidental. The analysis by Phillips *et al*. (Phillips *et al*., 2009a; Phillips *et al*., 2009b) indicated that a CT value <30 for both viruses was suggestive of a clinically significant result, that is, disease truly caused by these two organisms. For rotavirus, this cut-off point coincided well with results from ELISA testing, suggesting that rotavirus immunoassays are adequate for diagnosing disease due to rotavirus. In the IID2 study, we have therefore used a CT value <30 to define clinically significant infection for both norovirus and rotavirus.

Table 3.7: Summary of definitions for positive results for each pathogen investigated at CfI, based on quantitative PCR

Organism	Test	CT cut-off
Bacteria		
Campylobacter coli		<40
Campylobacter jejuni		<40
C. perfringens	Alpha toxin	<40
	Enterotoxin	<40
Enteroaggregative *E. coli*		<40
VT-producing *E. coli*	VT1	<40
	VT2	<40
L. monocytogenes		<40
Salmonella		<40
Protozoa		
Cryptosporidium		<40
Giardia		<40
Viruses		
Adenovirus		<40
Astrovirus		<40
Norovirus	Genogroup 1	<30
	Genogroup 2	<30
Rotavirus		<30
Sapovirus		<40

3.7 EXTERNAL SOURCES OF DATA USED IN ANALYSIS

3.7.1 Census and area-level data

Data on the age, sex, ethnic group and socioeconomic classification of the population in each of the four UK countries were obtained from CASWEB[8]. Data were obtained for the latest census in 2001.

Data on area-level deprivation were obtained from the Office for National Statistics Postcode Directory[9], which maps every UK postcode to a Super Output Area (SOA). SOAs comprise approximately 1,000 residents within defined geographic boundaries. They are ranked according to the Index of Multiple Deprivation (IMD) (Jordan *et al*., 2004) with the lowest rank denoting SOAs with the greatest level of deprivation, based on a composite score that uses information on seven domains: Income, Employment, Health, Education, Housing and Services, Crime, and Living Environment. Participants' postcodes were linked to their SOA of residence to obtain information on the deprivation and urban-rural classification of their area.

3.7.2 International Passenger Survey

The International Passenger Survey is a continuous survey of returning travellers conducted at UK ports of entry[10]. The survey gathers information from UK residents on the frequency, duration and purpose of visits to non-UK countries. We obtained aggregated data on the number of nights spent abroad by UK residents in 2008, by age and sex, from the Office for National Statistics. We used these data to estimate the average number of nights spent outside the UK by age group and sex.

3.7.3 Royal College of General Practitioners Weekly Returns Service

The Royal College of General Practitioners (RCGP) Research and Surveillance Centre collects information on all consultations from a network of 100 general practices distributed throughout England and Wales. Statistics on the weekly incidence of consultations, according to the 9th version of the International Classification of Diseases code, are published annually. We obtained information on the annual incidence of episodes of IID (ICD9 codes 001-009) presenting to network practices for the years 1996 and 2008[11], when the first and second IID studies were conducted, as an external comparison of rates of IID presenting to general practice.

3.8 DATA MANAGEMENT AND QUALITY CONTROL

3.8.1 Data management

Staff at each of the main study sites jointly co-ordinated data management. For the prospective studies this was primarily by use of a bespoke web-based data collection system.

The University of Manchester team (UoM) was responsible for developing the web-based data system with input from the London School of Hygiene and Tropical Medicine (LSHTM), MRC GPRF, HPA Manchester Laboratory and CfI. The University of Manchester was also responsible for day-to-day liaison with the development and hosting companies to ensure that any non-conforming issues or problems were dealt with in a timely manner.

The MRC GPRF Coordinating Centre was primarily responsible for day-to-day liaison with the Study Nurses in the study practices.

The HPA Manchester laboratory was responsible for day-to-day liaison with the GP practices on any sample-related queries and provision of positive results of microbiological testing.

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[8] Available at http://casweb.mimas.ac.uk / - Date accessed 19th June 2010
[9] Available at http://www.ons.gov.uk/about-statistics/geography/products/geog-products-postcode/nspd/index.html - Date accessed 25th June 2010
[10] Available at http://www.statistics.gov.uk/ssd/surveys/international_passenger_survey.asp - Date accessed 25th June 2010
[11] Available at: http://www.rcgp.org.uk/clinical_and_research/rsc/annual_reports.aspx - Date accessed 20th July 2010

The LSHTM and the MRC GPRF were responsible for the design of the study registers and dedicated databases to hold participant recruitment information from each practice. In addition, LSHTM was responsible for monitoring data quality and completeness and evaluating the accuracy of data entry.

The team at the University of East Anglia (UEA) was responsible for the design and development of the Telephone Survey database.

3.8.2 Questionnaires and Forms/Study Registers

3.8.2.1 Questionnaires

Several short questionnaires were used and have been summarised in Table 3.8. Copies of the full questionnaires are located in Appendix 9.

Table 3.8: IID2 Study Questionnaires

Version Number	Study component	Purpose
V06	Cohort Baseline questionnaire - Adult	Adult baseline data
V06	Cohort Baseline questionnaire - Child	Child baseline data
V09	Cohort Symptom questionnaire - Adult	Adult symptoms, consultations, hospital visits, travel
V09	Cohort Symptom questionnaire - Child	Child symptoms, consultations, hospital visits, travel
V07	GP Presentation questionnaire - Adult	Adult baseline data and symptoms, consultations, hospital visits, travel
V07	GP Presentation questionnaire - Child	Child baseline data and symptoms, consultations, hospital visits, travel
	Enumeration	Read codes, symptoms, consultations, hospital visits, travel, specimen results
	Validation	Read codes, symptoms, consultations, hospital visits, travel, specimen results
	Telephone Survey questionnaire	Baseline data and symptoms, consultations, hospital visits, travel

3.8.2.2 Study Registers

We monitored recruitment into the Prospective Cohort and GP Presentation Studies using standardised electronic registers, in which Study Nurses recorded details of individuals' eligibility, response to invitation, attendance at a recruitment interview, and consent to participate. Examples of each of the study registers are included in Appendix 11.

3.8.2.3 Study Newsletters

We sent regular updates on study progress via newsletters to Study Nurses and participants to try to maintain their interest in the study (Appendix 14).

3.8.3 Web-Based Data System for Prospective Studies

We developed a bespoke data system (Egton Software Systems) to enable the capture, storage and transfer of data within study sites collating all the study data in a highly secure web-based database. Once informed consent was obtained an individual record for each participant was created at the GP practice and a unique identifier number assigned. Data were entered directly into the web-based data system in each of the 88 participating practices, at the MRC GPRF Coordinating Centre, and in the two microbiology laboratories. Each user was assigned a level of access to the system

appropriate to their role in the study. This is described in detail in Appendix 15. In addition, for those cohort participants who opted for email follow-up, an automated email was sent each week and their response automatically logged in the system.

The system permitted real-time monitoring of Cohort and Presentation Study participation and real-time tracking of specimens and results.

3.8.3.1 Reports

Users at each study site had access to a range of reports which could be run on demand and were used throughout the study to monitor participation rates, follow-up, episodes and specimens.

3.8.3.2 Weekly Monitoring meetings

The UoM team hosted weekly telephone conferences. Representatives from each of the main study sites took part i.e. for the prospective studies the MRC GPRF, Manchester HPA Laboratory, HPA CfI, LSHTM and for the retrospective Telephone Survey from UEA.

Each of the main study sites provided detailed reports 24 hours prior to the meeting. For monitoring purposes these included recruitment, follow-up and drop-out figures for the previous week, as well as reporting of symptoms, submission of questionnaires and specimens by study participants, and microbiological findings.

For the prospective studies all sites used the report functionalities within the web-based system to generate reports. Additional reports on recruitment, follow-up and compliance were generated at LSHTM from the web-based data system and at MRC GPRF from the study registers that were compiled centrally into a Microsoft Access™ logging database. Reports which were generated using Microsoft Excel™ were provided by UEA to monitor the Telephone Survey.

These meetings provided real-time monitoring of all aspects of the study and enabled any inconsistencies or missing information to be identified and followed-up in a timely manner.

3.8.3.3 Data flow

For each participant who consented to take part in the Prospective Cohort or GP Presentation studies, the Study Nurse generated a record on the web-based data system, containing baseline demographic information and a unique identifier was attached automatically by the system. Authorised users from different study sites could upload additional information related to that record as necessary (Figure 3.7). Participants could appear in both the Prospective Cohort Study and the GP Presentation Study if they were a cohort member and they presented to the GP for IID-related symptoms during the study period. In this case, a separate record containing episode information relating to the GP presentation visit was created in the GP Presentation Study data.

Prospective Cohort Study participants who reported symptoms of diarrhoea and/or vomiting through the weekly follow-up system were asked to complete a paper-based questionnaire and mail it to the Study Nurse, who entered the information into the relevant record on the web-based data system.

GP Presentation Study participants completed a baseline and symptom questionnaire in person with the Study Nurse upon enrolment. The Study Nurse added the data directly to the relevant record on the web-based data system during the interview.

Once data for a record were entered and saved on the web-based system, Study Nurses could not amend the data for that record, but could request amendments to be made. When logging into the system the MRC GPRF were able to view any amendment requests and to update participant information as appropriate.

The system provided real-time tracking of specimens and results.

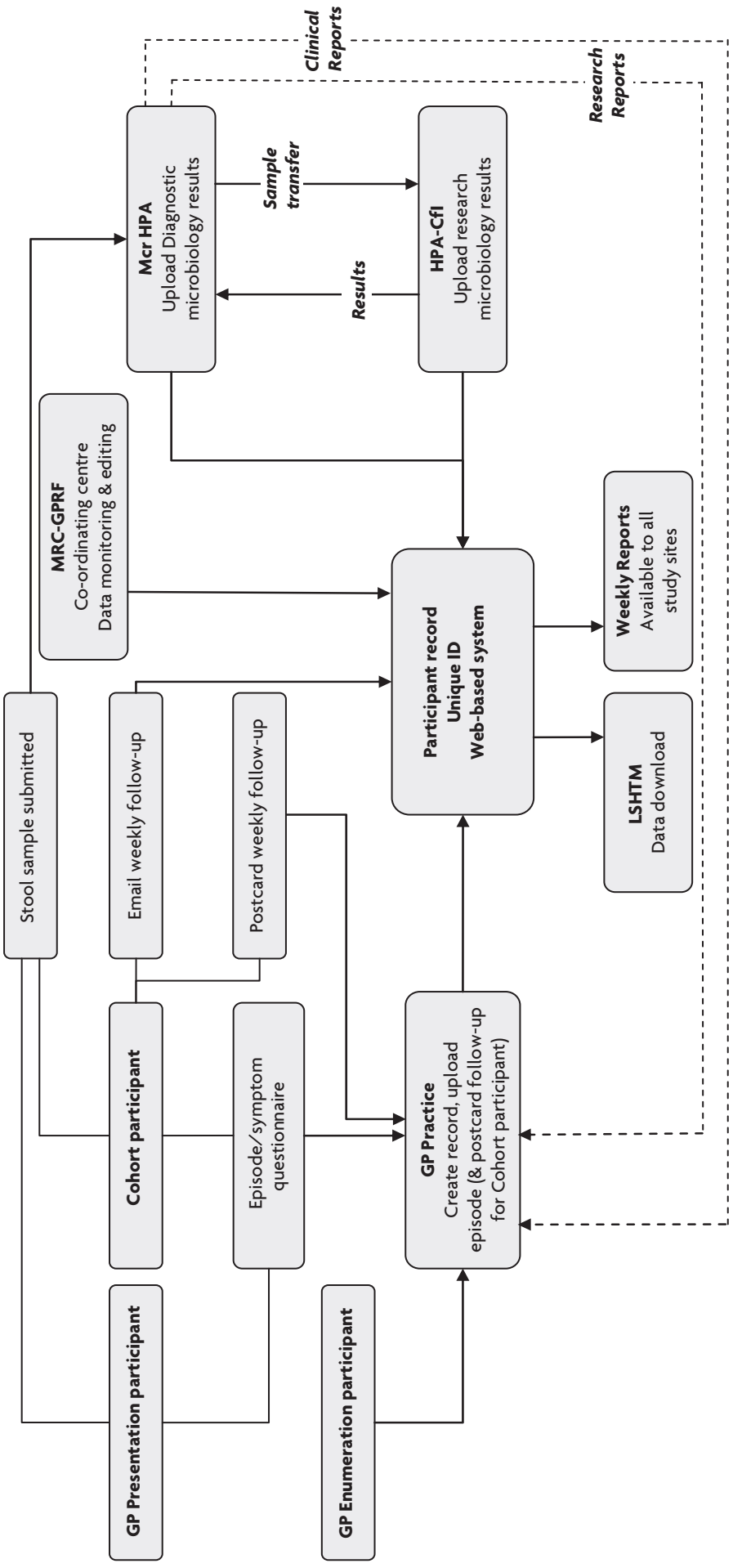


Figure 3.7 Web-Based Data flow

3.8.3.4 Data security

The data were stored on a dedicated server housed behind a dedicated Cisco (hardware) firewall. Access to the server was assigned through a secure shell (SSH) via unique user names and passwords. All information was encrypted prior to transfer using secure socket layer certificates (SSL's) providing 128 bit encryption. The range of Internet Protocol (IP) addresses was restricted to national IP ranges. A Redundant Array of Independent Disks (RAID 5 array) was employed for the server to provide additional fault tolerance and hence data security. A detailed account of the data security measures and back-up arrangements is presented in Appendix 15.

3.8.4 Telephone Survey Database

A bespoke, secure, Telephone Survey database was developed at UEA using Microsoft Access™. Number banks were generated from random telephone numbers by the Telephone Survey team. These numbers were uploaded to the Telephone Survey database. Calls were made according to the telephone calling algorithm (Appendix 3).

When telephonists opened the Access database and started a new call the selection of telephone number and recall period (7 or 28 days) were random. All calls were assigned a unique identifier and recorded using CopyCall Telephone Recorder or Retell 957 software, which generated a digital sound recording (wav file) of the call. In compliance with ethical requirements, only calls with an audible record of consent in the digital audio file were included in the study. The call recording was also used for quality control purposes and double data entry. Data were entered by the telephonists directly onto the database during the course of the interview.

3.8.4.1 Data security

The Telephone Survey database was encrypted and stored on a secure server centrally at the UEA. Whilst telephonists were able to access the Telephone Survey programme, enabling them to enter survey data, they were unable to access the database itself or to view or edit the data once it had been entered.

Access to the database itself was password protected and assigned to only the system developer and the researcher at UEA. The database was backed up on a daily basis at UEA. A full audit trail of all records on the database was available.

Copies of the database, from which telephone numbers had been removed, were transferred on a weekly basis to a secure server at LSHTM using a secure file transfer protocol.

3.8.5 Quality Control

3.8.5.1 Data Collection by Study Nurses

The MRC GPRF regional training nurses (RTNs) provided ongoing support for the Study Nurses whilst the field work was in progress. These nurses are experienced in practice-based research and were specifically trained in the IID2 study protocols and procedures. The RTNs contacted the Study Nurses at the practices at the beginning of the study to ensure that they were confident in the study procedures. Where there was a delay between nurse training and the start of fieldwork (e.g. due to R&D approval), the RTNs offered to visit the nurses for 'top up' training. They also visited all the nurses to carry out quality control (QC) checks, ensuring that the nurses were adhering to the protocol and collecting the data in a standardised way. The RTNs completed a quality control form for each practice visit (Appendix 16). They also discussed issues such as recruitment and RTNs liaised with the study team to resolve any difficulties that were raised. RTNs made a minimum of two visits to each practice during the recruitment period.

3.8.5.2 Web-Based Data System

Computerised and manual checks were implemented at every stage to ensure data accuracy.

Consistency checks were built into the web-based data collection fields, which flagged any inconsistencies at the data entry stage, to provide increased data integrity. A full audit trail of each record was available on the system.

An independent company (Abacus UK) double entered all Prospective Cohort Study, Enumeration Study and Validation Study questionnaires.

Completeness of the datasets was monitored on regular basis. Each of the main study sites (UoM, MRC GPRF, HPA Manchester, CfI, LSHTM and UEA) provided weekly reports which were discussed during the weekly telephone conferences. This enabled any inconsistencies or missing information to be identified and followed-up in a timely manner.

3.8.5.3 Study Registers

All study registers were locked to prevent formatting changes and data input masks used to ensure invalid data were not entered. Study Nurses sent their study registers electronically to the MRC GPRF Coordinating Centre on a weekly basis. Registers were automatically imported to a dedicated Microsoft Access logging database and the data updated weekly. Updates received by practices could be viewed by a specific date, allowing the MRC GPRF team to identify any practices that had not returned an updated study register. Queries were also setup to identify any missing information in the study registers and to monitor recruitment. The logging database was maintained by MRC GPRF and data were checked by the MRC GPRF and LSHTM.

3.8.5.4 Quality control at the HPA Manchester Laboratory

The responsibility for the laboratory section's internal quality assurance (IQA) remained with the individual heads of the section. The Quality Manager assisted in the maintenance of dedicated computer databases and by administration of some of the IQA schemes.

In each laboratory section designated staff produced reports on the results obtained in any IQA. IQA reports were discussed at management and staff meetings and copies were placed on notice boards and/or distributed via the Biomedical Scientist (BMS) network.

The internal quality control (IQC) procedures in place verified the quality of the agar media and broths that were used to isolate and identify the organisms in the enteric laboratory. All reagents, stains and equipment were also regularly monitored and recorded. IQC data were recorded on specific controlled documents that included all relevant auditable information. Both Medical Laboratory Assistant (MLA) and BMS staff were responsible for carrying out and documenting the IQC procedures and these were supervised by senior BMS staff.

Internal Quality Assurance (IQA) was also carried out during the study from receipt of sample to final results. IQA was performed weekly and involved both MLA and BMS staff. Findings were recorded. In addition assay controls were included in all immunoassays and acceptance limits, based on the analysis of IQA data and the acceptance criteria provided by the manufacturers of commercial assays, were used for all results.

3.8.5.5 Quality control at CfI

IQC was performed with pathogen-specific controls and PCR inhibition controls for RNA and DNA targets. IQC was monitored through the use of the Westgard rules and assays with target-specific controls +3SD from the expected value were repeated. Individual samples demonstrating inhibition in the RT-PCR or PCR assays were repeated following manual extraction of the nucleic acid (Boom *et al*., 1990).

Manchester HPA and CfI laboratories were accredited by Clinical Pathology Accreditation (UK) throughout the study. The laboratory staff at both Manchester HPA and at the CfI participated in audits and complied with local safety policies and procedures. Their competencies in sample

handling, assay performance and data handling were measured after training, and monitored throughout the project. All staff kept a detailed training record.

3.8.5.6 Quality control in the Telephone Survey

The Telephone Survey Co-ordinator monitored call quality on a continuous basis recording a minimum of two formal IQC assessments (Appendix 16).

Data entry clerks re-entered data from the telephone interviews by listening to the original digital recording. The LSHTM team then compared original and double-entered data for discrepancies. The Telephone Survey Co-ordinator at UEA resolved the discrepancies by referring to the original audio files where necessary.

3.8.6 Audit Programme

3.8.6.1 Internal Audit Programme

The Project Manager at Manchester developed and implemented an internal audit programme to ensure adherence to all study protocols and procedures. Aspects of the study were audited in turn once per quarter.

At each visit the Project Manager verified and recorded compliance against all audit items using quality audit forms (Appendix 16) which were completed on the day of the audit and included comments from the Project Manager and the researcher.

The Project Manager summarised the audit findings in a separate document and specified any improvement actions required. These included:

- Any non conformities or deficiencies found.
- Any recommendations and timescales for corrective action.
- Responsibilities for corrective action. Any recommendations for preventative action.

The Project Manager provided copies of the audit document and improvement actions to the site researcher, the Food Standards Agency and members of the IID2 Study Executive Committee. The Project Manager retained the original documents.

The Project Manager ensured that any improvement actions were completed within the agreed timescale. In the event that issues were not resolved within the agreed timescale, the contingency was to report non compliance to the IID2 Study Executive Committee at the next meeting or, if urgent, via correspondence. Internal audit was a standing item on the agenda of the IID2 Study Executive Committee.

3.8.6.2 External Audit

The Project Management team at the University of Manchester was subject to two external audits during the course of the study to ensure that all protocols and procedures were followed. The reports of these external audits may be found in Appendix 16.

3.9 STATISTICAL METHODS

3.9.1 Methods for participation, representativeness and compliance in the Telephone Survey, Prospective Cohort Study and GP Presentation Study

3.9.1.1 Participation

We computed participation in the Telephone Survey, Prospective Cohort Study and GP Presentation Study as the percentage of those invited who consented to take part in the study. For the Telephone Survey, only overall participation by country was calculated, as no additional information on non-

participants was available. For the Prospective Cohort and GP Presentation Studies, we calculated participation separately by age group and sex.

3.9.1.2 Representativeness

We assessed the representativeness of the study populations in each of the studies by comparing the characteristics of each study population with those of the 2001 census population. We used the 2001 census because this was the last census for which results were published. Age-sex structure estimates were available after 2001 (based on census projections) but data on population size by ethnic group, household size, NS-SEC and area-level deprivation were not.

We compared the age and sex distribution of the population registered with general practices participating in the GP Enumeration and GP Presentation Studies with that of the UK census population. In addition, we compared the area-level deprivation and urban-rural profiles of participating practices with those of all practices in the UK.

For the Prospective Cohort Study, we assessed representativeness by comparing the distribution of age group, sex, ethnic group, socioeconomic classification, area-level deprivation and urban-rural distribution of cohort participants with that of the UK census population. We used the National Statistics-Socioeconomic Classification (NS-SEC) to assign participants aged 16 to 74 to one of five socioeconomic groups based on the self-coded method[12], which uses information from five questions on employment type and status to classify working individuals into five socioeconomic groups.

For the Telephone Survey we compared the age, sex, ethnic group, household size, area-level deprivation and urban-rural characteristics of survey participants with those of the census population, separately for each of the four UK countries, and for the UK as a whole. To account for the differing populations in the four UK countries, we weighted the sample to reflect the relative size of the population in each country.

3.9.1.3 Compliance

For the Cohort and GP Presentation Studies, we computed compliance as the percentage of IID cases who submitted a questionnaire following the onset of symptoms. We estimated compliance separately by age group and sex. We investigated factors related to compliance using a logistic regression model, comparing compliant and non-compliant individuals in terms of demographic characteristics and type of follow-up (email or postcard).

3.9.1.4 Completeness of follow-up

We computed the median duration of follow-up among cohort participants. As recruitment occurred throughout the duration of the study, we computed the total follow-up time in the cohort as a percentage of the maximum achievable follow-up time, based on the number of weeks individuals could remain in the study between their start of follow-up and the end of the study on 31st August 2009. In addition, we calculated the percentage of participants who dropped out or were lost to follow-up during the course of the study, and investigated factors associated with not completing the study using logistic regression.

3.9.2 Incidence of IID in the community

3.9.2.1 Definition of cases

For a fraction of participants reporting diarrhoea and/or vomiting through the weekly follow-up system, information on symptom duration and foreign travel was not available, either because of missing responses, or because no questionnaire was submitted. We therefore defined cases as definite and possible cases. Definite cases were individuals meeting the case definition as described

[12] Available at: http://www.ons.gov.uk/about-statistics/classifications/current/ns-sec/index.html - Date accessed 21/06/2010

in section 3.3. Possible cases were defined as individuals who reported symptoms of diarrhoea and/or vomiting through the weekly follow-up system, but who did not submit a questionnaire or who submitted a questionnaire but could not be classified as definite cases because of missing information on the presence and/or duration of symptoms or recent foreign travel. We calculated incidence estimates using definite cases only, and using definite and possible cases.

3.9.2.2 Incidence calculations

We computed the incidence of IID in the community, per 1000 person-years, as the ratio of IID cases occurring in the cohort to the number of person-years at risk during the period of follow-up. We censored periods of follow-up during which individuals were not considered to be at risk according to the case definition. In particular, among cases who reported travel outside the UK in the 10 days prior to illness onset, we excluded from analysis the period between the date they left the UK until three weeks after their last reported symptomatic week, or three weeks after their return to the UK, whichever was latest. Among individuals reporting symptoms not related to travel, follow-up time was censored from the date of symptoms onset until three weeks after their last reported symptomatic week, at which point they were considered to be at risk again. If a person did not respond to follow-up for one or more consecutive weeks, their follow-up time was considered censored from the first week of non-response until three weeks after their last week of non-response. Individuals did not count towards the numerator or the denominator in the incidence calculations during censored periods. Participants who did not respond to follow-up for four or more consecutive weeks were considered dropped out of the study.

We did not make any adjustments to the denominator to account for time spent outside the UK during the follow-up period, as individuals in the cohort were instructed not to respond to weekly follow-ups on weeks during which they were outside the UK. Such weeks would, therefore, have automatically been excluded from analysis. Cohort participants were, however, not asked to report the specific weeks on which they were not in the UK.

We calculated incidence rates overall, by age group and sex, and by pathogen. We assumed that pathogens were independent; so that if a sample was positive for two pathogens, it contributed to the numerator in the incidence calculations for both pathogens (except for *C. difficile*).

We calculated overall rates of IID, and rates of IID by pathogen for England and for the UK. To account for differences in the age and sex structure of the IID2 cohort relative to the census population, we adjusted incidence estimates by means of post-stratification weighting. For each stratum of age group and sex we computed individuals' weights as the ratio of the size of the stratum in the census population to that in the Prospective Cohort Study. We then normalised the weights to sum to unity.

We calculated the weighted incidence as:

$$I = \sum_j \sum_i w_j \cdot I_{ij}$$

$$w_j = \frac{N_j / n_j}{N}$$

where:
I = weighted incidence of IID
Iij = rate in individual *i* in age-sex stratum *j*
wj = weight applied to observations in age-sex stratum *j*
Nj = size of census population in age-sex stratum *j*
nj = size of cohort in age-sex stratum *j*
N = size of census population

This effectively gave greater weight to those observations from under-represented strata.
We calculated 95% confidence intervals (CI) using jackknife methods, which involve repeatedly re-computing the rate estimate leaving out one observation each time.

3.9.3 Incidence of IID in the Telephone Survey

We calculated the incidence rate of self-reported IID as the number of cases of IID among survey participants divided by the total person-time of follow-up. As information on chronic illness was not available from non-cases, we adjusted the person-time at risk using the expected age-specific prevalence of Crohn's disease and inflammatory bowel disease, estimated from exclusions in the Prospective Cohort Study. Similarly, we adjusted the person-time at risk to discount the expected time spent outside the UK in each age and sex group, estimated using data from the 2008 ONS International Passenger Survey. The adjustments for chronic illness and foreign travel were both stratified by age group and sex.

We estimated the annual incidence rate, with corresponding 95% confidence intervals, separately for the 7-day and 28-day recall groups. We estimated incidence overall, and separately by age, sex and country. We weighted the incidence estimates so as to adjust for differences in the age and sex distribution of participants relative to the census population, as defined for the Cohort Study in section 3.9.2.

When calculating incidence for the UK as a whole, estimates were further adjusted to reflect the relative sizes of the populations in each UK country. Estimates were weighted to account for the fact that England comprises 83.6% of the UK population, Scotland 8.6%, Wales 4.9% and Northern Ireland 2.9%.

Finally, we adjusted for the number of interviews completed each month. This was done in order to avoid bias due to seasonal effects, because the number of interviews conducted varied by month, and there was some evidence that incidence of self-reported IID varied between months. We used jackknife re-sampling methods to calculate 95% confidence intervals.

To obtain estimates of differential recall between the 7-day and 28-day recall groups we calculated the rate ratio (RR) comparing the incidence between the two groups:

$$RR_j = \frac{{}_{7d}I_j}{{}_{28d}I_j}$$

where:
RRj = rate ratio in age-sex stratum *j*
${}_{7d}I_j$ = rate in age-sex stratum *j* of 7-day recall group
${}_{28d}I_j$ = rate in age-sex stratum *j* of 28-day recall group

We estimated the rate ratio and 95% confidence interval comparing incidence in the 7-day and 28-day recall groups overall, and for each age group and sex category, using a Poisson regression model with the logarithm of the rate as the outcome variable, and recall period as the dependent variable.

3.9.4 Comparing incidence rates in the Prospective Cohort Study and Telephone Survey

To provide a visual comparison of the rates estimated in the Cohort Study and the Telephone Survey, we plotted the age-specific rates of self-reported IID from the two components with corresponding 95% confidence intervals. We did not conduct any formal statistical comparisons between the two studies, because of the low power to estimate age-specific rates, particularly in the Telephone Survey.

To investigate further whether telescoping or differential recall took place in the Telephone Survey, we plotted the incidence estimates from the Cohort Study, and from the 7-day and 28-day recall groups of the Telephone Survey. We also plotted incidence estimates in the 28-day recall group splitting the recall period into two time bands: <2 weeks prior to the date of interview, and 2 to 4 weeks prior to the date of interview. This enabled us to see whether differences in rate estimates were related to the period over which participants were asked to recall symptoms.

3.9.5 Incidence of consultations to NHS Direct/NHS24 for diarrhoea and vomiting

We computed the annual incidence rate of telephone consultations to NHS Direct as the ratio of annual calls to the service (averaged over the two-year period 1st July 2007 to 30th June 2009) to the mid-year census population. We included calls from the following complaints in the numerator:

1. Diarrhoea (including diarrhoea in infants and toddlers).
2. Vomiting (including vomiting in infants and toddlers).
3. Food poisoning.

Calls for which the main complaint was vomiting blood were excluded, as these are unlikely to reflect IID.

We calculated rates of consultation to NHS Direct by age group and sex, separately for England and Wales. In addition, we calculated rates according to the following call outcomes, based on what the caller was advised to do:

1. Ambulance required as soon as possible (999);
2. Patient referred to Accident and Emergency (A&E);
3. Patient referred to GP surgery (GP);
4. Patient advised to be cared for at home (Home Care);
5. Any other call outcome (Other).

For NHS24, we calculated rates of consultation over the same time period by age group. We included calls in which the principal complaint was "Diarrhoea" or "Vomiting" in the numerator. Information on the patients' sex, and the outcome of the call, was not available.

3.9.6 Incidence of IID presenting to General Practice

We estimated the incidence of IID presenting to general practice from the GP Presentation and Validation studies. We computed the incidence rate of IID as the ratio of cases identified in the GP Presentation Study to the number of person-years of observation, adjusted for under-ascertainment and practice list inflation.

We defined the under-ascertainment ratio as the ratio between the number of cases identified in the Validation Study that were not recruited in the GP Presentation Study and the number of cases identified in the Validation Study and recruited in the GP Presentation Study. This ratio represents the expected number of additional consultations that actually occurred during the observation period for every case that was recruited into the GP Presentation Study.

We investigated factors related to under-ascertainment using a logistic regression model in which ascertainment into the GP Presentation Study was used as the outcome variable. We explored associations between ascertainment and age group, sex, and a number of practice-level factors, including practice size, number of GPs working in the practice, area-level deprivation based on the postcode of the practice, and the urban-rural classification of the practice. In addition, we investigated whether cases coded in the practice records under specific types of Read code were more likely to be ascertained in the GP Presentation Study. We grouped the Read codes assigned to each consultation in the Validation Study into seven broad categories: diarrhoea (D), vomiting (V), diarrhoea and vomiting (DV), gastroenteritis (G), codes denoting IID due to specific pathogens (P), codes indicating that a stool sample was sent for analysis (O), and codes relating to symptoms compatible with IID (S). In addition, we included in the logistic regression model a random intercept for practice as a second level variable, to account for additional variation between practices that was not accounted for by the above factors.

The analysis indicated that age group and Read code category were important predictors of under-ascertainment. No practice-level factors were related to under-ascertainment, although there

was strong statistical evidence for variation between practices that was not accounted for by these practice-level factors. The final under-ascertainment model included age group, sex, Read code category and a random intercept term for practice. From this model, we obtained under-ascertainment probabilities for each case recruited in the GP Presentation Study. We used the inverse of these probabilities as under-ascertainment weights, and adjusted the numerator in each age-sex stratum by multiplying the number of cases ascertained in the GP Presentation Study by the weight to obtain the expected number of cases. We used two sets of weights in the incidence calculations, based on separate under-ascertainment models for definite, and definite and probable cases.

We did not take organism into account in the under-ascertainment model, because information on causative pathogen in the GP Validation Study records was not reliably recorded and not available for the majority of cases. Similarly, we did not take into account the symptoms experienced by GP Validation Study cases in the under-ascertainment model because they were not reliably recorded in the medical records.

For each practice, we estimated the person-years as the size of the population registered with the practice multiplied by the period of observation. The denominator was further adjusted by a factor for list inflation, to discount individuals registered with the practice but no longer living in the catchment area of the practice. Practice-specific list inflation factors were estimated from the Prospective Cohort Study, by determining the proportion of individuals randomly selected from the practice list that had died or moved away. We estimated the logarithm of the incidence rate of IID using a Poisson model, accounting for the dependence of observations within practices in the calculation of 95% confidence intervals.

3.9.7 Triangulation of incidence rates presenting to primary care

As an external validation of incidence estimates obtained in the Cohort Study and Telephone Survey, we estimated the incidence of IID presenting to general practice, based on cases in these two studies who reported having consulted a GP for their illness. We compared these estimates with those obtained in the GP Presentation Study, the GP Enumeration Study, and the RCGP Weekly Returns Service.

For the Cohort Study, we also estimated the incidence of IID for which cases reported contacting NHS Direct. We compared this estimate with that obtained from actual calls to NHS Direct.

3.9.8 Organism-specific incidence of IID

3.9.8.1 Microbiological Findings in Cases

For the Prospective Cohort and GP Presentation Studies, we computed, by study, the percentage of specimens positive for each organism among IID cases for whom a stool sample was available for analysis. We assumed that infection with one organism was independent of infection with any other organism, i.e. if a sample was positive for two organisms we counted it as positive in the calculations for both organisms (except for *C. difficile*[13]). We computed the percentage of specimens positive for each organism based on routine diagnostic methods, and on routine and molecular diagnostic methods combined. In addition, we calculated the percentage of specimens that were negative for all organisms tested.

3.9.8.2 Imputation of missing data on microbiological testing

For a proportion of participants in both the Prospective Cohort and GP Presentation studies information on microbiological test results was missing. This was (a) because the participant had

[13] A case of *Clostridium difficile*-associated diarrhoea was defined as an individual with symptoms of diarrhoea **not attributable to another cause** (i.e. in the absence of other enteropathogens), occurring at the same time as a positive toxin assay.

not provided a stool specimen (b) because the specimen provided was insufficient to test for some of the pathogens or (c) because the specimen was not tested for one or more pathogens due to another reason. Ignoring the missing data would result in an under-estimate of pathogen-specific incidence. To account for the missing data, we used multiple imputations by chained equations (Rubin, 2004). Using this method, we first defined an imputation model for each microbiological test to predict the probability of positivity conditional on the observed data. The model used as predictors five categories of age group (<1 year, 1-4 years, 5-24 years, 25-64 years and 65+ years), sex and the presence of five symptoms likely to be related to pathogen, namely diarrhoea, vomiting, bloody diarrhoea, abdominal pain and fever. For each test in turn, the missing values were filled in using random draws from the parameter distribution defined by the imputation model. The imputation proceeded iteratively, updating the imputed variables each time, until the model converged and all missing values had been filled in. To account for uncertainty in the imputation, 20 imputed datasets were generated. For *E. coli* and *Salmonella*, for which the number of positives was very low, the missing data were instead filled in by sampling with replacement from the observed data within strata of age group and sex. Overall, 35% of records in the Cohort Study and 11% of records in the GP Presentation Study had values imputed for at least one variable.

We obtained incidence estimates for each pathogen by averaging the incidence across all 20 imputation datasets, taking into account the within- and between-imputation variances in the calculation of 95% confidence intervals. Multiple imputation and analysis of imputed data were implemented in Stata 11.0 (Statacorp) using the `ice` and `mi` suites of commands (Carlin *et al*., 2003; Royston, 2005).

3.9.9 Reporting patterns of IID

3.9.9.1 Incidence of IID reported to National Surveillance

We obtained records of IID cases reported to national surveillance during the period 1st April 2008 to 31st August 2009 from the national databases at CfI, Health Protection Scotland (HPS) and the Communicable Disease Surveillance Centre Northern Ireland (CDSC NI). We calculated incidence rates of reported IID by dividing the number of cases reported over a 12-month period by the mid-year census population. To account for seasonal variations in incidence, smooth out temporal fluctuations and delays in reporting, and because the study spanned more than one year, we calculated the numerator as a moving average of the number of reports over 22 consecutive 365-day periods between 1st April 2008 and 31st August 2009, with the 365-day window advancing by one week in each consecutive period. We then took the mean of these 22 values as the numerator in the incidence calculations.

We calculated the overall incidence rates and incidence by organism for England and for the UK as a whole.

3.9.9.2 Incidence of IID in the community, presenting to general practice, and reported to national surveillance

To investigate the relationship between the incidence of IID in the community, presenting to general practice, and reported to national surveillance, we calculated rate ratios comparing the incidence in the different components, both for all IID and for IID due to specific organisms.

For organism-specific IID, we calculated the ratio comparing the rate in the community with that presenting to general practice using a simulation approach. We assumed that the natural logarithm of the rates, estimated from the combined analysis of 20 imputed datasets, had an approximately normal distribution with mean equal to the logarithm of the observed rate, and standard deviation inferred from the width of the 95% confidence intervals. We performed 100,000 random draws from the distribution of each rate and calculated the difference between each pair of sampled values. The median and central 95% of the resulting distribution was obtained, and the exponential of these values used to estimate the rate ratio and 95% confidence bounds. Rate ratios comparing

organism-specific incidence in the community and presenting to general practice with that reported to national surveillance were estimated in a similar way.

In estimating the incidence of all IID in the community, we used distribution-free methods to calculate 95% confidence intervals. Accordingly, to estimate the rate ratio comparing the rate of all IID in the community with that presenting to general practice, we used distribution-free methods to account for variability in the rate estimate. We simulated the distribution of the rate in the community by performing 9,999 bootstrap replications. In each replication, we sampled with replacement a cohort of size equal to the observed data and calculated the rate. Similarly, the rate of all IID presenting to general practice was calculated from 9,999 bootstrap replications. The ratio of the rates was calculated for each pair of bootstrap replicates, and the median and central 95% of the resulting distribution obtained to provide estimates of the rate ratio and 95% confidence bounds.

3.9.10 Comparing aetiology and incidence of IID in the IID1 and IID2 studies

We compared the percentage of specimens positive for each organism, as well as the percentage of specimens positive for at least one organism, in the IID1 and IID2 studies. To account for differences in the organisms tested for in the two studies, we used only the subset of organisms tested for in both studies. For organisms that were additionally tested by PCR in the IID2 study, we compared the percentage positivity using conventional methods in IID1 to that using both conventional and PCR methods in IID2 to establish the added benefit of using molecular diagnostic methods.

To investigate whether the relationship between disease in the community, presenting to general practice and reported to national surveillance had changed in the intervening period between the IID1 and IID2 studies, we compared the reporting patterns for all IID, as well as for *Campylobacter* spp., *Salmonella* spp., norovirus and rotavirus, between the two studies. It should be noted that in IID1 two separate estimates of under-ascertainment by national surveillance were made. The first was based on direct linkage of cases among community cohort participants, and cases presenting to general practice, to cases reported to national surveillance. The second, indirect method was based on the overall ratios of incidence in the community and presenting to general practice to the incidence of reports to national surveillance. The difference is important because, for some organisms, notably norovirus, a large fraction of reports to national surveillance result from disease in hospitals and other institutions not included in the community cohort. Accordingly, in IID1 there was great divergence in the estimates for norovirus obtained by the two methods. Because of confidentiality restrictions and changes in the amount of personal identifiable information held on laboratory reports, direct linkage of cases identified in the IID2 study with reports to national surveillance was not possible. Reporting patterns presented in this report are, therefore, all based on the indirect method.

For *Campylobacter* spp. and *Salmonella* spp. we present reporting patterns for both studies based on diagnosis by culture, so as to enable direct comparison between the two studies. For norovirus, Phillips *et al*. (2010) recently published a modified reporting pattern based on PCR re-testing of archived specimens from the first IID study, and we have used those estimates as a comparison. For rotavirus, the original estimates in IID1 are based on diagnosis by ELISA. In IID2, ELISA testing was performed only on specimens from individuals aged <5 years, while all specimens were tested by PCR. Incidence estimates in IID2 are therefore based on cases with clinically significant rotavirus infection (CT value <30 by PCR) at all ages and/or a positive ELISA test in individuals <5 years of age.

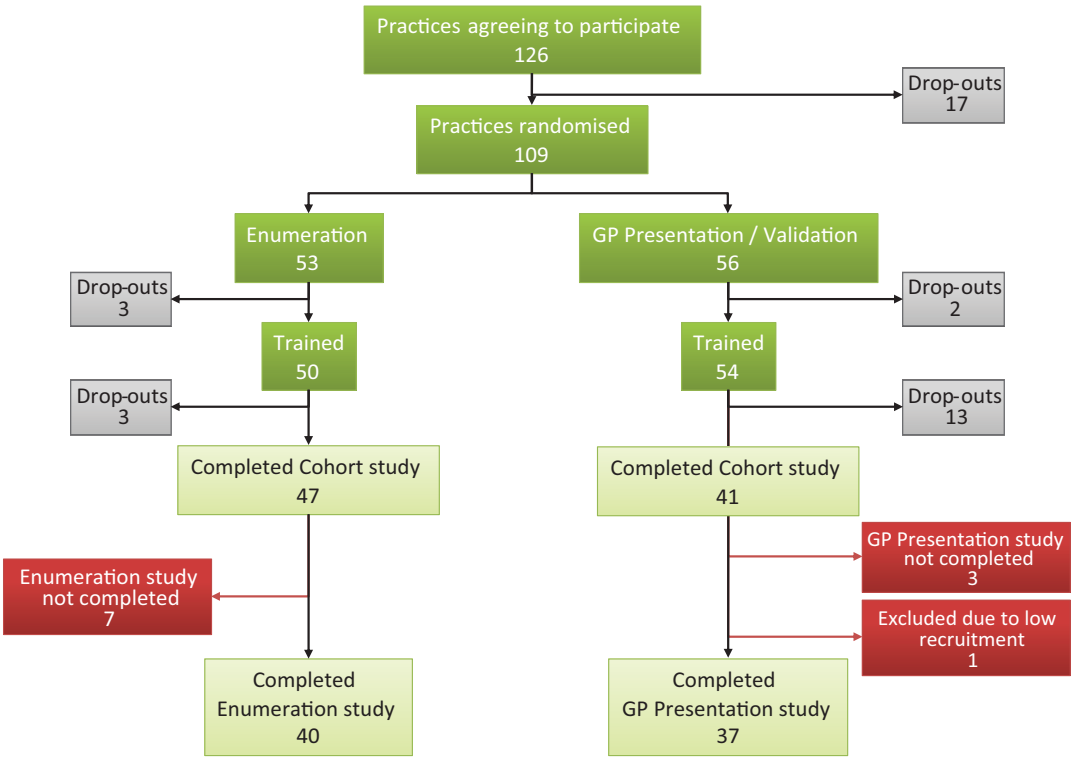
CHAPTER 4

PARTICIPATION, REPRESENTATIVENESS AND COMPLIANCE[14]

4.1 PRACTICE CHARACTERISTICS

Figure 4.1 presents a summary of practices recruited into the IID2 study. A total of 126 initially agreed to take part in the study (Table A4.1). Seventeen practices subsequently dropped out before being allocated to the GP Enumeration or GP Presentation Study. The majority of these practices cited lack of nurse time or resources as reasons for withdrawing from the study. Of the remaining 109 practices, 53 were randomly allocated to the GP Enumeration Study and 56 to the GP Presentation/Validation Study. Six GP Enumeration Study and 15 GP Presentation/Validation Study practices subsequently withdrew from the study, either prior to training or in the early stages of the study. Among the remaining practices, seven did not complete the GP Enumeration Study, three did not complete the GP Presentation/Validation Study and one was excluded from analysis of the GP Presentation/Validation Study because of low recruitment. Thus, after withdrawals and exclusions, 40 practices completed both the Cohort and GP Enumeration studies, and 37 practices completed both the Cohort and GP Presentation/Validation studies. Eleven practices did not complete either the GP Enumeration or GP Presentation Study, and contributed data only to the Cohort Study.

Figure 4.1: Recruitment and allocation of GP practices into the IID2 study



The populations registered with practices in the GP Enumeration and GP Presentation/GP Validation studies were representative of the UK census population with respect to age and sex (Figure 4.2). Practices in the third quintile of deprivation were over-represented in both the GP Enumeration and GP Presentation studies. In the GP Enumeration Study, there was deficit of practices in the most deprived areas, and there was only one practice from a rural area (Table 4.1).

[14] When reading this chapter please note that tables and figures pre-fixed "A" can be found in the annex to Chapter 4.

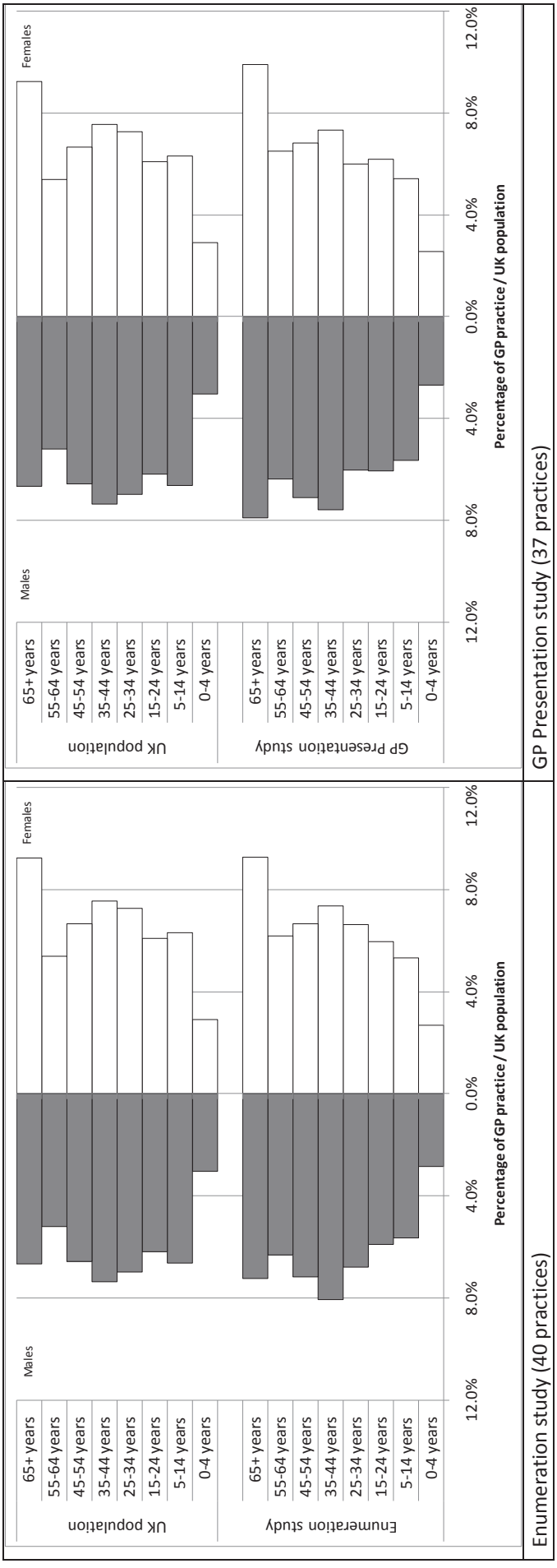


Figure 4.2: Age and sex profile of practice populations among practices in the Enumeration and GP Presentation studies compared with the UK census population

Table 4.1: Distribution of IID2 study practices by area-level deprivation and urban-rural classification, compared with all UK practices

	IID2 Study				UK[b]
	Enumeration	%	GP Presentation	%	%
IMD quintile[a]					
1 (most deprived)	5	13%	8	22%	26%
2	10	25%	6	16%	22%
3	12	30%	11	30%	20%
4	9	23%	7	19%	17%
5	4	10%	5	14%	14%
All	*40*	*100%*	*37*	*100%*	*100%*
Urban-rural classification					
Urban area	30	75%	25	68%	76%
Town	9	23%	5	14%	14%
Rural area	1	3%	7	19%	10%
All	*40*	*100%*	*37*	*100%*	*100%*

[a]IMD: Index of Multiple Deprivation; [b]General practices in the UK are not evenly distributed in each quintile of deprivation, because they tend to be more concentrated in areas of greater deprivation

4.2 PROSPECTIVE POPULATION-BASED COHORT STUDY

4.2.1 Recruitment and representativeness

In total 79,254 eligible individuals were selected at random from the patient registers of practices participating in the Cohort Study. Of these, 77,995 (98%) were invited to take part, of whom 8,336 (11%) responded positively. Of these 7,090 attended a baseline recruitment interview and 7,033 were recruited (Figure 4.3).

Figure 4.3: Recruitment of participants into the Cohort Study

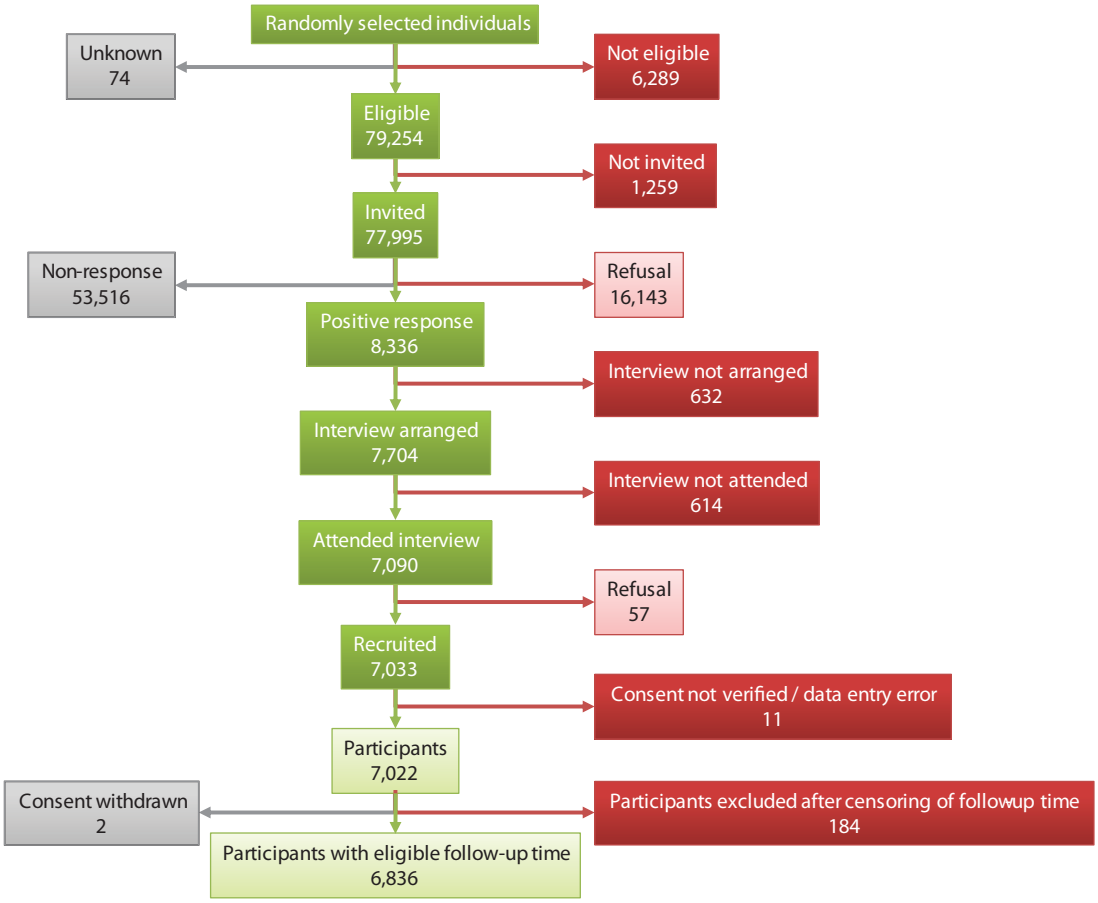


Table 4.2 shows the number and percentage of participants recruited into the Cohort Study by age group and sex. Overall participation was 9%, but was higher in females (10.9%) than in males (7.1%). For both sexes, participation was highest among those aged 55 and above, and lowest among those aged 15 to 34 years; among males, participation in this age group was less than 2%.

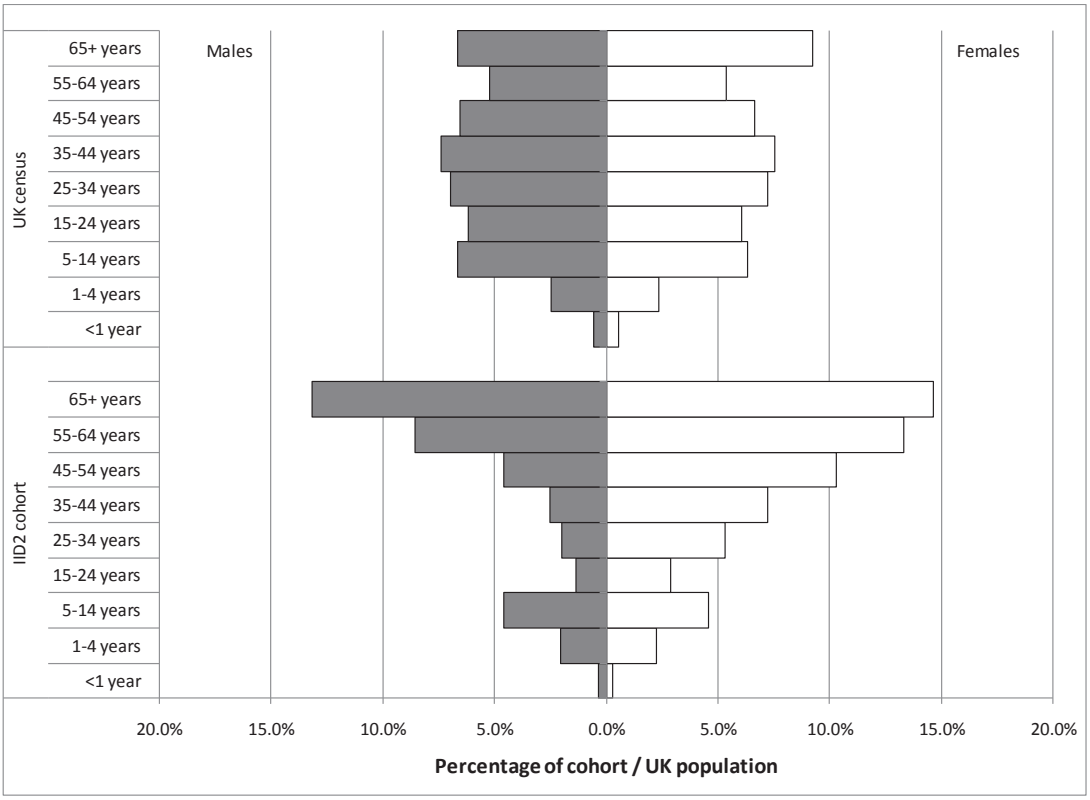
Table 4.2: Recruitment of participants into the Cohort Study by age group and sex

Sex	Age group	Eligible	Invited	Percentage of those invited				No. recruited
				Positive responses	Interview arranged	Interviewed	Recruited	
Males	<1 year	291	283	14.8%	13.8%	13.1%	13.1%	**37**
	1-4 years	1,372	1,332	14.1%	12.6%	11.2%	11.2%	**149**
	5-14 years	3,839	3,715	10.5%	9.4%	8.3%	8.3%	**308**
	15-24 years	7,669	7,557	2.0%	1.7%	1.4%	1.4%	**105**
	25-34 years	7,646	7,531	2.7%	2.4%	2.0%	1.9%	**146**
	35-44 years	5,181	5,097	4.8%	4.2%	3.6%	3.6%	**182**
	45-54 years	4,588	4,547	8.3%	7.4%	7.2%	7.2%	**326**
	55-64 years	4,101	4,062	17.1%	15.7%	15.1%	15.0%	**609**
	65+ years	4,643	4,601	21.3%	20.6%	19.8%	19.6%	**901**
	All ages	*39,330*	*38,725*	*8.4%*	*7.7%*	*7.2%*	*7.1%*	***2,763***
Females	<1 year	250	235	12.3%	12.3%	10.6%	10.6%	**25**
	1-4 years	1,296	1,256	15.5%	14.4%	12.7%	12.6%	**158**
	5-14 years	3,568	3,441	12.2%	11.1%	9.6%	9.4%	**324**
	15-24 years	7,744	7,614	4.0%	3.6%	2.9%	2.8%	**215**
	25-34 years	7,567	7,443	7.1%	6.4%	5.4%	5.4%	**400**
	35-44 years	5,000	4,940	12.5%	11.3%	10.4%	10.3%	**511**
	45-54 years	4,540	4,494	18.0%	16.9%	15.6%	15.5%	**698**
	55-64 years	4,245	4,202	25.1%	23.4%	22.5%	22.4%	**940**
	65+ years	5,617	5,548	19.9%	19.1%	18.3%	18.0%	**999**
	All ages	*39,827*	*39,173*	*12.9%*	*12.0%*	*11.0%*	*10.9%*	***4,270***

We excluded from analysis 184 participants who were recruited close to the end of the study and who, after censoring, did not contribute any follow-up time (Figure 4.3). In addition, two further participants withdrew consent during the study and were excluded.

Compared with the UK population, Cohort Study participants were generally older, with a particular deficit among males between the ages of 15 to 54 years (Figure 4.4; Table A4.2). Ninety eight percent of cohort participants were of White ethnicity, approximately 5% more than expected based on the UK census population, while other ethnic groups were slightly under-represented (Figure 4.5).

Figure 4.4: Age and sex structure of Cohort Study participants compared with the UK census population



Among those aged 16 to 74 years, the managerial and professional occupations were over-represented in the cohort; 52% of cohort participants were in this socioeconomic group, compared with 8% of the UK population. Conversely, the intermediate occupations, and semi-routine and routine occupations categories were under-represented in the cohort (Figure 4.6). Individuals living in areas of greater deprivation were under-represented in the cohort; 40% of the UK population live in areas in the two most deprived quintiles of deprivation, but less than 20% of cohort participants lived in these areas (Figure 4.7). By contrast, individuals living in rural areas were over-represented in the cohort compared with the UK census (Figure 4.8). The most likely explanation for this is that those living in rural areas have higher participation rates. Although there were some large differences in the UK census data and the sample in terms of socio-economic status and deprivation there was not much evidence that rates differed by NS-SEC.

Overall, 63% of cohort participants chose to be followed up by email and 37% by postcard. Email follow-up was preferred by more than two-thirds of participants in every age group, with the exception of those aged 65 years and above; 33% of participants in this age group chose email follow-up (Table A4.4)

Figure 4.5: Distribution of ethnic group among cohort participants relative to the UK census population

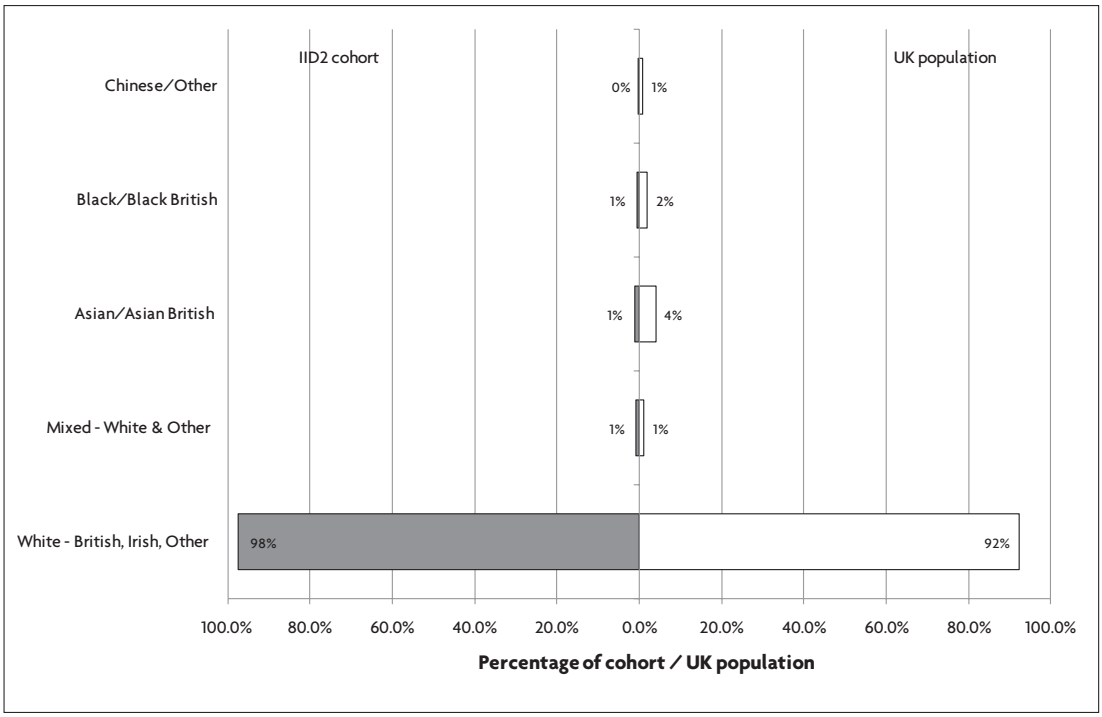


Figure 4.6: Distribution of National Statistics – Socioeconomic Classification among cohort participants aged 16-74 years compared with the UK population

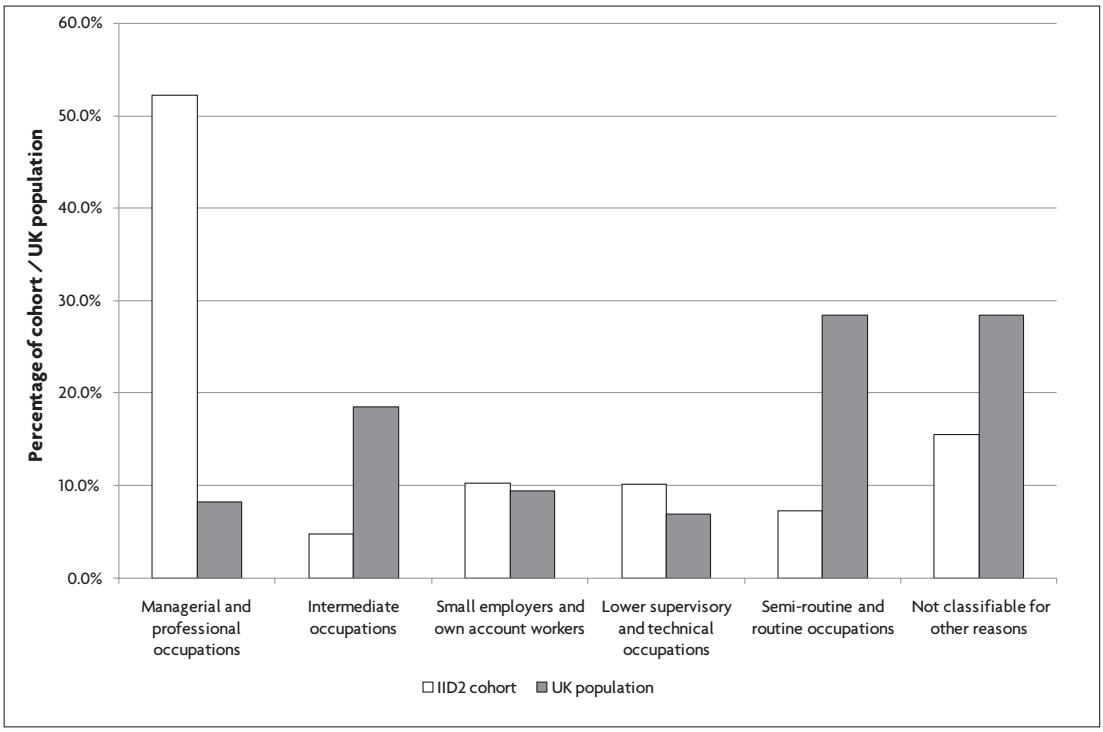
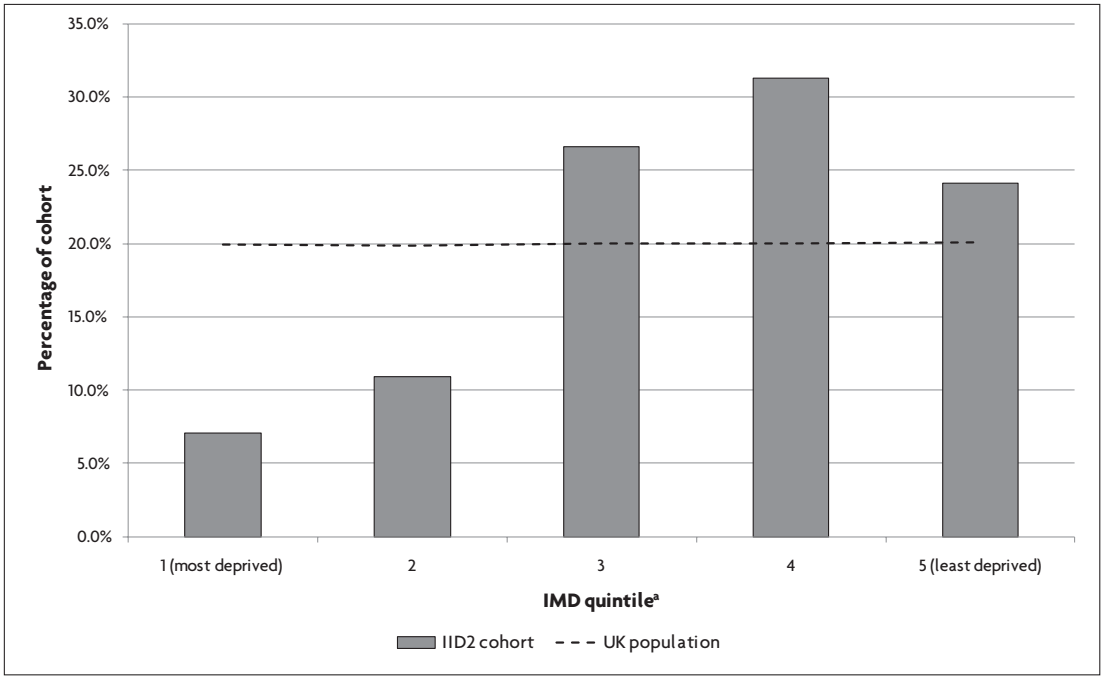
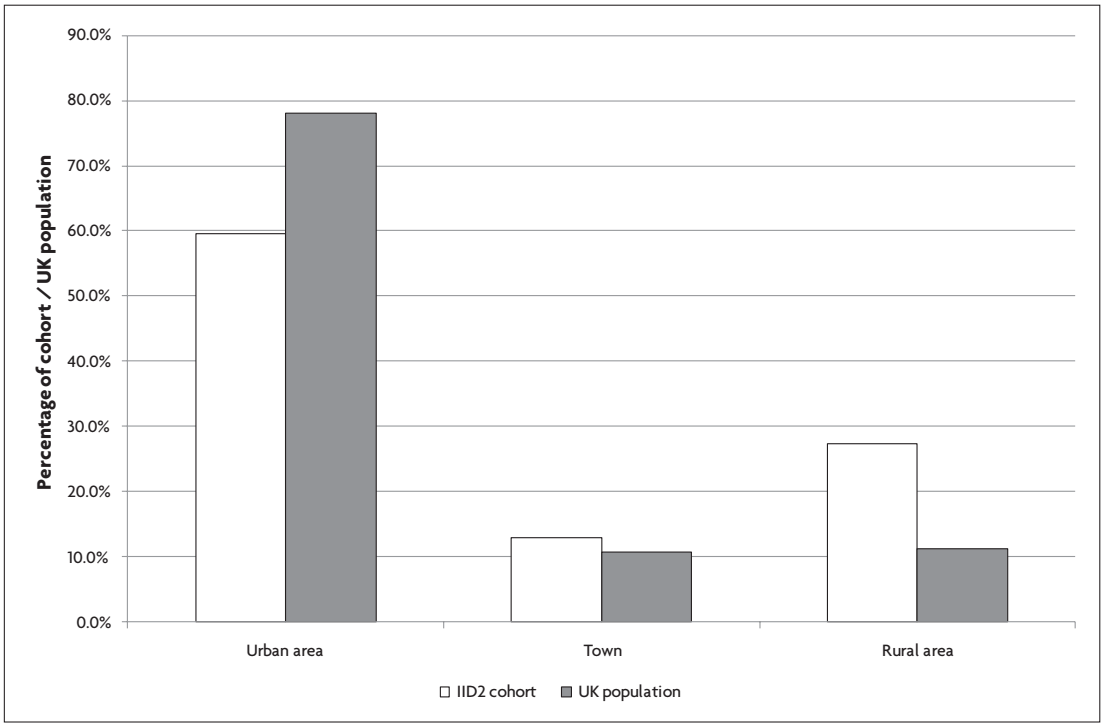


Figure 4.7: Distribution of area-level deprivation among cohort participants compared with the UK population



[a]IMD: Index of Multiple Deprivation, based on area of residence. Approximately 20% of the UK population is represented in each quintile of IMD

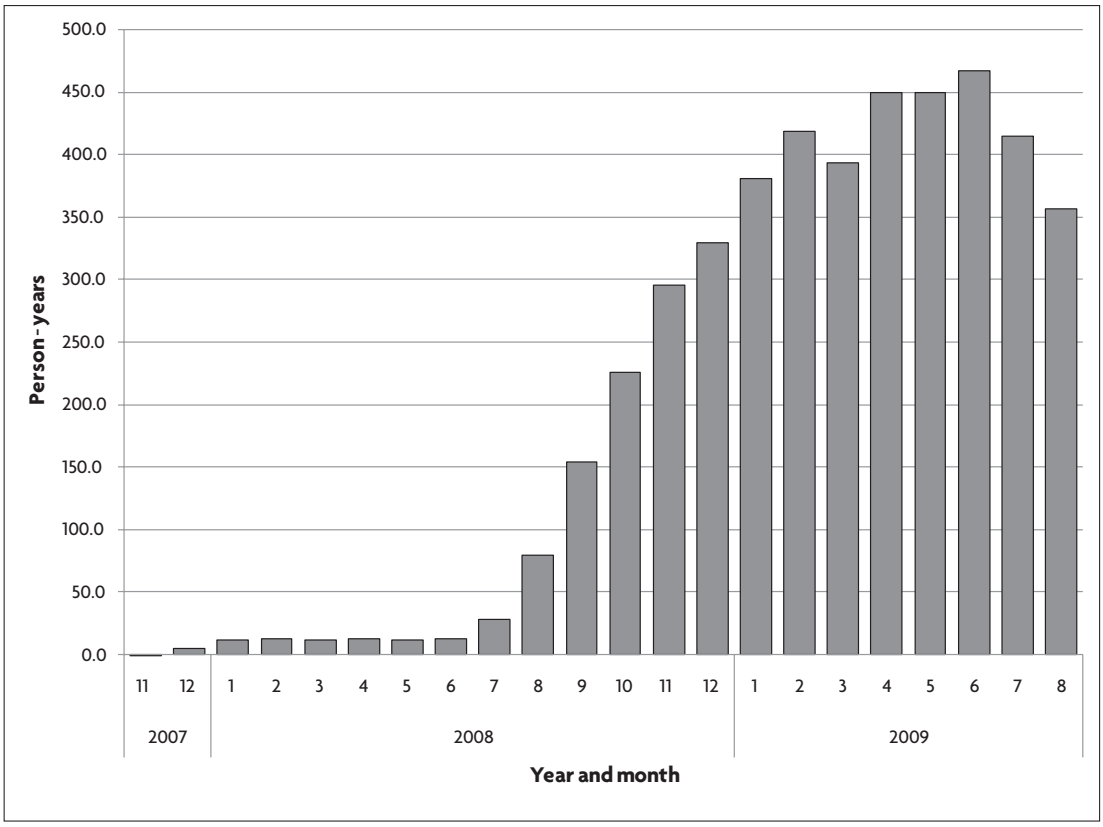
Figure 4.8: Distribution of urban-rural classification among cohort participants compared with the UK population



4.2.2 Follow-up

The 6,836 cohort participants contributed a total of 4,658 person-years of follow-up. The median duration of follow-up among cohort members was 39 weeks (interquartile range 27 – 45 weeks); overall, 86% of the maximum achievable follow-up time to 31st August 2009 was completed. The number of person-years of follow-up by study month is shown in Figure 4.9 and rises rapidly during the second half of 2008, reflecting the fact that most participants were recruited at that time.

Figure 4.9: Distribution of follow-up time in the Cohort Study by month



No major differences in median duration of follow-up were seen by sex, NS-SEC groups, deprivation quintile or urban-rural classification, although those from ethnic groups other than White British tended to have shorter duration of follow-up. Individuals aged 15 to 34 years also had shorter duration of follow-up (median 19 weeks), although this was influenced by the second wave of recruitment specifically in this age group. Among those recruited in the first wave, median duration of follow-up was comparable with that in the other age groups.

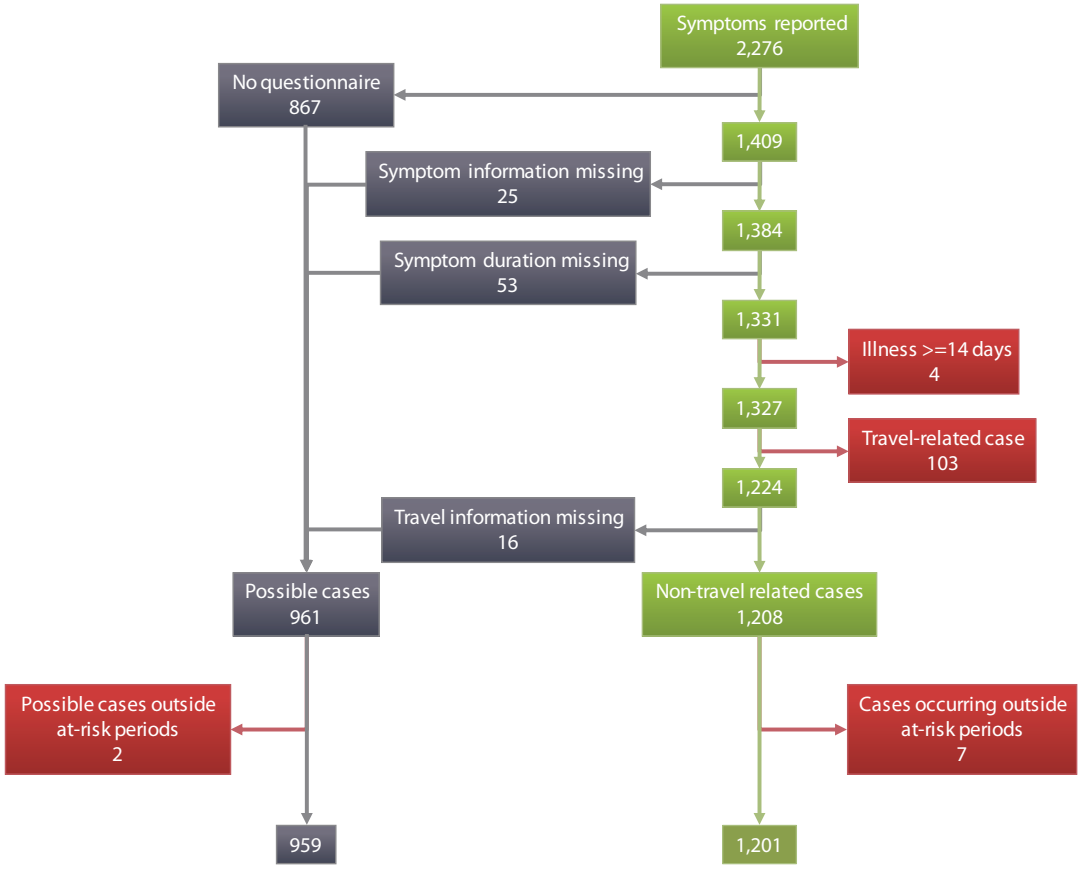
During the follow-up period, 610 (9%) participants dropped out of the study, accounting for a loss of 219 (9.5%) person-years of follow-up. The most common reasons for dropping out were failure to respond to follow-up for four or more consecutive weeks (77.7%) and health problems that prevented participants from continuing (6.2%) (Table A4.5). Drop-out was associated with younger age, increasing area-level deprivation, living in a town (as opposed to urban or rural areas) and, among those aged 16-74 years, lower supervisory and technical occupations (Table A4.6). Drop-out was more likely among those of non-White ethnicity, but the number of participants in these ethnic groups was small.

4.2.3 Compliance

Cohort participants reported 2,276 episodes of diarrhoea and/or vomiting on 2,276 occasions during the study period. Of these, symptom questionnaires were available for 1,409 (62%). Among those submitting a questionnaire, 1,201 met the definition for a case of UK-acquired IID. A further 959

episodes of diarrhoea and/or vomiting for which a questionnaire was not available, or for which information on symptoms and/or foreign travel was missing from the questionnaire, were classified as possible cases (Figure 4.10).

Figure 4.10: Cohort Study case definitions and exclusions



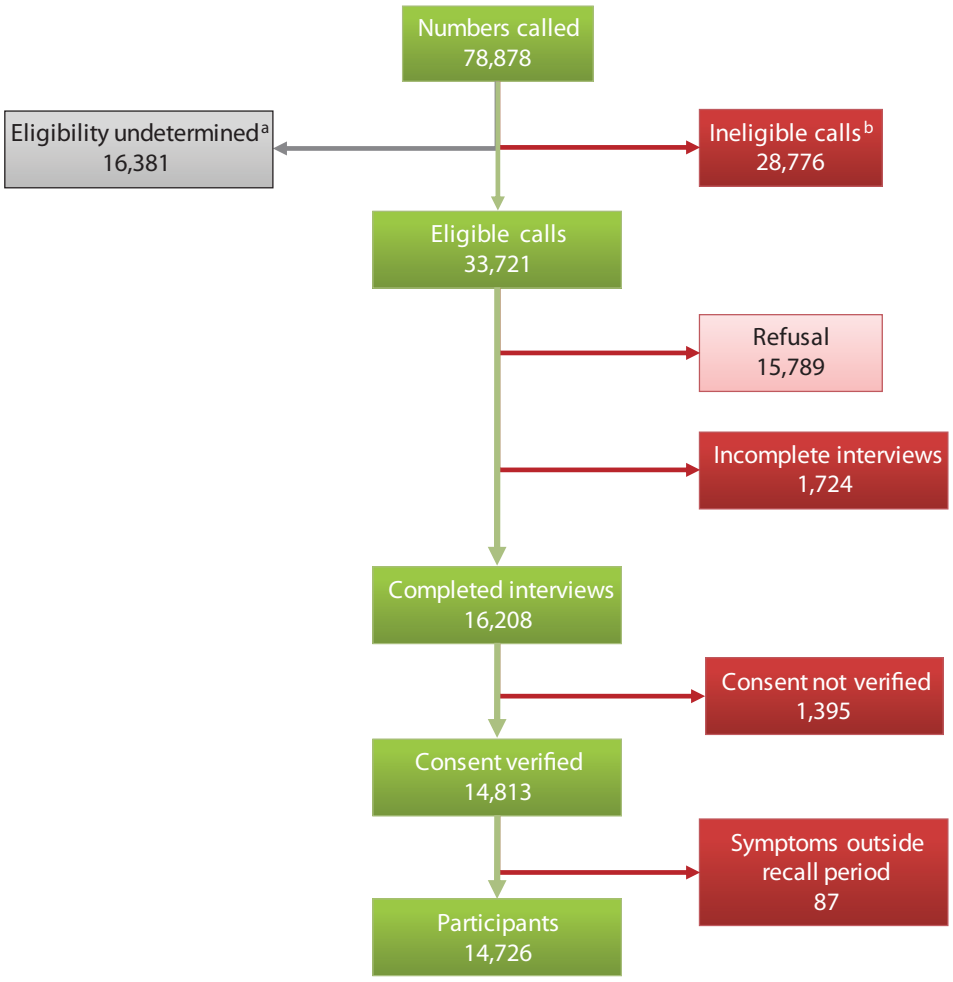
Submission of a questionnaire was related to age, sex, ethnicity, area-level deprivation and type of follow-up: among those who reported symptoms of diarrhoea and/or vomiting, individuals aged between 5 and 24 years and those of non-White ethnicity were less likely to submit questionnaires, compared with those aged 65 years and above, while female participants, those in the third and fourth quintiles of area-level deprivation, and those choosing postcard follow-up, were more likely to submit a questionnaire (Figure A4.1)

4.3 TELEPHONE SURVEY

4.3.1 Recruitment and representativeness

Over the period 1st February 2008 to 27th August 2009, a total of 78,878 telephone numbers were dialled across the four UK countries. Of these, 33,721 (42.7%) numbers belonged to households eligible to take part in the survey (Figure 4.11). A further 28,776 (36.5%) numbers were not eligible because they were invalid numbers (n=24,341, 30.9%), or commercial numbers (n=4,395, 5.6%), or because the person answering the telephone did not speak English (n=40, 0.05%). For 16,381 numbers (20.8%), it was not possible to ascertain whether the number dialled belonged to an eligible household, because the call was not answered (n=10,222, 13%), it reached an answering machine (n=3,693, 4.7%) or a fax machine (n=2,108, 2.7%), or the number was engaged (n=358, 0.4%).

Figure 4.11: Eligibility of calls made in the Telephone Survey, UK



a
- 10,222 no answer
- 3,693 answering machine
- 2,108 fax machine
- 358 engaged

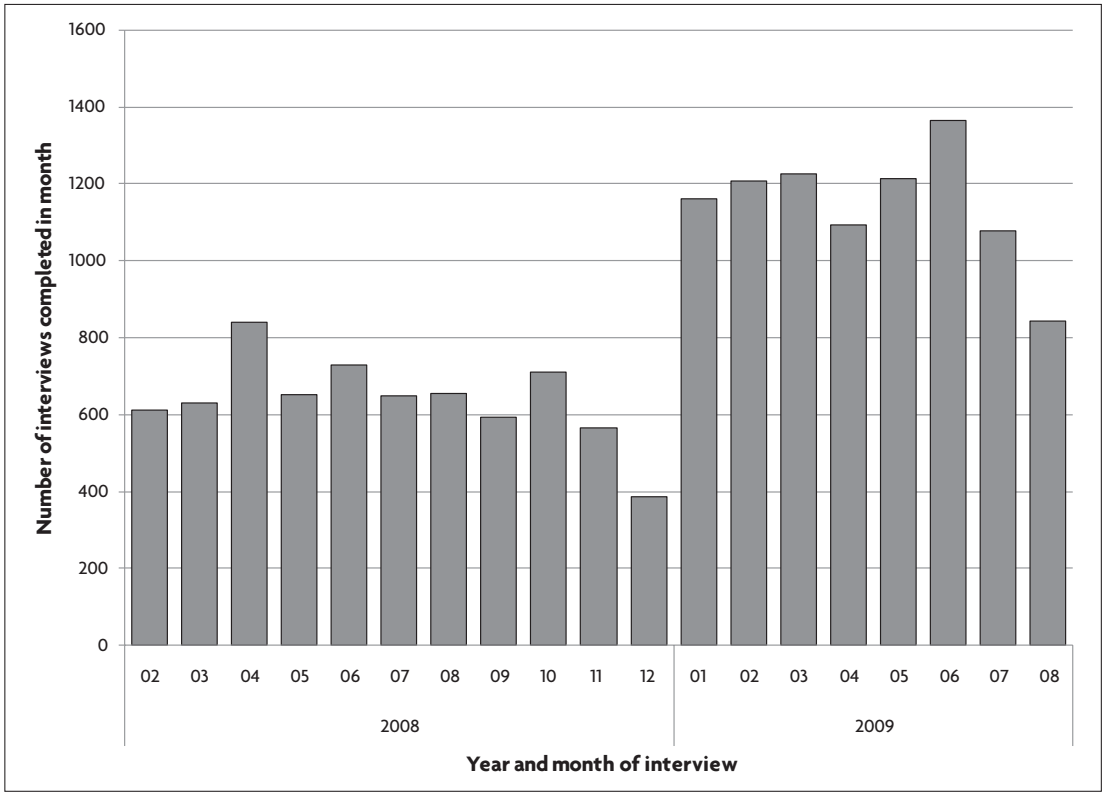
b
- 24,341 invalid number
- 4,395 commercial number
- 40 non-English speaker

Of the 33,721 eligible calls, 16,208 (48.1%) interviews were successfully completed, and similar completion proportions were observed by month of study and between the two recall periods (7 days and 28 days). The proportion of completed calls was similar in England (51.7%, 95% CI: 50.5% - 52.8%), Scotland (49.9%, 95% CI: 48.8% - 51.1%) and Wales (49.7%, 95% CI: 48.7% - 50.7%) but was lower in Northern Ireland (41.7%, 95% CI: 40.7% - 42.7%) (Table 4.3). Although the proportion of calls resulting in completed interviews was fairly constant over time, the number of interviews completed each month increased dramatically from January 2009 (Figure 4.12), because more calls per month were achieved during this period as a result of increased staffing.

Table 4.3: Percentage of eligible calls resulting in completed interviews by country

		Completed interviews	Refusals / Interviews not completed	Total
England	*N*	4,059	3,799	7,858
	% (95% CI)	*51.7 (50.5; 52.8)*		
Northern Ireland	*N*	3,752	5,245	8,997
	% (95% CI)	*41.7 (40.7; 42.7)*		
Scotland	*N*	3,642	3,652	7,294
	% (95% CI)	*49.9 (48.8; 51.1)*		
Wales	*N*	4,755	4,817	9,572
	% (95% CI)	*49.7 (48.7; 50.7)*		
Total	*N*	*16,208*	*17,513*	*33,721*
	% (95% CI)	48.1 (47.5; 48.6)		

Figure 4.12: Number of completed interviews by month

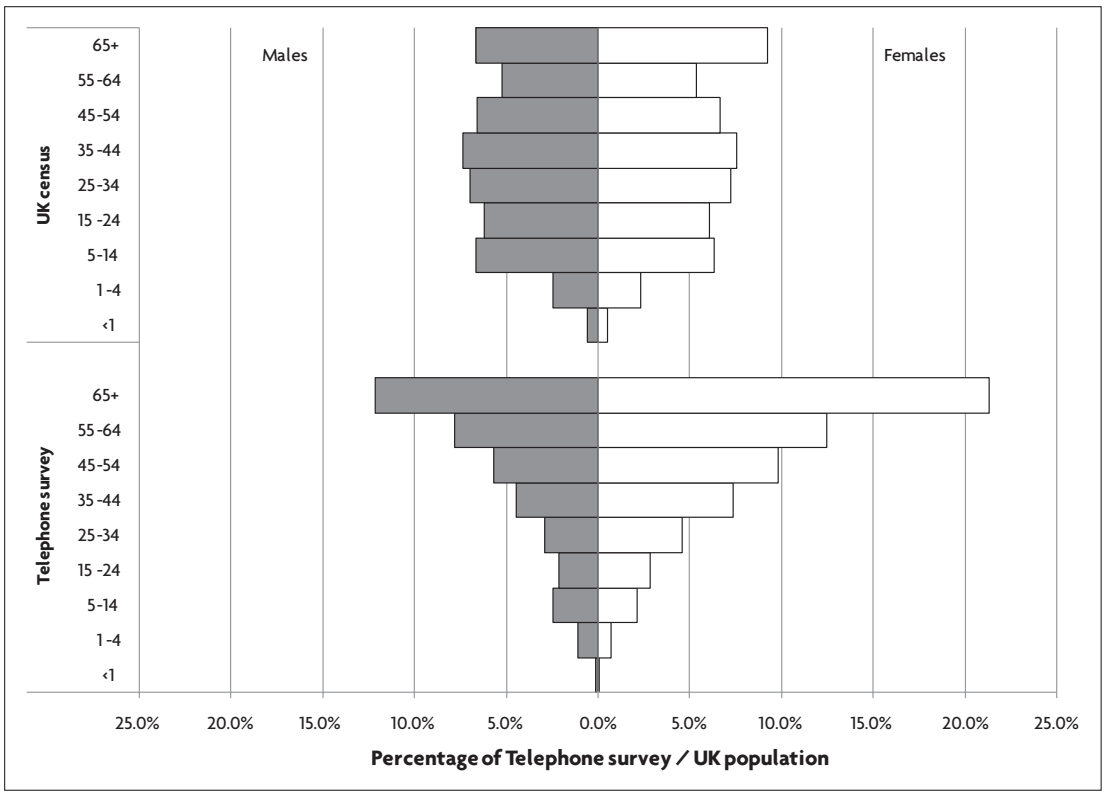


We restricted the analyses to the 14,813 calls for which evidence of consent was clearly recorded in the audio file. For 1,395 interviews, the audio recording was missing or damaged, or there was no recorded evidence of participant consent, and these interviews were excluded from the study. A further 87 calls were excluded from the analyses because the date of onset of symptoms was outside the period over which the participant was asked to recall. After exclusions, 14,726 interviews were available for analysis (Figure 4.11).

Among survey participants, there was evidence that the survey respondent was randomly selected from among those present in the household at the time for 45.7% in the 7-day recall group and for 45.2% in the 28-day recall group.

Figure 4.13 compares the age and sex structure of participants in the Telephone Survey with the UK census population. Females and elderly participants were over-represented in the survey sample.

Figure 4.13: Age and sex structure of Telephone Survey participants compared with the UK population



The majority of Telephone Survey participants (96.4%) were of White ethnicity, while other ethnic groups were slightly under-represented relative to the UK census population (Figure 4.14). Survey participants were broadly representative of the UK population in terms of household size, although there was a small deficit of single-person households and a slight excess of two-person households in the study (Figure 4.15).

Individuals living in the most deprived areas were under-represented in the Telephone Survey: approximately 25% of survey participants lived in areas in the first two quintiles of area-level deprivation, compared with 40% of the UK population (Figure 4.16). By contrast, individuals living in rural areas and towns were over-represented in the survey sample (Figure 4.17).

Figure 4.14: Distribution of ethnic group among Telephone Survey participants relative to the UK population

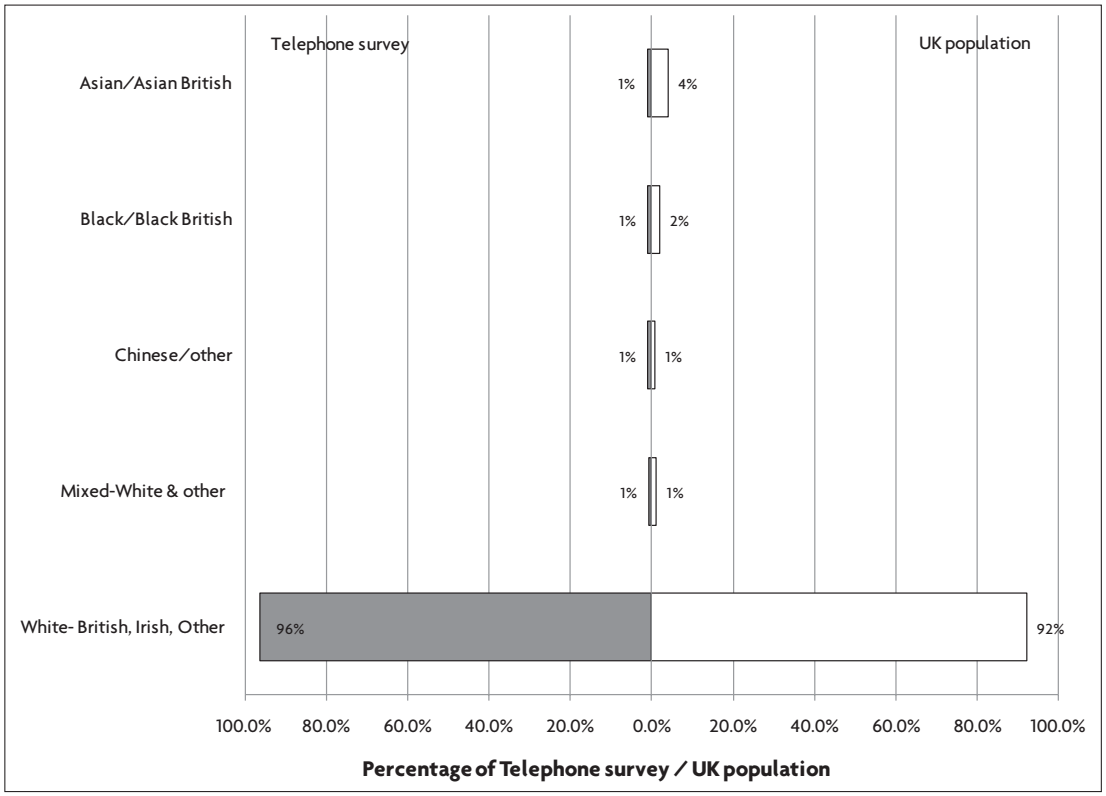
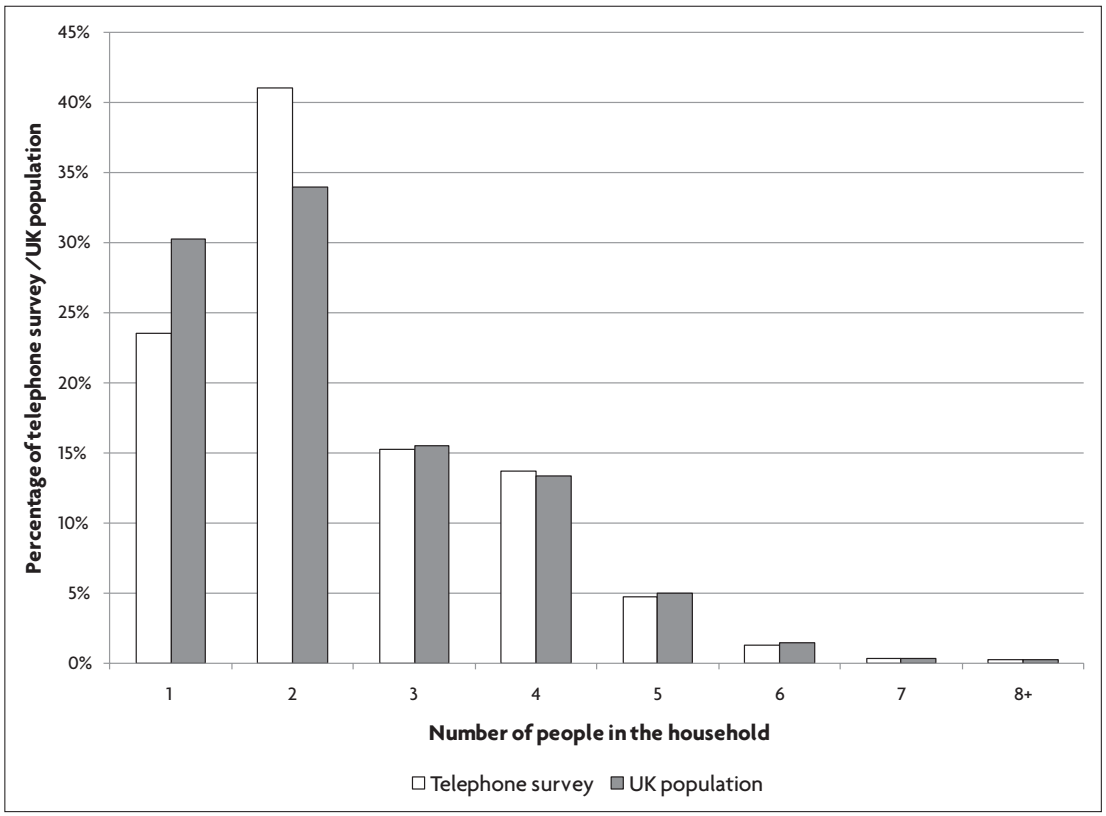
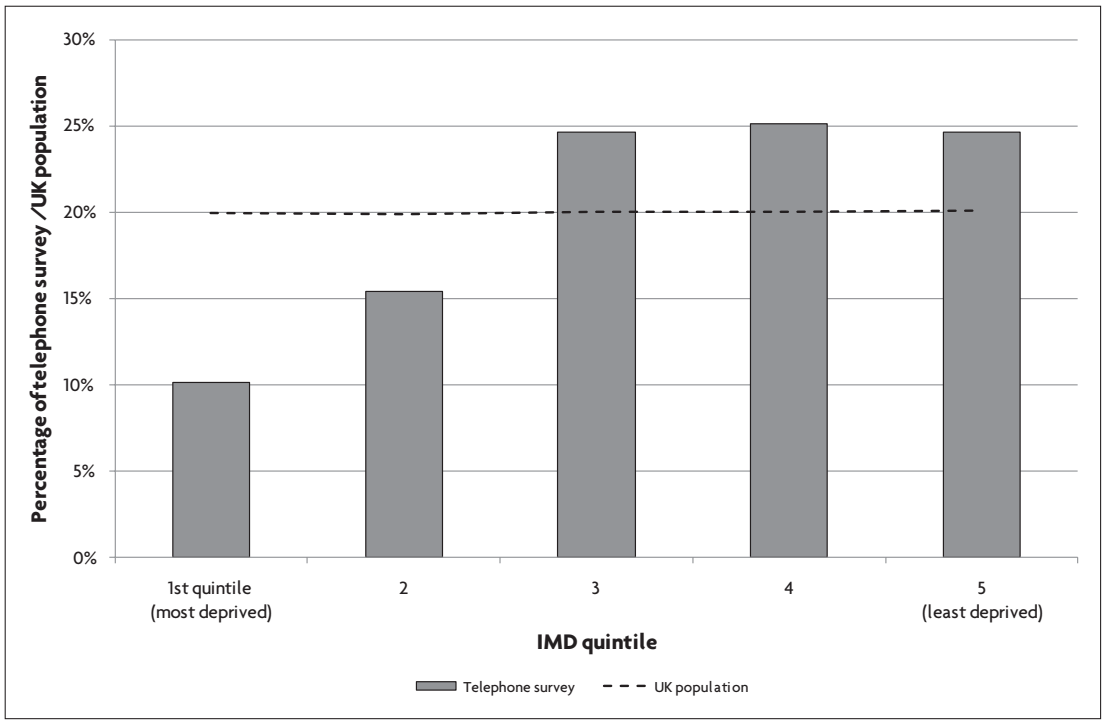


Figure 4.15: Distribution of household size among Telephone Survey participants compared with the UK population



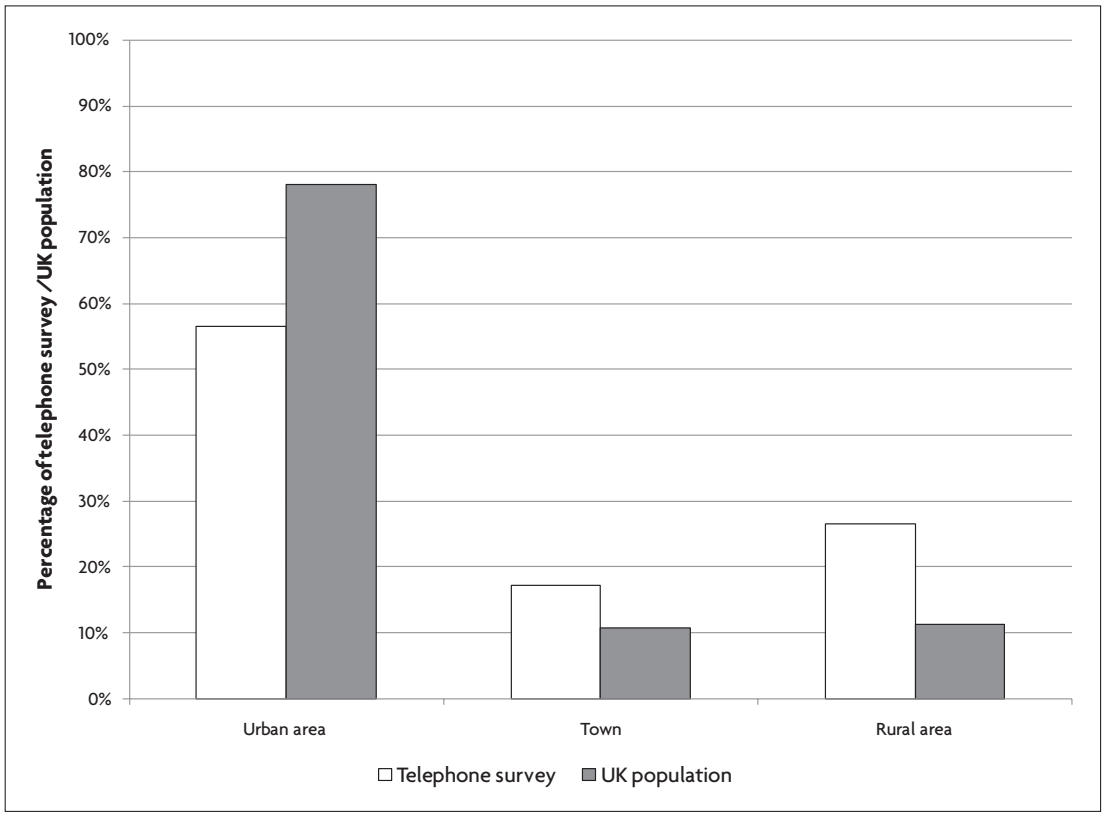
NOTE: The percentage of participants in each category is averaged across the 4 UK countries taking into account the relative size of the population in each country

Figure 4.16: Distribution of area-level deprivation among Telephone Survey participants compared with the UK population



NOTE: The proportion of participants in each category is a weighted average that takes into account the different distribution of participants across countries.

Figure 4.17: Distribution of urban-rural classification among Telephone Survey participants compared with the UK population



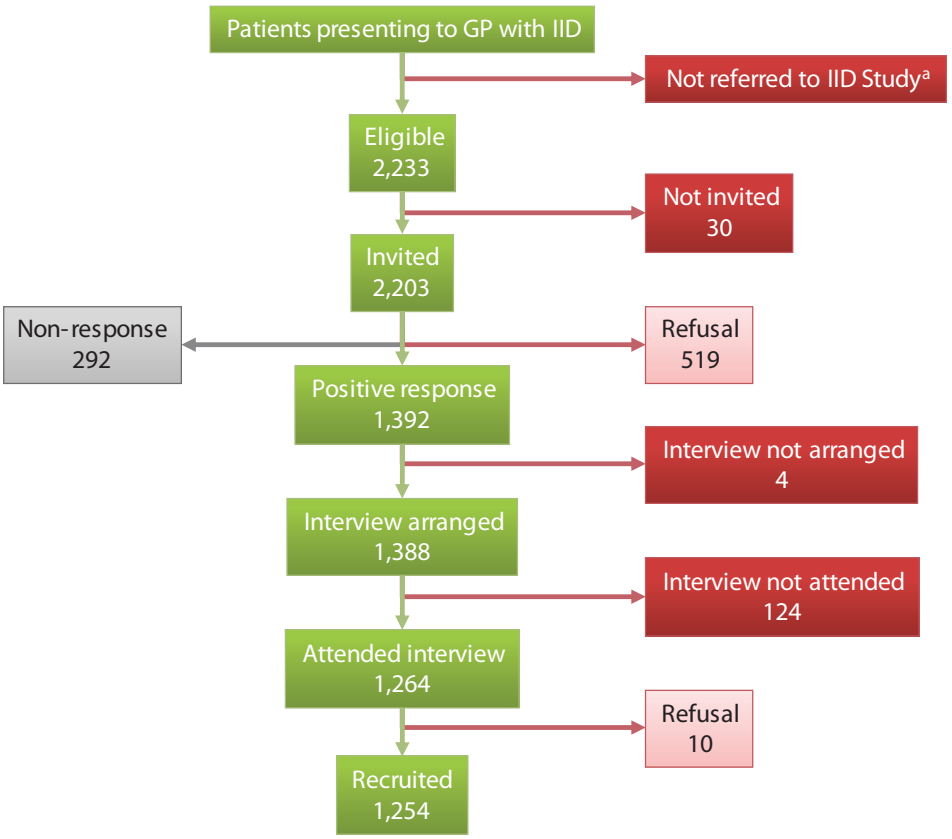
NOTE: The percentage of participants in each category is averaged across the 4 UK countries taking into account the relative size of the population in each country

4.4 GP PRESENTATION STUDY

4.4.1 Recruitment

In total 2,233 eligible patients were referred to the IID2 GP Presentation Study. Of these, 2,203 (99%) were invited to take part in the study. Among those invited to participate, 1,392 (63%) responded positively, 1,264 (57%) attended a baseline recruitment interview, and 1,254 (57%) were recruited (Figure 4.18).

Figure 4.18: Recruitment of participants into the GP Presentation Study



[a] The number not referred is not known and was estimated from the GP Validation Study

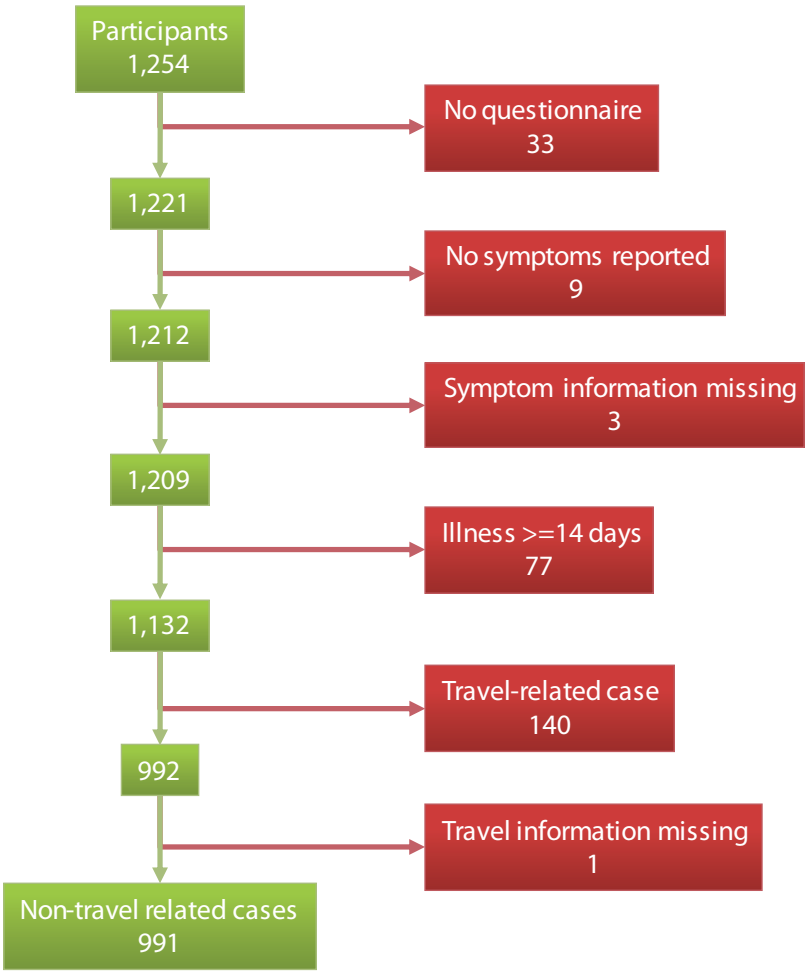
Table 4.4 shows the number and percentage of individuals recruited into the GP Presentation Study. Six hundred and sixty five (53%) participants were female. Among both males and females, participation was highest among those aged 45 years and above and lowest between the ages of 15 and 34 years. Practices recruited an average of 34 participants.

Table 4.4: Recruitment of participants into the GP Presentation Study by age group and sex

	Age group	Eligible	Invited	Percentage of those invited				No. Consented
				Positive response	Interview arranged	Attended interview	Consented	
Males	<1 year	98	96	59.4%	59.4%	51.0%	51.0%	**49**
	1-4 years	187	183	64.5%	62.8%	55.2%	54.6%	**100**
	5-14 years	92	91	60.4%	59.3%	52.7%	52.7%	**48**
	15-24 years	85	85	50.6%	48.2%	44.7%	42.4%	**36**
	25-34 years	95	94	56.4%	56.4%	52.1%	50.0%	**47**
	35-44 years	115	112	62.5%	58.0%	52.7%	52.7%	**59**
	45-54 years	112	110	68.2%	66.4%	63.6%	63.6%	**70**
	55-64 years	91	90	81.1%	77.8%	74.4%	73.3%	**66**
	65+ years	171	171	74.3%	70.8%	66.7%	66.7%	**114**
	All ages	*1,046*	*1,032*	*65.0%*	*62.9%*	*57.7%*	*57.1%*	***589***
Females	<1 year	61	61	54.1%	54.1%	49.2%	49.2%	**30**
	1-4 years	140	136	61.0%	59.6%	51.5%	51.5%	**70**
	5-14 years	84	84	63.1%	61.9%	56.0%	56.0%	**47**
	15-24 years	117	114	52.6%	50.9%	46.5%	45.6%	**52**
	25-34 years	168	166	63.9%	60.8%	50.6%	50.6%	**84**
	35-44 years	141	139	64.0%	62.6%	56.8%	56.8%	**79**
	45-54 years	117	114	69.3%	69.3%	63.2%	63.2%	**72**
	55-64 years	129	128	75.8%	72.7%	67.2%	65.6%	**84**
	65+ years	229	229	71.6%	67.7%	64.6%	64.2%	**147**
	All ages	*1,186*	*1,171*	*65.2%*	*63.1%*	*57.1%*	*56.8%*	***665***

Of the 1,254 participants recruited, 991 met the case definition for a non-travel related case of IID (Figure 4.19).

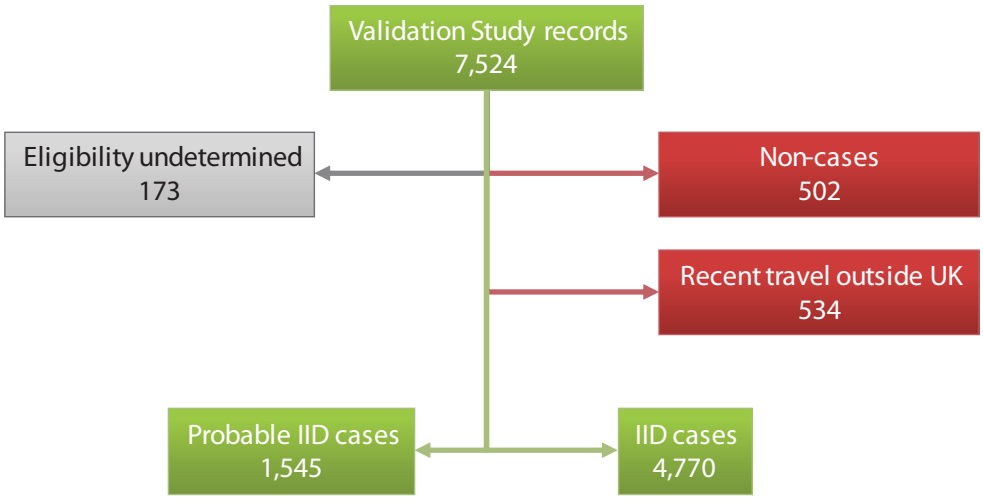
Figure 4.19: Case definition and exclusions among GP Presentation Study participants



4.4.2 Under-ascertainment

In total 7,524 records of consultations for IID-related symptoms were identified through the Read code search in the Validation Study. Of these, 4,770 met the case definition for IID. A further 1,545 consultations with relevant Read codes, but for which symptom information was missing from the medical records, were classified as probable cases (Figure 4.20).

Figure 4.20: Case definition and exclusions among the Validation Study records



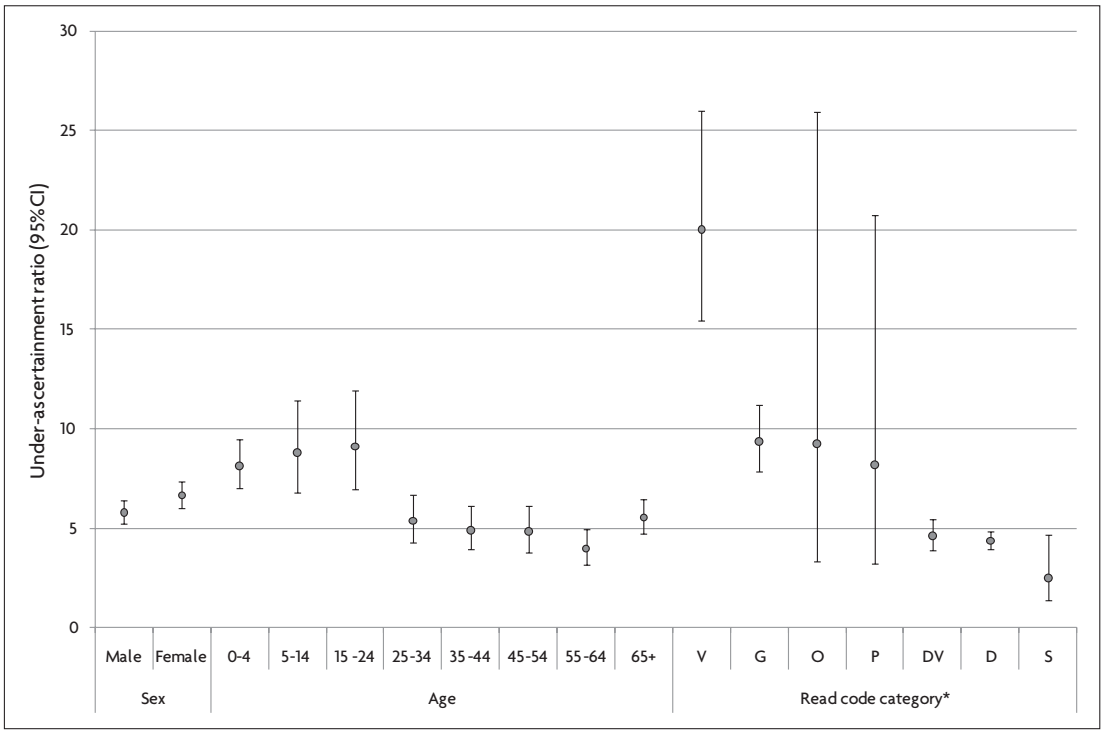
In the under-ascertainment analysis, we used 6,315 records for definite and probable cases identified in the Validation Study, of which 799 linked to a case in GP Presentation Study. A further 94 GP Presentation cases were not identified in the Validation search and 98 linked to a record in the Validation search that did not meet the case definition. These latter 192 records were not used in the development of the under-ascertainment model. Overall, 6 additional cases were identified in the Validation Study for every participant enrolled in the GP Presentation Study. Our final under-ascertainment model, used to derive under-ascertainment weights, included sex, age group, Read code category, and a random intercept variable to account for differences in ascertainment by practice. Figure 4.21 shows the ratio of Validation Study to GP Presentation Study cases by sex, age group and Read code category. A higher ratio indicates a greater degree of under-ascertainment, i.e. more cases identified in the Validation Study for every case enrolled in the GP Presentation Study. Under-ascertainment was higher among females than males, and among individuals <25 years compared with other age groups.

The under-ascertainment ratio also varied by the type of Read code used to code the consultation. In particular, the under-ascertainment ratio for codes related to vomiting (20:1) was more than double that for all the other Read code categories. This suggests that consultations coded under Read codes for vomiting are far less specific for IID and are likely to include a high proportion of consultations not related to IID. For this reason, for records with a Read code of "Vomiting", we used as the weights the mean under-ascertainment ratio across all other Read code categories instead. We thus made the assumption that for the fraction of consultations for "Vomiting" that was truly related to IID, the under-ascertainment ratio was similar to that for IID consultations coded under other categories of Read code (such as "Diarrhoea and vomiting" or "Gastroenteritis").

The under-ascertainment weights were applied to the 991 definite cases identified in the GP Presentation Study to compute the incidence. For the 192 GP Presentation records that were not used in developing the under-ascertainment model, we used the model-estimated weights for records in the same practice and in the corresponding stratum of age group, sex and Read code category. If no records in the same stratum occurred in that practice, then the mean of the weights across all other practices was applied.

It was not possible to assess misclassification amongst GP Presentation cases. Where GP Presentation cases did not link to a validation record this was often because the consultation had not been coded, or had been coded as something else. However, all the GP Presentation cases used in the analysis met the case definition.

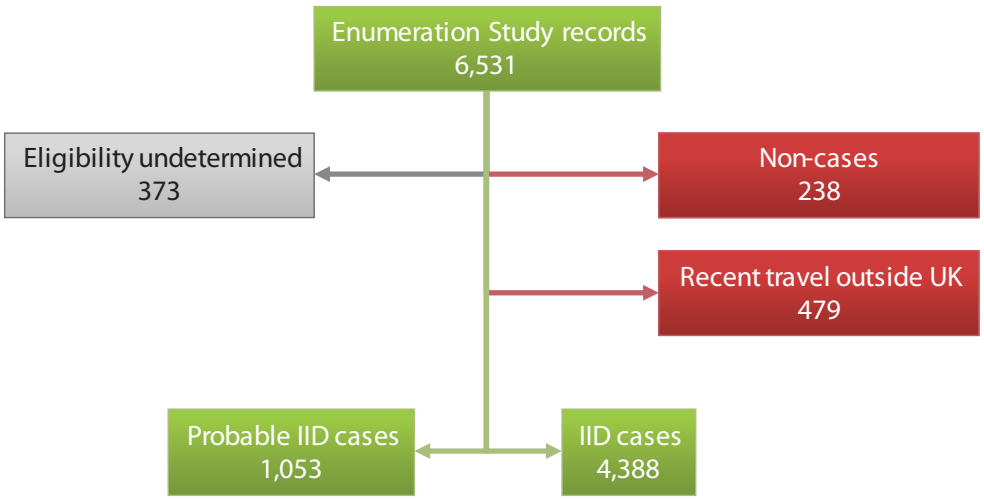
Figure 4.21: Under-ascertainment in the GP Presentation Study by sex, age group and Read code category



Each marker represents the number of cases not ascertained in the GP Presentation Study for every case recruited in the study. *Read code categories: V: codes for vomiting; G: codes for gastroenteritis; O: codes indicating stool sample sent for analysis; P: codes denoting IID due to specific pathogens; DV: codes for diarrhoea and vomiting; D: codes for diarrhoea; S: codes relating to symptoms compatible with IID; Error bars represent 95% CIs

4.5 GP ENUMERATION STUDY

Figure 4.22: Case definition and exclusions among GP Enumeration Study records



Between 1st September 2008 and 31st August 2009 4,388 definite cases of IID were identified through the Read code search in the GP Enumeration Study (Figure 4.22). Among these, a specimen for microbiological investigation was known to have been requested in 27% (n=1,174), although this ranged from 19% among cases aged 5-24 years, to 42% among cases aged 55-64 years (Table A4.12). Among the 1,174 cases from whom a specimen had been requested, a specimen was recorded as having been submitted in 34% (n=400), with little variation by age (Table A4.13). A positive result for one or more organisms was recorded in 71% (n=283) of the 400 submitted specimens (Table A4.14).

Overall, 24% of the 1,174 cases from whom a specimen was requested had a positive microbiological result recorded.

4.6 SPECIMEN COLLECTION

Among 1,201 definite cases in the Cohort Study, 783 specimens were submitted (65%). There was little difference between males and females in the percentage of cases submitting a specimen, but children <5 years and individuals aged 45+ years were more likely to submit a specimen (Table 4.5). The median time between illness onset and specimen collection was 1 day; 75% of specimens were collected within 3 days of symptom onset.

Among the 783 specimens submitted, 65% weighed <10 grams and 749 specimens (96%) were tested for all organisms in the first line testing at the HPA Manchester laboratory.

Table 4.5: Number and percentage of specimens submitted among definite cases in the Cohort Study by age group and sex

Variable	Cases	Specimen received	%
Age group			
<1 year	29	22	75.9%
1-4 years	136	98	72.1%
5-14 years	126	62	49.2%
15-24 years	20	11	55.0%
25-34 years	78	44	56.4%
35-44 years	136	79	58.1%
45-54 years	168	118	70.2%
55-64 years	241	176	73.0%
65+ years	267	173	64.8%
Sex			
Males	424	282	66.5%
Females	777	501	64.5%

Among 991 cases in the GP Presentation Study, 874 (88%) submitted a specimen. Again, there was little difference in specimen submission between males and females. More than 80% of cases in all age groups submitted a specimen, with the exception of individuals aged between 15 and 24 years, among whom 70% of cases submitted a specimen (Table 4.6). The median time between illness onset and specimen collection was 6 days; 75% of specimens were collected within 9 days of symptom onset. The greater delay between illness onset and specimen collection in the GP Presentation Study is due to the requirement for potential participants to be approached by the practice nurse and make an appointment for an interview before a specimen could be collected.

Among the 874 specimens submitted, 63% weighed <10 grams and 856 (98%) were tested for all organisms in the first line testing at the Manchester laboratory.

Table 4.6: Number and percentage of specimens submitted among cases in the GP Presentation Study by age group and sex

Variable	Cases	Specimen received	%
Age group			
<1 year	74	68	91.9%
1-4 years	141	124	87.9%
5-14 years	83	67	80.7%
15-24 years	63	44	69.8%
25-34 years	95	77	81.1%
35-44 years	102	83	81.4%
45-54 years	96	92	95.8%
55-64 years	122	116	95.1%
65+ years	215	203	94.4%
Sex			
Males	516	460	89.1%
Females	475	414	87.2%

CHAPTER 5

INCIDENCE RATES[15]

5.1 INCIDENCE RATES IN THE PROSPECTIVE POPULATION-BASED COHORT STUDY

There were 1,201 definite cases of IID and a total of 4,658 person-years of follow-up in the community cohort. The crude incidence rate of IID in the community in the UK was estimated at 258 cases per 1,000 person-years. The rate after adjustment to reflect the age and sex composition of the census population was 274 cases per 1,000 person-years (95% CI: 254 – 296). This indicates that just over a quarter of the population experience an episode of IID each year (Table 5.1).

Table 5.1: Incidence rate of overall IID in the Cohort Study

	Cases	PY	Rate	(95% CI)
Crude rate	1,201	4658.6	**257.8**	(243.6 - 272.8)
Age-sex standardised rate			**274.3**	(253.8 - 295.8)

[a]PY – person-years; [b]Cases per 1,000 person-years

Rates of IID were particularly high among those aged less than 5 years. Among infants, the rate in the community was 1,079 per 1,000 person-years, indicating that, on average, children experience one episode of IID in their first year of life. There was little variation in incidence with age among those aged more than 5 years (Table 5.2).

Rates of IID were higher overall among females than males, particularly in those aged between 25 and 34 years; female rates in this age group were more than double male rates.

[15] When reading this chapter please note that tables and figures pre-fixed "A" can be found in the annex to Chapter 5.

Table 5.2: Incidence rate of overall IID in the Cohort Study by age group and sex (definite cases only)

	Males				Females				All			
Age group	**Cases**	**PY[a]**	**Rate[b]**	**(95% CI)**	**Cases**	**PY[a]**	**Rate[b]**	**(95% CI)**	**Cases**	**PY[a]**	**Rate[b]**	**(95% CI)**
<1 year	15	14.9	**1009.2**	(608.4 - 1673.9)	14	12.0	**1166.4**	(690.8 - 1969.4)	29	26.9	**1,079.4**	(750.1 - 1553.3)
1-4 years	67	92.5	**724.1**	(569.9 - 920)	69	98.2	**702.3**	(554.7 - 889.2)	136	190.8	**712.8**	(602.5 - 843.2)
5-14 years	75	211.5	**354.7**	(282.8 - 444.7)	51	212.6	**239.9**	(182.3 - 315.6)	126	424.2	**297.1**	(249.5 - 353.7)
15-24 years	9	42.2	**213.1**	(110.9 - 409.5)	11	90.3	**121.8**	(67.5 - 220)	20	132.6	**150.9**	(97.4 - 233.9)
25-34 years	11	59.7	**184.1**	(102 - 332.5)	67	172.9	**387.4**	(304.9 - 492.2)	78	232.8	**335.1**	(268.4 - 418.4)
35-44 years	30	118.4	**253.4**	(177.1 - 362.4)	106	345.8	**306.5**	(253.4 - 370.8)	136	464.2	**293.0**	(247.6 - 346.6)
45-54 years	47	221.0	**212.6**	(159.8 - 283)	121	509.0	**237.7**	(198.9 - 284.1)	168	730.2	**230.1**	(197.8 - 267.7)
55-64 years	77	428.5	**179.7**	(143.7 - 224.7)	164	659.8	**248.5**	(213.3 - 289.7)	241	1,088.3	**221.4**	(195.2 - 251.2)
65+ years	93	651.9	**142.7**	(116.4 - 174.8)	174	717.2	**242.6**	(209.1 - 281.5)	267	1,369.1	**195.0**	(173 - 219.9)
All ages[c]	*424*	*1840.6*	***230.4***	*(209.4 - 253.4)*	*777*	*2818.0*	***275.7***	*(257 - 295.8)*	*1201*	*4,658.6*	***257.8***	*(243.6 - 272.8)*

[a]PY – person-years; [b]Cases per 1,000 person-years; [c]Unadjusted rates

After adjusting for age and sex, there was little evidence of variation in IID rates by type of follow-up (email or postcard), area-level deprivation, urban-rural classification or socioeconomic classification, although for the latter, there was some evidence that the rate in the lower supervisory and technical occupations group was lower when compared with the rate in the Managerial and professional occupations group. Those belonging to non-White ethnic groups reported lower rates of IID, although there were very few participants in these groups and the uncertainty in the corresponding rate estimates was high (Figure A5.1).

The rate of IID decreased with time in study. Among participants who were in the study for <26 weeks, the rate of IID was 442 cases per 1,000 person-years (95% CI: 370 – 533). Among those who were in the study for 26 weeks or more, the rate in the first 26 weeks was 282 cases per 1,000 person-years (95% CI: 257 – 311), while the rate after 26 weeks was 198 cases per 1,000 person-years (95% CI: 74 – 227) (Figure A5.2). There was a gradual decrease in the rate by week of follow-up (Figure A5.3)

When both definite and possible cases were considered, the crude rate estimate was 464 cases per 1,000 person-years. After standardising for age and sex, this estimate rose to 523 cases per 1,000 person-years. The difference between crude and standardised rates arises because individuals in certain age groups were more likely to be missing a questionnaire and hence be classified as possible cases, despite reporting a higher frequency of episodes of diarrhoea and/or vomiting.

5.2 INCIDENCE RATES IN THE TELEPHONE SURVEY

The estimates of IID incidence in the Telephone Survey for the 7-day and 28-day recall groups are shown in Table 5.3 Among participants in the 7-day recall group, there were a total of 300 cases and 212 person-years, resulting in a crude incidence of IID of 1,414 cases per 1,000 person-years (95% CI: 1263 – 1583). Among the 28-day recall group, 107 cases occurred in 158 person-years, giving a crude incidence of IID of 676 cases per 1,000 person-years (95% CI: 559 – 817). After standardising for age and sex, and adjusting for the number of interviews completed each month and the relative size of each UK country, the estimated rate of IID in the 7-day recall group was 1,530 cases per 1,000 person-years (95% CI: 1135 – 2113), while in the 28-day recall group it was 533 cases per 1000 person-years (95% CI: 377 – 778).

Table 5.3: Incidence rate of overall IID in the Telephone Survey by recall period

Recall period	Cases	PY[a]	Crude rate		Adjusted rate		RR[c]	(95% CI)
			Rate[b]	(95% CI)	Rate[b]	(95% CI)		
7 days	300	212.2	**1413.9**	(1262.6 - 1583.3)	**1529.6**	(1135.1 - 2112.6)	**2.9**	(1.8 - 4.6)
28 days	107	158.4	**675.5**	(558.9 - 816.5)	**533.2**	(377.0 - 777.5)		

[a]PY – person-years; [b]Cases per 1,000 person-years; [c]RR – Rate ratio comparing incidence in 7-day and 28-day recall groups

Table 5.4 presents incidence estimates by age group and sex. Rates decreased with age in the 7-day recall period. For the 28-day recall period the pattern was less clear, but the number of cases identified in each age group was small.

Overall, the rate estimated in the 7-day recall group was approximately 3 times higher than that estimated in the 28-day recall group (Table 5.3). There was considerable variation by age: the rate ratios comparing incidence in the 7-day and 28-day recall groups were generally higher among those aged <35 years, although much of this variation is likely to result from uncertainty in the age-specific rate estimates, particularly in the 28-day recall group, in which the number of cases was small (Table 5.4). The rates in males and females were similar for both recall periods.

Table 5.4: Incidence rate of overall IID in the Telephone Survey by recall period, age group and sex

	7-day recall			28-day recall			Rate ratio	
	PY[a]	Rate[b]	(95% CI)	PY[a]	Rate[b]	(95% CI)	RR[c]	(95% CI)
Age group								
<1 year[d]	0.4	---	---	0.4	**790**	(13 - 2670)	---	---
1-4 years	4.1	**2,910**	(1,218 - 8,534)	3.7	**336**	(130 - 977)	**8.7**	(2.4 - 31.1)
5-14 years	10.7	**2,020**	(538 - 12,986)	6.9	**1,037**	(389 - 3,463)	**1.9**	(0.4 - 8.5)
15-24 years	11.7	**1,194**	(556 - 3,016)	7.9	**60**	(23 - 191)	**20.0**	(5.9 - 67.8)
25-34 years	15.3	**2,177**	(1,025 - 5,467)	11.3	**292**	(51 - 4,051)	**7.5**	(1.6 - 35.8)
35-44 years	25.1	**1,369**	(828 - 2,426)	18.0	**809**	(375 - 2,022)	**1.7**	(0.7 - 4.3)
45-54 years	35.1	**1,633**	(958 - 3,014)	27.4	**726**	(347 - 1,775)	**2.2**	(0.9 - 5.6)
55-64 years	43.3	**799**	(505 - 1,343)	31.7	**764**	(340 - 2,069)	**1.0**	(0.4 - 2.7)
65+ years	66.4	**1,028**	(687 - 1,607)	51.0	**247**	(120 - 594)	**4.2**	(1.8 - 9.6)
Sex								
Males	81.8	**1,669**	(1,173 - 2,457)	60.4	**545**	(306 - 1,067)	**3.1**	(1.5 - 6.1)
Females	130.3	**1,401**	(846 - 2,497)	98.0	**523**	(346 - 822)	**2.7**	(1.4 - 5.1)

[a]PY – person-years; [b]Cases per 1,000 person-years, adjusted for number of interviews completed each month and the relative size of each UK country; [c]Rate ratio comparing 7-days and 28-day recall groups; [d]No cases reported so rate not calculable

The rates by country are shown in Table 5.5. There was variation in the rates between countries for both recall periods. However, the patterns were not consistent and there was considerable overlap in the 95% CIs.

Table 5.5: Incidence rate of overall IID in the Telephone Survey by recall period and country

	7-day recall		28-day recall	
Country	Rate	(95% CI)	Rate	(95% CI)
England	**1,463.4**	(994.3 - 2,246.5)	**449.4**	(279.8 - 766.7)
Northern Ireland	**1,269.9**	(932.4 - 1,774.9)	**801.8**	(512.9 - 1,324.9)
Scotland	**2,052.9**	(1,444.2 - 3,020.1)	**1,195.5**	(756.4 - 2,007.0)
Wales	**2,066.4**	(1,578.5 - 2,758.8)	**661.6**	(397.6 - 1,183.5)

There was no clear pattern in incidence by household size, area-level deprivation or urban-rural classification (Tables A5.1 – A5.3). Incidence estimates were highest among participants living in households with 4 people. By contrast, participants living in rural areas reported the lowest rates of IID in the 7-day recall group, but the highest rates in the 28-day recall group. It should be noted, however, that there was considerable uncertainty around these rate estimates.

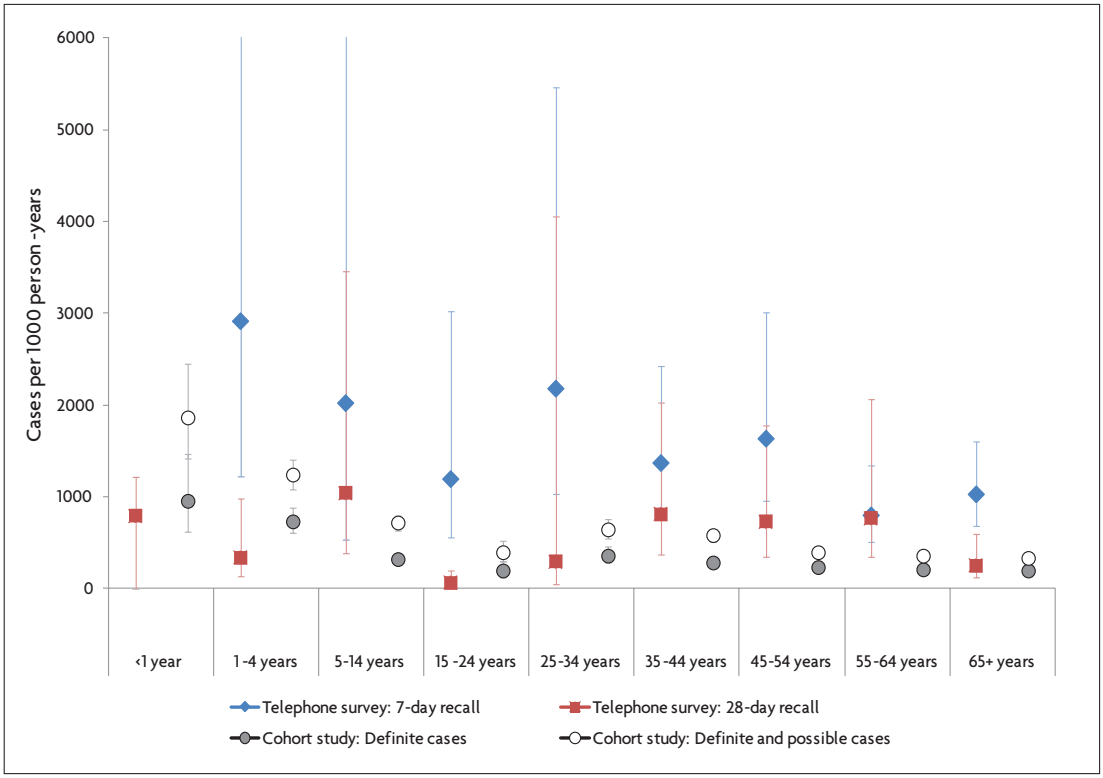
For both the 7-day and 28-day recall, there was evidence of variation in recall of IID symptoms according to time since illness onset. Participants reported a higher number of episodes with onset in the 3 days prior to interview, but there was a rapid decline in the number of episodes reported with onset beyond this period (Figure A5.4). For the 28-day recall group, there was also clear evidence of digit preference, with a greater number of episodes reported with onset 7, 14 and 21 days prior to the date of interview than on other days.

5.3 COMPARING INCIDENCE RATES OF OVERALL IID IN THE PROSPECTIVE POPULATION-BASED COHORT STUDY AND TELEPHONE SURVEY

Figure 5.1 compares the age-specific estimates of IID incidence in the Cohort Study and Telephone Survey. Incidence rates decreased with age until the ages of 15 to 24 years, with a subsequent secondary peak in adults between 25 and 44 years.

For all age groups, incidence estimates were higher in the 7-day recall Telephone Survey component than in all the other components.

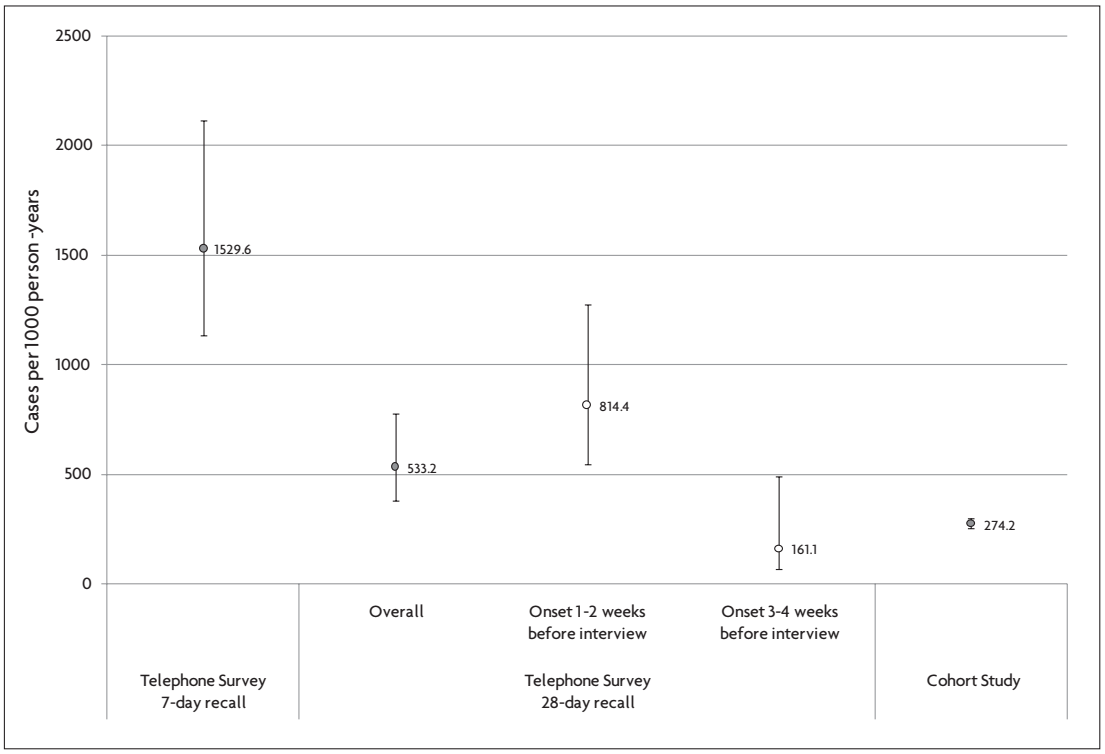
Figure 5.1: Incidence rates of overall IID by age group in the Cohort Study and Telephone Survey



Note: Error bars represent 95% CIs

There was evidence that reporting of symptoms in the Telephone Survey was related to the period of recall. The rate of IID in the 28-day recall group was 3 times lower than that in the 7-day recall group. Moreover, even within the 28-day recall group, participants reported a significantly higher rate of IID in the 2 weeks prior to the date of interview (814 cases per 1,000 person-years, 95% CI: 543 – 1276) compared with both the 2 to 4 weeks prior to the date of interview (161 cases per 1,000 person-years, 95% CI: 670 – 490), and the rate estimated in the Cohort Study (Figure 5.2).

Figure 5.2: Incidence rates of overall IID in the Telephone Survey, by recall period, and in the Cohort Study



Note: Error bars represent 95% CIs

5.4 INCIDENCE RATES IN NHS DIRECT

In the 24-month period between 1st July 2007 and 30th June 2009, a total of 623,732 calls were made to NHS Direct in England and Wales for diarrhoea, vomiting or food poisoning. In Scotland, 145,096 calls for diarrhoea or vomiting were made to NHS24 over the same time period.

The overall rates of consultation to these telephone services, per 1,000 person-years, were 6.1 in England, 3.6 in Wales and 14.3 in Scotland (Table 5.6). Rates in Scotland were higher than in England and Wales in all age groups, and particularly among those aged 65 years and above, in whom the rates in Scotland were more than 5 times higher than in the other two countries. Rates were highest among infants and children under 5 years in all three countries.

Table 5.6: Incidence of consultations to NHS Direct/NHS24 by age group in England, Wales and Scotland (rate per 1,000 person-years)

	England		Wales		Scotland	
Age group	**Rate**	**(95% CI)**	**Rate**	**(95% CI)**	**Rate**	**(95% CI)**
<1 year	113.3	(112.7 - 114)	65.8	(63.9 - 67.9)	208.3	(205.5 - 211.1)
1-4 years	31.9	(31.7 - 32)	20.6	(20 - 21.1)	64.7	(64 - 65.5)
5-14 years	3.4	(3.4 - 3.5)	2.0	(1.9 - 2.1)	7.7	(7.5 - 7.8)
15-44 years	4.1	(4.1 - 4.2)	2.4	(2.3 - 2.4)	9.0	(8.9 - 9.1)
45-64 years	2.4	(2.4 - 2.4)	1.4	(1.3 - 1.4)	7.4	(7.3 - 7.6)
65+ years	3.5	(3.5 - 3.5)	1.9	(1.8 - 1.9)	17.6	(17.4 - 17.8)
All ages	*6.1*	*(6.1 - 6.2)*	*3.6*	*(3.5 - 3.6)*	*14.3*	*(14.3 - 14.4)*

In both England and Wales, rates were slightly higher among females than males, although there was notable variation with age: among infants, rates were higher among males than females, but this pattern was reversed in the 15 to 44 year age group, among whom female rates were approximately double those in males (Table 5.7).

Table 5.7: Incidence of consultations to NHS Direct by age group and sex in England and Wales

	England		Wales	
Age group	**Males**	**Females**	**Males**	**Females**
<1 year	116.7	109.8	68.3	63.2
1-4 years	32.0	31.7	20.6	20.5
5-14 years	3.4	3.4	2.0	2.0
15-44 years	2.9	6.2	1.7	3.6
45-64 years	3.4	6.5	2.0	3.6
65+ years	2.3	3.6	1.3	2.1
All ages	1.7	2.6	1.0	1.4
55-64	2.0	3.3	1.3	1.9
65+	2.8	4.0	1.5	2.1
All ages	*5.6*	*6.7*	*3.3*	*3.8*

More than half of callers to NHS Direct with symptoms of diarrhoea and vomiting were advised home care, while approximately 40% were advised to consult their GP. Other call outcomes were rare (Table 5.8).

Table 5.8: Percentage of calls to NHS Direct by outcome of call, England and Wales

Call outcome*	**England**	**Wales**
999	0.7	0.6
A&E	2.8	2.3
GP	39.6	37.9
Home Care	54.1	56.5
Other	2.8	2.7
All outcomes	*100.0*	*100.0*

*999: Referred to emergency services; A&E: Referred to Accident & Emergency department; GP: Referred to general practice

The rate of consultations to NHS Direct for which the caller was advised to contact their GP was 2.43 per 1,000 persons per year, and the rate of IID presenting to general practice – as estimated in the GP Presentation Study – in which cases reported having contacted NHS Direct for their illness was 1.10 per 1,000 person-years. These estimates suggest that of those who contact NHS Direct for diarrhoea and vomiting and were advised to consult their GP; approximately 40% actually did so.

5.5 INCIDENCE RATES IN THE GP PRESENTATION STUDY

After adjusting for under-ascertainment and practice list inflation, there were an estimated 5,546 definite cases of IID and 312,232 person-years of follow-up in the GP Presentation Study. The corresponding incidence estimate was 17.7 cases per 1,000 person-years. When both definite and probable cases were considered, the incidence estimate was 19.1 cases per 1,000 person-years (Table 5.9).

Table 5.9: Incidence rate of overall IID presenting to general practice

	Cases	**PY[a]**	**Rate[b]**	**(95% CI)**
Definite cases	5546	312,232	**17.7**	(14.4 - 21.8)
Definite and probable cases	5968	312,232	**19.1**	(15.7 - 23.2)

[a]PY – Person-years; [b]Cases per 1,000 person-years

Estimates of IID incidence by age group and sex are shown in Table 5.10. Rates were generally higher among females than males at all ages with the exception of the 0-4 and 5-14 year age groups. The rate among women aged 25 to 34 years was more than double that of males in the same age group. A second peak in incidence occurred among those aged 65 years and above.

Table 5.10: Incidence rates of overall IID presenting to general practice by age group and sex (definite cases only)

	Males		Females		All	
Age group	Rate[a]	(95% CI)	Rate[a]	(95% CI)	Rate[a]	(95% CI)
0-4 years	**91.7**	(64.7 - 129.9)	**77.1**	(49.5 - 120.1)	**84.6**	(58.5 - 122.3)
5-14 years	**14.4**	(9 - 22.8)	**13.3**	(8.4 - 20.9)	**13.8**	(9.5 - 20.2)
15-24 years	**13.4**	(7.3 - 24.9)	**15.7**	(9.8 - 25.3)	**14.6**	(9.6 - 22.2)
25-34 years	**8.7**	(5.2 - 14.8)	**17.5**	(12.6 - 24.4)	**13.2**	(10.2 - 17)
35-44 years	**9.8**	(7.2 - 13.3)	**10.3**	(7.5 - 14.3)	**10.1**	(8 - 12.6)
45-54 years	**9.7**	(6.4 - 14.5)	**13.6**	(9.7 - 19)	**11.6**	(8.5 - 15.9)
55-64 years	**10.7**	(6.7 - 17.2)	**15.1**	(10.7 - 21.3)	**12.9**	(9.1 - 18.3)
65+ years	**18.0**	(13.2 - 24.5)	**22.0**	(14.8 - 32.6)	**20.2**	(15 - 27.3)
All ages	***16.6***	*(13.4 - 20.6)*	***18.9***	*(15.2 - 23.5)*	***17.7***	*(14.4 - 21.8)*

[a]Cases per 1,000 person-years

Only age group and sex were found to be important predictors of incidence. No practice-level characteristics, including urban-rural classification, area-level deprivation and number of GPs, were associated with differences in IID incidence, although there was weak evidence that incidence in larger practices (10,000+ registered patients) was lower than in smaller practices (<6,000 registered patients) (RR = 0.70, 95% CI: 0.48 – 1.02, p = 0.062) (Figure A5.5). Adjustment for practice size, however, made little difference to the overall rates. Incidence estimates for the GP Presentation Study have, therefore, not been adjusted for practice size.

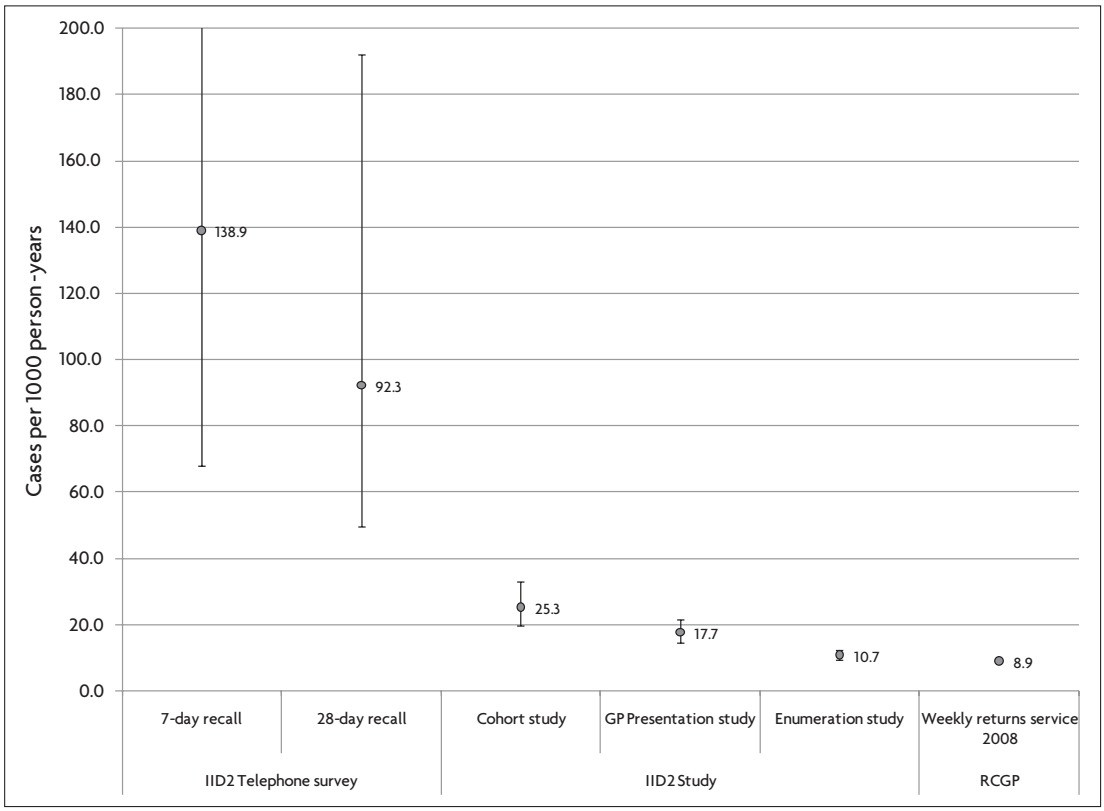
5.6 TRIANGULATION OF INCIDENCE RATES

5.6.1 Comparing estimates of incidence of IID presenting to general practice and consulting NHS Direct from different studies

Figure 5.3 shows estimates of the incidence of IID presenting to general practice from the Telephone Survey, the Prospective Cohort Study, the GP Presentation Study and the GP Enumeration Study. As an external comparison, we also present an estimate based on the incidence of new episodes of IID presenting to practices in the RCGP Weekly Returns Service network.

The estimates based on self-report of presentation to general practice, from the Telephone Survey and Cohort Study, were higher than those based on general practice records of consultations. The estimates were highest in the Telephone Survey: in the 7-day recall group, the incidence rate was estimated at 138.9 per 1,000 person-years (95%CI: 68.2; 328.5) and in the 28-day recall period as 92.3 per 1,000 person-years (95% CI: 49.3; 193.1). By contrast, the estimate based on cases in the Cohort Study who reported consulting a GP for their illness was 25.3 cases per 1,000 person-years (95% CI: 20.7 – 31.3), and was closer to estimates obtained from the GP Presentation Study (17.7 cases per 1,000 person-years, 95% CI: 14.4 – 21.8), the Enumeration Study (10.7 cases per 1,000 person-years, 95% CI: 9.3 – 12.4), and the RCGP Weekly Returns Service (8.9 cases per 1,000 person-years).

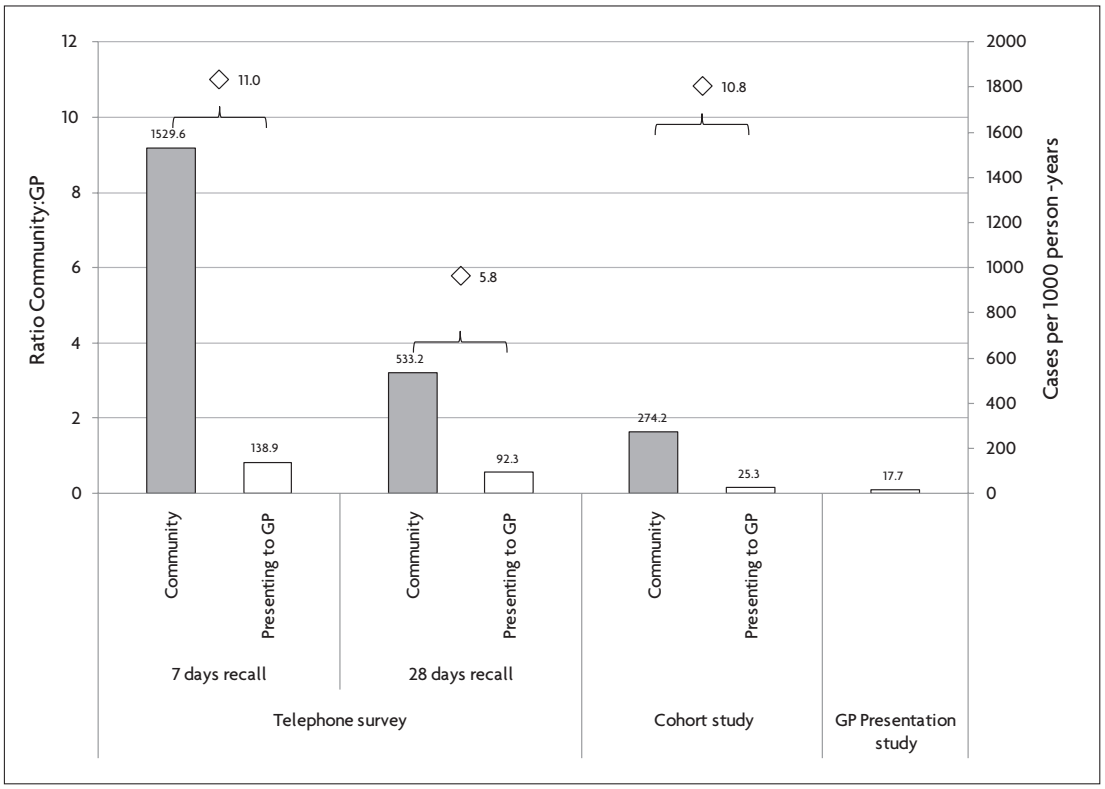
Figure 5.3: Incidence rate of overall IID presenting to general practice – Estimates from different studies



Note: Error bars represent 95% CIs

Figure 5.4 shows the estimated rates of IID in the community and presenting to general practice from the two recall groups in the Telephone Survey and from the Prospective Cohort Study. The ratios comparing the rate in the community with that presenting to general practice in each study component is also shown. For the Telephone Survey 7-day recall group, 1 in 11 cases reported having consulted a GP for their illness, and this ratio was similar to that in the Prospective Cohort Study. By contrast, in the 28-day recall group, 1 in 6 cases reported having consulted a GP.

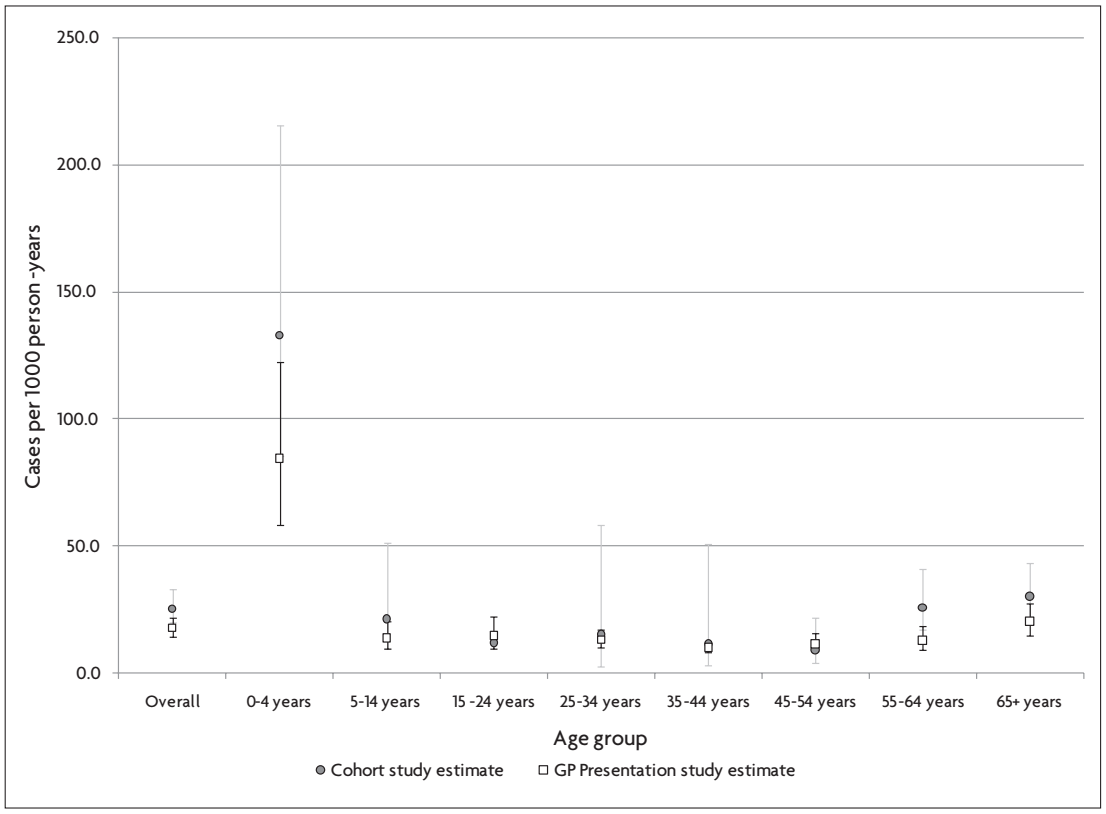
Figure 5.4: Incidence of IID in the community and presenting to general practice – Estimates from the Telephone Survey and Cohort Study



Note: Grey bars show estimates of incidence in the community, white bars show estimates of incidence presenting to general practice, white diamonds represent the ratio of incidence in the community to that presenting to general practice. Estimates from the GP Presentation Study are included for comparison.

In Figure 5.5, age-specific incidence rates of IID presenting to general practice, as estimated from the Prospective Cohort and GP Presentation studies, are presented. Comparison with age-specific rates from the Telephone Survey was not possible, due to the small number of cases who reported having consulted a GP. The figure shows that estimates from the Cohort Study and the GP Presentation Study are similar between the ages of 15 and 54 years, but estimates based on self-report in children and the elderly are generally higher compared with practice record-based estimates.

Figure 5.5: Incidence of IID presenting to general practice by age group – Estimates from the Prospective Cohort and GP Presentation studies



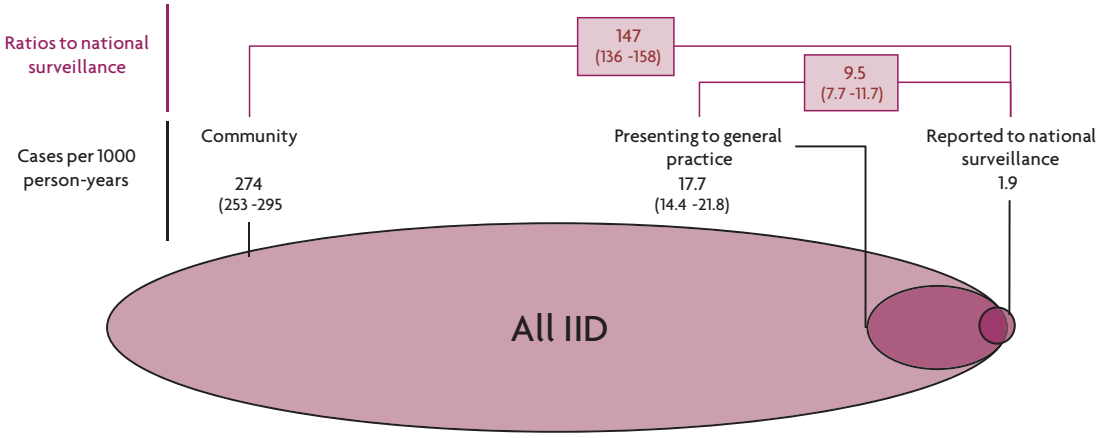
Note: Error bars represent 95% CIs. A CI around the cohort study estimate for 15-24 year olds has been omitted intentionally. This is because CIs are calculated by jackknife, which involves excluding one observation at a time and re-estimating the rate. Where numbers of cases are very small, this can sometimes result in unreliable estimates, e.g. both limits being below (or above) the point estimate.

The estimated rate of self-reported consultation to NHS Direct in England obtained from the Prospective Cohort Study was 5.5 per 1,000 person-years (95% CI: 3.4 – 9.5) and was also in agreement with that estimated from calls to NHS Direct in England (6.1 per 1,000 person-years).

5.6.2 Reporting pattern for overall IID in the UK

Figure 5.6 shows the reporting pattern for all IID in the UK. It represents the relationship between the incidence of IID in the community, presenting to general practice and reported to national surveillance. The figure is based on the incidence of overall IID in the community as estimated from definite cases in the Prospective Cohort Study, the incidence of IID presenting to general practice as estimated from the GP Presentation Study, and the incidence of IID reported to national surveillance as estimated from laboratory reports of positive identifications for IID-related pathogens. The incidence estimates of IID in the community and presenting to general practice, together with 95% CIs, are shown in black inside the corresponding ellipses. The numbers in red outside the ellipses represent, respectively, the ratio of incidence of IID in the community to that reported to national surveillance, and the ratio of incidence of IID presenting to general practice to that reported to national surveillance.

Figure 5.6: Reporting pattern for overall IID, UK



The estimated rate of IID in the community was 274 per 1,000 person-years, 147 times higher than that of IID reported to national surveillance. The rate of IID presenting to general practice was 17.7 per 1,000 person-years, a figure 9.5 times higher than that of IID reported to national surveillance. This indicates that for every case of IID reported to national surveillance, approximately 150 cases occur in the community, and about 10 of these present to general practice for their illness.

The ratio comparing the incidence of IID in the community with that presenting to general practice was 15.4 (95% CI: 12.4 – 19.3), indicating that approximately 1 in every 15 cases of IID occurring in the community consults a GP for their illness.

5.6.3 Travel-related IID

In the Prospective Cohort Study, 8% of IID cases reported having travelled outside the UK in the 10 days prior to illness onset. The proportion reporting recent foreign travel was lower among children, and there was little variation among those aged 15 years and above. The corresponding figure among cases of IID presenting to general practice was 12%, with a similar pattern by age (Tables A5.4 and A5.5).

In the Prospective Cohort Study, we estimated that the rate of IID for which recent foreign travel is reported was 22 cases per 1,000 person-years (95% CI: 17.5 - 28.0) (Table A5.6), suggesting that approximately 2% of UK residents acquire IID putatively related to recent foreign travel.

CHAPTER 6

ORGANISM-SPECIFIC INCIDENCE RATES OF IID[16]

6.1 MICROBIOLOGICAL FINDINGS IN THE PROSPECTIVE POPULATION-BASED COHORT AND GP PRESENTATION CASES

6.1.1 Prospective Population-Based Cohort Study

Microbiological findings among cases in the cohort are shown in Table 6.1. Viruses were the most commonly identified pathogens: clinically significant norovirus and rotavirus infection was identified in 16.5% and 4.1% of specimens respectively, while evidence of sapovirus infection was found in 9.2% of specimens. Adenovirus and astrovirus were identified in 3.6% and 1.8% of specimens respectively. Among children aged <5 years, norovirus was identified in 20% of specimens, sapovirus in 18%, and rotavirus in 10% (Table A6.1). *Campylobacter* was the most commonly identified bacterial agent among cohort cases, with 3.7% of specimens testing positive for this pathogen by culture methods. Overall, 4.6% of specimens tested positive for *Campylobacter* by either culture or PCR. Enteroaggregative *E. coli* was found by PCR in 1.9% of specimens overall (Table 6.1) and in 5% of specimens among those aged less than 5 years (Table A6.1). Other pathogens were identified in less than 1% of specimens. For *C. difficile*, only one specimen tested positive by PCR. No *C. difficile* positive specimens were identified using immunoassay methods.

Overall, 60.2% of samples from confirmed cases had no pathogen identified, although this varied by age group; among those aged less than 5 years, 40% of specimens had no pathogen identified (Table A6.1).

[16] When reading this chapter please note that tables and figures pre-fixed "A" can be found in the annex to Chapter 6.

Table 6.1: Microbiological findings in stool samples submitted by Cohort cases

Pathogen	Test	No. identified	Tested	% identified	(95% CI)
Bacteria					
C. difficile[a]	All	1	715	0.1%	(0% - 0.8%)
	EIA	*0*	*715*	*0.0%*	*(0% - 0.5%)*
	PCR	*1*	*693*	*0.1%*	*(0% - 0.8%)*
C. perfringens	Culture	6	772	0.8%	(0.3% - 1.7%)
Campylobacter	All	36	782	4.6%	(3.2% - 6.3%)
	All culture	*28*	*767*	*3.7%*	*(2.4% - 5.2%)*
	Direct culture	*18*	*766*	*2.3%*	*(1.4% - 3.7%)*
	Enrichment	*27*	*766*	*3.5%*	*(2.3% - 5.1%)*
	PCR	*31*	*782*	*4.0%*	*(2.7% - 5.6%)*
E. coli O157 VTEC	Culture	1	768	0.1%	(0% - 0.7%)
E. coli non-O157 VTEC	Culture	6	781	0.8%	(0.3% - 1.7%)
Enteroaggregative *E. coli*	PCR	15	782	1.9%	(1.1% - 3.1%)
Listeria	Culture and/or PCR	0	769	0.0%	(0% - 0.5%)
Salmonella	All	2	782	0.3%	(0% - 0.9%)
	Culture	*2*	*768*	*0.3%*	*(0% - 0.9%)*
	PCR	*1*	*782*	*0.1%*	*(0% - 0.7%)*
Shigella	Culture	0	768	0.0%	(0% - 0.5%)
Yersinia	All culture	0	769	0.0%	(0% - 0.5%)
	Direct culture	*0*	*769*	*0.0%*	*(0% - 0.5%)*
	Enrichment	*0*	*769*	*0.0%*	*(0% - 0.5%)*
Protozoa					
Cryptosporidium	All	3	782	0.4%	(0.1% - 1.1%)
	EIA	*2*	*768*	*0.3%*	*(0% - 0.9%)*
	PCR	*3*	*782*	*0.4%*	*(0.1% - 1.1%)*
Cyclospora	Microscopy	0	768	0.0%	(0% - 0.5%)
Giardia	All	6	782	0.8%	(0.3% - 1.7%)
	EIA	*3*	*768*	*0.4%*	*(0.1% - 1.1%)*
	PCR	*6*	*782*	*0.8%*	*(0.3% - 1.7%)*
Viruses					
Adenovirus	ELISA and/or PCR[b]	28	782	3.6%	(2.4% - 5.1%)
Astrovirus	PCR	14	782	1.8%	(1% - 3%)
Norovirus	PCR	129	782	16.5%	(14% - 19.3%)
Rotavirus	ELISA and/or PCR[b]	32	782	4.1%	(2.8% - 5.7%)
Sapovirus	PCR	72	782	9.2%	(7.3% - 11.5%)
No pathogen identified		471	782	60.2%	(56.7% - 63.7%)

[a] Only specimens from cases aged 2 years and above were tested for *C. difficile*

[b] ELISA for adenovirus and rotavirus was conducted in specimens from cases aged <5 years

6.1.2 GP Presentation Study

Among cases in the GP Presentation Study, *Campylobacter* was the most commonly identified agent, with 13% of specimens testing positive for this pathogen by either culture or PCR (8% by culture alone) (Table 6.2). Among cases aged 5 years and above, 15% of specimens were positive for *Campylobacter* by either culture or PCR, compared with 5% among cases aged less than 5 years (Tables A6.3 and A6.4)

Viruses were also common among GP Presentation Study cases, with evidence of clinically significant norovirus or rotavirus infection identified in 12.4% and 7.3% of specimens respectively (Table 6.2). Nearly 20% of specimens in cases aged less than 5 years had evidence of clinically significant norovirus infection, with a similar figure for rotavirus (Table A6.3). Sapovirus infection was identified in 8.8% of cases overall (Table 6.2), with similar prevalences in cases less than 5 years and cases aged 5 years and above (Tables A6.3 and A6.4).

Salmonella were detected in only 0.8% of cases. This was less than cases with *C. difficile* (1.4%), *C. perfringens* (2.2%), Enteroaggregative *E. coli* (1.4%), *Cryptosporidium* (1.4%) or *Giardia* (1.0%).

No pathogen was identified in 48.6% of specimens (Table 6.2). Among cases less than 5 years, 36% of specimens were negative for all pathogens tested, compared with 52% among specimens from cases aged 5 years and above (Tables A6.3 and A6.4).

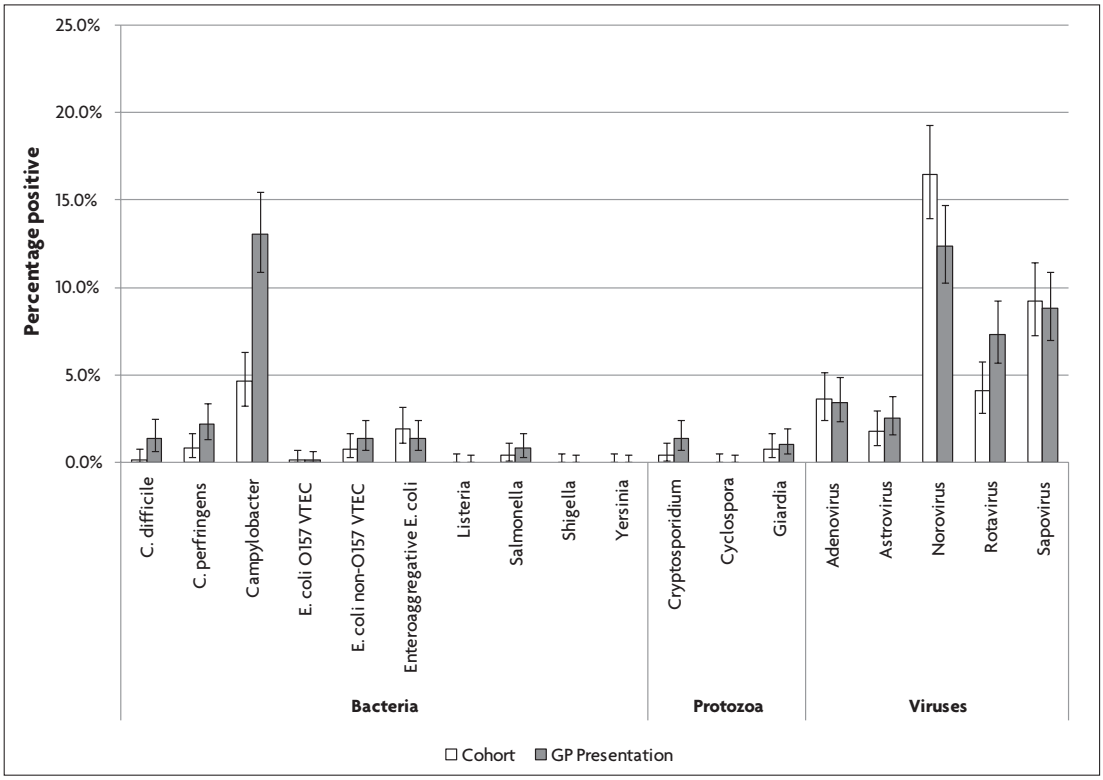
Table 6.2: Microbiological findings in stool samples submitted by GP Presentation cases

Pathogen	Test	No. identified	Tested	% identified	(95% CI)
Bacteria					
C. difficile[a]	All	10	738	1.4%	(0.7% - 2.5%)
	EIA	*1*	*736*	*0.1%*	*(0% - 0.8%)*
	PCR	*9*	*719*	*1.3%*	*(0.6% - 2.4%)*
C. perfringens	Culture	19	868	2.2%	(1.3% - 3.4%)
Campylobacter	All	114	874	13.0%	(10.9% - 15.5%)
	All culture	*69*	*866*	*8.0%*	*(6.3% - 10%)*
	Direct culture	*48*	*866*	*5.5%*	*(4.1% - 7.3%)*
	Enrichment	*65*	*863*	*7.5%*	*(5.9% - 9.5%)*
	PCR	*105*	*874*	*12.0%*	*(9.9% - 14.4%)*
E. coli O157 VTEC	Culture	1	866	0.1%	(0% - 0.6%)
E. coli non-O157 VTEC	Culture	7	866	0.8%	(0.3% - 1.6%)
Enteroaggregative *E. coli*	PCR	12	874	1.4%	(0.7% - 2.4%)
Listeria	Culture and/or PCR	0	865	0.0%	(0% - 0.4%)
Salmonella	All	7	874	0.8%	(0.3% - 1.6%)
	Culture	*7*	*866*	*0.8%*	*(0.3% - 1.7%)*
	PCR	*6*	*874*	*0.7%*	*(0.3% - 1.5%)*
Shigella	Culture	0	866	0.0%	(0% - 0.4%)
Yersinia	All	1	866	0.1%	(0% - 0.6%)
	Direct culture	*0*	*865*	*0.0%*	*(0% - 0.4%)*
	Enrichment	*1*	*866*	*0.1%*	*(0% - 0.6%)*
Protozoa					
Cryptosporidium	All	12	874	1.4%	(0.7% - 2.4%)
	EIA	*9*	*863*	*1.0%*	*(0.5% - 2%)*
	PCR	*12*	*874*	*1.4%*	*(0.7% - 2.4%)*
Cyclospora	Microscopy	0	861	0.0%	(0% - 0.4%)
Giardia	All	9	874	1.0%	(0.5% - 1.9%)
	EIA	*6*	*863*	*0.7%*	*(0.3% - 1.5%)*
	PCR	*9*	*874*	*1.0%*	*(0.5% - 1.9%)*
Viruses					
Adenovirus	ELISA and/or PCR[b]	30	874	3.4%	(2.3% - 4.9%)
Astrovirus	PCR	22	874	2.5%	(1.6% - 3.8%)
Norovirus	PCR	108	874	12.4%	(10.2% - 14.7%)
Rotavirus	ELISA and/or PCR[b]	64	874	7.3%	(5.7% - 9.3%)
Sapovirus	PCR	77	874	8.8%	(7% - 10.9%)
No pathogen identified		425	874	48.6%	(45.3% - 52%)

[a] Only specimens from cases aged 2 years and above were tested for *C. difficile*
[b] ELISA for adenovirus and rotavirus was conducted in specimens from cases aged <5 years

Figure 6.1 compares the microbiological results in Cohort and GP Presentation Study cases. For each organism, all specimens testing positive by any test for that organism are presented. Interestingly, norovirus and sapovirus, viruses typically thought to cause mild illness, feature prominently among GP Presentation cases.

Figure 6.1: Microbiological findings in Cohort and GP Presentation cases



Note: Error bars represent 95% CIs

6.1.3 Factors associated with negative specimens

Based on logistic regression analysis, the likelihood of a negative stool specimen among Cohort Study cases was strongly associated with age, with cases under 5 years being less likely to have a negative stool specimen than those aged 65 years and above. There was also evidence that cases who did not experience vomiting and loss of appetite were more likely to have a negative stool specimen (Table A6.5)

Among GP Presentation Study cases, males were less likely than females to have a negative stool specimen, while those who did not experience vomiting, loss of appetite or headache were more likely to have a negative stool specimen (Table A6.6). In addition, cases who no longer had diarrhoea at the time of questionnaire completion were more likely to have a negative stool specimen, as were those who collected a stool specimen 10 or more days after onset of symptoms. Among those aged 16 years and above, there was evidence that the likelihood of a negative stool specimen was related to socioeconomic group, with those in non-managerial and professional occupations being more likely to have a negative stool specimen (Table A6.6).

6.1.4 Mixed infections

Among 782 specimens from Cohort Study cases, infections with two or more organisms were identified in 37 (4.7%). The majority of these mixed infections involved adenovirus, norovirus or sapovirus (Tables A6.7 and A6.8). Among 874 specimens from GP Presentation Study cases, 40 (4.6%) had evidence of infection with two or more organisms. Mixed infections involving adenovirus, norovirus, sapovirus or *Campylobacter* accounted for the majority of these (Tables A6.9 and A6.10).

6.2 ORGANISM-SPECIFIC INCIDENCE RATES OF IID IN THE COMMUNITY AND PRESENTING TO GENERAL PRACTICE

Table 6.3 shows UK incidence rates of IID in the community and presenting to general practice by organism. For *Campylobacter* spp., *Salmonella* spp., *Cryptosporidium* spp., and *Giardia* spp., incidence rates are presented for conventional diagnostic methods, and for conventional and PCR diagnostic methods combined. For adenovirus and rotavirus, incidence rates are presented based on ELISA and PCR diagnostic methods combined, although diagnosis by ELISA was performed only in children under 5 years. The last three columns of the table show the ratio of incidence rates in the community to rates of IID presenting to general practice, with corresponding 95% CIs.

The most common organism causing IID in the community was norovirus, with an incidence of 47 cases per 1,000 person-years. Approximately one case of norovirus IID presented to general practice for every 23 cases occurring in the community. Other viral agents, particularly sapovirus and rotavirus, were also common. One in nine cases of rotavirus IID in the community presented to general practice.

Among the bacteria, *Campylobacter* had the highest incidence in the community, at approximately 10 cases per 1,000 person-years. When considering culture methods only, about one in seven community cases of *Campylobacter* IID presented to general practice; when both culture and PCR methods were considered, the corresponding ratio was one in five. The incidence of *Salmonella* IID in the community was 0.6 cases per 1,000 person-years; approximately one in four cases in the community presented to general practice. Enteroaggregative *E. coli* was the second most common bacterial agent, with an incidence of 5.9 cases per 1,000 person-years.

Table 6.3: Incidence rates of IID in the community and presenting to general practice by organism

		Community				Presenting to GP				Ratio Community:GP	
Organism		**Cases[1]**	**PY[2]**	**Rate[3]**	**(95% CI)**	**Cases[1]**	**PY[2]**	**Rate[3]**	**(95% CI)**	**RR**	**(95% CI)**
Bacteria											
C. perfringens	a	7	4,658.6	**1.5**	(0.5 - 3.9)	78	312,232	**0.24**	(0.11 - 0.52)	**6.0**	(1.7 - 20.9)
Campylobacter spp.	a	43	4,658.6	**9.3**	(6 - 14.3)	400	312,232	**1.28**	(0.90 - 1.82)	**7.2**	(4.1 - 12.7)
	e	51	4,658.6	**10.9**	(7.4 - 15.9)	693	312,232	**2.22**	(1.65 - 2.97)	**4.9**	(3 - 7.9)
E. coli O157 VTEC	a	1	4,658.6	**0.3**	(0 - 4.3)	4	312,232	**0.01**	(0.00 - 0.09)	**22.8**	(0.9 - 610)
Enteroaggregative *E. coli*	d	28	4,658.6	**5.9**	(3.4 - 10.2)	66	312,232	**0.21**	(0.11 - 0.41)	**28.4**	(11.8 - 68.2)
Salmonella spp.	a	3	4,658.6	**0.6**	(0.2 - 2.4)	57	312,232	**0.18**	(0.08 - 0.44)	**3.4**	(0.7 – 17.4)
	e	3	4,658.6	**0.6**	(0.2 – 2.4)	56	312,232	**0.18**	(0.07 - 0.44)	**3.5**	(0.7 – 17.9)
Protozoa											
Cryptosporidium	b	3	4,658.6	**0.7**	(0.2 - 2.7)	65	312,232	**0.20**	(0.08 - 0.48)	**3.5**	(0.7 - 17.6)
	c	6	4,658.6	**1.2**	(0.4 - 3.9)	80	312,232	**0.25**	(0.11 - 0.58)	**4.9**	(1.2 - 20.6)
Giardia	b	4	4,658.6	**0.8**	(0.2 - 3)	29	312,232	**0.09**	(0.03 - 0.27)	**9.3**	(1.8 - 49.2)
	c	9	4,658.6	**2.0**	(0.7 - 5.6)	35	312,232	**0.11**	(0.05 - 0.26)	**18.2**	(4.8 - 69.6)
Viruses											
Adenovirus[4]	c	48	4,658.6	**10.2**	(6.8 - 15.4)	265	312,232	**0.84**	(0.49 - 1.45)	**12.1**	(6.1 - 23.9)
Astrovirus	d	25	4,658.6	**5.3**	(3 - 9.4)	127	312,232	**0.40**	(0.20 - 0.82)	**13.1**	(5.2 - 32.7)
Norovirus	d	219	4,658.6	**47.0**	(39.1 - 56.5)	648	312,232	**2.07**	(1.44 - 2.99)	**22.7**	(15.1 - 34.2)
Rotavirus[4]	c	59	4,658.6	**12.7**	(8.7 - 18.4)	424	312,232	**1.36**	(0.89 - 2.07)	**9.4**	(5.3 - 16.5)
Sapovirus	d	121	4,658.6	**26.1**	(20.1 - 33.8)	491	312,232	**1.57**	(1.08 - 2.29)	**16.6**	(10.5 - 26.2)
All IID		1,277	4,658.6	**274.1**	(253.8 - 295.8)	5,546.0	312,232	**17.7**	(14.40 - 21.80)	**15.4**	(12.4 - 19.3)

a – Culture; b – EIA; c – ELISA and/or PCR; d – PCR; e – Culture and/or PCR; [1]Mean number of cases from 20 imputations; [2]Person-years; [3]Cases per 1,000 person-years based on organism data from 20 imputed datasets; [4]ELISA for adenovirus and rotavirus was conducted in specimens from cases aged <5 years

6.3 REPORTING PATTERNS OF IID BY ORGANISM AND REPORTING ELLIPSES

Table 6.4 shows the incidence rates of IID in the community, presenting to general practice and reported to national surveillance, by organism. The rate ratios comparing community and general practice incidences with incidence of IID reported to national surveillance are also presented.

In general, viral agents had higher ratios of community to national surveillance rates, reflecting the fact that these viruses, while occurring with high frequency in the community, are less likely to be reported to national surveillance.

Figures 6.2 to 6.5 show the reporting patterns for *Campylobacter*, *Salmonella*, norovirus and rotavirus. For each organism, the area of the community, general practice and national surveillance ellipses are proportional to the incidence, so as to enable visual comparison of the rates. The areas of the ellipses are, however, not comparable between organisms, as each diagram is scaled differently.

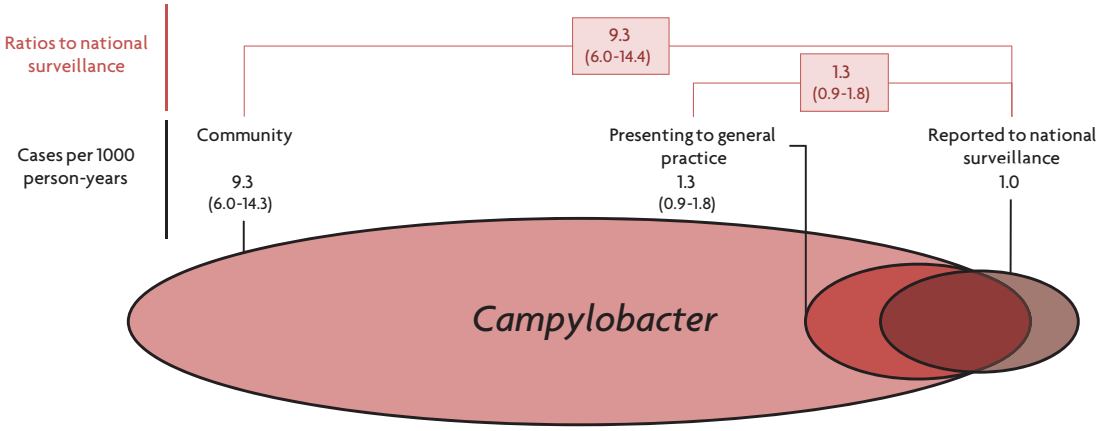
Table 6.4: Incidence rates of IID in the community, presenting to general practice, and reported to national surveillance, by organism

		Community		Presenting to GP		Reported to national surveillance	
Organism		**Rate[1]**	**(95% CI)**	**Rate[1]**	**(95% CI)**	**Rate[1]**	**(95% CI)**
Bacteria							
C. perfringens	a	1.5	(0.5 - 3.9)	0.2	(0.1 - 0.5)	0.001	(0 - 0.001)
Ratios to last column		*2518.7*	(890.7 - 7179.4)	*419.1*	(181.9 - 962.8)	*1.0*	
Campylobacter	a	9.3	(6 - 14.3)	1.3	(0.9 - 1.8)	0.997	(0.989 - 1.005)
Ratios to last column		*9.3*	(6 - 14.4)	*1.3*	(0.9 - 1.8)	*1.0*	
E. coli O157 VTEC	a	0.3	(0 - 4.3)	0.0	(0 - 0.1)	0.042	(0.04 - 0.043)
Ratios to last column		*7.4*	(0.5 - 104.4)	--	--	*1.0*	
Salmonella	a	0.6	(0.2 - 2.4)	0.2	(0.1 - 0.4)	0.133	(0.13 - 0.136)
Ratios to last column		*4.7*	(1.2 – 18.2)	*1.4*	(0.6 - 3.3)	*1.0*	
Protozoa							
Cryptosporidium	b	0.7	(0.2 - 2.7)	0.2	(0.1 - 0.5)	0.086	(0.084 - 0.089)
Ratios to last column		*8.2*	(2.1 - 31.7)	*2.3*	(1 - 5.6)	*1.0*	
Giardia	b	0.8	(0.2 - 3)	0.1	(0 - 0.3)	0.061	(0.059 - 0.063)
Ratios to last column		*14.0*	(4 - 49)	*1.5*	(0.5 - 4.5)	*1.0*	
Viruses							
Adenovirus	c	10.2	(6.8 - 15.4)	0.8	(0.5 - 1.5)	0.055	(0.053 - 0.057)
Ratios to last column		*184.5*	(122 - 279.3)	*15.3*	(8.8 - 26.3)	*1.0*	
Astrovirus	d	5.3	(3 - 9.4)	0.4	(0.2 - 0.8)	0.003	(0.003 - 0.003)
Ratios to last column		*1763.5*	(970.1 - 3218.1)	*135.1*	(65.5 - 278.9)	*1.0*	
Norovirus	d	47.0	(39.1 - 56.5)	2.1	(1.4 - 3)	0.164	(0.011 - 0.02)
Ratios to last column		*287.6*	(239.1 - 346)	*12.7*	(8.8 - 18.3)	*1.0*	
Rotavirus	c	12.7	(8.7 - 18.4)	1.4	(0.9 - 2.1)	0.296	(0.232 - 0.268)
Ratios to last column		*42.9*	(29.5 - 62.4)	*4.6*	(3 - 7)	*1.0*	
All IID		274.1	(253.8 - 295.8)	17.7	(14.4 - 21.8)	1.87	(1.86 - 1.88)
Ratios to last column		*146.5*	(135.6 - 158.1)	*9.5*	(7.7 - 11.7)	*1.0*	

a – Culture; b – EIA ; c – ELISA and/or PCR; d – PCR; [1]Cases per 1,000 person-years based on organism data from 20 imputed datasets; Sapovirus is omitted from this table as data on this organism are not routinely collected at national level in all UK countries

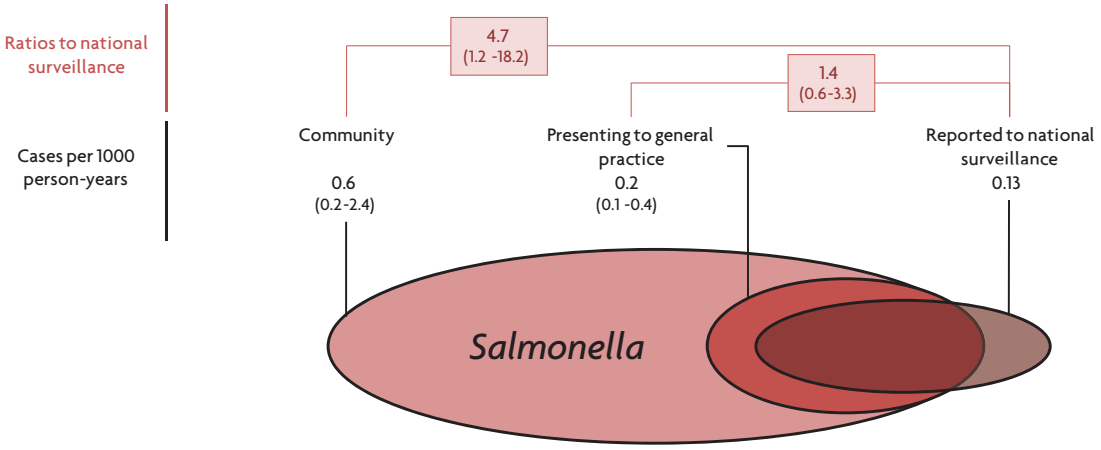
For *Campylobacter*, the reporting pattern indicates that 1 case is reported to national surveillance for every 9 cases occurring in the community (Figure 6.2).

Figure 6.2: Reporting ellipse for IID due to Campylobacter



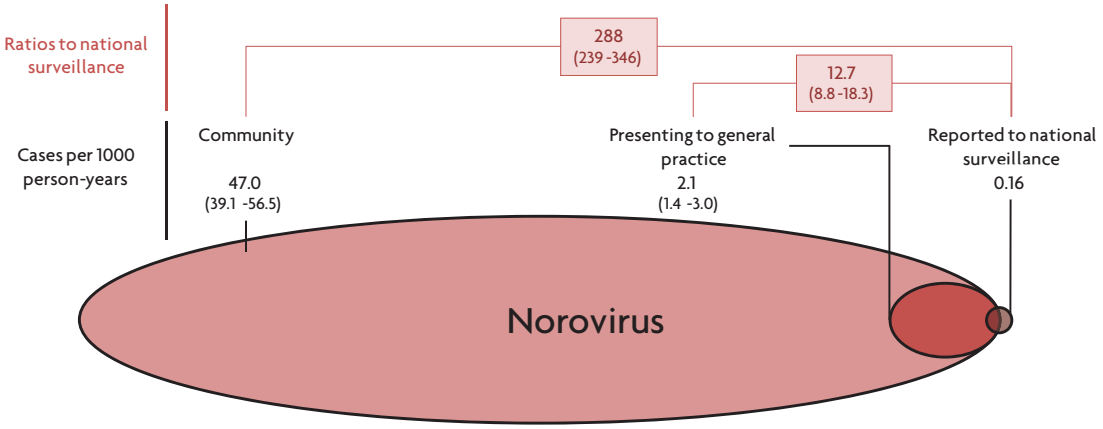
For *Salmonella*, the corresponding ratio is 1 in 5 (Figure 6.3). By contrast, fewer than 1.5 cases of *Campylobacter* IID and *Salmonella* IID presented to general practice for every case reported to national surveillance. This suggests that most cases of IID due to *Campylobacter* and *Salmonella* that consult a GP are reported to national surveillance.

Figure 6.3: Reporting ellipse for IID due to Salmonella



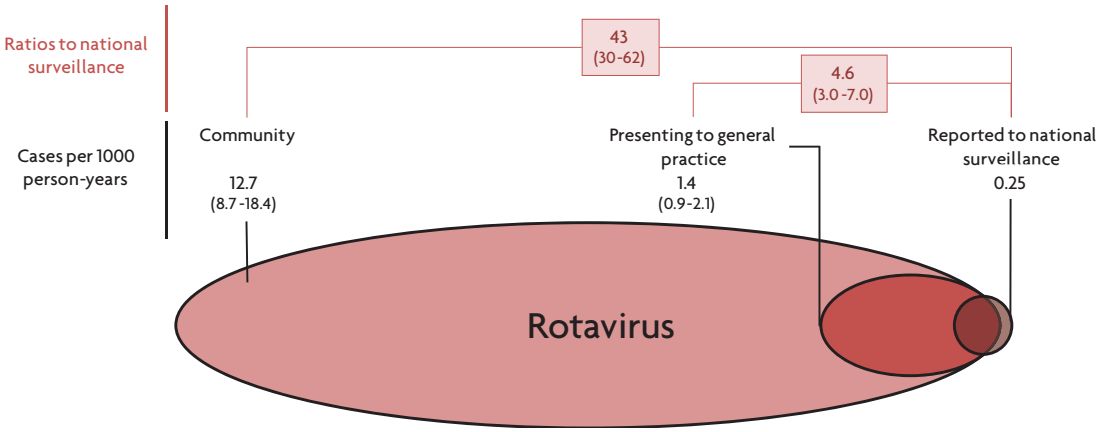
For norovirus, a very different pattern is seen. Approximately 290 cases of norovirus IID occur in the community for every case reported to national surveillance, while only 1 in 13 norovirus IID cases presenting to general practice is reported to national surveillance (Figure 6.4). However, these ratios should be interpreted with caution. The majority of national surveillance reports for norovirus IID result were from outbreaks in hospitals and other institutional settings not included in the IID2 Study. The ratio of norovirus IID incidence in the community to the incidence of reported norovirus IID that actually originates from sporadic cases in the community rather than from institutional outbreaks is, therefore, likely to be higher than reported here.

Figure 6.4: Reporting pattern of IID due to norovirus



Approximately 1 in 40 cases of rotavirus IID in the community and 1 in 5 cases of rotavirus IID presenting to general practice, is reported to national surveillance (Figure 6.5).

Figure 6.5: Reporting pattern of IID due to rotavirus



CHAPTER 7

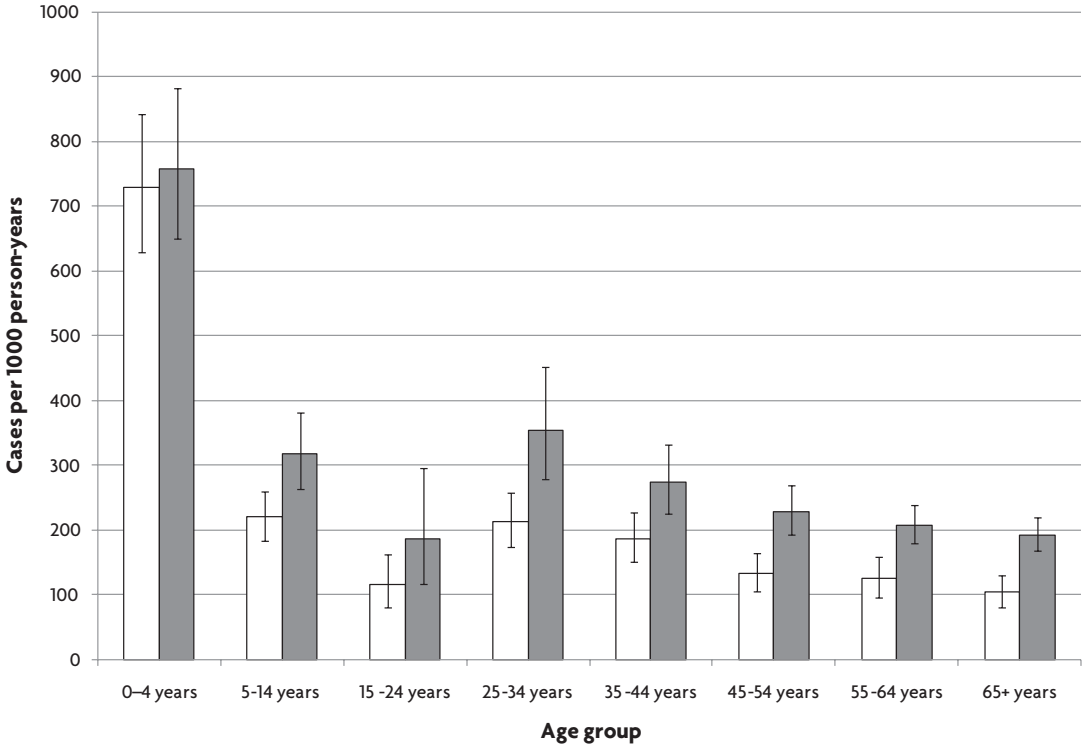
COMPARING AETIOLOGY AND INCIDENCE RATES OF IID IN ENGLAND IN THE IID1 AND IID2 STUDIES

The information presented in this chapter incorporates re-analysis of IID1 Study data so that comparisons with IID2 Study findings are based on equivalent data from both studies.

7.1 INCIDENCE RATES OF OVERALL IID IN IID1 AND IID2 STUDIES

Figure 7.1 compares the age-specific rates of overall IID in the community as estimated in the IID1 and IID2 studies. Rates in IID2 were higher in every age group with the exception of children under 5 years of age, which were similar.

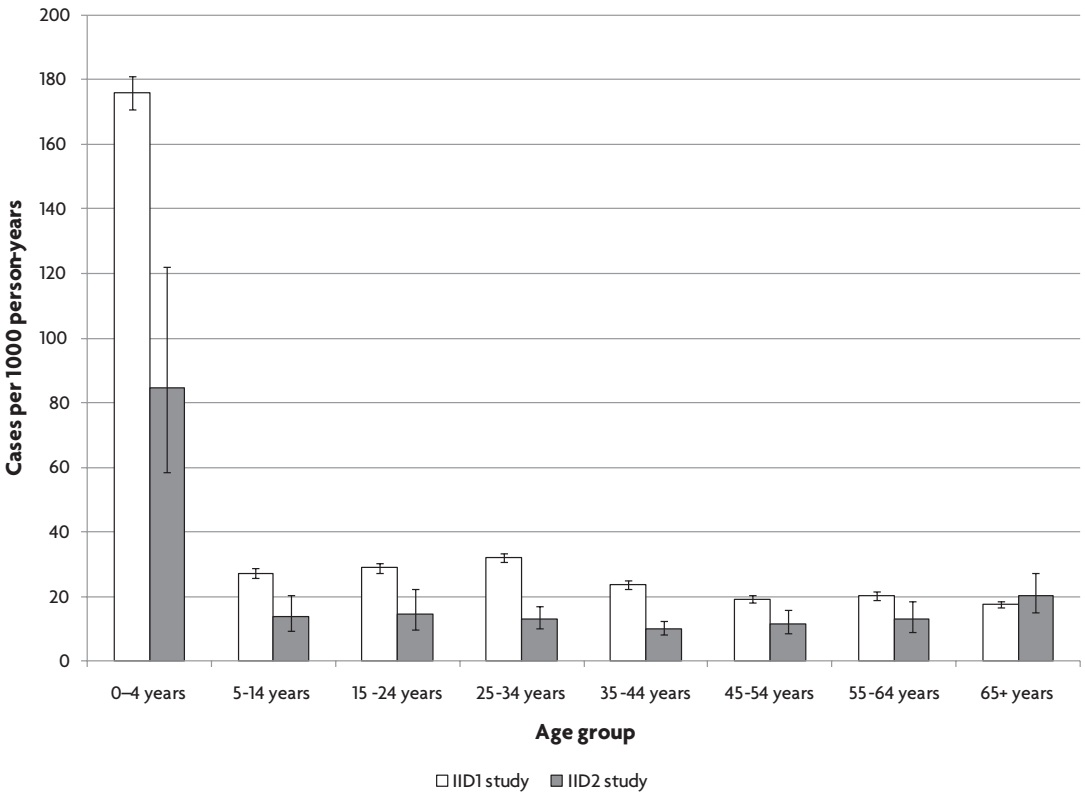
Figure 7.1: Incidence rates of overall IID in the community by age group, IID1 and IID2 studies



Note: Error bars represent 95% CIs

In Figure 7.2, the rates of IID presenting to general practice in the IID1 and IID2 studies are compared. The rates in IID1 were considerably higher than in the IID2 Study in all age groups, with the exception of those aged 65 years and above, in which the rates in the two studies were similar. Rates of IID presenting to general practice were highest in both studies in children under the age of 5 years.

Figure 7.2: Incidence rates of overall IID presenting to general practice by age group, IID1 and IID2 studies

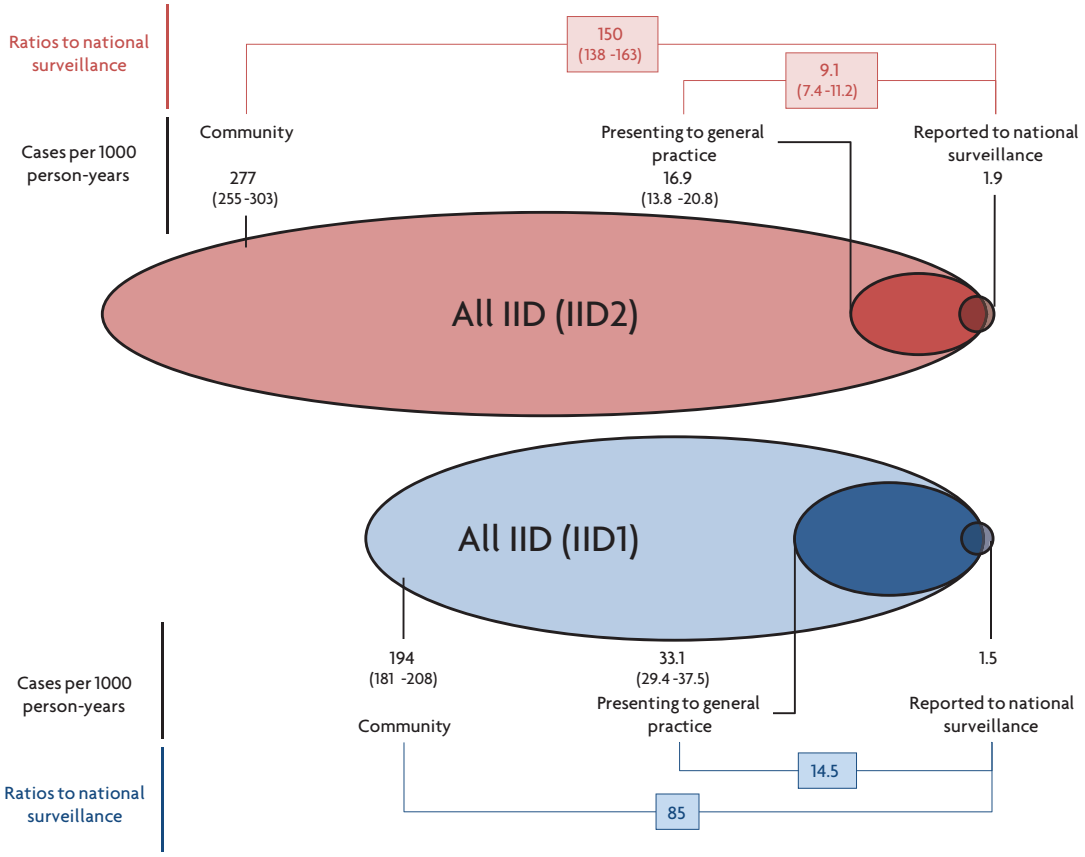


Note: Error bars represent 95% CIs

The corresponding reporting patterns for all IID in the two studies are shown in Figure 7.3. To enable comparability between the two studies, the area of ellipses is proportional to the incidence, and the IID2 estimates are based on data from England only, as the first IID study did not include participants from other UK countries.

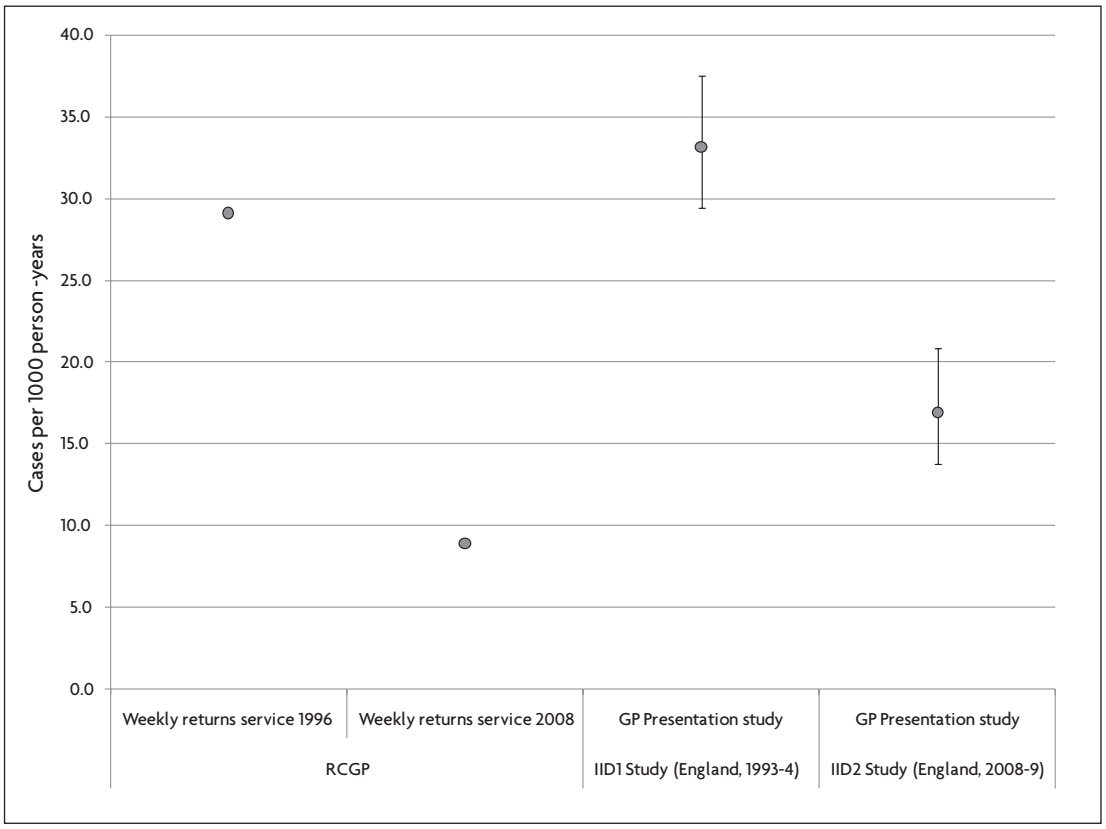
As can be seen from the reporting patterns, the incidence of IID in the community is higher in IID2 than in IID1, but the rate of IID presenting to general practice in IID2 is about half that estimated in IID1.

Figure 7.3: Reporting patterns for overall IID in England, IID1 and IID2 studies



In Figure 7.4, the rates of IID presenting to general practice estimated in IID1 and IID2 are plotted alongside estimates from the RCGP Weekly Returns Service. It can be seen that the decrease in the rate of IID-related GP presentation in IID2 relative to IID1 is also reflected in the RCGP data, in which rates have decreased 3-fold between 1996, just after the end of the IID1 study, and 2008, during the period of the IID2 study.

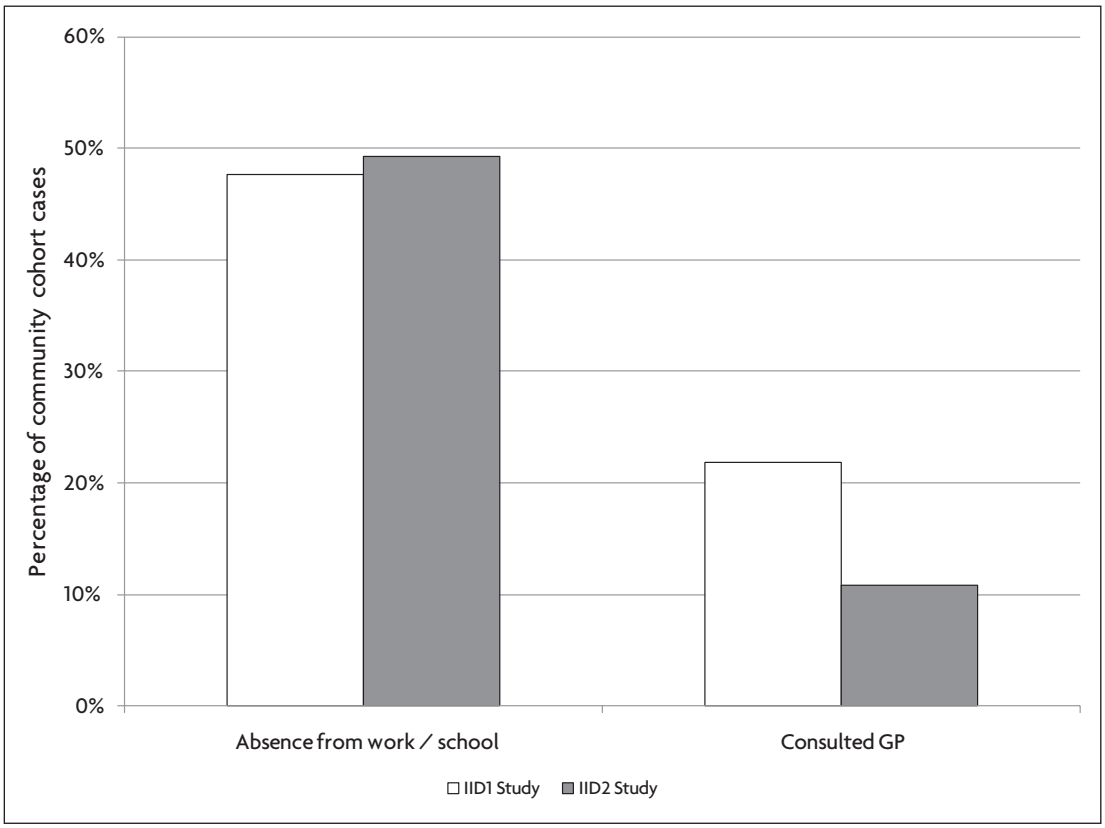
Figure 7.4: Incidence rates of IID presenting to general practice – Estimates from RCGP Weekly Returns Service, IID1 and IID2



Note: Error bars represent 95% CIs

In Figure 7.5 we compare two indicators of disease severity in the IID1 and IID2 studies. The figure shows, respectively, the proportion of cases in the community cohort who reported being absent from work or school and consulting a GP as a result of their illness. Although just under half of community cases in both studies reported being absent from work or school, the proportion of cases reporting having consulted a GP in the IID2 Study was half that in the IID1 Study.

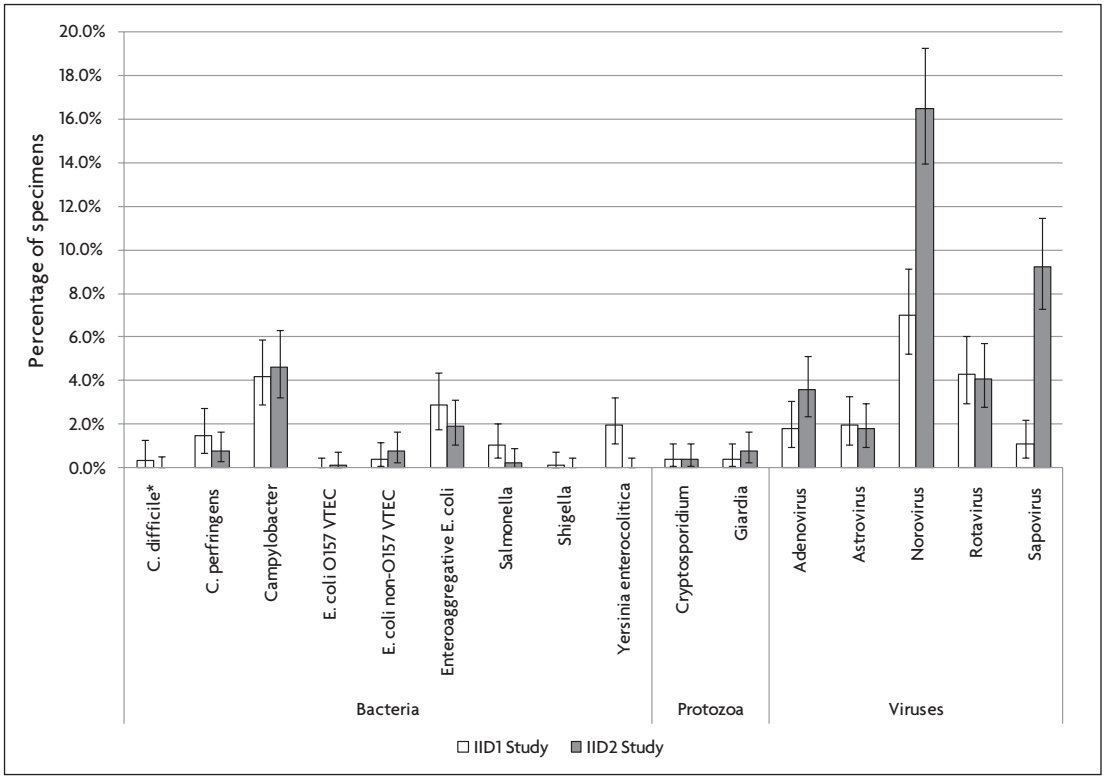
Figure 7.5: Proportion of IID cases reporting absence from work or school and consulting their GP, IID1 and IID2 studies



7.2 AETIOLOGY OF IID IN IID1 AND IID2 STUDIES

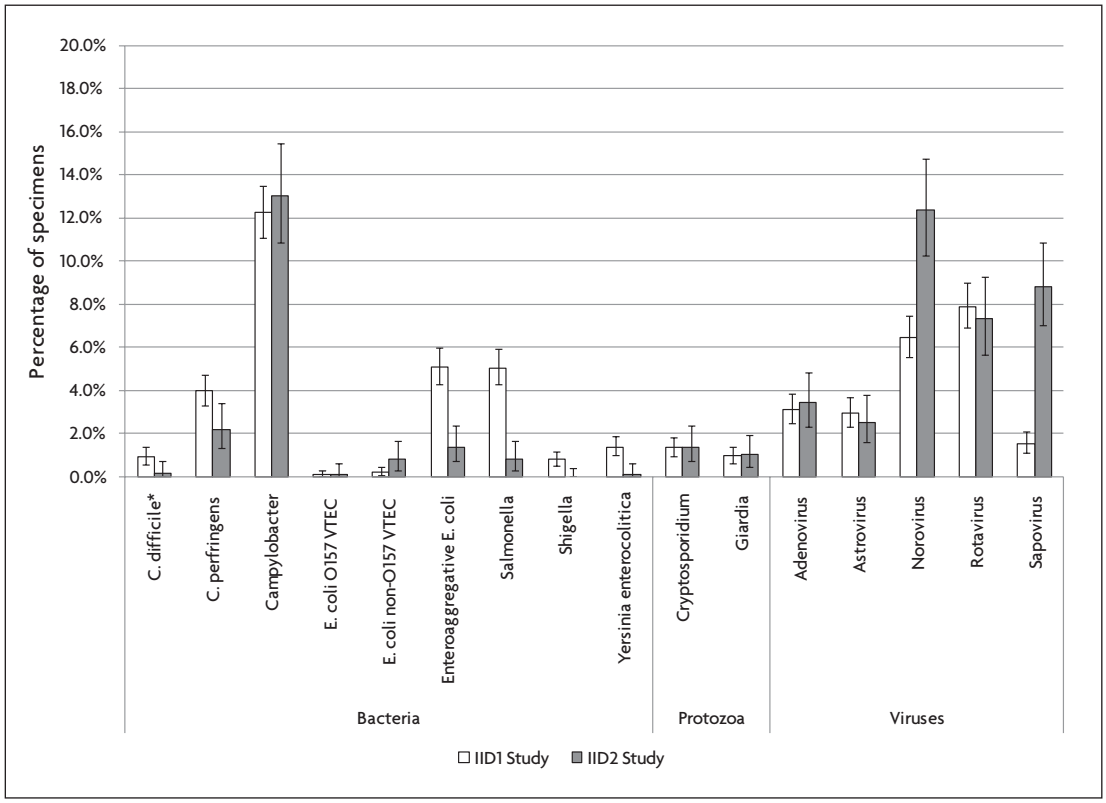
Comparison of the aetiology of IID in the IID1 and IID2 studies shows that the major difference between the studies is the greater identification of norovirus and sapovirus, among both community cases and cases presenting to general practice (Figures 7.6 and 7.7). This difference is due primarily to the greater sensitivity of PCR-based methods used in IID2 for the detection of these viruses compared with electron microscopy, which was the diagnostic method used in IID1. Although there were decreases in the detection of *C. perfringens*, *Salmonella* spp., Enteroaggregative *E. coli* and *Y. enterocolitica* in IID2 compared with IID1 it should be noted that there were insufficient person-years of follow-up to determine significant changes in incidence between the two studies.

Figure 7.6: Microbiological findings among community cases of IID in IID1 and IID2 studies



Note: Error bars represent 95% CIs

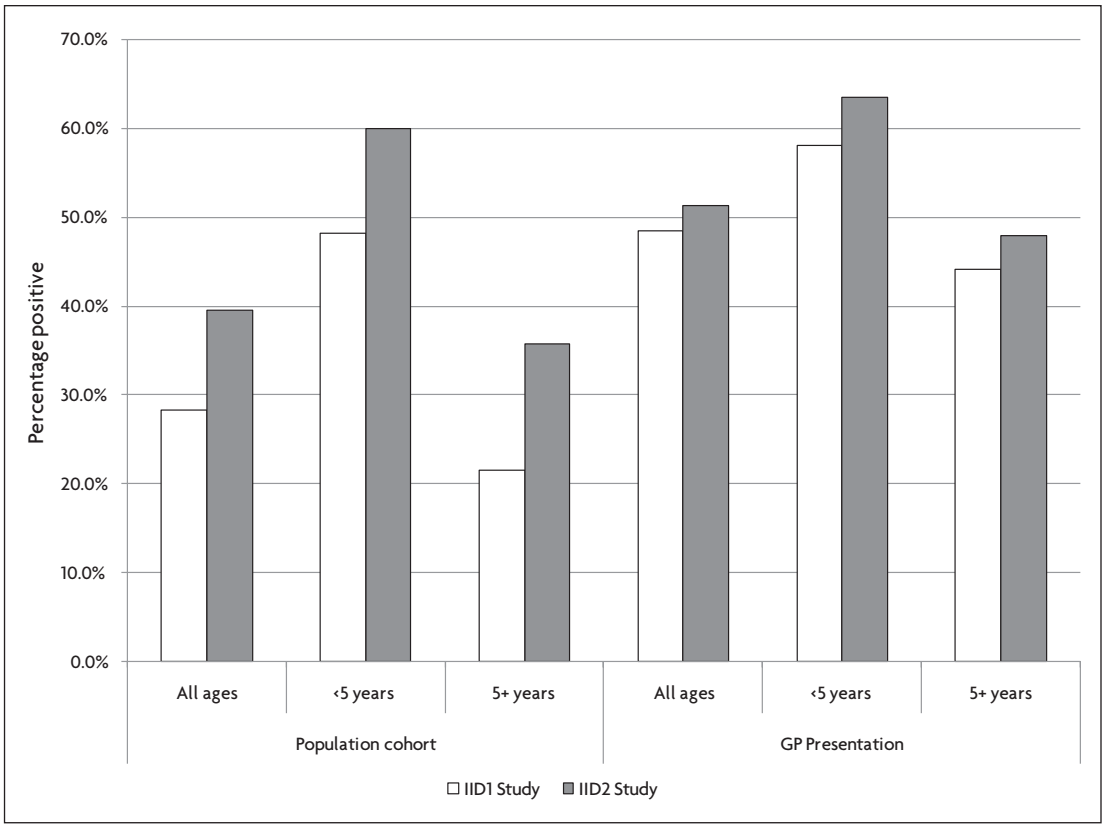
Figure 7.7: Microbiological findings among IID cases presenting to general practice in IID1 and IID2 studies



Note: Error bars represent 95% CIs

The use of PCR methods in IID2 resulted in a slight increase in the detection of organisms, particularly among community cases of IID. When the same set of organisms is compared between the two studies, approximately 40% of specimens from community cases had at least one organism detected in IID2 compared with fewer than 30% in IID1. For cases aged <5 years, the corresponding percentages were 60% and less than 50% respectively. This difference is primarily due to the greater detection of viruses among community cases. Among cases presenting to general practice, the difference in detection between the two studies is less marked, because the relative increase in detection of viruses in IID2 is offset by the greater frequency of bacterial agents in IID1 (Figure 7.8).

Figure 7.8: Percentage of specimens from IID cases in the community and presenting to general practice with one or more pathogens identified in IID1 and IID2 studies

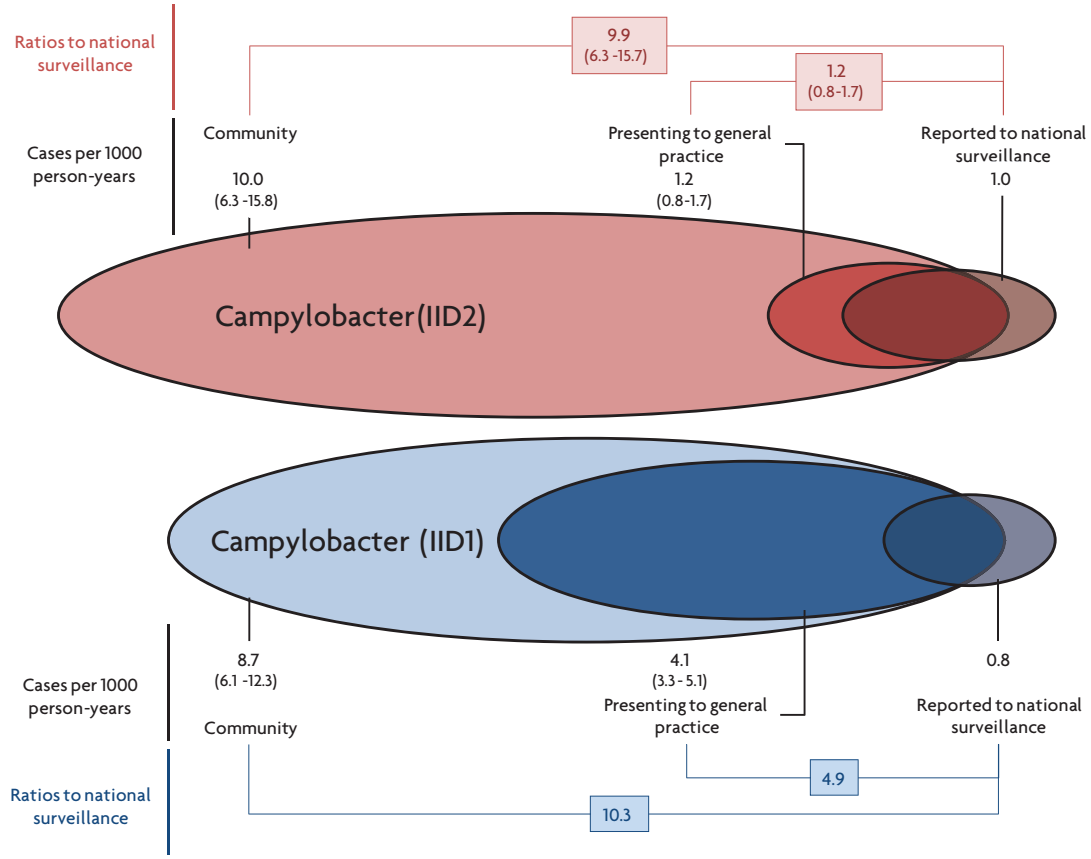


7.3 REPORTING PATTERNS BY ORGANISM IN THE IID1 AND IID2 STUDIES

In Figures 7.9 to 7.12, we compare the reporting patterns for *Campylobacter*, *Salmonella*, norovirus and rotavirus between the IID1 and IID2 studies. To enable direct comparison, incidence estimates in both studies are for England only. As with previous figures, numbers inside the ellipses represent the estimated rates and numbers outside the ellipses are the ratios of incidence in the community and presenting to general practice relative to the incidence of IID reported to national surveillance. For each organism, the area of the ellipses is proportional to the incidence, so as to enable a visual comparison between the two studies. The area of the ellipses cannot be compared between organisms, however, as each figure is scaled differently. For norovirus, the estimates for IID1 in Figure 7.11 are taken from work carried out by Phillips *et al*. (2010), who have produced revised norovirus incidence estimates based on re-testing of archived IID1 specimens using quantitative PCR. This enables direct comparison between the two studies using the same diagnostic method, which has far greater sensitivity than the electron microscopy methods originally used for norovirus diagnosis in IID1.

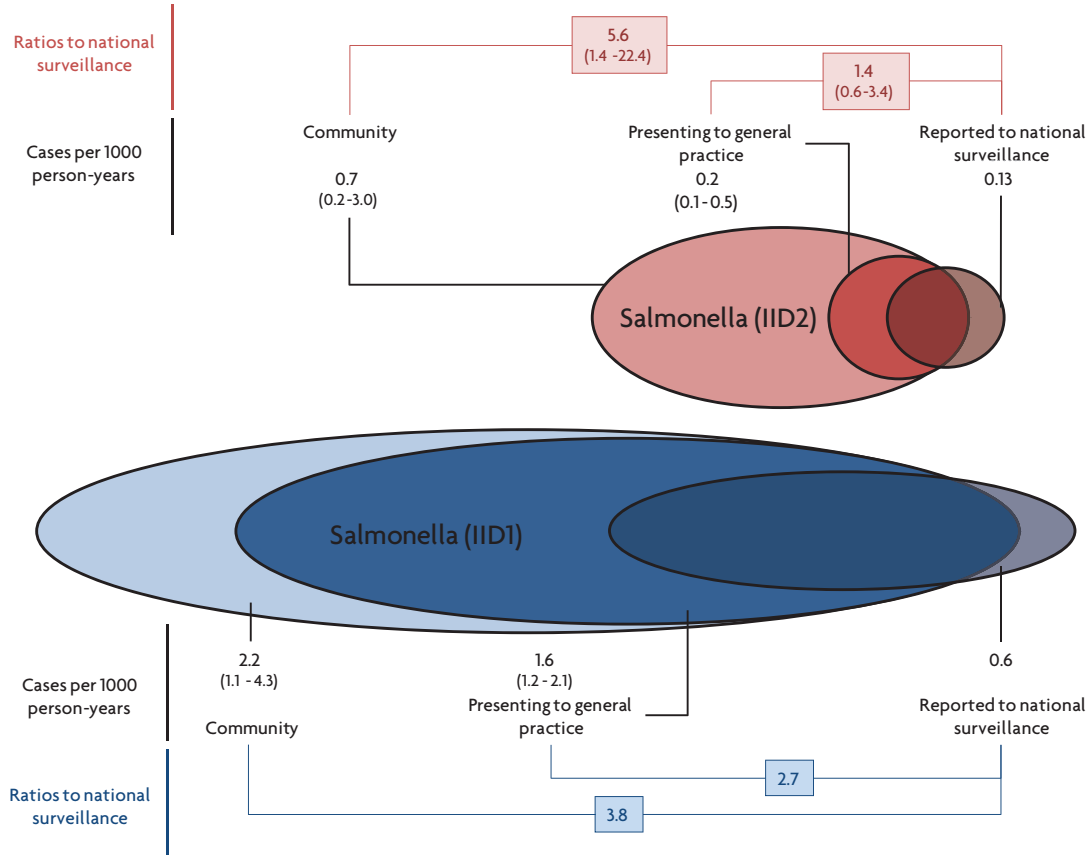
For *Campylobacter*, the rate estimated in the community in IID2 is 10 cases per 1,000 person-years, similar to that estimated in the IID1 study. Approximately 1 in 10 cases of *Campylobacter* IID in the community is reported to national surveillance, also similar to the estimate in IID1. By contrast, the rate of *Campylobacter* IID presenting to general practice was 1.2 cases per 1,000 person-years, more than 3 times lower in IID2 compared with the IID1 (Figure 7.9).

Figure 7.9: Reporting pattern of IID due to Campylobacter in England, IID1 and IID2 studies



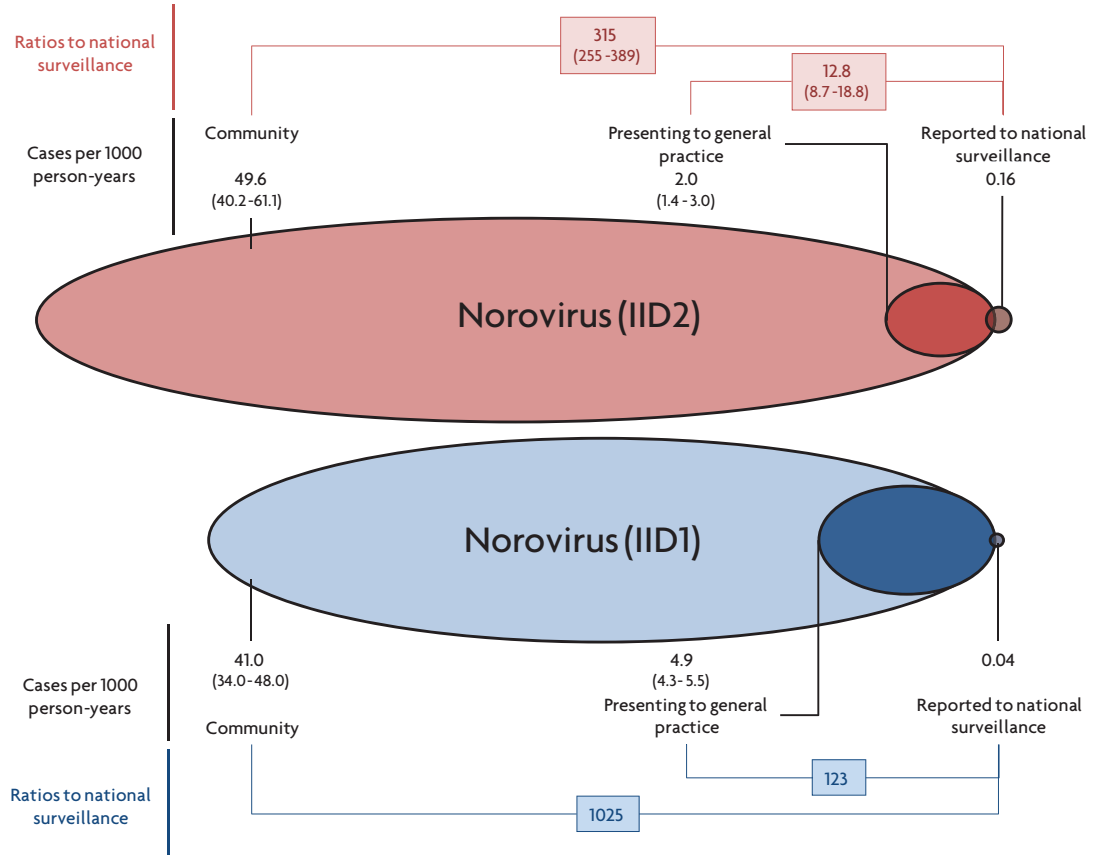
The incidence of *Salmonella* IID appears to have decreased dramatically since the IID1 study was conducted. The rate estimated in the IID2 study for *Salmonella* IID in the community was 0.7 cases per 1,000 person-years. This is less than a third of that estimated in the IID1 study, although it should be noted that there is considerable overlap in the 95% CIs, and the difference in the two estimates could be due to chance; the number of community cases with *Salmonella* IID in the two studies was small. However, there were corresponding decreases in the incidence of *Salmonella* IID presenting to general practice and reported to national surveillance between the first and second IID studies. The rate of *Salmonella* IID presenting to general practice was 0.2 cases per 1,000 person-years in the IID2 study, 8 times lower than in the IID1 study, and this was reflected in a greater than 4-fold decrease in the frequency of reports to national surveillance for salmonellosis (Figure 7.10).

Figure 7.10: Reporting pattern of IID due to Salmonella in England, IID1 and IID2 studies



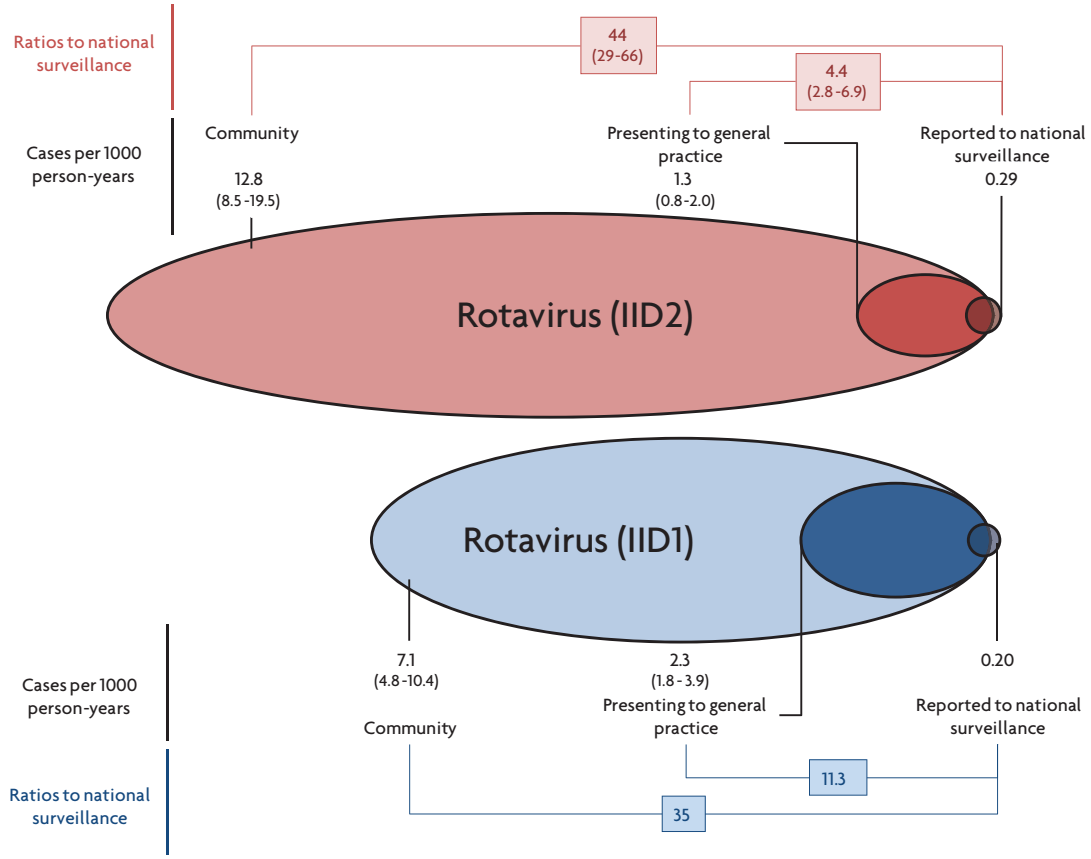
For norovirus, the rate in the community was slightly higher in the IID2 study compared with the IID1 study, although there is considerable overlap in the 95% CIs By contrast, the ratio of community to reported cases has changed dramatically. At the time of the first IID study, an estimated 1,025 cases of norovirus IID occurred in the community for every case reported to national surveillance. However, at the time of the IID2 study, this ratio had changed to 315 to 1. This is the result of a 4-fold increase in laboratory reports to national surveillance in the intervening period. The rate of norovirus IID presenting to general practice has decreased 2.5 fold between the IID1 and IID2 studies (Figure 7.11).

Figure 7.11 Reporting pattern of IID due to norovirus in England, IID1 and IID2 studies



The reporting figures for rotavirus suggest that the incidence of rotavirus IID in the community has nearly doubled between the IID1 and IID2 studies, although there is considerable uncertainty in the incidence estimates since the study was not powered to detect changes in pathogen-specific disease incidence. Accordingly, data from the IID2 study indicate that 1 in every 44 cases of rotavirus IID in the community is reported to national surveillance, a slightly higher ratio than that estimated in the first IID study. By contrast, the rate of rotavirus IID presenting to general practice has decreased by approximately 40%, and between one quarter and one fifth of cases of rotavirus IID presenting to general practice are now reported to national surveillance, compared with 1 in 11 cases at the time of the IID1 study (Figure 7.12).

Figure 7.12: Reporting pattern of IID due to rotavirus in England, IID1 and IID2 studies



CHAPTER 8

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

This chapter is arranged in five sections. In the first section we present a summary of the main study findings. The second section describes the strengths and limitations of the study. The third section contains our interpretation of the study results in the context of the worldwide literature. We present our overall conclusions in the fourth section and the final section contains the implications of the study and our recommendations.

8.1 SUMMARY OF MAIN FINDINGS

- In the Prospective Cohort Study the estimated rate of IID in the community in the UK was 274 cases per 1,000 person-years, meaning that around a quarter of the population suffer from IID in a year. The most commonly identified pathogens were, in order of frequency, norovirus, sapovirus, *Campylobacter* spp. and rotavirus.
- In the Telephone Survey the estimated rate of IID in the community using 7-day recall was 1,530 cases per 1000 person-years, which was five times higher than the rate estimated in the Prospective Cohort Study. This would correspond to the average person having IID between once and twice a year. Using 28-day recall the estimated rate of IID in the community in the Telephone Survey was 533 cases per 1000 person-years, which was twice as high as the rate estimated in the Prospective Cohort Study and would mean half the population suffering from IID in a year. There was variation in estimated rates between countries. The rate of reported symptoms was different in the two recall periods.
- Around 8% of people in the Prospective Cohort Study IID and 12% of people in the GP Presentation Study reported having travelled outside the UK in the 10 days prior to illness onset.
- In the Prospective Cohort Study the estimated rate of overall IID in the community in England was 43% higher in 2008-9 than in 1993-96 (estimated in IID1).
- The estimated rate of IID presenting to general practice in England in 2008-9 was 50% lower than in 1993-6 (estimated in IID1). The most commonly identified pathogens were, in order of frequency, *Campylobacter* spp., norovirus, sapovirus and rotavirus.
- *C. difficile*–associated diarrhoea was uncommon.
- Approximately 50% of people with an episode of IID in IID1 and IID2 reported absence from work or school because of their symptoms.
- In England, the ratio of cases reported to national surveillance to cases in the community has changed from ≈1:85 in IID1 to ≈1:150 in IID2. For norovirus, the change was from ≈1:1000 in IID1 to ≈1:300 in IID2. The ratios for *Campylobacter*, *Salmonella* and rotavirus were similar in both studies.
- In the IID2 Study, in which molecular methods were used, the diagnostic yield was 10% higher than in IID1.
- The ratio of cases reported to national surveillance to cases presenting to primary care had improved for all IID and for all the pathogens that we considered.
- The rate of contact with NHS Direct/24 by people with IID was very low (<2%). Less than half of IID cases contacting NHS Direct were advised to contact their General Practitioner and approximately 40% of people receiving this advice actually did so.

8.2 STRENGTHS AND LIMITATIONS OF THE STUDY

8.2.1 Prospective Cohort Study

8.2.1.1 Person-Years of Follow-Up and Study Power

We set out to include 8,400 person-years of follow-up based on the sample size needed to detect a 20% change in IID incidence from a baseline incidence of 6%. The follow-up time achieved in the Prospective Cohort Study was just under 5,000 person-years of follow-up. Research ethics and governance procedures (and in particular the time taken by NHS R&D Offices to communicate decisions) meant a much more staggered start to recruitment than we had anticipated. This meant that we were recruiting to the Prospective Cohort Study during the entire study period. However, since the differences in rates observed in IID1 and IID2 were much higher than anticipated (with the rate in the community being much higher, and the rate of GP Presentation much lower), the study objectives were still met despite fewer person-years of follow-up.

It should also be noted that the study was not powered to detect changes in the incidence of specific organisms over time since, to have done this, we would have needed a minimum of 106,000 person-years of follow-up in the Prospective Cohort Study, which was considered unaffordable.

8.2.1.2 Participation and Cohort Population

The proportion of people who agreed to take part in the Prospective Cohort Study was low (9%), and considerably lower than in IID1 in which around one third of people approached (35%) agreed to participate (Food Standards Agency, 2000). The most commonly cited reasons for not participating included lack of interest and lack of time. It should be noted that Ethics Committee requirements in the UK do not allow follow-up of non-responders since this is considered to be harassment. People may refuse to take part in research without giving a reason. Even in studies where incentives are used, participation rates are generally lower than they were 10 years ago. The low participation in the IID2 Prospective Cohort Study is similar to those in other large, population-based studies conducted in the UK at around the same time. In "Flu Watch", in which researchers recruited a healthy cohort of all ages and collected swabs when individuals developed respiratory symptoms, the participation rate was around 11% (Andrew Hayward – Personal Communication). Similarly in UK Biobank, a multi-million pound prospective Cohort Study with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses, the overall attendance rate for an assessment visit during the pilot was 8% (UK Biobank Co-ordinating Centre, 2006). Nevertheless, low participation might limit the generalisability of the study findings if those who chose to take part in the study had very different risks of IID compared with the general population and this was not controlled for.

The characteristics of the cohort population differed from the UK population, in particular by age and sex. As expected, teenagers and young adults (and especially males) proved the most difficult groups to recruit so we approached a professional marketing company with a view to helping us to create study material more appealing to them. Despite using the new material at re-recruitment the participation amongst these groups remained low (data available but not shown). To compensate for differences in the demographic profile of the cohort and the general population we standardised rates according to the age and sex distribution of the 2001 census population. We used data from the last census because they allow for comparison of a number of other important variables, including socioeconomic classification, ethnic composition and household size. Although changes in the population structure of the UK might have occurred in the intervening period, such changes are likely to be minor and should not invalidate our comparisons and adjustments.

8.2.1.3 Weekly Follow-Up and Reporting Fatigue

People who agreed to take part in the study complied well with follow-up as witnessed by the high proportion of people who responded each week (whether using the weekly automated e-mail or postcards). Drop-outs among participants were even rarer than in IID1. Over the entire study period there was evidence of a small decline in the reported incidence of symptoms consistent

with reporting fatigue. However, the rate of decline was small and even less marked than in IID1 (FSA, 2000). So, although participation in IID2 was lower than in IID1, the retention was higher and participants were followed up for a longer time.

8.2.1.4 Questionnaire and stool sample submission from participants reporting symptoms

More than half of the people reporting symptoms in the Prospective Cohort Study completed a questionnaire but the proportion not returning a questionnaire was higher in the e-mail follow-up group. This persisted despite follow up by the Study Nurses to ensure that participants had reported symptoms correctly and not inadvertently clicked on the wrong link in the automated e-mail. People who reported symptoms but did not return questionnaire were defined as possible cases since, without knowing details of their illness, we could not include them as definite cases of IID according to our case definition. Rates were presented including and excluding the possible cases.

Most of the people who did not return a questionnaire also failed to submit a stool specimen (data available but not shown). They might have recovered before getting round to submitting either stool specimen or questionnaire. We might, therefore, have underestimated the frequency of mild IID in the Prospective Cohort Study. However, the good agreement between the Prospective Cohort Study and other study components in the rates of IID that resulted in contact with a General Practitioner or NHS Direct suggests that we captured adequately episodes of illness that participants considered significant.

8.2.2 GP Presentation and Validation Studies

8.2.2.1 Practice Population Characteristics

The practice populations were representative of the UK in terms of age and sex. Although we randomly allocated practices to the GP Enumeration and the GP Presentation/Validation studies, a larger number of practices dropped out or failed to complete the GP Presentation/Validation Study than the GP Enumeration Study. The majority of practices that withdrew from the GP Presentation/Validation Study did so after random allocation to the study and after their training session. The GP Presentation/Validation Study involved considerably more work, which dissuaded some practices from taking part. This could have introduced bias if the rate of consultation for IID differed between participating and non-participating practices. Practices completing the GP Enumeration Study tended to be larger than those completing the GP Presentation Study. The estimated rate of IID presenting to general practice was lower in the GP Enumeration Study than the GP Presentation Study, although adjusting for practice size did not account for this difference. It is also possible that the difference in the estimated rates occurred by chance, as the number of practices in each study arm was relatively small.

8.2.2.2 Participation and Compliance

Amongst those invited to take part in the GP Presentation Study, just less than 60% chose to participate, and commonly cited reasons for not taking part were lack of interest or lack of time. The Ethics Committee required that we allowed symptomatic people a 24-hour "cooling-off" period before enrolling them into the study. In practice, however, this meant they had to make another appointment at the surgery if they were interested in taking part in the study. Given that IID is an acute, generally short-lived illness many patients who might have participated probably did not want to return to the practice on another day, but we have no means of verifying this.

People who enrolled in the GP Presentation Study complied well with the study procedures and approximately 90% submitted a stool sample.

8.2.2.3 Under-ascertainment

Under-ascertainment is frequently encountered in epidemiological studies, disease registers and surveillance and so results need to be adjusted to obtain accurate estimates of incidence (Doll, 1991). In the Validation Study the Study Nurses undertook a Read code search once a month in order to

identify patients who should have been referred into the study but were not. The purpose of this was to work out the degree of under-ascertainment in the GP Presentation Study.

Read codes are a hierarchical coding system that is employed in primary care to code consultations. They comprise a variety of signs and symptoms and capture a clinician's interpretation of a patient's presenting complaint. The use of these codes for IID in primary care is not standardised within or between practices. The clinician may code the consultation using codes that may refer to symptoms, diagnoses, investigations or treatment. Alternatively they might not code the consultation at all. Since data on symptom duration, frequency or severity are not collected in a standardised manner some Read codes in our search are likely to be more sensitive and less specific than our epidemiological case definition. Thus some Read codes, particularly those related to vomiting symptoms, were not sufficiently specific and were likely to include consultations for conditions other than IID. We accounted for this in our under-ascertainment analysis by assuming that the degree of under-ascertainment for IID cases coded as vomiting should be similar to the degree of under-ascertainment for cases coded under other IID-related codes. Different clinical management software (or different versions of the same software) may also affect how codes are used. We developed a Read code search using EMIS software (LV 5.2) and this was adapted for use with different versions of EMIS and for the various other electronic clinical management systems employed in participating practices. Although we attempted to be as comprehensive as possible it is possible that the translation into different versions was incomplete.

Overall, we estimated that about 1 in 6 people presenting to general practice with IID were recruited into the GP Presentation Study. To account for this, we adjusted for under-ascertainment in our analysis, taking into account variations in the degree of under-ascertainment by age, sex, study practice, and the type of condition for which the patient presented. Including both definite and probable cases had little impact on our incidence estimates (a difference of 1.4 cases per 1,000 person-years compared with definite cases only). However, we were unable to account for other, potentially relevant, determinants of under-ascertainment in our adjustments, particularly causative organism and symptom severity, as the information available on these in consultation records is limited. Our analysis indicated that there was considerable variation in ascertainment between practices that was not accounted for by practice size, number of GPs, or the area-level deprivation and urban-rural profile of the practice. This suggests that under-ascertainment was largely related to efficiency of referral and recruitment within practices. Methods used to correct for under-ascertainment were sufficiently similar (albeit not identical), to those used in IID1.

8.2.3 Advantages and Disadvantages of the Prospective Cohort Study and the GP Presentation Study

A major strength of the two studies was garnering information on the aetiology of IID, which is impossible in a Telephone Survey of self-reported illness. It would have been impossible for us to re-calibrate national surveillance data by pathogen without information on the aetiology of IID. However, weekly follow-up and obtaining and testing stool samples are very costly procedures. We could not, therefore, produce independent incidence rate estimates or reporting pyramids for each UK nation since it would have been prohibitively expensive.

8.2.4 GP Enumeration Study

8.2.4.1 Read code searches

We encountered the same issues with Read code searches in the GP Enumeration Study as we did in the GP Presentation Study (see Section 8.2.2.3). It is possible that variations in coding of IID consultations and implementing Read code searches between the two different groups of practices resulted in differences in the sensitivity of Read code searches for capturing IID-related consultations. Given the considerable difference in estimated rates, and the fact that practices were randomly allocated to the two study arms, this is unlikely.
We had originally intended to use GP Enumeration study data to link with national surveillance data.

However, during the course of the study the national surveillance systems changed from capturing personally identifiable information to electronic anonymised data so that record linkage was impossible. We attempted to overcome this problem using probability linkage but, unfortunately, this did not work (see Section 8.2.6.1).

8.2.5 Microbiology Studies

8.2.5.1 Diagnostic Methods

The time to submission of stool samples was generally short. In the Prospective Cohort Study 75% of participants submitted stool samples within three days of illness onset. In the GP Presentation Study 75% of people submitted stool samples within nine days of illness onset. In a logistic regression analysis, only specimens submitted 10 or more days after onset were more likely to test negative for all pathogens tested, after adjusting for other factors.

The inclusion of molecular methods in IID2 increased the diagnostic yield by around 10% overall compared with IID1. To undertake this comparison we re-calculated the diagnostic yield in IID1 according to the pathogens sought in IID2. The gain was most obvious for the enteric viruses. Using molecular methods also meant that we could test low volume samples for the complete range of IID2 study tests. The sample collection methods used (unrefrigerated, unpreserved samples transported by mail) mimicked routine community specimen collection and transportation. The lack of significant increases in detection of bacteria using PCR suggests that organisms were viable where present.

During the course of the study we noticed that the *Campylobacter* PCR was failing to detect the organism in stool samples that were positive on culture in the HPA Manchester Laboratory. This is not necessarily surprising since there is high variability in the *Campylobacter* genome (Parkhill *et al*., 2000) meaning that the sensitivity of a PCR based on any one genome target might be sub-optimal. A second PCR, specific for C. *jejuni* and containing alternative primers and probe, specific for the mapA gene was developed in Manchester (Fox, A, 2009, Pers comm.) and was used on all samples to optimise the detection of C. *jejuni* (Forward primer, reverse primer and probe, 5'- GTG GTT TTG AAG CAA AGA TTA AAG G3', 5'-GCG TTT ATT GGC ACA ACA TTG A-3', FAM5'-ATA CAT TAG CGA TGT TGG A-3'MGB, respectively). Similarly, an alternatively labelled probe was included in the *C. coli*-specific PCR (YY5'-TTG GAC CTC AAT CTC GCT TTG GAA TCA TT-3'BHQ1). Therefore every sample was tested using two C. *jejuni* and *C. coli* PCR assays. The *Campylobacter* results presented in this report are based on samples positive by either PCR method.

The immunoassay test used for *C. perfringens* was different in IID2 compared with IID1, so differences between the two sets of study findings should be interpreted with caution.

8.2.5.2 Lack of controls and implications for defining positive results

A major difference in study design was the inclusion of controls in IID1 but not in IID2. One of the consequences of this is that it hindered the identification of an appropriate cut of value for the definition of a positive result when PCR-based methods were used (since we did not have the distribution of CT values in controls). This might have led to overestimations of incidence of IID by specific organisms. Previous work on the analysis of archived specimens from IID1 by PCR has shown that in those data, CT cut-off value of <30 is a good indicator of IID genuinely caused by norovirus and rotavirus, and we used these published cut-off points to define norovirus and rotavirus positive specimens in IID2 (Phillips *et al*., 2009; Phillips *et al*., 2010). In the original work by Phillips *et al*., cut-off points were derived using only cases with specimens collected within 3 days of symptom onset, to minimise the possibility that low viral loads in cases were related to late specimen collection. In our data, we found no differences in viral load between specimens collected within and after 3 days of illness onset (data available but not shown), so we have made no adjustments for timing of specimen collection. In the absence of similar data on CT value cut-offs for other organisms, we used a more sensitive cut-off value of <40 for other pathogens, which is standard practice in diagnostic laboratories. We found good agreement between PCR and culture results for both *Campylobacter*

and *Salmonella*, but might have over-estimated incidence for other pathogens, particularly some viruses, if disease in IID cases with high CT values (low pathogen loads) was not actually due to infection with those organisms.

The absence of controls also had implications for searching for a broader range of pathogens. For example, in IID2 we did not look for other pathogenic *E. coli* such as Diffusely Adherent *E. coli*, Enteropathogenic *E. coli* or Enteroinvasive *E. coli*. In IID1 these organisms were almost as prevalent in controls as cases (Tompkins *et al*., 1999) so that there was the potential to overestimate the prevalence of these pathogens.

8.2.5.3 Missing specimens

A large proportion of IID cases in both the Prospective Cohort and GP Presentation studies failed to supply a stool sample. We used multiple imputation methods to account for missing data on specimen results. In the first IID study, the distribution of pathogens for IID cases not providing a stool specimen was assumed to be the same as that among cases with specimens available. The multiple imputation method used in IID2 is an improvement on this, in that it enables additional information to be used in determining the probability that a case with missing specimen information is positive for a given organism. In particular, we included age and symptoms experienced in our imputation model, which are likely to be related to the infecting organism. In addition, by using data from 20 imputed datasets in our analysis, we were able to account for uncertainty in the imputation process, to better reflect the uncertainty introduced by the missing data in the estimation of organism-specific incidence rates. Nevertheless, our analysis could still have resulted in inaccurate estimates if important variables were omitted from the imputation model. For example, cases with and without specimens might differ in ways, other than age and symptoms, that are related to the risk of infection with specific organisms. Another assumption of our imputation process is that infection with a given organism is independent of infection with all other organisms, which might not be reasonable if, for example, certain groups of organisms share common routes of infection. This assumption was necessary because of the large number of organisms involved, which would have made the imputation process unwieldy. Among cases with specimens available, the proportion with mixed infections was low, so this is unlikely to have had a marked difference to the results. The need for the independence assumption, however, means that we could not reliably estimate the incidence of IID in which no organism is identified.

8.2.5.4 Mixed infections

Less than 5% of cases who provided a specimen had an infection with more than one organism. In both studies, adenovirus, norovirus and sapovirus were the organisms most commonly involved in mixed infections. This means that we might have slightly overestimated the burden of disease cause by these viruses.

We did not consider it appropriate to exclude those cases with more than one pathogen found because, if mixed infections are common, incidence is potentially underestimated for many pathogens. In addition, for cases with mixed infections there is currently no reliable way of determining which pathogen was responsible for symptoms. For norovirus and rotavirus there is some evidence that in patients with lower viral loads the infection is more likely to be coincidental than clinically relevant but these data are not available for other pathogens. It might not be reasonable to assume that the principle would also apply to bacterial and protozoal pathogens. Furthermore, it is possible that mixed infections reflect common routes of infection. For example, sewage contamination of food or water, with multiple pathogens likely to be present, could lead to clinical disease from more than one organism simultaneously. Given current scientific constraints, our approach represents the most transparent way of presenting the data.

8.2.6 National Surveillance Study

8.2.6.1 Inability to perform data linkage

In the IID2 Study we were unable to link directly information from cases in the Prospective Cohort and GP Presentation Studies to laboratory reports to the four national surveillance centres to calibrate the national surveillance data, as was done in IID1. All data held at the national surveillance centres are now anonymised so that direct linkage was, in practice, impossible. To overcome this we used the indirect method to compare estimated rates of IID in the IID1 and IID2 studies.

It should be noted that national surveillance data contain information about outbreak cases of IID as well as sporadic cases although outbreak cases are not necessarily flagged as such. This is particularly important for norovirus for which the majority of reported cases are from outbreaks, most of which will be reported in institutions like hospitals and nursing homes rather than in the community. National surveillance data might also contain information from repeat samples, which we could not identify from anonymised data. Finally, we could not exclude travel-related cases from our analysis, which might have inflated the numerator and denominator.

There are no UK surveillance data for Enteroaggregative *E. coli* or for non-O157 VTEC (except in Scotland) and national surveillance data for *C. perfringens* is confined to enterotoxin detection in cases of suspected food poisoning.

8.2.6.2 Inclusion in national surveillance data of organisms of doubtful pathogenicity

Inclusion of organisms of doubtful pathogenicity in national surveillance systems might also inflate rates of sporadic, UK-acquired IID in those systems. This is particularly the case for *Yersinia* spp. (only certain types are known to be pathogenic) and adenovirus where the viruses of interest belong only to group F.

8.2.6.3 Recording dates

We found that the dates attached to stool samples were recorded in several different ways in the various national surveillance systems – date of onset (often poorly captured), specimen date, date received in the laboratory or date (week) uploaded into the national surveillance system. However, since we were averaging rates over more than a calendar year, and since we took account of reporting delays in extracting the data, this is unlikely to have affected the rate estimates.

8.2.7 Telephone Survey

8.2.7.1 Participation

In the Telephone Survey nearly 50% of individuals invited to take part completed a survey questionnaire. Participation was highest in England and lowest in Northern Ireland. This is similar to recently published Telephone Surveys from British Columbia (44%) (Thomas *et al*., 2006), Canada (34.7%) and the United States (37.1%) but is lower than levels of participation achieved in Ireland (84.1%) and Australia (68.2%) (Scallan *et al*., 2005). However, in a study by Boland and colleagues (2006), examining three Telephone Surveys on the island of Ireland conducted between 2000 and 2005, participation fell from 84.1% to 40.5% over this time period.

Participation in the Telephone Survey was higher than in the Prospective Cohort Study although the two study samples were very similar in terms of age group, sex, ethnicity, area-level deprivation and urban-rural classification. In the Telephone Survey, however, we could not measure NS-SEC because of the difficulty, identified in the pilot study, of implementing the full set of questions over the phone.

Those least likely to participate were in the younger age groups, and especially young males. This group is well known to be the hardest group to recruit into research studies. Younger people are more likely to use mobile phones but, mainly for ethical reasons, we were unable to make calls to

mobile numbers. Among participants in the Prospective Cohort Study 95% still used a landline as their main method of making phone calls. This suggests that the potential for bias from exclusion of mobile telephones was small, provided that the low participation in the Cohort Study has not led to an overestimate of landline usage. To account for under-representation among males and among certain age groups, we standardised rates according to the age and sex distribution of the census population.

In this telephone survey we recorded calls electronically. We discovered during double data entry (DDE) that a proportion of the calls could not be used because the audio recording was missing or damaged or there was no evidence that the participant had consented to proceed with the interview. This highlights the need to monitor call recordings continuously, to commence DDE early in the study and to test recording software rigorously during the pilot phase.

8.2.7.2 Sampling within households

Random sampling of people within the household proved very difficult to implement. For both recall periods the proportion of survey participants selected at random was less than 50%. A similar pattern was seen in a Telephone Survey in Northern Ireland where the person who answered the call was most likely to complete the survey, even in two people households when the likelihood of their completing the call should have been 50% (Scallan *et al*., 2004). However, in our study, the rate estimates among those sampled at random and those not sampled at random were very similar (data not shown), which suggests that among those present in the household at the time of the call, the decision about who responds to the survey is not primarily influenced by whether participants recently had symptoms. However, people at home at the time of the survey might be at home because they are recovering from IID. One of the consequences of restricting sampling to people in the household at the time of the call, rather than calling back at another time once the participant is identified, especially using a 7-day recall period, is that people who recently have been unwell with IID might still be at home recovering from their symptoms and are, therefore, available to answer the phone. The population sampled might over-represent individuals who have generally worse health and, perhaps, a higher risk of IID so that we might have overestimated the rate of IID.

8.2.7.3 Case definition of IID

We matched the case definitions in the Telephone Survey and the Prospective Cohort Study as closely as possible, because we aimed to compare the rate estimates between the two study types. However, one of the implications of this was that we did not define the term “diarrhoea” to participants. Most investigators who use Telephone Surveys to estimate illness burden define diarrhoea as three or more loose stools in a 24 hour period. Our case definition was probably more sensitive than that used in other Telephone Surveys of self-reported illness. Since we did not specifically provide a definition to our Telephone Survey participants they might have interpreted the term diarrhoea differently from each other and from us. In addition we were unable to exclude episodes occurring less than three weeks apart, among cases in the Telephone Survey, and this could have inflated rate estimates, especially in the 7-day recall group.

8.2.7.4 Inaccurate recall and digit preference

There was a decline in reporting of symptoms by number of days prior to the interview and this occurred regardless of recall period. However, during the 28-day recall period there was clear evidence of digit preference. Participants were much more likely to report symptoms on days 7, 14 and 21 suggesting, perhaps, that people remember events in blocks of a week. There was also evidence that reporting of symptoms is related to the period of recall; in the 28-day recall group, participants were more than four times more likely to report symptoms in the one to two weeks preceding the interview than in the period three to four weeks prior to the interview.

8.2.7.5 Advantages and Disadvantages of the Telephone Survey

A major advantage of telephone surveys is the ability to study large sample sizes relatively cheaply. This meant that we were able to calculate independent IID rate estimates for each UK country in the Telephone Survey. The main disadvantages are lack of information on the aetiology of IID, which means that telephone surveys cannot be used to calibrate national surveillance systems by pathogen, and the potential for inaccurate recall leading to inaccurate rate estimates.

8.2.8. NHS Direct/NHS24

8.2.8.1 Population covered

The nurse-led telephone information and advice systems do not cover the entire UK population. NHS Direct covers England and Wales whilst NHS24 covers Scotland. There is no telephone service in Northern Ireland although the NHS Direct website is available. However, we found that the proportion of the population in our studies that had contacted NHS Direct/NHS24 was very small.

8.2.8.2 Algorithms

We captured IID presenting to NHS Direct/NHS24 using calls for three main complaints – diarrhoea, vomiting and food poisoning. These were relatively crude groupings and could have included non-IID related causes of diarrhoea and vomiting. It seems that the food poisoning algorithm is rarely used by the nurses to avoid attributing a particular cause to a constellation of symptoms.

8.2.8.3 Data availability

In Scotland NHS24 data only aggregated data were available to us and we had no information on the sex of the caller or on call outcome. This limited our analysis of those data, in particular with regard to the proportion of calls relating to diarrhoea and vomiting in which the caller is advised to consult their GP.

8.2.9 Simulation Methods

We used simulation as a consistent framework for calculating uncertainty around reporting ratios, both for overall IID and for organism-specific estimates. While less intensive methods are available, we considered that simulation requires similar assumptions to other methods, is equally valid and is more flexible, allowing data from differents sources to be combined regardless of how the estimates in the individual study components were derived.

8.3 INTERPRETATION

8.3.1 Estimated rates of IID in the community in the UK

We used two methods to estimate rates of IID in the community – a Prospective Cohort Study and a Telephone Survey of self-reported illness. The estimated rate of IID in the community in the Prospective Cohort Study was within the range of estimates from other prospective studies (Roy *et al*., 2006) and similar to the rates obtained by de Wit *et al*. (2001) in the SENSOR study in the Netherlands (280 per 1,000 person-years) and Fox *et al*. (1972) in the United States (300 per 1,000 person-years). However, as with all international rate comparisons, case definitions, recruitment, participation and follow-up in the various studies were different. Similarly the estimated rates from the Telephone Survey (28-day recall) were within the range reported in the international literature (Roy *et al*., 2006) but the same caveats as those mentioned above apply. The rate estimates in the Telephone Survey using a 28-day recall period were very close to the rates reported by Wheeler *et al*. (1999) in the retrospective element of the IID1 Study (533 per 1,000 person-years in IID2 versus 550 per 1,000 person-years in IID1). However, the Prospective Cohort and Telephone Survey Studies in IID2 yielded very different results, which might reflect differences in the methods of data collection in the two studies.

Although there was variation in the rate estimates by country in the Telephone Survey the confidence intervals were wide so that there was little evidence that differences between countries were important. We could find no external sources of data that might have helped with further interpretation of these findings.

The annual rates from the Telephone Survey were between two and five times higher than the rates from the Prospective Cohort Study, depending upon the period of recall used. There are several possible explanations for the differences in rates obtained.

First, sampling from people in the household at the time of the telephone call might have meant that we selectively sampled people more likely to have had IID (especially for 7-day recall) if they were at home recovering from their illness and therefore available to answer the phone.

Secondly, the people who signed up to the Prospective Cohort Study were given a detailed briefing about the study prior to giving consent to take part. It is possible, therefore, that they developed a better understanding of the definition of IID and might have been more selective about what they reported than participants in the Telephone Survey. Indeed there is some evidence that people in the Telephone Survey might have reported milder illness – 31% reported two or less bouts of diarrhoea on the worst day of their illness compared with 22% in the Prospective Cohort Study. However, this difference was not enough to explain the discrepancy in rates.

Thirdly, it is possible that the two study populations were different. The type of person that agrees to comply with the procedures required to be a member of the cohort is likely to be different from someone who is prepared to answer a short duration, one-off telephone call.

Several factors indicate that rates from the Telephone Survey might overestimate the incidence of IID. First, the estimated rates appear to be highly sensitive to the period of recall used, suggesting that factors related to recall of symptoms play an important role. Secondly, the rate of IID presenting to general practice estimated from the Cohort Study was slightly higher than that estimated from the GP Presentation Study, and both were within the same order of magnitude as estimates from the GP Enumeration Study and an external estimate from the RCGP Weekly Returns Service. Similarly, the rate of IID-related calls to NHS Direct estimated in the Cohort is very close to that estimated from NHS Direct data. By contrast, rates of IID presenting to general practice in the Telephone Survey were considerably higher. Indeed, extrapolating the estimated rate based on 7-day results in a projected eight million general practice consultations for IID in the UK, an implausibly high figure. These findings suggest that the cohort approach provides more reliable estimates, certainly for episodes of IID that involve health care contact.

Interestingly, 1 in 11 cases of IID reported having contacted their GP in both the Cohort Study and the 7-day recall group of the Telephone Survey, while in the 28-day recall group the corresponding ratio was 1 in 6. This suggests that Telephone Survey data results in consistently higher estimates of incidence and that the phenomena of telescoping and selective recall appear to operate at different timescales. Our findings indicate that IID is consistently reported with greater frequency in the 7-day recall group relative to the Cohort Study, regardless of whether contact with a GP is involved. This is consistent with findings reported by Cantwell *et al*. (2010). By contrast, a greater proportion of cases in the 28-day recall group reported contacting their GP, suggesting that over this longer period of recall, participants are more likely to recall illness that involved healthcare contact.

Consultation rates to NHS Direct in England and Wales and to NHS24 Scotland were a fraction of the incidence rates recorded in the telephone survey by country. This probably reflects being prompted to recall illness in the telephone survey, which the case might not have judged severe enough to contact healthcare services.

It might be argued that we have chosen the most conservative rate estimate as our study outcome. In our opinion, definite cases of IID provide the most relevant measure of disease burden and are

also most relevant for guiding policy. People in the IID2 Study were asked to report symptoms that were presumed to be of infectious origin, but neither the participants, nor we, can be certain that this was this case in the absence of positive laboratory results. From a policy perspective, cases that are laboratory negative are not particularly amenable to control measures. For example, if a clinical definition of IID is very sensitive, incidence estimates will be higher. However, if most cases are negative on laboratory testing how useful is that clinical definition? It is noteworthy that the patterns and magnitude of incidence estimates based on definite cases in IID2 showed good agreement with IID1 for all organisms expect *Salmonella*, where a decline was expected (see Section 8.3.3).

8.3.2 Estimated rates of IID presenting to primary care in the UK

From the GP Presentation Study, we estimated the incidence of IID presenting to general practice at 18 per 1,000 person-years. This equates to less than 2% of the population consulting a GP for symptoms of IID every year, or about 1 million consultations per year in the UK. Our estimate was about double that obtained from the RCGP Weekly Returns Service, although it should be noted that these two sets of data were collected using different methodologies. In particular, the diagnostic codes used to capture IID are likely to be different. In addition, data from the RCGP Weekly Returns Service can be used to exclude repeat consultations for the same episode of illness, which was not possible in the IID2 GP Presentation Study. This might have resulted in a slight overestimate of incidence.

The incidence of IID case presenting to primary care in our study is around twice as high as in a similar study in the Netherlands (8 per 1,000 person-years) (de Wit *et al*., 2001a) but around half as much as that found in north-west Germany (40 per 1,000 person years) (Karsten *et al*., 2009). Differences in case definitions and healthcare systems might explain at least part of the difference observed.

Less than half of the people who contacted NHS Direct and were advised to contact their GP subsequently did so. However, callers with uncomplicated diarrhoea and/or vomiting are advised to self-care with home treatment. Callers are only advised to contact their primary care service if their symptoms are complex or worsen. The short-lived nature of diarrhoea and vomiting is likely to mean that a significant percentage of callers will have identified their symptoms as non-worsening, been able to self-care to manage their symptoms, or recovered sufficiently, so that contacting their GP becomes unnecessary. This is likely to account for the relatively low percentage of people advised to contact their GP who are estimated by the study to have actually done so.

8.3.3 Aetiology of IID in the UK

No pathogen was detected in a large percentage of stool samples submitted by people who reported symptoms of IID. This was despite the fact that the majority of people submitted their sample within 10 days of symptom onset. The case definition in the IID2 Study was very sensitive but, in order to compare IID2 Study data with IID1, we needed to use the same case definition. We did not define the term "diarrhoea" to participants so it is possible that we detected transient changes in bowel habit not caused by IID. Alternatively, we might have missed cases of IID due to organisms that we did not include in our diagnostic algorithms.

Norovirus was the most common viral cause of IID in the community in the UK and *Campylobacter* spp., one of the Food Standards Agency's target organisms, was the most common bacterial cause. The high proportion of sapovirus identifications is consistent with the fact that the IID2 Study data collection coincided with the introduction of a completely new genotype into the population (Jim Gray, Tom McDonnell - personal communication).

Norovirus, sapovirus and *Campylobacter* infection all featured prominently in GP Presentation Study samples. As regards norovirus and sapovirus this probably reflects the fact that young children were more likely to be affected. *Campylobacter* infection, on the other hand, might lead to more severe symptoms prompting the case to present to their GP (Tam *et al*., 2003).

The prevalence of norovirus can fluctuate quite widely from year to year (Siebenga *et al*., 2009) so it might be argued studying a one-year cohort would either over- or under-estimate viral IID burden. We note that, compared with the revised incidence estimates for IID1 (Phillips *et al*., 2010), the IID2 study incidence estimates are quite similar. The proportion of samples positive for norovirus in cases presenting to primary care in our study was similar to studies conducted in Germany (Karsten *et al*., 2009), Switzerland (Fretz *et al*., 2005), Australia (Sinclair *et al*., 2005) and the Netherlands in 1999 (de Wit *et al*., 2001a) but less that in an Austrian study conducted in 2007 (Huhulescu *et al*., 2009). The incidence of norovirus IID presenting to primary care in our study (210 cases per 100,000) was around a third of that found in north-west Germany in 2004 (626 cases per 100,000) (Karsten *et al*., 2009). As well as the emergence of new genotypes (Siebenga *et al*., 2009) differences in study design, sample sizes and case definitions might also explain at least some of the differences described here.

In relation to the findings on rotavirus it should be noted that routine vaccination had not been implemented in the UK at the time of the IID2 Study. These data will provide useful background information for assessing the effectiveness of a vaccine if it is introduced into the UK schedule.

The proportion of samples positive for the Food Standards Agency's remaining target organisms in the community was very low (*C. perfringens*, *Salmonella* spp., *Listeria monocytogenes*, *E. coli* O157 (all <1% and *Listeria monocytogenes* (0%)) and the findings were similar for cases presenting to general practice (*Salmonella* spp. <1%, *C. difficile* 1.4%, *C. perfringens* 2.2% and *Listeria monocytogenes* 0%).

There was only one case of *C. difficile*-associated diarrhoea in the Prospective Cohort Study and 10 cases in the GP Presentation Study, which suggests that in unselected community samples, i.e. from people who have not necessarily had recent or frequent contact with health or social care, the incidence of *C. difficile*-associated diarrhoea is very low. However, based on the study design and case definition, we could only detect the fraction of listeriosis and *C. difficile* infection that was associated with diarrhoeal disease. We did not capture the systemic complications associated with either infection so we have underestimated their clinical impact. Similarly, we did not collect any risk factor data in the IID2 Study (e.g. hospital stays or antibiotic usage) that might have been useful in interpreting the *C. difficile* results.

8.3.4 Comparing IID1 with IID2 in England

8.3.4.1 IID rates in the community

A major consideration when assessing rates from the IID1 and IID2 studies relates to the comparability of the two cohorts. Participation in IID1 was higher than in IID2 but the reporting fatigue was also more marked. It is difficult to assess the impact these differences in participation and follow-up, which might or might not influence the validity of the comparisons between the two studies. Rates in both studies were standardised to account for differences between the cohort populations and the UK census populations at the time of each study. The UK age-sex structure had not changed much between IID1 and IID2.

To the degree that comparing the two cohorts is valid, the estimated rate of IID in the community in England was high (274 per 1,000 person-years) and over 40% higher than in IID1 (194 per 1,000 person-years).

8.3.4.2 IID rates presenting to primary care

The estimated rate of IID presenting to primary care was approximately half that in IID1 for all IID and across all organisms that we looked for. This might reflect the changes in healthcare usage that have taken place between the two study periods since we observed similar reductions in consultation rates in the RCGP Weekly Returns Service. We noted that although the consultation rates had, in general, halved the consultation rates for people with *Salmonella* infection had reduced eight-fold. There have been major changes in the epidemiology of salmonellosis in the intervening years, mainly a large decline in *S.* Enteritidis Phage Type 4, and it is possible that the illness is milder

than it was, leading to fewer consultations. The fall in GP Presentation rates that we observed is not attributable to NHS Direct/NHS24 since the proportion of people with IID in the community contacting those services was very small (≈2%).

8.3.4.3 Re-calibrating national surveillance – reporting patterns

Introducing molecular methods into the IID2 Study improved diagnostic yield by approximately 10%. Given the improvements in detection methods that have taken place between the IID1 and IID2 studies, especially for viruses, we used a revised reporting pattern for norovirus, based on PCR-based testing of archived specimens from IID1 (Phillips *et al*., 2010).

The ratio of IID cases in the community to those reported to national surveillance has changed. In the IID1 Study the ratio was ≈1:85 compared with ≈1:150 in the IID2 Study. This means that, not only has the overall incidence of IID increased, but the proportion that is hidden from national surveillance systems has also increased. The reason that the hidden burden has increased appears to be because fewer cases are presenting to, and are therefore visible to, health services. It was notable that the ratio of cases reported to national surveillance to cases presenting to primary care had improved for all IID and for all the pathogens that we considered. It suggests that a greater proportion of cases presenting to the GP are being reported and, presumably, also reflects better data capture from diagnostic laboratories reporting to national surveillance systems.

For *Salmonella* the ratio of cases in the community to those reported to national surveillance was similar (≈1:4 in IID1 to ≈1:5 in IID2). The reporting patterns for rotavirus and *Campylobacter* were similar in the two studies but the ratio of cases of norovirus reported to national surveillance to cases in the community had changed from ≈1:1000 to ≈1:300. This might be due to improvements in diagnostic methods used in routine practice. However, it needs to be interpreted cautiously since norovirus cases reported to national surveillance tend to reflect outbreak cases rather than sporadic cases.

We were unable to determine if changes in the community rates of particular organisms were greater than could be explained by chance alone, because the IID2 study was not powered for these outcomes. Although not designed specifically to measure changes in individual pathogens, particularly in the cohort, in the context of other evidence (e.g. Gillespie *et al*., 2005; Matheson *et al*., 2010; Gormley *et al*., 2011), the IID2 Study provides support for a decline in *Salmonella* incidence in recent years. To have detected statistically significant changes in incidence for individual pathogens would have required several hundred thousand person-years of follow-up, which was considered to be unaffordable.

8.3.4.4 IID acquired outside the UK

Around 8% of people in the Prospective Cohort Study and 12% of people in the GP Presentation Study with IID reported having travelled outside the UK in the 10 days prior to illness onset. It should be noted, however, that this study was not specifically designed to estimate the incidence of travel-related IID. In particular, we did not have an estimate for the frequency of recent foreign travel from a similar group of individuals without IID for comparison, and our study might not have captured cases that occurred outside the UK but had already resolved by the time individuals returned to the UK. In addition, participants might not have reported symptoms while they were abroad. It should be noted that we excluded travel-related cases from all the incidence calculations.

8.4 CONCLUSIONS

We conclude that:-

- Around 25% of people in the UK suffer from an episode of IID in a year. Approximately 50% of people with IID reported absence from work or school because of their symptoms. We estimated that for every case of IID in the UK reported to national surveillance systems there were 147 in the community. The most commonly identified pathogens were, in order of frequency, norovirus, sapovirus, rotavirus and *Campylobacter* spp.. *C. perfringens*, *Salmonella* spp. was found in <1% of samples from IID cases. *L. monocytogenes* was not found.
- Less than 2% of people in the UK consulted their General Practitioner for an episode of IID and about 1 in 18 of these is reported to national surveillance in the UK. The most commonly identified pathogens were *Campylobacter* spp., norovirus, sapovirus and rotavirus. *Salmonella* were detected in only 0.8% of cases. This was less than cases of *C. perfringens* (2.2%), Enteroaggregative *E. coli* (1.4%), *Cryptosporidium* (1.4%) or *Giardia* (1.0%).
- There was only one case of *C. difficile*-associated diarrhoea in the Prospective Cohort Study and 10 cases in the GP Presentation Study.
- Approximately 8% of community IID cases reported having travelled outside the UK in the 10 days prior to illness onset. Among cases of IID presenting to general practice, the corresponding figure was 12%.
- There was variation in the IID rate estimates by country in the Telephone Survey but the confidence intervals were wide and there was insufficient evidence to determine if these differences were important.
- The estimated rate of IID in England was 43% higher in 2008-9 (IID2) than in 1993-6 (IID1) whilst the estimated rate of IID presenting to General Practice in England in IID2 was 50% lower than in IID1.
- Approximately 50% of people with an episode of IID in IID1 and IID2 reported absence from work or school because of their symptoms.
- In England, the ratio between cases reported to national surveillance to those occurring in the community had changed from ≈1:85 in IID1 to ≈1:150 in IID2. For norovirus, the change was from ≈1:1000 in IID1 to ≈1:300 in IID2. The ratios for *Campylobacter*, *Salmonella* and rotavirus were similar in both studies.
- Based on a re-analysis of IID1 Study data, using molecular methods in the IID2 Study increased the diagnostic yield to 40% compared with IID1 (30%) in the Prospective Cohort Study.
- Although the hidden burden of IID had increased between the two study periods, because fewer people with IID present to general practice, reporting to national surveillance of cases presenting to general practice had improved i.e. national surveillance data capture of cases presenting to healthcare had improved between IID1 and IID2 for all the pathogens that we considered.
- A very small proportion of people with IID (≈2%) contacted NHS Direct or NHS24, and this was insufficient to account for the observed drop in rates of consultation to general practice.
- From the Telephone Survey we estimated that the rate of IID in the community in the UK was 1,530 cases per 1,000 person-years using 7-day recall (i.e. five times higher than the rate in the Prospective Cohort Study) and 533 cases per 1,000 person-years using 28-day recall i.e. twice as high as in the Prospective Cohort Study). We also found evidence that rates differ according to the period of recall.
- To attempt to understand the variation in community rates in the two types of study we triangulated rates around presentation to General Practice. The rates from the Prospective Cohort Study, the GP Presentation Study, the GP Enumeration Study and an external data source (the RCGP Weekly Returns Service) were all of a similar order of magnitude and substantially less than in the Telephone Survey. We suggest, therefore, that the cohort approach might provide more reliable estimates, at least for episodes of IID that involve healthcare contact.

8.5 RECOMMENDATIONS

8.5.1 Recommendations for laboratory diagnostics

- As diagnostic methods become more sensitive, there is a need to define adequate cut-off points for the diagnosis of clinically significant positive results based on real time PCR methods. Preliminary work on this has been undertaken for norovirus and rotavirus and similar work, using samples from appropriate controls, is necessary for other organisms.
- If cut-off points of sufficient sensitivity and specificity are found, given the improvement in diagnostic yield witnessed in this study, the cost-effectiveness of introducing PCR-based methods in routine diagnostics needs to be investigated.

8.5.2 Recommendations for estimating illness burden and trends

- The appropriate methods to estimate illness burden and trends depend on the question to be answered.
  - Measuring disease incidence is difficult whichever method is chosen. Both telephone surveys and cohort studies are subject to bias. An alternative to measuring incidence would be to measure longitudinal prevalence (Morris *et al*., 1996) i.e. the proportion of people with IID on the day of the survey, with no recall involved. In certain circumstances, longitudinal prevalence can be a more useful measure of disease burden, as it measures the proportion of time during which individuals are ill. The advantages of this method are that it avoids difficulties in defining incident (new) cases of illness, and can potentially eliminate inaccurate recall if participants are asked about illness on the day of contact. Although this requires larger studies, continuous syndromic surveillance mechanisms can be set up to estimate longitudinal prevalence of many conditions simultaneously, and the data analysed cumulatively. It should be noted, however, that longitudinal prevalence is influenced not just by risk of illness, but also by illness duration, and so is not appropriate for studies in which the distinction between these two features is important.
  - Trend information on overall IID can be captured through telephone surveys or cohort studies but telephone surveys are, of course, considerably cheaper. The drawbacks of using telephone surveys, however, are inaccuracy in burden estimation and lack of information on the aetiology of IID, which is important for policy-making.
  - In future, capturing information on the frequency of illness through internet-based surveys using volunteers is likely to become more commonplace.
- Calibrating national surveillance data requires knowledge of the organisms causing IID.
  - An alternative to an IID3 Study would be to implement some form of continuous sentinel surveillance including stool sample requests from all cases, for example attached to the RCGP WRS. It is possible that primary care electronic datasets might provide an alternative to GP Presentation studies if data entry can be improved although stool samples for laboratory examination are not always requested from (or provided by) all IID cases.
  - Interpreting positive laboratory results in the absence of a control group is challenging. Cycle threshold cut-off values need to be validated in this context, taking into account variations in laboratory techniques and sample populations. In future studies, and depending on available funding, cohort members could be used as their own controls e.g. obtaining samples at baseline or at other times during follow-up when participants are not symptomatic.
  - The increasing use of electronic methods, such as e-mail, for collecting health information is accompanied by concerns that those taking part in epidemiological studies are an increasingly selected subset of the population. The gradual uptake of these electronic forms of communication should, however, offset some of these concerns. In our study, two-thirds of participants elected to be followed up weekly by e-mail. Those choosing e-mail were generally younger, but weekly response rates between the two groups were comparable. Our experience suggests that offering participants a range of options for collecting information can improve response rates by allowing them to choose the most convenient form of communication, while substantially reducing workload and providing more timely information.

8.5.3 Recommendations for Policy

Our findings suggest that:-

- IID continues to represent a significant disease burden in the UK, so that further efforts to control the pathogens causing IID are needed.
- *Campylobacter* spp. remains an important public health problem so that the Food Standards Agency continued focus on tackling foodborne *Campylobacter* to reduce levels of IID is warranted.
- From the point of view of the Food Standards Agency, further work is needed to understand the burden of norovirus infection, in particular the proportion of norovirus infection that might be food-related.
- The increase in sapovirus due to the emergence of a new genotype highlights the need for continual surveillance and horizon scanning to identify new and emerging pathogens.

REFERENCES

ACMSF, 2009. Ad Hoc Group on Vulnerable Groups: Report on the Increased Incidence of Listeriosis in the UK. London: Food Standards Agency (FSA/1439/0709).

Adak GK, Long SM, O'Brien SJ (2002). Trends in indigenous foodborne disease and deaths, England and Wales: 1992 to 2000. *Gut* **51**: 832-41.

Amar CFL, Dear PH, McLauchlin J (2003). Detection and genotyping by real-time PCR/RFLP analyses of *Giardia duodenalis* from human faeces. *J Med Microbiol* **52**:681-683.

Amar CFL, Dear PH, McLauchlin J (2004a). Detection and identification by real-time PCR/RFLP analyses of *Cryptosporidium* species from human faeces. *Lett Appl Microbiol* **38**: 217-222.

Amar CFL, East CL, Grant KA, Gray J, Iturriza-Gomara M, Maclure EA, McLauchlin J (2005). Detection of viral, bacterial and parasitological RNA or DNA of nine intestinal pathogens in faecal samples archived as part of the English Infectious Intestinal Disease Study: assessment of the stability of target nucleic acid. *Diagn Mol Pathol* **14**: 90-6.

Amar CF, East CL, Gray J, Iturriza-Gomara M, Maclure EA, McLauchlin J (2007). Detection by PCR of eight groups of enteric pathogens in 4,627 faecal samples: re-examination of the English case-control Infectious Intestinal Disease Study (1993-1996). *Eur J Clin Microbiol Infect Dis* **26(5)**: 311-23.

Atchison CJ, Lopman BA, Harris CJ, Tam CC, Iturriza Gómara M, Gray JJ (2009). Clinical laboratory practices for the detection of rotavirus in England and Wales: can surveillance based on routine laboratory testing data be used to evaluate the impact of vaccination. *Euro Surveill* **14**: 1-6.

Best EL, Powell EJ, Swift C, Grant KA, Frost JA (2003) Applicability of a rapid duplex real-time PCR assay for speciation of *Campylobacter jejuni* and *Campylobacter coli* directly from culture plates. *FEMS Microbiol Let*. **229**: 237-241.

Boland M, Sweeney MR, Scallan E, Harrington M, Staines A (2006). Emerging advantages and drawbacks of telephone surveyingTelephone Surveying in public health research in Ireland and the U.K. *BMC Public Health* **6**: 208.

Boom R, Sol CJ, Salimans MM, Jansen CL, Wertheim-van Dillen PM, van der Noordaa J. (1990)Rapid and simple method for purification of nucleic acids. *J Clin Microbiol* **28(3)**: 495–503.

Brazier JS, Raybould R, Patel B, Duckworth G, Pearson A, Charlett A, Duerden BI (2008). Distribution and antimicrobial susceptibility patterns of *Clostridium difficile* PCR ribotypes in English hospitals, 2007-08. *Euro Surveill* **13:** 41.

Buzby JC, Roberts T. (2009). The economics of enteric infections: human foodborne disease costs. *Gastroenterology* **136:** 1851-1862.

Cantwell LB, Henao OL, Hoekstra RM, Scallan E (2010). The effect of different recall periods on estimates of acute gastroenteritis in the United States, FoodNet Population Survey 2006-2007.

Foodborne Pathog Dis. Jun 26 [E-pub ahead of print].

Carlin JB, Li N, Greenwood P, Coffey C. (2003). Tools for analyzing multiple imputed datasets. *Stata Journal*; **3(3)**: 226-244.

Chief Medical Officer. (1992). *Definition of food poisoning* (PL/CMO(92)14). Department of Health: London.

Chisholm J (1990). The Read clinical classification. *BMJ* **300(6732):** 1092.

Cooper DL, Smith GE, O'Brien SJ, Hollyoak VA, Baker M (2003). What can analysis of calls to NHS direct tell us about the epidemiology of gastrointestinal infections in the community? *J Infect* **46:** 101-5.

Doll R (1991). Progress against cancer. An epidemiological assessment. The 1991 John C Cassel Memorial Lecture. *Am J Epidemiol* **134:** 675-88.

Fleming DM, Smith GE, Charlton JR, Charlton J, Nicoll A (2002). Impact of infections on primary care – greater than expected. *Commun Dis Public Health* **5:** 7-12.

Flint JA, Duynhoven YT, Angulo FJ, DeLong SM, Braun P, Kirk M, Scallan E, Fitzgerald M, Adak GK, Sockett P, Ellis A, Hall G, Walke H, Braam P (2005). Estimating the burden of acute gastroenteritis, foodborne disease, and pathogens commonly transmitted by food: an international review. *Clin Infect Dis* **41:** 693-704.

Food Standards Agency (2000). A report of the study of infectious intestinal disease in England. London: The Stationery Office.

Food Standards Agency (2001). Strategic Plan 2001-2006: Putting Consumers First. Available at < http://www.food.gov.uk/multimedia/pdfs/stratplan.pdf> Accessed 21st July 2010.

Food Standards Agency (2002). Measuring foodborne illness levels. Available at < http://www.food.gov.uk/safereating/microbiology/58736> Accessed 21st July 2010.

Fox JP, Hall CE, Cooney MK, Luce RE, Kronmal RA (1972). The Seattle virus watch. II. Objectives, study population and its observation, data processing and summary of illnesses. *Am J Epidemiol* **96(4):** 270-85.

Frahm E, Obst U (2003). Application of the fluorogenic probe technique (TaqMan PCR) to the detection of *Enterococcus* spp. and *Escherichia coli* in water samples. *J Microbiol Methods* **52:**123-131.

Fretz R, Herrmann L, Christen A, Svoboda P, Dubuis O, Viollier EH, Tanner M, Baumgartner A (2005). Frequency of Norovirus in stool samples from patients with gastrointestinal symptoms in Switzerland. *Eur J Clin Microbiol Infect Dis* **24(3):**214-6.

Gill LJ, Shand PAX, Fuggle P, Dugan B, Davies SC (1997). Pain assessment for children with sickle cell disease: improved validity of diary keeping versus interview ratings. *Br J Health Psychol* **2:** 131–140.

Gillespie IA, O'Brien SJ, Adak GK, Ward LR, Smith HR (2005). Foodborne general outbreaks of *Salmonella* Enteritidis phage type 4 infection, England and Wales, 1992-2002: where are the risks? *Epidemiol Infect.* **133(5):**795-801.

Gillespie IA, McLauchlin J, Little CL, Penman C, Mook P, Grant K, O'Brien SJ (2009). Disease presentation in relation to infection foci for non-pregnancy-associated human listeriosis in England and Wales, 2001 to 2007. *J Clin Microbiol* **47(10):** 3301-7.

Gormley FJ, Little CL, Rawal N, Gillespie IA, Lebaigue S, Adak GK (2011). A 17-year review of foodborne outbreaks: describing the continuing decline in England and Wales (1992-2008). *Epidemiol Infect.* **139(5):**688-99.

Green J, Norcott JP, Lewis D, Arnold C, Brown DW (1993). Norwalk-like viruses: demonstration of genomic diversity by polymerase chain reaction. *J Clin Microbiol* **31:** 3007-3012.

Grif K, Patscheider G, Dierich MP, Allerberger F (2003). Incidence of fecal carriage of *Listeria monocytogenes* in three healthy volunteers: a one-year prospective stool survey. Euro J Clin *Microbiol Infect Dis*. **22:**16-20.

Huang H, Weintraub A, Fang H, Nord CE (2009). Comparison of a commercial multiplex real-time PCR to the cell cytotoxicity neutralization assay for diagnosis of *Clostridium difficile* infections. *J Clin Microbiol* **47(11):** 3729-31.

Huhulescu S, Kiss R, Brettlecker M, Cerny RJ, Hess C, Wewalka G, Allerberger F (2009) . Etiology of acute gastroenteritis in three sentinel general practices, Austria 2007. *Infection* **37(2):**103-8.

Iturriza Gomara M, Wong C, Blome S, Desselberger U, Gray J (2002). Molecular characterization of VP6 genes of human rotavirus isolates: correlation of genogroups with subgroups and evidence of independent segregation. *J Virol* **76:** 6596-6601.

Iturriza Gómara M, Simpson R, Perault AM, Redpath C, Lorgelly P, Joshi D, Mugford M, Hughes CA, Dalrymple J, Desselberger U, Gray J (2008). Structured surveillance of infantile gastroenteritis in East Anglia, UK: incidence of infection with common viral gastroenteric pathogens. *Epidemiol Infect* **136(1):** 23-33.

Iturriza-Gómara M, Elliot AJ, Dockery C, Fleming DM, Gray JJ (2009). Structured surveillance of infectious intestinal disease in pre-school children in the community: 'The Nappy Study'. *Epidemiol Infect* **137(7):** 922-31.

Jensen A (1993). *Listeria monocytogenes* isolation from human faecal specimens: experiments with the selective media, PALCAM and L-PALCAMY. *Lett Appl Microbiol* **16(1):** 32-5.

Jordan H, Roderick P, Martin D (2004). The Index of Multiple Deprivation 2000 and accessibility effects on health. *J Epidemiol Community Health* **58(3):** 250-7.

Kageyama T, Kojima S, Shinohara M, Uchida K, Fukushi S, Hoshino FB, Takeda N, Katayama K (2003). Broadly reactive and highly sensitive assay for Norwalk-like viruses based on real-time quantitative reverse transcription-PCR. *J Clin Microbiol* **41:** 1548-1557.

Karsten C, Baumgarte S, Friedrich AW, von Eiff C, Becker K, Wosniok W, Ammon A, Bockemühl J, Karch H, Huppertz HI (2009). Incidence and risk factors for community-acquired acute gastroenteritis in north-west Germany in 2004. *Eur J Clin Microbiol Infect Dis* **28(8):**935-43.

Marcus AC (1982). Memory aids in longitudinal health surveys: results from a field experiment. *American Journal of Public Health* **72:** 567–573.

Majowicz SE, Hall G, Scallan E, Adak GK, Gauci C, Jones TF, O'Brien S, Henao O, Sockett PN (2008). A common, symptom-based case definition for gastroenteritis. *Epidemiol Infect* **136:** 886-894.

Matheson N, Kingsley RA, Sturgess K, Aliyu SH, Wain J, Dougan G, Cooke FJ (2010). Ten years experience of *Salmonella* infections in Cambridge, UK. *J Infect*. **60(1):**21-5.

McCormick A (1993). The notification of infectious diseases in England and Wales. *Communicable Disease Report CDR Review* **2:** R19-R25.

McLauchlin J, Pedraza-Díaz S, Amar-Hoetzeneder C, Nichols GL (1999). Genetic characterization of *Cryptosporidium* strains from 218 patients with diarrhea diagnosed as having sporadic cryptosporidiosis. *J Clin Microbiol* **37:** 3153-3158.

Morris SS, Cousens SN, Kirkwood BR, Arthur P, Ross DA (1996). Is prevalence of diarrhea a better predictor of subsequent mortality and weight gain than diarrhea incidence? *Am J Epidemiol* **144(6):** 582-8.

Møller Nielsen E and Thorup Andersen M (2003). Detection and Characterization of Verocytotoxin-Producing *Escherichia coli* by Automated 5' Nuclease PCR assay. *J Clin Microbiol* **41:** 2884-2893.

Murphy NM, McLauchlin J, Ohai C, Grant KA (2007). Construction and evaluation of a microbiological positive process internal control for PCR-based examination of food samples for *Listeria monocytogenes* and *Salmonella enterica*. *Int J Food Microbiol*. **120(1-2):** 110-9.

Musher DM (2004). Contagious acute gastrointestinal infections. *N Engl J Med* **351:** 2417-2427.

Noel JS, Liu BL, Humphrey CD, Rodriguez EM, Lambden PR, Clarke IN, Dwyer DM, Ando T, Glass RI, Monroe SS (1997). Parkville virus: a novel genetic variant of human calicivirus in the Sapporo virus

clade, associated with an outbreak of gastroenteritis in adults. *J Med Virol* **52:**173-178.

Novak-Weekley SM, Marlowe EM, Miller JM, Cumpio J, Nomura JH, Vance PH, Weissfeld A (2010). *Clostridium difficile* testing in the clinical laboratory using multiple testing algorithms. *J Clin Microbiol* **48(3):** 889-893.

O'Brien SJ, Elson R, Gillespie IA, Adak GK, Cowden JM (2002). Surveillance of foodborne outbreaks of infectious intestinal disease in England and Wales 1992-1999: contributing to evidence-based food policy? *Public Health* **116(2):** 75-80.

O'Brien SJ, Rait G, Hunter PR, Gray JJ, Bolton FJ, Tompkins DS, McLauchlin J, Letley LH, Adak GK, Cowden JM, Evans MR, Neal KR, Smith GE, Smyth B, Tam CC, Rodrigues LC (2010). Methods for determining disease burden and calibrating national surveillance data in the United Kingdom: the second study of infectious intestinal disease in the community (IID2 study). *BMC Med Res Methodol* **10:** 39.

Oka T, Katayama K, Hansman GS, Kageyama T, Ogawa S, Wu FT, White PA, Takeda N. (2006). Detection of human sapovirus by real-time reverse transcription-polymerase chain reaction. *J Med Virol* **78(10):** 1347-53.

Parkhill J, Wren BW, Mungall K, Ketley JM, Churcher C, Basham D, Chillingworth T, Davies RM, Feltwell T, Holroyd S, Jagels K, Karlyshev AV, Moule S, Pallen MJ, Penn CW, Quail MA, Rajandream MA, Rutherford KM, van Vliet AH, Whitehead S, Barrell BG (2000). The genome sequence of the food-borne pathogen *Campylobacter jejuni* reveals hypervariable sequences. *Nature* **403(6770):** 665-8.

Pawlowski SW, Warren CA, Guerrant R (2009). Diagnosis and treatment of acute or persistent diarrhea. *Gastroenterology* **136:** 1874-1886.

Phillips G, Lopman B, Tam CC, Iturriza-Gomara M, Brown D, Gray J (2009a). Diagnosing norovirus-associated infectious intestinal disease using viral load. *BMC Infect Dis* **9:** 63.

Phillips G, Lopman B, Tam CC, Iturriza-Gomara M, Brown D, Gray J (2009b). Diagnosing rotavirus A associated IID: Using ELISA to identify a cut-off for real time RT-PCR. *J Clin Virol* **44(3):** 242-5.

Phillips G, Tam CC, Conti S, Rodrigues L C, Brown D, Iturriza-Gomara M, Gray J, Lopman B (2010). Community Incidence of Norovirus-associated Infectious Intestinal Disease in England: Improved Estimates Using Viral Load for Norovirus Diagnosis. *Am J Epidemiol* **171(9):** 1014-1022.

Roberts JA, Cumberland PA, Sockett P, Rodrigues LC, Wheeler JG, Sethi D, Roderick PJ (2003). The study of infectious intestinal disease in England: socio-economic impact. *Epidemiol Infect* **130 (3):** 1-11.

Roy SL, Scallan E, Beach MJ (2006). The rate of acute gastrointestinal illness in developed countries. *J Water Health* **4(Suppl. 2):** 31-70.

Royston P (2005). Multiple imputation of missing values: update. *Stata Journal* **5(2):** 1-14.

Rubin DB (2004). Multiple imputation for nonresponse in surveys (2nd Ed.). Wiley-Blackwell.

Scallan E, Fitzgerald M, Collins C, Crowley D, Daly L, Devine M, Igoe D, Quigley T, Robinson T, Smyth B (2004). Acute gastroenteritis in northern Ireland and the Republic of Ireland: a telephone survey. *Commun Dis Public Health* **7(1):** 61-7.

Scallan E, Majowicz SE, Hall G, Banerjee A, Bowman CL, Daly L, Jones T, Kirk MD, Fitzgerald M, Angulo FJ (2005). Prevalence of diarrhoea in the community in Australia, Canada, Ireland, and the United States. *Int J Epidemiol* **34:** 454-60.

Siebenga JJ, Vennema H, Zheng DP, Vinjé J, Lee BE, Pang XL, Ho EC, Lim W, Choudekar A, Broor S, Halperin T, Rasool NB, Hewitt J, Greening GE, Jin M, Duan ZJ, Lucero Y, O'Ryan M, Hoehne M, Schreier E, Ratcliff RM, White PA, Iritani N, Reuter G, Koopmans M (2009). Norovirus illness is a global problem: emergence and spread of norovirus GII.4 variants, 2001-2007. *J Infect Dis* **200(5):**802-12.

Simpson R, Aliyu S, Iturriza-Gómara M, Desselberger U, Gray J (2003). Infantile viral gastroenteritis: on the way to closing the diagnostic gap. *J Med Virol* **70:** 258-62.

Sinclair MI, Hellard ME, Wolfe R, Mitakakis TZ, Leder K, Fairley CK (2005). Pathogens causing community gastroenteritis in Australia. *J Gastroenterol Hepatol.* **20(11):**1685-90.

Smith G, Hippisley-Cox J, Harcourt S, Heaps M, Painter M, Porter A, Pringle M (2007). Developing a national primary care-based early warning system for health protection – a surveillance tool for the future? *J Public Health (Oxf)* **29:** 75-82.

Strickland MJ, Crawford JM, Shen L, Wilkins JR 3rd (2006). Time-dependent record keeping fatigue among youth completing health diaries of unintentional injuries. *J Safety Res* **37:** 487-492.

Swindells J, Brenwald N, Reading N, Oppenheim B. (2010). An Evaluation of Diagnostic Tests for *Clostridium difficile* Infection. *J Clin Microbiol* **48(2):** 606-608.

Tam CC, Rodrigues LC, O'Brien SJ (2003). The study of infectious intestinal disease in England: what risk factors for presentation to general practice tell us about potential for selection bias in case-control studies of reported cases of diarrhoea. *Int J Epidemiol* **32(1):** 99-105.

Thomas MK, Majowicz SE, MacDougall L, Sockett PN, Kovacs SJ, Fyfe M, Edge VL, Doré K, Flint JA, Henson S, Jones AQ (2006). Population distribution and burden of acute gastrointestinal illness in British Columbia, Canada. *BMC Public Health* **6:** 307.

Tiemessen CT, Nel MJ (1996). Detection and typing of subgroup F adenoviruses using the polymerase chain reaction. *J Virol Methods* **59(1-2):**73-82.

Tompkins DS, Hudson MJ, Smith HR, Eglin RP, Wheeler JG, Brett MM, Owen RJ, Brazier JS, Cumberland P, King V, Cook PE. (1999). A study of infectious intestinal disease in England: microbiological findings in cases and controls. *Commun Dis Public Health* **2(2):** 108-13.

UK Biobank Co-ordinating Centre (2006). UK Biobank: Report of the integrated pilot phase. Available at <http://www.ukbiobank.ac.uk/docs/IntegratedPilotReport.pdf>. Accessed 20th July 2010.

Verbrugge LM (1980). Health diaries. *Med Care* **18:** 73–95.

Wall PG, de Louvois J, Gilbert RJ, Rowe B. (1996). Food poisoning: notifications, laboratory reports, and outbreaks – where do the statistics come from and what do they mean? *Communicable Disease Report CDR Review* **6:** R93-R100.

Westgard JO, Groth T, Aronsson T, Falk H, de Verdier C-H (1997). Performance characteristics of rules for internal quality control : probabilities for false rejection and error detection. *Clin Chem* **23:** 1857-67.

Wheeler JG, Sethi D, Cowden JM, Wall PG, Rodrigues LC, Tompkins DS, Hudson MJ, Roderick PJ (1999). Study of infectious intestinal disease in England: rates in the community, presenting to general practice, and reported to national surveillance. The Infectious Intestinal Disease Study Executive. *BMJ* **318(7190):** 1046-50.

de Wit MA, Koopmans MP, Kortbeek LM, Wannet WJ, Vinje J, van Leusden F, Bartelds AI, van Duynhoven YT (2001). Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. *Am J Epidemiol* **154:** 666-74.

de Wit MA, Koopmans MP, Kortbeek LM, van Leeuwen NJ, Bartelds AI, van Duynhoven YT (2001a). Gastroenteritis in sentinel general practices, The Netherlands. *Emerg Infect Dis.* **7(1):** 82-91.

de Wit MA, Koopmans MP, Kortbeek LM, van Leeuwen NJ, Vinjé J, van Duynhoven YT (2001b). Etiology of gastroenteritis in sentinel general practices in The Netherlands. *Clin Infect Dis* **33(3):**280-8.

ANNEX: SUPPLEMENTARY RESULTS

Chapter 4 Annex

Chapter 4 Annex

Table A4.1: Distribution of IID2 Enumeration and GP Presentation practices by practice list size and number of GPs

	Enumeration Study		GP Presentation Study	
Variable	**Number of practices**	**%**	**Number of practices**	**%**
Practice list size				
<6,000 patients	8	20	14	38
6,000-9,999 patients	11	28	11	30
10,000+ patients	21	53	12	32
Number of GPs				
1	9	23	9	24
4	13	33	14	38
7	13	33	8	22
10+	5	13	6	16
Total	*40*		*37*	

Table A4.2: Age and sex distribution of Cohort Study participants compared with the UK census population

	IID2 Cohort			Comparison with UK census population					
				Males		Females		All persons	
Age group	Males	Females	All	Cohort	UK	Cohort	UK	Cohort	UK
<1 year	23	19	42	0.3%	0.6%	0.3%	0.5%	0.6%	1.1%
1-4 years	139	152	291	2.0%	2.5%	2.2%	2.3%	4.3%	4.8%
5-14 years	312	312	624	4.6%	6.6%	4.6%	6.3%	9.1%	13.0%
15-24 years	94	198	292	1.4%	6.2%	2.9%	6.1%	4.3%	12.3%
25-34 years	135	364	499	2.0%	7.0%	5.3%	7.3%	7.3%	14.2%
35-44 years	174	494	668	2.5%	7.4%	7.2%	7.6%	9.8%	14.9%
45-54 years	312	706	1,018	4.6%	6.6%	10.3%	6.7%	14.9%	13.2%
55-64 years	585	912	1,497	8.6%	5.2%	13.3%	5.4%	21.9%	10.6%
65+ years	902	1,003	1,905	13.2%	6.7%	14.7%	9.2%	27.9%	15.9%
All ages	*2,676*	*4,160*	*6,836*	*39.1%*	*48.6%*	*60.9%*	*51.4%*	*100.0%*	*100.0%*

Table A4.3: Distribution of Cohort Study participants by ethnic group, socioeconomic classification, area-level deprivation and urban-rural classification, compared with the UK population

	IID2 Cohort		UK
Variable	**No.**	**%**	**%**
Ethnic group			
White - British, Irish, Other	6,667	97.5%	92%
Mixed - White & Other	46	0.7%	1%
Asian/Asian British	80	1.2%	4%
Black/Black British	33	0.5%	2%
Chinese/Other	10	0.1%	1%
All	*6,836*	*100.0%*	*100%*
NS-SEC, 16-74 year-olds			
Managerial and professional occupations	2,692	52.2%	8%
Intermediate occupations	247	4.8%	18%
Small employers and own account workers	527	10.2%	9%
Lower supervisory and technical occupations	520	10.1%	7%
Semi-routine and routine occupations	374	7.2%	28%
Not classifiable for other reasons	799	15.5%	28%
All	*5,159*	*100.0%*	*100%*
Quintile of deprivation[a]			
1 (most deprived)	482	7.1%	20%
2	747	10.9%	20%
3	1,818	26.6%	20%
4	2,142	31.3%	20%
5 (least deprived)	1,644	24.1%	20%
All	*6,833*	*100.0%*	*100%*
Urban-rural classification[a]			
Urban area	4,075	59.6%	78%
Town	888	13.0%	11%
Rural area	1,870	27.4%	11%
All	*6,833*	*100.0%*	*100%*

[a] Information on area-level deprivation and urban-rural classification missing for 3 participants

Table A4.4: Number and percentage of Cohort Study participants choosing email and postcard follow-up

	Follow-up type				
Age group	**Email**	**%**	**Postcard**	**%**	**Total**
<1 year	28	67	14	33	42
1-4 years	231	79	60	21	291
5-14 years	501	80	123	20	624
15-24 years	243	83	49	17	292
25-34 years	440	88	59	12	499
35-44 years	527	79	141	21	668
45-54 years	760	75	258	25	1,018
55-64 years	950	64	547	37	1,497
65+ years	626	33	1,279	67	1,905
All ages	*4,306*	*63*	*2,530*	*37*	*6,836*

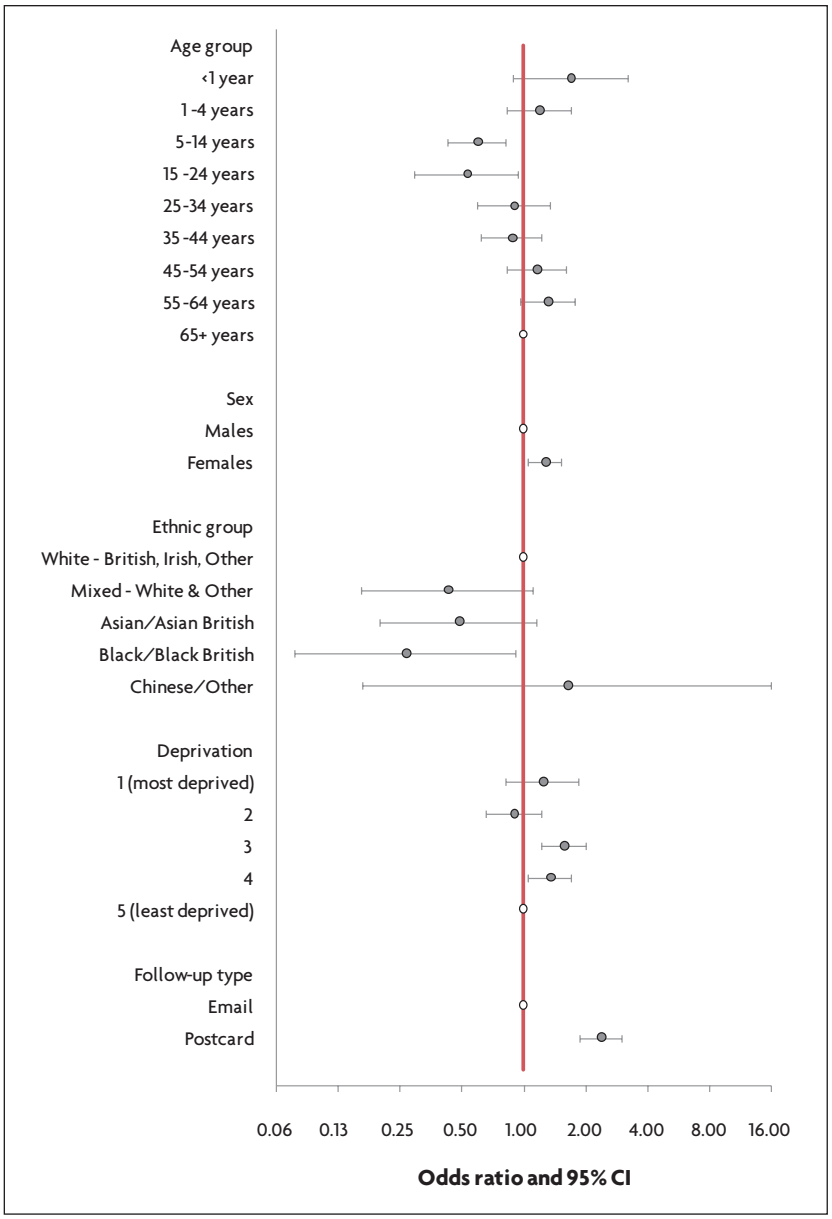
Table A4.5: Reasons for dropping out among IID2 Cohort participants

Drop-out reason	**No.**	**%**
Away for extended period	3	0.5
Deceased	10	1.6
Email problems	9	1.5
Health problems	38	6.2
Left practice	22	3.6
Moving away	7	1.1
No longer interested	13	2.1
No reason given	8	1.3
Non-response	474	77.7
Personal problems	10	1.6
Study too demanding	5	0.8
Too busy	4	0.7
Other	7	1.1
Total	*610*	*100*

Table A4.6: Factors associated with dropping out of the Cohort Study – Results from multivariable logistic regression (Each variable is adjusted for all the other variables in the model)

	All ages			16-74 years		
	OR	**(95% CI)**	**p**	**OR**	**(95% CI)**	**p**
Age group						
<1 year	1.48	(0.57 - 3.84)	0.423	--	--	--
1-4 years	1.64	(1.13 - 2.38)	0.009	--	--	--
5-14 years	1.51	(1.13 - 2.01)	0.005	--	--	--
15-24 years	1.44	(0.98 - 2.11)	0.064	1.59	(1 - 2.52)	0.051
25-34 years	0.69	(0.46 - 1.01)	0.059	0.96	(0.63 - 1.47)	0.850
35-44 years	1.11	(0.82 - 1.51)	0.481	1.56	(1.11 - 2.19)	0.011
45-54 years	0.77	(0.57 - 1.03)	0.073	1.07	(0.77 - 1.49)	0.689
55-64 years	0.82	(0.64 - 1.06)	0.133	1.12	(0.83 - 1.5)	0.466
65+ years	*1.00*	--	--	*1.00*	--	--
Ethnic group						
White - British, Irish, Other	*1.00*	--	--	*1.00*	--	--
Mixed - White & Other	1.52	(0.67 - 3.45)	0.320	1.62	(0.47 - 5.54)	0.443
Asian/Asian British	1.58	(0.85 - 2.95)	0.148	1.05	(0.41 - 2.71)	0.919
Black/Black British	2.36	(1 - 5.57)	0.051	3.58	(1.4 - 9.19)	0.008
Chinese/Other	3.30	(0.69 - 15.81)	0.136	1.94	(0.24 - 15.66)	0.536
Quintile of deprivation						
1 (most deprived)	2.05	(1.45 - 2.88)	<0.001	1.93	(1.26 - 2.98)	0.003
2	1.77	(1.31 - 2.4)	<0.001	1.44	(0.96 - 2.15)	0.077
3	1.51	(1.17 - 1.95)	0.002	1.62	(1.18 - 2.24)	0.003
4	1.32	(1.03 - 1.7)	0.028	1.43	(1.04 - 1.97)	0.027
5 (least deprived)	*1.00*	--	--	*1.00*	--	--
Urban-rural classification						
Urban area	*1.00*	--	--	*1.00*	--	--
Town	1.33	(1.04 - 1.71)	0.025	1.35	(1 - 1.83)	0.052
Rural area	0.94	(0.76 - 1.18)	0.609	0.89	(0.68 - 1.17)	0.394
NS-SEC						
Managerial and professional occupations	--	--	--	*1.00*	--	--
Intermediate occupations	--	--	--	1.06	(0.64 - 1.76)	0.829
Small employers and own account workers	--	--	--	0.99	(0.68 - 1.45)	0.959
Lower supervisory and technical occupations	--	--	--	1.59	(1.15 - 2.2)	0.005
Semi-routine and routine occupations	--	--	--	1.07	(0.71 - 1.62)	0.749
Not classifiable for other reasons	--	--	--	1.44	(1.08 - 1.92)	0.012

Figure A4.1: Factors associated with submitting a questionnaire among Cohort Study participants reporting symptoms of diarrhoea and/or vomiting – Odds ratios (ORs) and 95% CIs from multivariable logistic regression



For each factor, the white circles lying on the vertical line indicate the baseline comparison group. ORs >1 (to the right of the vertical line) indicate that individuals in that group were more likely to submit a questionnaire than individuals in the baseline comparison group; OR<1 (to the left of the vertical line) indicate that individuals in that group were less likely to submit a questionnaire than individuals in the baseline comparison group

Table A4.7: Age and sex structure of Telephone Survey participants compared with the UK census population

	England				Northern Ireland			
	Males		Females		Males		Females	
Age group[a]	Survey	Census	Survey	Census	Survey	Census	Survey	Census
<1	4		3		2		4	
(%)	(0.1)	(0.6)	(0.1)	(0.6)	(0.1)	(0.7)	(0.1)	(0.6)
1-4	39		26		37		45	
(%)	(1.1)	(2.5)	(0.7)	(2.4)	(1.1)	(2.9)	(1.3)	(2.7)
5-14	90		75		101		91	
(%)	(2.5)	(6.6)	(2.1)	(6.3)	(3.0)	(7.8)	(2.7)	(7.4)
15-24	76		104		124		141	
(%)	(2.1)	(6.1)	(2.9)	(6.0)	(3.6)	(7.2)	(4.1)	(7.0)
25-34	105		167		99		176	
(%)	(2.9)	(7.0)	(4.6)	(7.3)	(2.9)	(7.1)	(5.2)	(7.3)
35-44	162		270		176		276	
(%)	(4.5)	(7.4)	(7.4)	(7.5)	(5.2)	(7.2)	(8.1)	(7.5)
45-54	201		348		227		379	
(%)	(5.5)	(6.6)	(9.6)	(6.7)	(6.7)	(5.9)	(11.1)	(6.0)
55-64	279		448		234		469	
(%)	(7.7)	(5.2)	(12.4)	(5.3)	(6.9)	(4.7)	(13.8)	(4.9)
65+	448		780		283		543	
(%)	(12.4)	(6.7)	(21.5)	(9.2)	(8.3)	(5.4)	(15.9)	(7.8)
Total	*1,404*		*2,221*		*1,283*		*2,124*	
(%)	*(38.7)*	*(48.7)*	*(61.3)*	*(51.3)*	*(37.7)*	*(48.7)*	*(62.3)*	*(51.3)*

	Scotland				Wales			
	Males		Females		Males		Females	
Age group[a]	Survey	Census	Survey	Census	Survey	Census	Survey	Census
<1	0		4		5		4	
(%)	(0.0)	(0.5)	(0.1)	(0.5)	(0.1)	(0.6)	(0.1)	(0.5)
1-4	36		20		35		47	
(%)	(1.1)	(2.3)	(0.6)	(2.2)	(0.8)	(2.4)	(1.1)	(2.3)
5-14	74		68		80		103	
(%)	(2.3)	(6.4)	(2.1)	(6.1)	(1.9)	(6.7)	(2.4)	(6.4)
15-24	71		68		81		114	
(%)	(2.2)	(6.3)	(2.1)	(6.2)	(1.9)	(6.1)	(2.6)	(6.1)
25-34	97		140		96		183	
(%)	(3.0)	(6.7)	(4.3)	(7.1)	(2.2)	(6.1)	(4.2)	(6.5)
35-44	133		217		186		310	
(%)	(4.1)	(7.5)	(6.6)	(7.9)	(4.3)	(6.9)	(7.2)	(7.2)
45-54	213		382		264		433	
(%)	(6.5)	(6.7)	(11.7)	(6.9)	(6.1)	(6.7)	(10.1)	(6.8)
55-64	282		414		373		546	
(%)	(8.6)	(5.2)	(12.7)	(5.6)	(8.7)	(5.6)	(12.7)	(5.8)
65+	359		686		550		896	
(%)	(11.0)	(6.4)	(21.0)	(9.5)	(12.8)	(7.3)	(20.8)	(10.1)
Total	*1,265*		*1,999*		*1670*		*2636*	
(%)	*(38.8)*	*(48.1)*	*(61.2)*	*(51.9)*	*(38.8)*	*(48.4)*	*(61.2)*	*(51.6)*

[a] Information on age/sex missing for 124 participants

Table A4.8: Distribution of ethnic group among Telephone Survey participants relative to the UK census population

	England		Northern Ireland		Scotland		Wales		Total	
Ethnic group[a]	**Survey**	**Census**	**Survey**	**Census**	**Survey**	**Census**	**Survey**	**Census**	**Survey[b]**	**Census**
White	3,489		3,402		3,232		4,249			
(%)	(96.0)	(90.9)	(99.4)	(99.3)	(98.6)	(98.0)	(98.7)	(98.1)	(96.4)	(92.2)
Asian or Asian British	46		7		15		16			
(%)	(1.3)	(4.6)	(0.2)	(0.2)	(0.5)	(1.1)	(0.4)	(0.8)	(1.1)	(3.9)
Black or Black British	37		3		7		8			
(%)	(1.0)	(2.3)	(0.1)	(0.1)	(0.2)	(0.2)	(0.2)	(0.2)	(0.9)	(1.9)
Mixed	27		6		11		11			
(%)	(0.7)	(1.3)	(0.2)	(0.2)	(0.3)	(0.2)	(0.3)	(0.5)	(0.7)	(1.1)
Other	36		6		14		22			
(%)	(1.0)	(0.9)	(0.2)	(0.3)	(0.4)	(0.5)	(0.5)	(0.3)	(0.9)	(0.8)
Total	*3,635*		*3,424*		*3,279*		*4,306*		*14,644*	
(%)	*(100.0)*	*(100.00)*	*(100.0)*	*(100.00)*	*(100.0)*	*(100.00)*	*(100.0)*	*(100.00)*	*(100.0)*	*(100.00)*

[a]Information on ethnic group missing for 82 participants; [b]Percentage weighted according to the relative size of the population in each country

Table A4.9: Distribution of household size among Telephone Survey participants compared with the UK census population

Number of people living in the household[a]	England		Northern Ireland		Scotland		Wales		Total	
	Survey	Census	Survey	Census	Survey	Census	Survey	Census	Survey*	Census
1	854		610		827		1,065			
(%)	(23.5)	(30.1)	(17.8)	(27.4)	(25.2)	(32.9)	(24.7)	(29.1)	(23.5)	(30.2)
2	1,500		1,088		1,347		1,793			
(%)	(41.3)	(34.2)	(31.8)	(28.1)	(41.1)	(33.1)	(41.5)	(34.4)	(41.0)	(33.9)
3	553		584		491		629			
(%)	(15.2)	(15.5)	(17.1)	(16.5)	(15.0)	(15.6)	(14.6)	(16.3)	(15.2)	(15.5)
4	496		590		429		580			
(%)	(13.6)	(13.4)	(17.3)	(15.2)	(13.1)	(12.9)	(13.4)	(13.4)	(13.7)	(13.4)
5	170		330		142		173			
(%)	(4.7)	(4.9)	(9.7)	(8.0)	(4.3)	(4.3)	(4.0)	(5.0)	(4.8)	(5.0)
6	44		140		23		52			
(%)	(1.2)	(1.5)	(4.1)	(3.5)	(0.7)	(1.0)	(1.2)	(1.3)	(1.2	(1.5)
7	10		52		9		18			
(%)	(0.3)	(0.3)	(1.5)	(0.9)	(0.3)	(0.2)	(0.4)	(0.3)	(0.3)	(0.3)
8+	7		25		9		6			
(%)	(0.2)	(0.2)	(0.7)	(0.5)	(0.3)	(0.1)	(0.1)	(0.1)	(0.2)	(0.2)
Total	*3,634*		*3,419*		*3,277*		*4,316*		*14,646*	
(%)	*(100.0)*	*(100.0)*	*(100.0)*	*100.0)*	*(100.0)*	*(100.0)*	*(100.0)*	*(100.0)*	*(100.0)*	*(100.0)*

[a]Information on household size missing for 80 participants ; [b]Percentage weighted according to the relative size of the population in each country

Table A4.10: Distribution of area-level deprivation among Telephone Survey participants compared with the UK census population

IMD quintile[a]	England	Northern Ireland	Scotland	Wales	Total[b]
1 (most deprived)	272	318	263	471	
(%)	(9.9%)	(11.7%)	(10.2%)	(13.7%)	(10.2%)
2	398	627	512	680	
(%)	(14.5%)	(23.0%)	(19.8%)	(19.8%)	(15.4%)
3	672	759	658	860	
(%)	(24.4%)	(27.8%)	(25.4%)	(25.0%)	(24.7%)
4	694	602	668	799	
(%)	(25.2%)	(22.1%)	(25.8%)	(23.2%)	(25.1%)
5 (least deprived)	713	423	486	632	
(%)	(25.9%)	(15.5%)	(18.8%)	(18.4%)	(24.6%)
Total	*2,749*	*2,729*	*2,587*	*3,442*	*11,507*
(%)	*(100.0%)*	*(100.0%)*	*(100.0%)*	*(100.0%)*	*(100.0%)*

[a]Each IMD quintile comprises approximately 20% of the population in each country, information IMD quintile missing for 3,219 participants; [b]Percentage weighted according to the relative size of the population in each country

Table A4.11: Distribution of urban-rural classification among Telephone Survey participants compared with the UK census population

	England		NI		Scotland		Wales		UK[a]	
Area[a]	**Survey**	**Census**	**Survey**	**Census**	**Survey**	**Census**	**Survey**	**Census**	**Survey**	**Census**
Rural area	672		1,579		880		1,068			
(%)	(24.3)	(9.4)	(57.9)	(34.9)	(34.0)	(18.7)	(30.7)	(17.2)	(26.4)	(11.3)
Town	463		634		444		663			
(%)	(16.8)	(9.6)	(23.2)	(25.3)	(17.2)	(13.1)	(19.0)	(17.9)	(17.1)	(10.7)
Urban area	1,627		516		1,263		1,753			
(%)	(58.9)	(81.1)	(18.9)	(39.8)	(48.8)	(68.3)	(50.3)	(65.0)	(56.5)	(78.0)
Total	*2,762*		*2,729*		*2,587*		*3,484*		*11,562*	
(%)	*(100.0)*		*(100.0)*		*(100.0)*		*(100.0)*		*(100.0)*	

[a]Information on urban-rural classification missing for 3,164 participants; [b]Average weighted for the relative size of the population of each UK country

Table A4.12: Percentage of definite cases with specimens requested by age group – GP Enumeration Study

Age group	Specimen requested	%	Specimen not requested	Not known	Total
0-4 years	323	23	791	278	1,392
5-14 years	94	19	319	94	507
15-24 years	82	19	256	85	423
25-34 years	128	26	293	67	488
35-44 years	123	30	228	55	406
45-54 years	111	37	138	48	297
55-64 years	125	42	120	56	301
65+ years	188	33	268	116	572
Not known	0	0	0	2	2
All ages	*1,174*	*27*	*2,413*	*801*	*4,388*

Table A4.13: Percentage of specimens submitted among definite cases with specimens requested – GP Enumeration Study

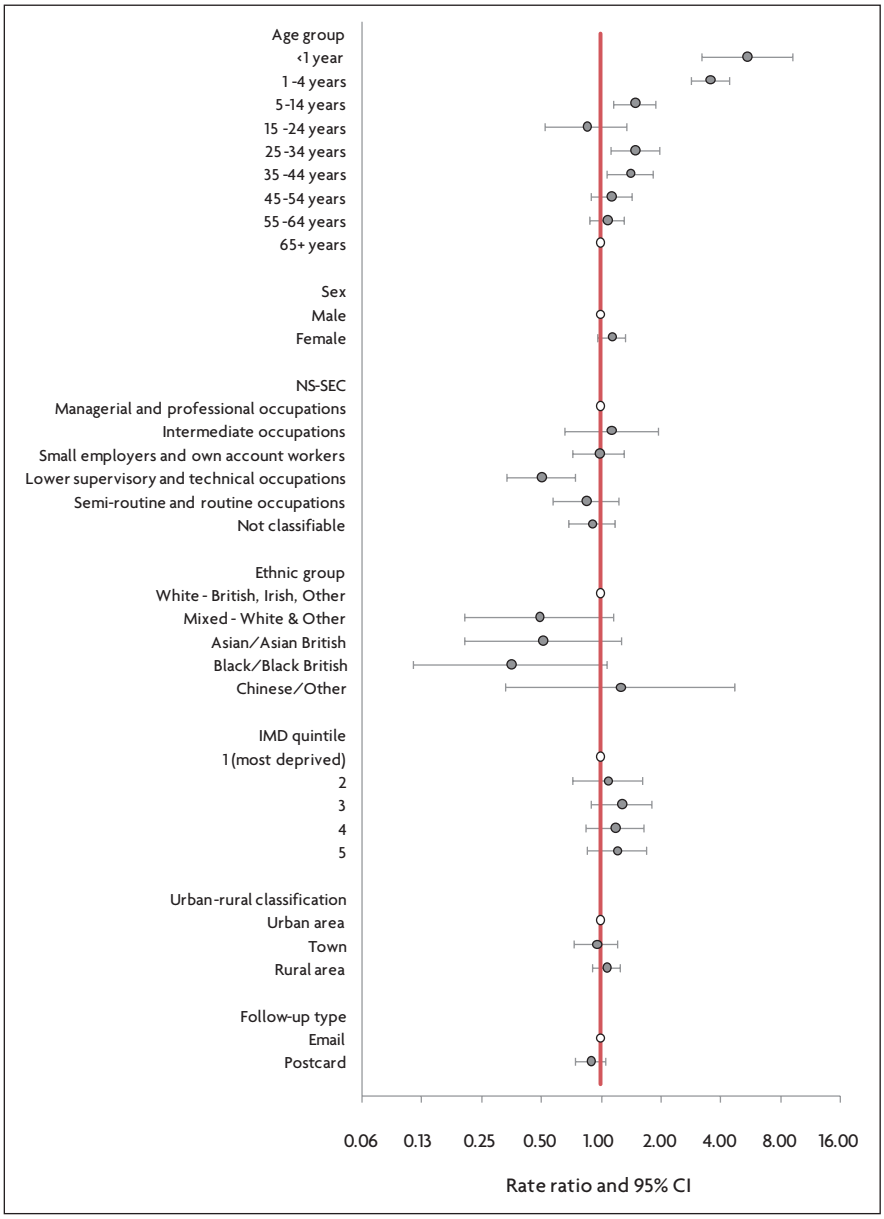
Age group	Specimen submitted	%	Specimen not submitted	Not known	Total
0-4 years	116	36	30	177	323
5-14 years	33	35	14	47	94
15-24 years	24	29	14	44	82
25-34 years	49	38	19	60	128
35-44 years	41	33	12	70	123
45-54 years	38	34	9	64	111
55-64 years	42	34	8	75	125
65+ years	57	30	11	120	188
All ages	*400*	*34*	*117*	*657*	*1,174*

Table A4.14: Percentage of cases with a recorded microbiological result among definite cases known to have submitted a specimen – GP Enumeration Study

Age group	Positive result recorded	%	Negative / No result recorded	Total
0-4 years	70	60	46	116
5-14 years	24	73	9	33
15-24 years	17	71	7	24
25-34 years	34	69	15	49
35-44 years	30	73	11	41
45-54 years	30	79	8	38
55-64 years	32	76	10	42
65+ years	46	81	11	57
All ages	*283*	*71*	*117*	*400*

Chapter 5 Annex

Figure A5.1: Variation in rates of IID in the Cohort Study – Rate ratios (RRs) and 95% confidence intervals



For each factor, the white circles lying on the vertical line indicate the baseline comparison group. RRs >1 (to the right of the vertical line) indicate that the rate in that group was higher than in the baseline comparison group; RRs <1 (to the left of the vertical line) indicate that the rate among individuals in that group was lower than in the baseline comparison group. RRs for NS-SEC, Ethnic group, IMD quintile, Urban-rural classification and Follow-up type are adjusted for age group and sex

Figure A5.2: Incidence rates of IID in the community cohort by time in study

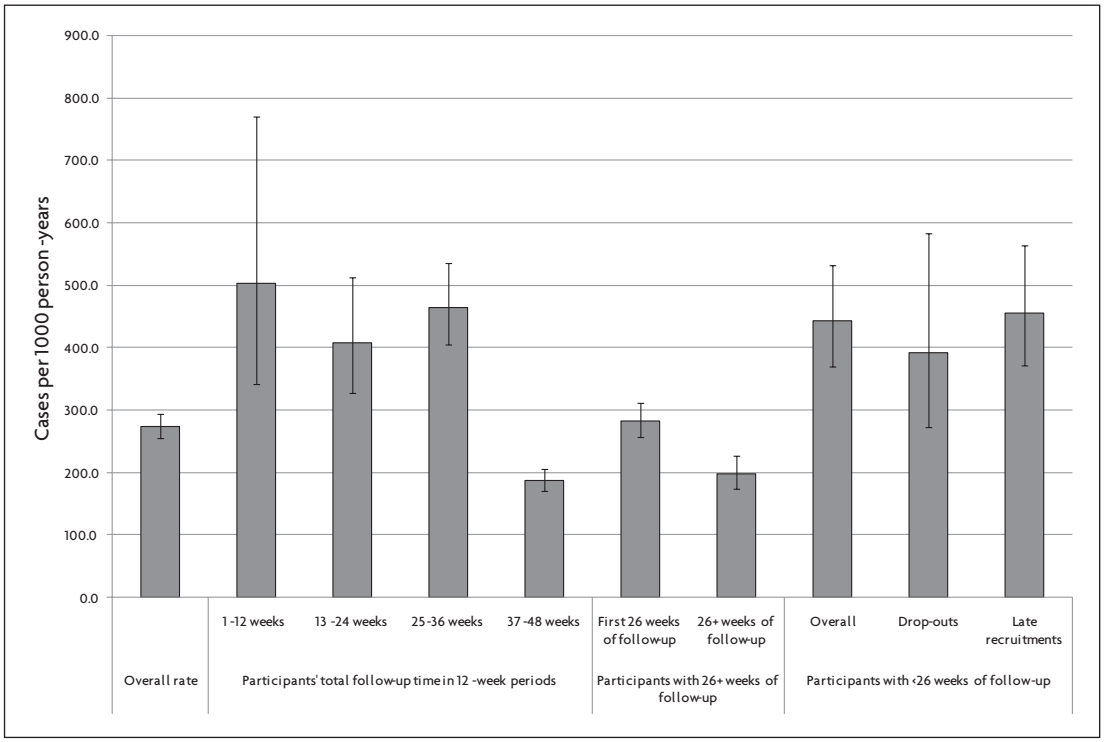


Figure A5.3: Incidence rate of IID in the community cohort by participants' week of follow-up

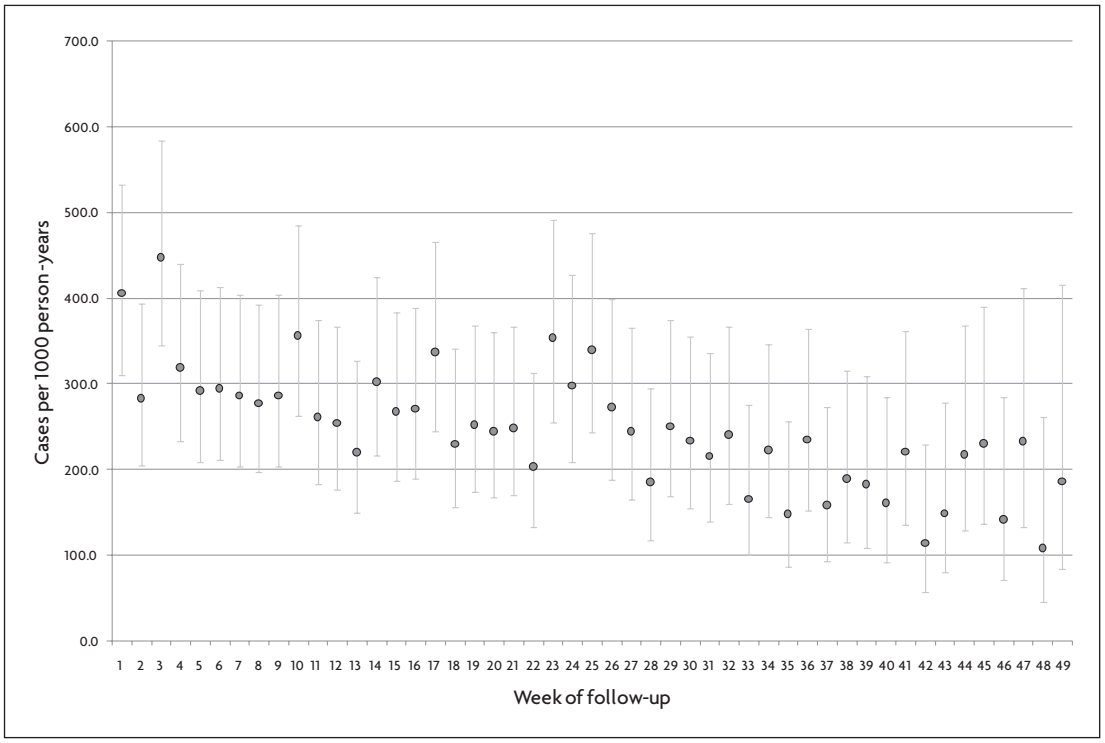


Table A5.1: Incidence rate of overall IID in the Telephone Survey by recall period and household size

	7- day recall		28-day recall	
Household size	**Rate[a]**	**(95% CI)**	**Rate[a]**	**(95% CI)**
1	1,486.4	(911.6 - 2,591.7)	353.3	(166.0 - 882.9)
2	1,395.9	(815.5 - 2,594.6)	506.2	(271.5 - 1,050.8)
3	1,565.1	(925.7 - 2,854.8)	371.7	(176.3 - 901.3)
4	2,025.0	(947.5 - 5,135.1)	889.5	(447.7 - 1,996.8)
5+	909.3	(405.7 - 2,456.2)	377.4	(91.4 - 2,612.2)

[a]Cases per 1,000 person-years

Table A5.2: Incidence rate of overall IID in the Telephone Survey by recall period and area-level deprivation

	7- day recall		28-day recall	
IMD quintile	**Rate[a]**	**(95% CI)**	**Rate[a]**	**(95% CI)**
1 (most deprived)	1,043.7	(502.3 - 2,509.8)	494.0	(170.8 - 1,829.9)
2	2,224.2	(561.1 - 15,778.0)	286.2	(91.7 - 1,254.9)
3	1,428.9	(652.8 - 3,735.6)	747.7	(351.7 - 1,866.3)
4	1,605.8	(1,052.4 - 2,567.6)	752.0	(388.7 - 1,614.6)
5 (least deprived)	1,994.0	(1,182.3 - 3,632.9)	178.1	(53.3 - 903.4)

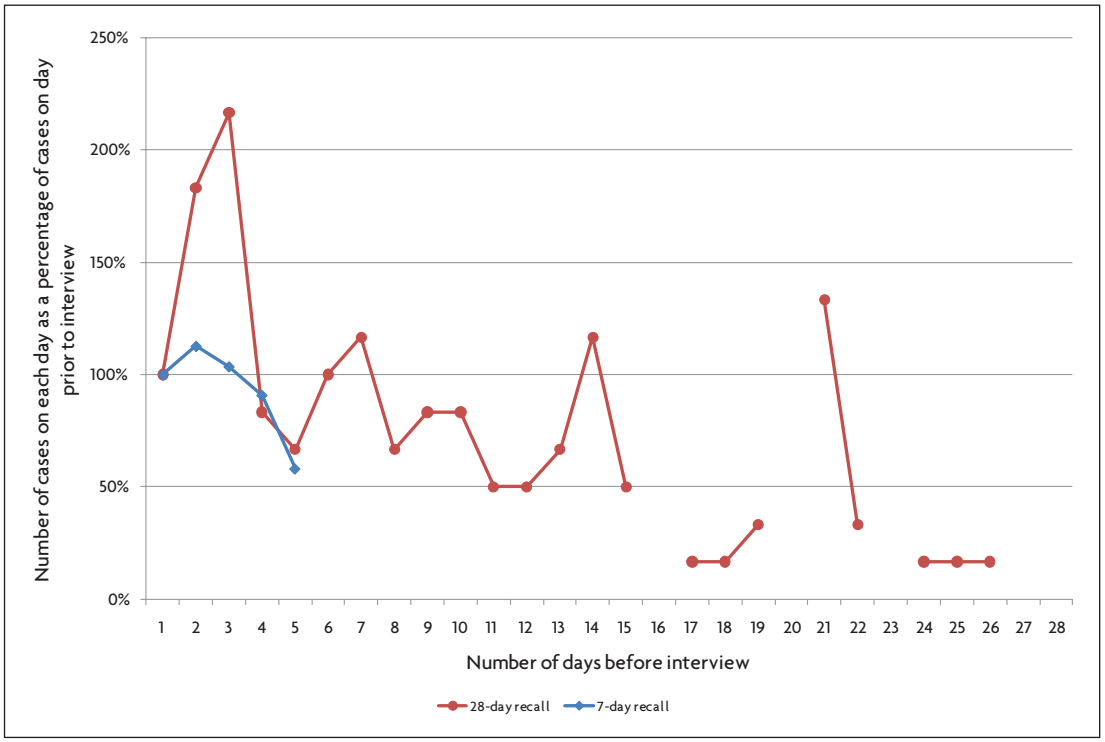
[a]Cases per 1,000 person-years

Table A5.3: Incidence rate of overall IID in the Telephone Survey by recall period and urban-rural classification

	7- day recall		28-day recall	
Area	**Rate[a]**	**(95% CI)**	**Rate[a]**	**(95% CI)**
Rural	1,087.5	(668.8 - 1,882.9)	786.0	(405.9 - 1,717.3)
Town	1,965.9	(1,086.0 - 3,925.1)	432.9	(174.3 - 1,341.6)
Urban	1,859.7	(1,149.3 - 3,217.8)	365.7	(209.6 - 689.0)

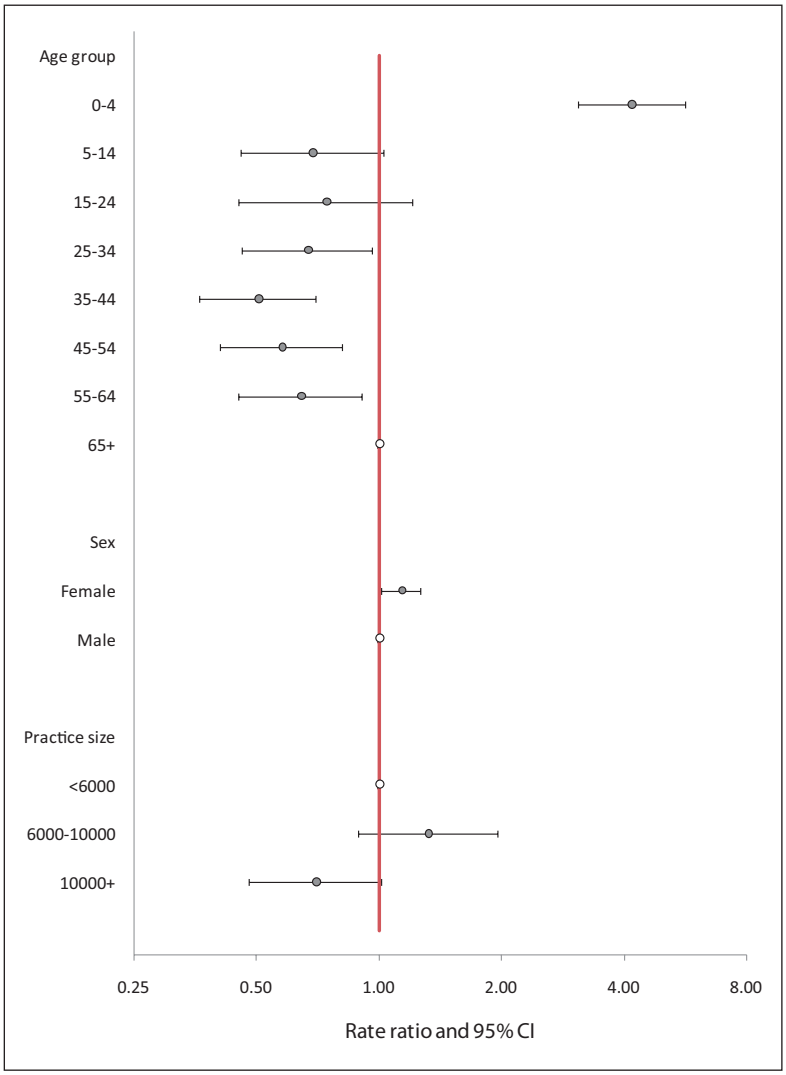
[a]Cases per 1,000 person-years

Figure A5.4: Decay in the reporting of symptoms among Telephone Survey participants by recall group



Each data point represents the number of participants reporting onset of symptoms on each day prior to the date of interview, expressed as a percentage of cases with onset on the day prior to interview

Figure A5.5: Variation in rates of IID in the GP Presentation Study – Rate ratios and 95% CIs



For each factor, the white circles lying on the vertical line indicate the baseline comparison group. RRs >1 (to the right of the vertical line) indicate that the rate in that group was higher than in the baseline comparison group; RRs <1 (to the left of the vertical line) indicate that the rate among individuals in that group was lower than in the baseline comparison group. RRs for each factor are adjusted for all the other factors

Table A5.4: Number and percentage of definite IID cases reporting having travelled outside the UK in the 10 days prior to illness onset by age group – Cohort Study

Age group	UK case	Travel case	%	Total
<1 year	29	3	9	32
1-4 years	136	1	1	137
5-14 years	126	3	2	129
15-24 years	20	3	13	23
25-34 years	78	5	6	83
35-44 years	136	16	11	152
45-54 years	168	25	13	193
55-64 years	241	30	11	271
65+ years	267	17	6	284
All ages	*1,201*	*103*	*8*	*1,304*

Table A5.5: Number and percentage of definite IID cases reporting having travelled outside the UK in the 10 days prior to illness onset by age group – GP Presentation Study

Age group	UK case	Travel case	%	Total
<1 year	74	3	4	77
1-4 years	141	5	3	146
5-14 years	83	6	7	89
15-24 years	63	13	17	76
25-34 years	95	19	17	114
35-44 years	102	23	18	125
45-54 years	96	27	22	123
55-64 years	122	17	12	139
65+ years	215	27	11	242
All ages	*991*	*140*	*12*	*1,131*

Table A5.6: Incidence rate of putatively travel-related IID by age group – Cohort Study

Age group	Rate[a]	(95% CI)
<1	104.2	(32.7 - 501.3)
1-4	5.6	(1.9 - 2.2)
5-14	7.0	(2.2 - 34.4)
15-24	16.6	(5.2 - 81.5)
25-34	15.3	(6.4 - 45.5)
35-44	36.9	(21.5 - 68.9)
45-54	34.8	(23.1 – 55.0)
55-64	26.1	(18.3 - 38.5)
65+	12.4	(7.8 – 21.0)
All ages	*22.0*	*(17.5 – 28.0)*

[a]Cases per 1,000 person-years; Only definite IID cases who reported having travelled outside the UK in the 10 days prior to illness onset are included in the numerator.

Chapter 6 Annex

Table A6.1: Microbiological findings among cohort cases, under 5 years

Pathogen	Test	No. identified	Tested	% identified	(95% CI)
Bacteria					
C. difficile[a]	All	0	64	0.0%	(0% - 5.6%)
	EIA	*0*	*64*	*0.0%*	*(0% - 5.6%)*
	PCR	*0*	*63*	*0.0%*	*(0% - 5.7%)*
C. perfringens	Culture	0	118	0.0%	(0% - 3.1%)
Campylobacter	All	2	120	1.7%	(0.2% - 5.9%)
	All culture	*2*	*117*	*1.7%*	*(0.2% - 6%)*
	Direct culture	*2*	*117*	*1.7%*	*(0.2% - 6%)*
	Enrichment	*2*	*117*	*1.7%*	*(0.2% - 6%)*
	PCR	*2*	*120*	*1.7%*	*(0.2% - 5.9%)*
E. coli O157 VTEC	Culture	0	117	0.0%	(0% - 3.1%)
E. coli non-O157 VTEC	Culture	0	120	0.0%	(0% - 3.0%)
Enteroaggregative *E. coli*	PCR	6	120	5.0%	(1.9% - 10.6%)
Listeria	Culture and/or PCR	0	117	0.0%	(0% - 3.1%)
Salmonella	All	0	120	0.0%	(0% - 3%)
	Culture	*0*	*117*	*0.0%*	*(0% - 3.1%)*
	PCR	*0*	*120*	*0.0%*	*(0% - 3%)*
Shigella	Culture	0	117	0.0%	(0% - 3.1%)
Yersinia	All culture	0	117	0.0%	(0% - 3.1%)
	Direct culture	*0*	*117*	*0.0%*	*(0% - 3.1%)*
	Enrichment	*0*	*117*	*0.0%*	*(0% - 3.1%)*
Protozoa					(0% - 0%)
Cryptosporidium	All	2	120	1.7%	(0.2% - 5.9%)
	EIA	*2*	*117*	*1.7%*	*(0.2% - 6%)*
	PCR	*2*	*120*	*1.7%*	*(0.2% - 5.9%)*
Cyclospora	Microscopy	0	117	0.0%	(0% - 3.1%)
Giardia	All	1	120	0.8%	(0% - 4.6%)
	EIA	*1*	*117*	*0.9%*	*(0% - 4.7%)*
	PCR	*1*	*120*	*0.8%*	*(0% - 4.6%)*
Viruses					(0% - 0%)
Adenovirus	ELISA[b]	5	104	4.8%	(1.6% - 10.9%)
	ELISA and/or PCR[b]	10	120	8.3%	(4.1% - 14.8%)
Astrovirus	PCR	10	120	8.3%	(4.1% - 14.8%)
Norovirus	PCR	24	120	20.0%	(13.3% - 28.3%)
Rotavirus	ELISA[b]	11	104	10.6%	(5.4% - 18.1%)
	ELISA and/or PCR[b]	12	120	10.0%	(5.3% - 16.8%)
Sapovirus	PCR	22	120	18.3%	(11.9% - 26.4%)
No pathogen identified		48	120	40.0%	(31.2% - 49.3%)

[a] Only specimens from cases aged 2 years and above were tested for *C. difficile*

[b] ELISA for adenovirus and rotavirus was conducted in specimens from cases aged <5 years

Table A6.2: Microbiological findings among cohort cases, 5+ years

Pathogen	Test	No. identified	Tested	% positive	(95% CI)
Bacteria					
C. difficile[a]	All	1	651	0.2%	(0% - 0.9%)
	EIA	*0*	*651*	*0.0%*	*(0% - 0.6%)*
	PCR	*1*	*630*	*0.2%*	*(0% - 0.9%)*
C. perfringens	Culture	6	654	0.9%	(0.3% - 2%)
Campylobacter	All	34	662	5.1%	(3.6% - 7.1%)
	All culture	*26*	*650*	*4.0%*	*(2.6% - 5.8%)*
	Direct culture	*16*	*649*	*2.5%*	*(1.4% - 4%)*
	Enrichment	*25*	*649*	*3.9%*	*(2.5% - 5.6%)*
	PCR	*29*	*662*	*4.4%*	*(3% - 6.2%)*
E. coli O157 VTEC	Culture	1	651	0.2%	(0% - 0.9%)
E. coli non-O157 VTEC	Culture	6	661	0.9%	(0.3% - 2.0%)
Enteroaggregative *E. coli*	PCR	9	662	1.4%	(0.6% - 2.6%)
Listeria	Culture and/or PCR	0	652	0.0%	(0% - 0.6%)
Salmonella	All	2	662	0.3%	(0% - 1.1%)
	Culture	*2*	*651*	*0.3%*	*(0.% - 1.1%)*
	PCR	*1*	*662*	*0.2%*	*(0% - 0.8%)*
Shigella	Culture	0	651	0.0%	(0% - 0.6%)
Yersinia	All culture	0	652	0.0%	(0% - 0.6%)
	Direct culture	0	652	0.0%	(0% - 0.6%)
	Enrichment	0	652	0.0%	(0% - 0.6%)
Protozoa					
Cryptosporidium	All	1	662	0.2%	(0% - 0.8%)
	EIA	*0*	*651*	*0.0%*	*(0% - 0.6%)*
	PCR	*1*	*662*	*0.2%*	*(0% - 0.8%)*
Cyclospora	Microscopy	0	651	0.0%	(0% - 0.6%)
Giardia	All	5	662	0.8%	(0.2% - 1.8%)
	EIA	*2*	*651*	*0.3%*	*(0% - 1.1%)*
	PCR	*5*	*662*	*0.8%*	*(0.2% - 1.8%)*
Viruses					
Adenovirus	ELISA and/or PCR[b]	18	662	2.7%	(1.6% - 4.3%)
Astrovirus	PCR	4	662	0.6%	(0.2% - 1.5%)
Norovirus	PCR	105	662	15.9%	(13.2% - 18.9%)
Rotavirus	ELISA and/or PCR[b]	20	662	3.0%	(1.9% - 4.6%)
Sapovirus	PCR	50	662	7.6%	(5.7% - 9.8%)
No pathogen identified		423	662	63.9%	(60.1% - 67.6%)

[a] Only specimens from cases aged 2 years and above were tested for *C. difficile*
[b] ELISA for adenovirus and rotavirus was conducted in specimens from cases aged <5 years

Table A6.3: Microbiological findings among GP Presentation cases, under 5 years

Pathogen	Test	No. identified	Tested	% positive	(95% CI)
Bacteria					
C. difficile[a]	All	0	62	0.0%	(0% - 5.8%)
	EIA	*0*	*62*	*0.0%*	*(0% - 5.8%)*
	PCR	*0*	*62*	*0.0%*	*(0% - 5.8%)*
C. perfringens	Culture	2	192	1.0%	(0.1% - 3.7%)
Campylobacter	All	10	192	5.2%	(2.5% - 9.4%)
	All culture	*5*	*191*	*2.6%*	*(0.9% - 6%)*
	Direct culture	*4*	*191*	*2.1%*	*(0.6% - 5.3%)*
	Enrichment	*5*	*191*	*2.6%*	*(0.9% - 6%)*
	PCR	*10*	*192*	*5.2%*	*(2.5% - 9.4%)*
E. coli O157 VTEC	Culture	0	191	0.0%	(0% - 1.9%)
E. coli non-O157 VTEC	Culture	1	191	0.0%	(0% - 1.9%)
Enteroaggregative *E. coli*	PCR	2	192	1.0%	(0.1% - 3.7%)
Listeria	Culture and/or PCR	0	191	0.0%	(0% - 1.9%)
Salmonella	All	1	192	0.5%	(0% - 2.9%)
	Culture	*1*	*191*	*0.5%*	*(0% - 2.9%)*
	PCR	*1*	*192*	*0.5%*	*(0% - 2.9%)*
Shigella		0	191	0.0%	(0% - 1.9%)
Yersinia	All culture	1	191	0.5%	(0% - 2.9%)
	Direct culture	*0*	*191*	*0.0%*	*(0% - 1.9%)*
	Enrichment	*1*	*191*	*0.5%*	*(0% - 2.9%)*
Protozoa					
Cryptosporidium	All	2	192	1.0%	(0.1% - 3.7%)
	EIA	*2*	*190*	*1.1%*	*(0.1% - 3.8%)*
	PCR	*2*	*192*	*1.0%*	*(0.1% - 3.7%)*
Cyclospora	Microscopy	0	188	0.0%	(0% - 1.9%)
Giardia	All	2	192	1.0%	(0.1% - 3.7%)
	EIA	*1*	*190*	*0.5%*	*(0% - 2.9%)*
	PCR	*2*	*192*	*1.0%*	*(0.1% - 3.7%)*
Viruses					
Adenovirus	ELISA[b]	9	189	4.8%	(2.2% - 8.8%)
	ELISA and/orPCR[b]	15	192	7.8%	(4.4% - 12.6%)
Astrovirus	PCR	10	192	5.2%	(2.5% - 9.4%)
Norovirus	PCR	37	192	19.3%	(13.9% - 25.6%)
Rotavirus	ELISA[b]	27	189	14.3%	(9.6% - 20.1%)
	ELISA and/or PCR[b]	36	192	18.8%	(13.5% - 25%)
Sapovirus	PCR	21	192	10.9%	(6.9% - 16.2%)
No pathogen identified		70	192	36.5%	(29.6% - 43.7%)

[a] Only specimens from cases aged 2 years and above were tested for *C. difficile*
[b] ELISA for adenovirus and rotavirus was conducted in specimens from cases aged <5 years

Table A6.4: Microbiological findings among GP Presentation cases, 5+ years

Pathogen	Test	No. identified	Tested	% positive	(95% CI)
Bacteria					
C. difficile[a]	All	10	676	1.5%	(0.7% - 2.7%)
	EIA	*1*	*674*	*0.1%*	*(0% - 0.8%)*
	PCR	*9*	*657*	*1.4%*	*(0.6% - 2.6%)*
C. perfringens	Culture	17	676	2.5%	(1.5% - 4%)
Campylobacter	All	104	682	15.2%	(12.6% - 18.2%)
	All culture	*64*	*675*	*9.5%*	*(7.4% - 11.9%)*
	Direct culture	*44*	*675*	*6.5%*	*(4.8% - 8.7%)*
	Enrichment	*60*	*672*	*8.9%*	*(6.9% - 11.3%)*
	PCR	*95*	*682*	*13.9%*	*(11.4% - 16.8%)*
E. coli O157 VTEC	Culture	1	675	0.1%	(0% - 0.8%)
E. coli non-O157 VTEC	Culture	6	681	0.9%	(0.3% - 1.9%)
Enteroaggregative *E. coli*	PCR	10	682	1.5%	(0.7% - 2.7%)
Listeria	Culture and/or PCR	0	674	0.0%	(0% - 0.5%)
Salmonella	All	6	682	0.9%	(0.3% - 1.9%)
	Culture	*6*	*675*	*0.9%*	*(0.3% - 1.9%)*
	PCR	*5*	*682*	*0.7%*	*(0.2% - 1.7%)*
Shigella	Culture	0	675	0.0%	(0% - 0.5%)
Yersinia	All culture	0	675	0.0%	(0% - 0.5%)
	Direct culture	*0*	*675*	*0.0%*	*(0% - 0.5%)*
	Enrichment	*0*	*670*	*0.0%*	*(0% - 0.5%)*
Protozoa					
Cryptosporidium	All	10	682	1.5%	(0.7% - 2.7%)
	EIA	*7*	*673*	*1.0%*	*(0.4% - 2.1%)*
	PCR	*10*	*682*	*1.5%*	*(0.7% - 2.7%)*
Cyclospora	Microscopy	0	673	0.0%	(0% - 0.5%)
Giardia	All	7	682	1.0%	(0.4% - 2.1%)
	EIA	*5*	*673*	*0.7%*	*(0.2% - 1.7%)*
	PCR	*7*	*682*	*1.0%*	*(0.4% - 2.1%)*
Viruses					
Adenovirus	ELISA and/or PCR[b]	15	682	2.2%	(1.2% - 3.6%)
Astrovirus	PCR	12	682	1.8%	(0.9% - 3.1%)
Norovirus	PCR	71	682	10.4%	(8.2% - 12.9%)
Rotavirus	ELISA and/or PCR[b]	28	682	4.1%	(2.7% - 5.9%)
Sapovirus	PCR	56	682	8.2%	(6.3% - 10.5%)
No pathogen identified		355	682	52.1%	(48.2% - 55.9%)

[a] Only specimens from cases aged 2 years and above were tested for *C. difficile*

[b] ELISA for adenovirus and rotavirus was conducted in specimens from cases aged <5 years

Table A6.5: Factors associated with a negative stool specimen – Prospective Cohort Study

Variable	OR	(95% CI)	p
Age group			
<1 year	0.12	(0.03 - 0.44)	0.001
1-4 years	0.34	(0.17 - 0.67)	0.002
5-14 years	0.73	(0.3 - 1.79)	0.494
15-24 years	--	--	--
25-34 years	0.84	(0.34 - 2.07)	0.707
35-44 years	1.52	(0.76 - 3.07)	0.239
45-54 years	0.99	(0.54 - 1.81)	0.963
55-64 years	0.69	(0.4 - 1.21)	0.199
65+ years	*1.00*	--	--
Vomiting			
Yes	*1.00*	--	--
No	4.26	(2.73 - 6.65)	<0.001
Loss of appetite			
Yes	*1.00*	--	--
No	2.44	(1.56 - 3.81)	<0.001
Not sure	1.85	(0.61 - 5.59)	0.273
Absence from work/school			
Yes	*1.00*	--	--
No	1.73	(1.13 - 2.66)	0.012
Not sure	1.81	(0.33 - 9.91)	0.495
Diarrhoea present at time of questionnaire completion			
Yes	*1.00*	--	--
No	1.54	(1.01 - 2.37)	0.046
Not sure	2.36	(1.18 - 4.74)	0.015

Table A6.6: Factors associated with negative stool specimens - GP Presentation Study

	All ages			16+ years		
Variable	OR	(95% CI)	p	OR	(95% CI)	p
Age group						
<1 year	0.92	(0.4 – 2.15)	0.852			
1-4 years	0.60	(0.32 – 1.12)	0.108			
5-14 years	1.17	(0.62 – 2.23)	0.628			
15-24 years	1.59	(0.76 – 3.32)	0.221			
25-34 years	1.57	(0.87 – 2.86)	0.138			
35-44 years	1.29	(0.73 – 2.29)	0.380			
45-54 years	1.32	(0.75 – 2.31)	0.332			
55-64 years	1.41	(0.85 – 2.34)	0.186			
65+ years	*1.00*	--	--			
Sex						
Female	*1.00*	--	--			
Male	0.66	(0.48 – 0.9)	0.008			
Loss of appetite						
Yes	*1.00*	--	--	*1.00*	--	--
No	2.71	(1.76 – 4.2)	<0.001	3.25	(1.91 – 5.52)	<0.001
Not sure	2.01	(0.56 – 7.22)	0.286	3.92	(0.77 – 19.95)	0.100
Vomiting						
Yes	*1.00*	--	--			
No	1.95	(1.41 – 2.71)	<0.001			
Not sure	3.85	(0.2 – 73.78)	0.371			
Headache						
Yes	*1.00*	--	--	*1.00*	--	--
No	1.53	(1.08 – 2.15)	0.016	1.44		0.050
Not sure	1.08	(0.53 – 2.18)	0.841	6.38	(0.7 – 58.28)	0.101
Diarrhoea present at time questionnaire completion						
Yes	*1.00*	--	--			
No	1.55	(1.11 - 2.15)	0.009			
Not sure	0.68	(0.38 - 1.23)	0.201			
Delay between onset and specimen collection						
0-3 days	*1.00*	--	--	*1.00*	--	--
4-6 days	0.95	(0.63 - 1.45)	0.815	0.98	(0.61 - 1.57)	0.922
7-9 days	1.13	(0.72 - 1.77)	0.587	1.30	(0.78 - 2.17)	0.308
10+ days	1.77	(1.1 - 2.84)	0.019	2.74	(1.58 - 4.76)	<0.001
NS-SEC[a]						
Managerial and professional occupations				*1.00*	--	--
Intermediate occupations				2.85	(1.37 - 5.95)	0.005
Small employers and own account workers				2.03	(1.12 - 3.65)	0.019
Lower supervisory and technical occupations				1.47	(0.84 - 2.58)	0.179
Semi-routine and routine occupations				2.54	(1.41 - 4.56)	0.002
Not classifiable for other reasons				1.65	(0.98 - 2.78)	0.059

[a] NS-SEC – National Statistics – Socioeconomic Classification

Table A6.7: Organisms occurring in dual infections among Prospective Cohort Study cases

Organism 1	Organism 2	Frequency
Adenovirus	Astrovirus	1
Adenovirus	*C. perfringens*	1
Adenovirus	Norovirus	5
Adenovirus	Rotavirus	1
Adenovirus	Sapovirus	2
Astrovirus	Rotavirus	1
Campylobacter	*E. coli* non-O157 VTEC	1
Norovirus	Astrovirus	2
Norovirus	*C. perfringens*	1
Norovirus	*E. coli* non-O157 VTEC	1
Norovirus	Enteroaggregative *E. coli*	2
Norovirus	*Giardia*	3
Rotavirus	*Giardia*	1
Sapovirus	Astrovirus	3
Sapovirus	*Campylobacter*	2
Sapovirus	Enteroaggregative *E. coli*	1
Sapovirus	Norovirus	3
Sapovirus	Rotavirus	2
Total		33

Table A6.8: Organisms occurring in triple infections among Prospective Cohort Study cases

Organism 1	Organism 2	Organism 3	Frequency
Norovirus	Sapovirus	Adenovirus	2
Sapovirus	*Campylobacter*	*E. coli* O157 VTEC	1
Adenovirus	*Campylobacter*	*C. perfringens*	1
Total			4

Table A6.9: Organisms occurring in dual infections among GP Presentation Study cases

Organism 1	Organism 2	Frequency
Sapovirus	Adenovirus	4
Sapovirus	*C. perfringens*	1
Sapovirus	*Campylobacter*	1
Sapovirus	*Giardia*	1
Sapovirus	Norovirus	3
Sapovirus	Rotavirus	3
Adenovirus	*Campylobacter*	3
Adenovirus	*Cryptosporidium*	1
Adenovirus	Norovirus	1
Adenovirus	Rotavirus	2
Campylobacter	Astrovirus	2
Campylobacter	*C. difficile*	3
Campylobacter	*Cryptosporidium*	1
Campylobacter	Enteroaggregative *E. coli*	1
Campylobacter	Norovirus	1
Norovirus	Astrovirus	2
Norovirus	*C. perfringens*	1
Norovirus	*E. coli* non-O157 VTEC	1
Norovirus	Enteroaggregative *E. coli*	1
Rotavirus	*C. perfringens*	1
Rotavirus	Enteroaggregative *E. coli*	1
C. perfringens	*C. difficile*	1
Total		36

Table A6.10: Organisms occurring in triple infections among GP Presentation Study cases

Organism 1	Organism 2	Organism 3	Frequency
Sapovirus	Adenovirus	*Cryptosporidium*	1
Sapovirus	Astrovirus	Enteroaggregative *E. coli*	1
Adenovirus	*Campylobacter*	*E. coli* non-O157 VTEC	1
Norovirus	Rotavirus	Enteroaggregative *E. coli*	1
Total			4

Table A6.11: Salmonella serotypes identified in Prospective Cohort Study cases

Serotype[a]	Frequency
Salmonella Szentes	1
Salmonella Bareilly	1
Total	*2*

[a]Excludes 1 *Salmonella* Paratyphi A

Table A6.12: Salmonella serotypes identified in GP Presentation Study cases

Serotype	Frequency
Salmonella Hadar	1
Salmonella Enteritidis PT1	1
Salmonella Enteritidis PT3	1
Salmonella Enteritidis PT8	2
Salmonella Typhimurium DT56	1
Salmonella unnamed (Group B)	1
Total	*7*

Table A6.13: Campylobacter species identified in Prospective Cohort Study cases

Species	Frequency
C. jejuni	30
C. coli	2
C. jejuni/C. coli mixed infection	3
Species not known	1
Total	*36*

Table A6.14: Campylobacter species identified in GP Presentation Study cases

Species	Frequency
C. jejuni	106
C. coli	6
C. jejuni/C. coli mixed infection	2
Total	*114*

Table A6.15: Norovirus genogroups identified in Prospective Cohort Study cases

Genotype	Frequency
Norovirus genogroup 1	11
Norovirus genogroup 2	118
Total	*129*

Table A6.16: Norovirus genogroups identified in GP Presentation Study cases

Genogroup	Frequency
Norovirus genogroup 1	4
Norovirus genogroup 2	104
Total	*108*

Table A6.17: E. coli subtypes identified in Prospective Cohort Study cases

Organism	Serotype	Phage type	VT genes	Frequency
E. coli O157	O157	PT8	VT1	1
E. coli non-O157	O8	Not determined	VT1	1
E. coli non-O157	O79	Not determined	VT1	1
E. coli non-O157	O117	Not determined	VT1	1
E. coli non-O157	Not determined	Not determined	VT1	1
E. coli non-O157	Not isolated[a]	Not isolated[a]	VT2	1
E. coli non-O157	Not isolated[a]	Not isolated[a]	VT1+VT2	1
Total				7

[a]*E. coli* not isolated at reference laboratory

Table A6.18: E. coli subtypes identified in GP Presentation Study cases

Organism	Serotype	Phage type	VT genes	Frequency
E. coli O157	O157	Not determined	VT1+VT2	1
E. coli non-O157	O76	Not determined	VT1	1
E. coli non-O157	O113:H11	Not determined	VT2	1
E. coli non-O157	O unidentifiable	Not determined	VT1	3
E. coli non-O157	Not isolated[a]	Not isolated[a]	VT1	2
E. coli non-O157	Not isolated[a]	Not isolated[a]	VT1+VT2	2
Total				*8*

[a]*E. coli* not isolated at reference laboratory

Table A6.19: C. difficile results among Prospective Cohort Study participants aged 2+ years

	Test			
Case definition	**Culture**	**ELISA**	**PCR**	**O27 serotype**
UK case	Positive	Negative	Positive	Positive
Travel-related case	Positive	Negative	Positive	Negative
Illness 14+ days	Not tested	Negative	Positive	Negative
Illness 14+ days	Not tested	Negative	Positive	Negative
Illness 14+ days	Positive	Positive	Positive	Negative

Table A6.20: C. difficile results among GP Presentation Study participants aged 2+ years

	Test			
Case definition	**Culture**	**ELISA**	**PCR**	**O27 serotype**
UK case	Positive	Positive	Negative	Negative
UK case	Positive	Negative	Positive	Negative
UK case	Positive	Negative	Positive	Negative
UK case	Not tested	Negative	Positive	Negative
UK case	Not tested	Negative	Positive	Negative
UK case	Positive	Negative	Positive	Negative
UK case	Positive	Negative	Positive	Negative
UK case	Not tested	Negative	Positive	Negative
UK case	Positive	Negative	Positive	Negative
UK case	Not tested	Negative	Positive	Negative
Travel-related case	Not tested	Positive	Negative	Negative
Illness 14+ days	Negative	Positive	Negative	Negative
Illness 14+ days	Negative	Positive	Negative	Negative
Illness 14+ days	Positive	Negative	Positive	Negative

APPENDICES – TABLE OF CONTENTS

Appendix 1: Pathogens that commonly cause IID

IID may be caused by a range of bacteria, viruses, and protozoa although the list of common causes is relatively short.

Pathogens that commonly cause IID
Bacteria
Campylobacter
Salmonella
Shigella
Escherichia coli O157
Clostridium difficile
Clostridium perfringens
Viruses
Norovirus
Sapovirus
Rotavirus
Adenovirus types 40 and 41
Astrovirus
Protozoa
Giardia
Cryptosporidium

Appendix 2: List of Read Codes

Appendix 2.1: List of Read codes used by the Study Nurses when performing searches of the General Practice database

J43-1	(Gastroenteritis)	
J4313-1	(Pseudomembranous colitis)	
A78y1	(Epidemic vomiting syndrome)	
A78y1-1	(Winter vomiting disease)	
65V1	(Notification of vomiting)	
65V2	(Notification of food poisoning)	
R0701-1	(Sickness)	
19G	(Diarrhoea & vomiting)	
199-1	(c/o vomiting)	
199-2	(Emesis)	
199-4	(Vomiting symptoms)	
1992-1	(Throwing up)	
4141	(Stool sample sent to lab)	
4J13	(Sample: no organism cultured)	
41D2	(Stool sample obtained)	
41B3	(Faeces test due)	
J431	(Toxic gastroenteritis)	+ daughter codes J4310, J4311, J4312, J4313, J431z
A0	(Infectious intestinal disease)	+ all daughter codes
Ayu0	([X] Intestinal Infectious diseases)	+ all daughter codes
4JH4	(Stool sample for C/S)	+ all daughter codes
199	(Vomiting)	+ all daughter codes except: 1991, 1994, 1995, 1997, 1998
R070	(Nausea & vomiting)	+ all daughter codes except R0703 (drug induced vomiting)
19F	(Diarrhoea symptoms)	+ all daughter codes except 19F1 (Diarrhoea not present), 19F3 (Spurious (overflow) diarrhoea)
19Z	(Gastrointestinal symptoms NOS)	+ all daughter codes except 19Z1 (no gastrointestinal symptoms)

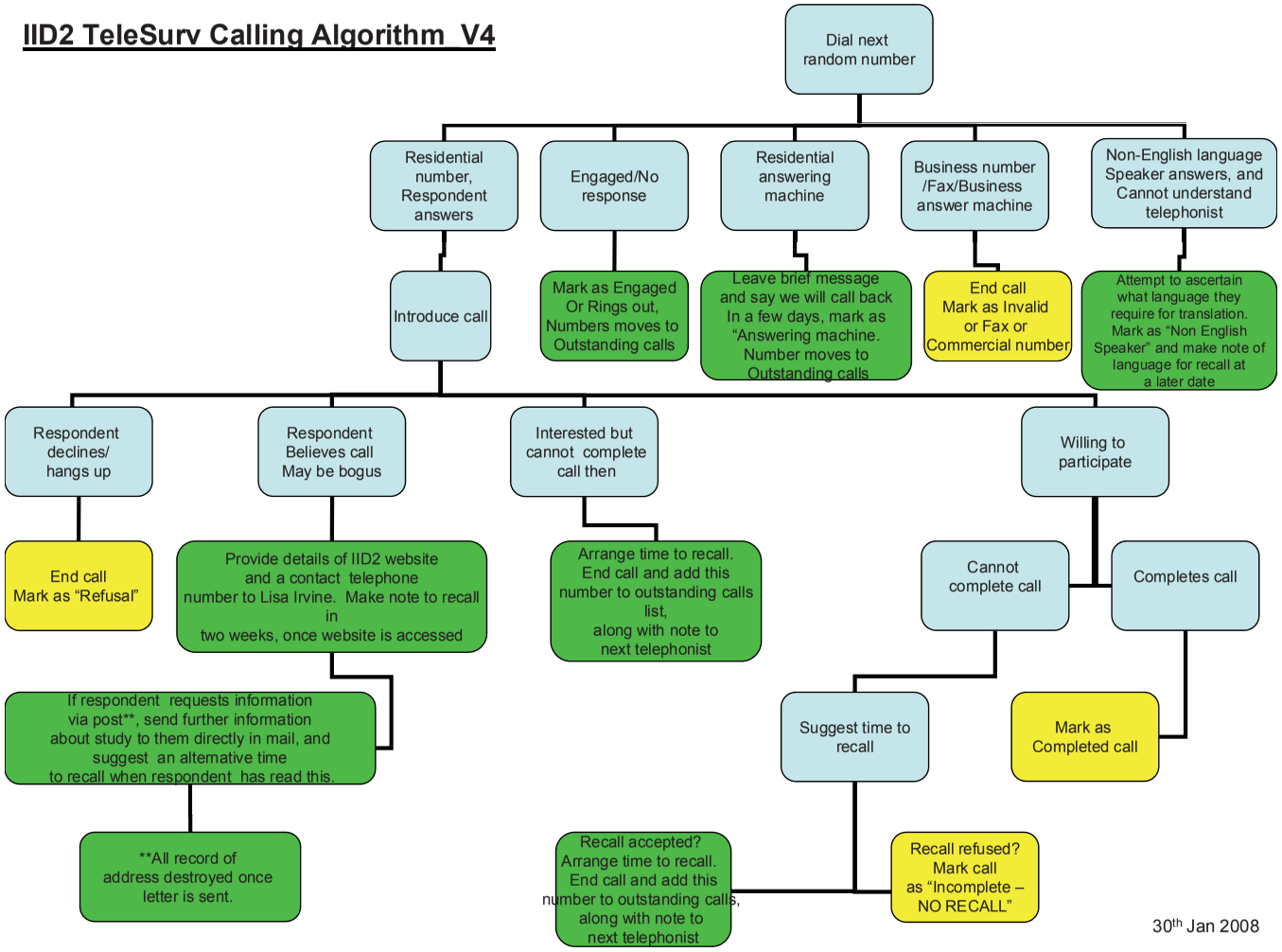
Appendix 2.2: List of Read codes which were excluded from the IID2 database

16E..00	Feels unwell
1962	Colicky abdominal pain
1972	Epigastric pain
19E3.00	Incontinent of faeces
19F1.00	Diarrhoea not present
19F4.00	Toddlers diarrhoea
1A55.00	Dysuria
1B1G.00	Headache
1D28.11	C/O - ankle symptom
1J4..00	Suspected UTI
81H..00	Dressing of wound
9N1C.11	Home visit
9N31.00	Telephone encounter
9N4F.00	Failed encounter - message left on answer machine
9Na..00	Consultation
A074313	Helicobacter gastritis
A074500	Helicobacter pylori gastrointestinal tract infection
A082.11	Travellers diarrhoea
B590.11	Carcinomatosis
H02..00	Acute pharyngitis
H03..00	Acute tonsillitis
J155.00	Gastritis unspecified
J43..00	Other non-infective inflammatory gastroenteritis and colitis
J430300	Radiation colitis
J436100	Lymphocytic colitis
J43z.00	Other non-infective gastroenteritis and colitis NOS
J521.00	Irritable colon - Irritable bowel syndrome
J573011	Rectal bleeding
J680.11	Vomiting of blood
L13Z.00	Unspecified pregnancy vomiting
R006.00	[D]Pyrexia of unknown origin
R070z11	[D]Posseting
R070z12	[D]Retching
R2y3.00	[D]Debility, unspecified

Six records (shown below) for which vomiting/diarrhoea was related to another cause were also excluded from the analyses

198.001992.00	NAUSEA & VOMITING - GASTRIC CA - BREAST CA
19F2	DIARRHOEA /ADEVERSE REACTION TO CLARITHROMYCIN
999	LOOSE STOOLS CA BOWEL
999	NAUSEA & PAIN - TERMINAL
999	NAUSEA - DRUG INDUCED / ALLERGY
999	NAUSEA - TERMINAL CA CAECUM

Appendix 3: Telephone Survey – Telephonist algorithm



Appendix 4: Telephone Survey questionnaire

The Second Study of Infectious Intestinal Disease in the Community (IID2)

Interviewer _____ Telephone number _____

Date of interview_____ Day of interview_____

Call ID _____

OPENING STATEMENT – Background information on research

- *I am calling from University of East Anglia medical school on behalf of Food Standards Agency.*
- *We would like to find out about illness experienced in the last seven days/four weeks.*
- *We would be very grateful if you could answer a brief questionnaire, which should take no longer than five minutes.*

"Do you consent to take part?"

Yes ☐ No ☐

"This call will be recorded for monitoring purposes".

All information you provide is anonymous and will be treated in strict confidence".

Computer generated info: Please select which:

Is this survey an example of: 1 week recall / 4 week recall

Survey call going to: England, Scotland, Wales, N Ireland.

Section A: Household Characteristics

A1. How many people usually live in your household? _____

A2. How many are under 18 years old? _____

A3. How many are over 18 years old? _____ [A4 see end]

A5. How many people are at home at the time of the call _____

(Consult Randomisation tables)

Do you know who at home at the moment is the Nth oldest?

Yes ☐ No ☐

(If they do not know who is the oldest, continue to interview the initial respondent)

A6b Were you able to carry out the randomization with this household?
Yes ☐ No ☐

A7 If the subject of the survey is under 17 years, please tick one of the boxes below:

Child under 12 years ☐
Teenager aged 12-16 years ☐
Adult > 16 years ☐

A8 ***Parent / guardian must answer on behalf of a child [< 12 years old].***
Is the questionnaire being answered by another person on behalf of the selected respondent? [No consent, interview halts]

Yes ☐ No ☐

A9 If the respondent is aged 12-16yrs, was parental consent given to interview the child:
Was parental consent given? [No consent, interview halts]

Yes ☐ No ☐

Section B. Demographic information on respondent

(Explain that we only require this information to assess whether the people participating in this Telephone Survey are representative of the general population. All responses will remain anonymous).

B1 Age in years: _____

B2 **Sex** Male ☐ Female ☐

B3. **Ethnic group** *(tick one of the following)*

Group 1: White	British or Irish	
	Other White	
Group2: Mixed	White & Black Caribbean	
	White and Black African	
	White and Asian	
	Other Mixed	
Group 3: Asian or Asian British	Indian	
	Pakistani	
	Bangladeshi	
	Other Asian	
Group 4: Black or Black British	Black Caribbean	
	Black African	
	Other Black	
Group 5: Other	Chinese	
	Other ethnic group	

B4 What is the **current or most recent occupation** of the main earner in the household?

B5. "What is the **current employment status** of the main earner in the household?"

Working	
Retired	
Student	
Looking after home or family	
Long-term sick or disabled	
Other	

Section C: Recent experience with diarrhoea and/or vomiting

C1 In the past week (4 weeks) have you (your child) experienced any of the following symptoms?

Please tick all that apply.

Symptom	Yes	No	Not Sure
Diarrhoea (loose watery bowel movements)			
Diarrhoea with blood in it			
Vomiting (being sick)			

(**Only answer secondary symptoms if one of above symptoms ticked**)

Secondary Symptoms	Yes	No	Not Sure
Nausea (feeling sick)			
Abdominal pain (tummy pain)			
Loss of appetite			
High temperature (shivering and sweating)			
Cough, runny/blocked nose, sore throat			
Headache			

****** For no symptoms – go straight to section E1 ******

C2 How many days did these symptoms last? Please write the number of days in the box.

Symptom	Number of Days	Not Sure
Diarrhoea (loose watery bowel movements)		
Diarrhoea with blood in it		
Vomiting (being sick)		

C3 Are any of these symptoms still present? Please tick

Symptom	Yes	No	Not sure
Diarrhoea (loose watery bowel movements)			
Bloody diarrhea			
Vomiting (being sick)			

C4 On what *date* (dd/mm/yyyy) did the diarrhoea and/or vomiting begin?

___ / ____ / _____

C5 If you answered "yes" to having diarrhoea in Question C.1., how many times did you go to the toilet on the worst day (24 hours) of your illness?

Number of times ☐☐ Not sure ☐

(NB – Do not prompt "Not Sure" as a response –we will always try to get an estimate of frequency)

C6 If you answered "yes" to vomiting in Question C.1., how many times did you vomit on the worst day (24 hours) of your illness?

Number of times ☐☐ Not sure ☐

C7 Have you been to **see** your doctor about this illness?

Yes ☐ ☐

C8 If "yes", on what date (dd/mm/yyyy) did you first see your doctor about these symptoms?

_____/_____/_____

C9 ***If you consulted your GP*****,** was it to seek diagnosis and treatment or because you required a medical certificate for work?

Diagnosis & treatment ☐ Certificate for work ☐

C10 Have you **spoken to your doctor over the telephone** about this illness?

Yes ☐ No ☐

C11 If "yes", on what date (dd/mm/yyyy) did you first speak to them about these symptoms?

_____/_____/_____

C12 Have you phoned NHS Direct/NHS 24 about this illness?

Yes ☐ No ☐

C13 If “yes”, on what date (dd/mm/yyyy) did you call NHS Direct?
_____/_____/_____

C14 Did you contact any other service during the course of your (your child’s) illness?

Out of hours provider	
Walk in centre	
Advice from pharmacist	
NHS Direct website	
Other health related websites	
Discuss with practice nurse	
None	

Burden of illness

C15 Did your (*your child’s*) illness prevent you from going about your normal daily activities?

Yes ☐ No ☐ Not sure ☐

C16 Did your (*your child’s*) illness stop you from going to work or to school?

Yes ☐ No ☐ Not sure ☐

If “yes”, how many days? ☐☐

Medications used

C17 Did you *(your child)* take any medications for your symptoms?

Yes ☐ No ☐

C18 Did you get the medication over the counter or on prescription?

(a) Over the counter

Yes ☐ No ☐

(b) On prescription

Yes ☐ No ☐

(c) Other, please specify

_____

C19 Name of medication(s)?

_____

C20 How many days were medications taken for? ☐☐

Hospitalisation

C21 Did you go *(take your child)* to any hospital department due to these symptoms?

Yes ☐ No ☐

C22 Were you *(was your child)* admitted to hospital?

Yes ☐ No ☐

C23 How many days did you *(your child)* spend in hospital
(enter '0' if none) ☐☐

C24 Were you *(your child)* asked to submit a stool sample for testing?

Yes ☐ No ☐ Not Sure ☐

C.25 If yes, what was the result of your (*your child's* test?

_____

Non-infectious diarrhoea

C26A Do you suffer from any relapsing diarrhoea or other chronic illness related to intestinal disease?

Yes ☐ No ☐

C26B. If yes, please specify:

_____

_____

Irritable Bowel disease/syndrome:

IBS1 Have you ever been told you have IBS? Yes/no

Yes ☐ No ☐

IBS2 If yes, how long have you suffered from it? _____(*free text*)

IBS3 Who told you, you had IBS? [*dropdown menu*]

_____ GP
_____ Other medical staff
_____ Self-diagnosed
_____ Other

IBS4 Have you had your IBS symptoms in the past month?

Yes ☐ No ☐

C27A Have you had any stomach or bowel surgery which may have caused diarrhoeal illness as a consequence in the past six months?

Yes ☐ No ☐

C27B If yes, please specify: _____

C28 What do you think was responsible for your illness?

C28A food [Subject thinks infection from food]	
C28A water [Subject thinks infection from water]	
C28B Infection - person to person spread	
C28C Morning sickness	
C28D Hangover	
C28E Obstruction in throat (causing vomiting)	
C28F Chronic illness (e.g. IBS, Crohns disease)	
C28G Recent stomach/bowel surgery	
C28H Medication	
C28 I Other	

Section D. Foreign travel in the two weeks before your illness started

D1 Did you travel outside the UK in the last two weeks, or in the two weeks before you became ill?

Yes ☐ No ☐

If "yes", please answer the next section

D2 If yes how long weeks ☐☐

D2 If yes, how long days ☐☐

D3 What dates were you away?

D3 Start date: _____ DD/MM/YYYY__/__/__

D3 End date : _____DD/MM/YYYY__/__/__

D4 If you stayed aboard please state which country/countries:

Do you mind providing your postcode?

A4. Postcode _____

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

Appendix 5: Nurse training agenda

09:30-09:40	Introduction to training day • Agenda • Study Manual issue
09:40-10:00	IID2 Study • Introduction, Background and Study Outline Questions and Answers
10:00-11:00	Prospective Cohort Study • Randomisation Identification and recruitment of sample • Study Register and practical. • Inviting the sample • Appointment for baseline interview
11:00-11:15	Coffee
11.15-11:50	Prospective Cohort Study • Pre consent • Consent procedures • Baseline interview
11:50-12:15	Prospective Cohort Study Weekly follow up procedures • By email • By postcard
12:15-12:35	Prospective Cohort Study • Patients with symptoms of diarrhoea and vomiting. • Specimen collection
12:35-13:15	Lunch
13:15-15:00	Prospective Cohort Study Web based data collection • Data entry • Recording follow-up • Generating reports • Trouble shooting
15:00-15:15	Coffee
15:15-15:45	Validation Study • Read code search • Data extraction
15:45-15:50	Study supplies
15:50- 16:05	Quality control Payment and claims process Questions and Answers
16:05- 16:20	GP Presentation Study
16:20-16:30	Q and A/Close

Appendix 6: Participant invitation packs

Appendix 6.1 Prospective Cohort Study – Invitation Pack – Adult – Phase 1 recruitment

App 6.1.1: Letter of invitation

GP Practice Headed Paper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

Our surgery is taking part in an important national study about the gut health of our communities and we are contacting you to see whether you would be prepared to help us.

What's involved?
We simply need to ask you a few questions at the start of the study about yourself. Then, all you need to do is keep in touch with us once a week for a year. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

Who can take part?
We are looking for people of all ages.

What are we looking for?
We want to find out how often people get diarrhoea and vomiting (D&V) and, if they do, which germs are causing it. This will help us find ways of preventing the infections. YOU DO NOT NEED TO HAVE SYMPTOMS OF D&V TO GET INVOLVED WITH THE STUDY.

Can you help us?
If you think this sounds interesting, we'd really like to talk to you so we've enclosed some more details about what's involved.

How to find out more
Please spare a little time to read the enclosed information pack which explains why we're doing the study and what will happen if you agree to help us. You can take your time to decide whether to take part and also talk to other people about the study. If you have any more questions just contact xxxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you are interested please return the enclosed form in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your care in any way and we won't contact you again about this study. If we don't hear from you the nurse may contact you again to see if you might be interested.

Thank you for taking the time to read this letter and the information enclosed.

Yours sincerely

Signed by Patient's GP

Appendix 6.1.2: Information sheet

Information Sheet (Weekly Follow-up Study)

Protocol Reference:
Version Number: 11
Date: 31/12/07

Introduction to the Diarrhoea and Vomiting Study

Please read this information leaflet about the study before you decide whether or not to take part.

This leaflet will tell you:

- Why the study is being done.
- What you will have to do if you decide to take part in this study.

Please note, that even if you never have or very rarely have diarrhoea or vomiting we would still like you to take part.

We would also still like you to take part even if you regularly have diarrhoea or vomiting.

What is the Diarrhoea and Vomiting Study about?

It will find out how many people have diarrhoea or vomiting during a year. We also would like to know how many of these people go to their doctor when they have diarrhoea and what germs are causing the diarrhoea.

Other names for diarrhoea and vomiting are “infectious intestinal disease”, “food poisoning”, “gastroenteritis” and “gastric flu”.

Although there is some official information about how big a problem diarrhoea is, we want to find out how good this information is.

What sort of Study is this?

This is a large study. There will be around 8,400 people from England, Northern Ireland, Scotland and Wales taking part.

Who is organising and paying for this Study?

The study is being organised by the University of Manchester and other partners from all over the UK who are working with your doctor (Further information about our partners is available on the website: www.iid2.org.uk). The research is being funded by the Food Standards Agency (the body that is responsible for making our food safe) (see www.food.gov.uk).

Why have I been chosen and do I have to take part?

You are 1 of around 800 people who have been picked at random from your doctor's list of patients.

We are inviting you to take part in this study, but **it is up to you to decide** whether or not you want to take part.

If you decide not to take part your health care will not be affected in any way.

What happens next if I agree to take part in this Study?

If you do agree to take part, you will be asked to:

1. Fill in a consent form. This is to show that you are happy to take part in the study.
2. Fill in a short questionnaire at the start of the Study to tell us about yourself.
3. Tell us as soon as possible if you are ill with diarrhoea or vomiting.

In case you forget, we will contact you every week for one year to check that you have not had diarrhoea or vomiting. A simple yes or no answer is all we need.

If you do become ill with diarrhoea or vomiting, we will ask you to:

- Contact the nurse at your doctor's surgery as soon as you become ill.
- Complete a symptom questionnaire about your illness.
- Give us a faeces (poo) sample so we can test for germs.

What will happen to the sample?

The faeces sample that you give us will be tested for germs. The results will be sent back to your doctor. The sample and any germs that are found will be stored and these may be used in future studies, if you agree.

What kind of information will be collected about me?

In the first questionnaire we will collect information like your name, age, ethnic group, post code, job, and any relevant medical history (e.g. a history of diarrhoea problems).
In the second questionnaire we will ask about your symptoms and details of any foreign travel.
We will keep a record of the results of your faeces sample.

How will this information be kept confidential?

The law called the Data Protection Act (1998) tells us how to keep the Study information secure.

We will store the information that you give us on a highly secure web-based electronic database. The system has been built to the standards used by the high street banks for internet banking and can only be accessed by authorised members of the Study Team using special passwords. We will not give your details to anyone else. When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept anonymous.

What are the benefits in taking part in this Study?

This Study will help the Food Standards Agency to decide whether current food safety measures have worked or if they need to make changes to food safety policy.

Are there any risks in taking part in this Study?

No. There are no risks in taking part in this Study.

After the Study starts, can I change my mind?

You can leave the Study at any time. If you do leave the information you have given up to that time will still be helpful.

What if I have a question or there is a problem?

If you are not sure about any aspect of this Study you should ask to speak to the research nurse who will try to answer your questions.

If you are unhappy and wish to complain you can do this through the NHS Complaints Procedure. You can get information about this from your doctor's surgery.

What happens when the Study finishes?

You will be involved in the study for one year. The results will be published as a report, in medical journals and presented at conferences. Your name and information that can identify you will not be used. If you would like us to send you a summary of the results, please tick the box on the consent form. This will be available from April 2010.

We will ask your permission to contact you in the future to find out if you are interested in taking part in related research.

Who has checked the Study?

Before a study like this goes ahead it has to be checked by an NHS Ethics Committee. This Study has been checked by the North West Research Ethics Committee.

Contact Details

During office hours: *Julie Dodds* (IID2 Study Manager): *0207 670 4869*
(Please leave a message out of office hours)

Complaints: *Kathryn Jackson* (IID2 Project Manager): *0161 206 4394*

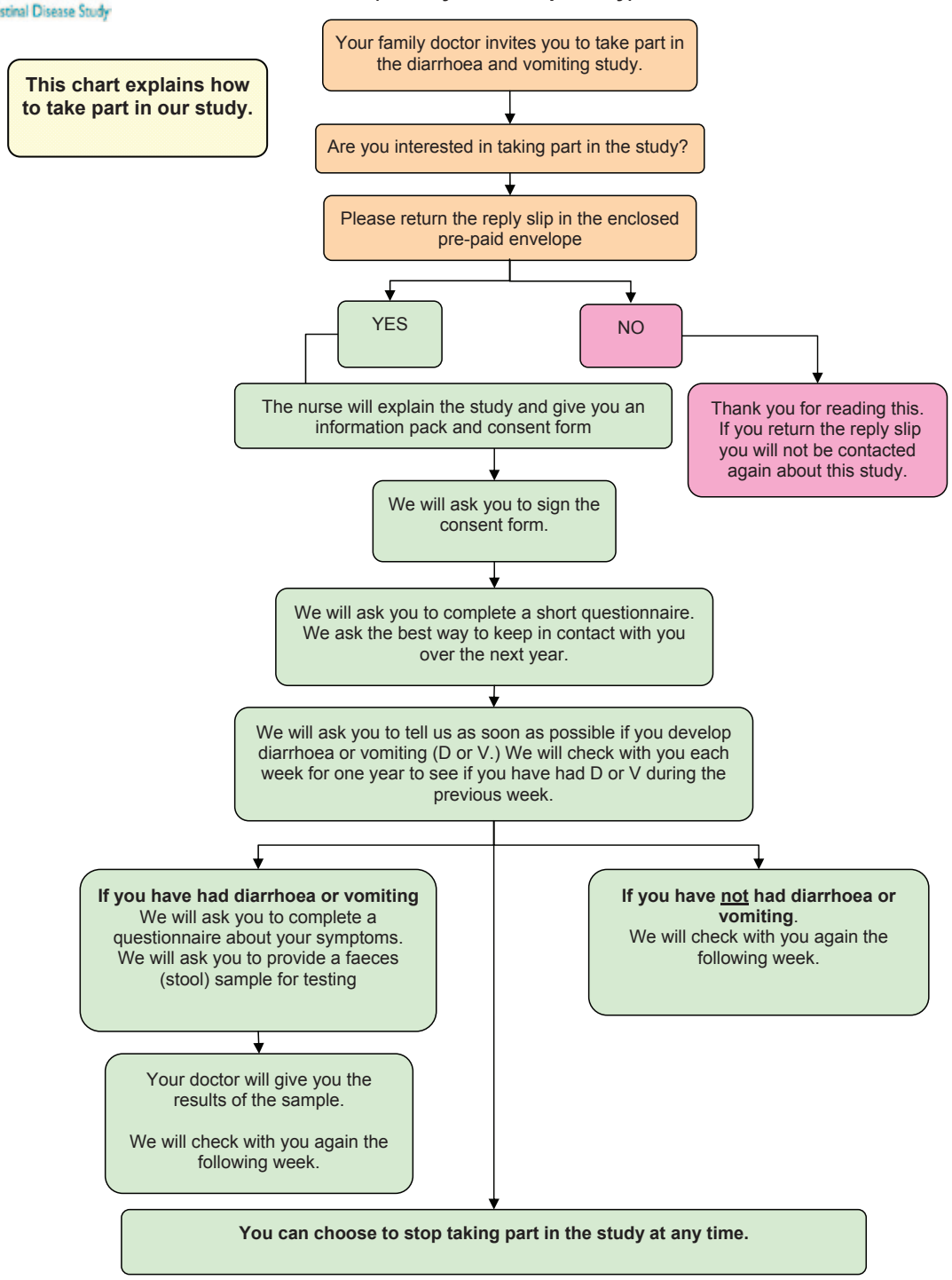
If you decide to take part in the Study, you can keep this information sheet and a signed copy of the consent form.

Finally, we would like to thank you for taking the time to read this information sheet.

App 6.1.3 Flow Chart

ProsStu_Cohort_Flowchart Adults_07

The Second Study of Diarrhoea and Vomiting (D&V) in the Community (Weekly Follow-up Study)



11th February 2008

App 6.1.4: Reply Slip

ProsStu_Cohort_ReplySlip_Adult_04

The Second Study of Diarrhoea and Vomiting in the Community

Reply Slip

Thank you for taking the time to read the letter and information sheet about this study.

Please let us know if you want to find out more about the study or not by completing this form below and sending it back to us in the enclosed pre-paid envelope.

Your surname: _____ forename: _____

Your date of birth (dd/mm/yyyy): _____/____/____

Your sex: Male ☐ Female ☐

Today's date (dd/mm/yyyy): _____/____/____

YES please, I want to find out more about the study ☐

If Yes, please give best mobile and landline contact numbers:

Mobile No: _____ Landline No:_____

NO thank you, I do not want to find out more about the study ☐

If NO, please to let us know why not by ticking one of the boxes below

No time ☐ Not interested ☐

Often away ☐ Other (please state below) ☐

Other_____

Appendix 6.2: Prospective Cohort Study – Invitation Pack – Child – Phase 1 recruitment

App 6.2.1: Letter of invitation

GP Practice Headed Paper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

Our surgery is taking part in an important national study about the gut health of our communities and we are contacting you to see whether you would be prepared to help us.

We are inviting your child: …….. **to take part.** If your child is old enough please discuss this with them.

What's involved?
We simply need to ask you a few questions at the start of the study about your child. Then, all you need to do is keep in touch with us once a week for a year. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

Who can take part?
We are looking for people of all ages including children.

What are we looking for?
We want to find out how often people get diarrhoea and vomiting (D&V) and, if they do, which germs are causing it. This will help us find ways of preventing the infections. YOUR CHILD DOES NOT NEED TO HAVE SYMPTOMS OF D&V TO GET INVOLVED WITH THE STUDY.

Can you help us?
If you think this sounds interesting, we'd really like to talk to you so we've enclosed some more details about what's involved.

How to find out more
Please spare a little time to read the enclosed information pack which explains why we're doing the study and what will happen if you agree to help us. You can take your time to decide whether to

take part and also talk to other people about the study. If you have any more questions just contact xxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you are interested please return the enclosed form in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your or your child's care in any way and we won't contact you again about this study. If we don't hear from you the nurse may contact you again to see if you might be interested.

Thank you for taking the time to read this letter and the information enclosed.

Yours sincerely

Signed by Patient's GP

App 6.2.2: Information Sheet

ProsStu_Cohort_Info Sheet Child_09

iid2
The Second Infectious Intestinal Disease Study

"The Tummy Bug Study"
Information Sheet
(Weekly Follow-up)

Protocol Reference:
Version Number: 09
Date: 31/12/07

Please read this information leaflet about the Tummy Bug Study also known as The Second Study of Diarrhoea and Vomiting in the Community. This will help you decide if you want to help us.

This leaflet will tell you:

- Why the doctors want to find out more about tummy bugs.
- What you will have to do if you decide to join in.

We would still like you to take part even if you have never had or rarely had diarrhoea or vomiting. We would also still like you to take part even if you often have these symptoms.

Why do doctors want to know more about tummy bugs?

We want to find out how many people are ill because of tummy bugs in a year. We would also like to know how many of these people go to their doctor when they are ill.

Other names for tummy bugs are "diarrhoea", "vomiting" and "food poisoning".

There is official information, about how big a problem diarrhoea or vomiting is and we want to find out how good this information is.

How many people will be helping the Tummy Bug Study?

This is a very big study. There will be around 8,400 people from England, Northern Ireland, Scotland and Wales taking part.

Why have you asked me to help?

We asked your doctor to choose 800 people from their list of patients.

Your name was picked by chance.

Do I have to join in?

It is up to you if you want to join in. If you do not want to join in, that's no problem. It will not change how your doctor and nurse treat you.

If I join in, what will happen to me?

We just want you to tell us when you are ill because of diarrhoea or vomiting.

Your nurse will ask your parent or guardian to sign a form. This will tell us that you agree to join in.

You, or your parent or guardian, will fill in a form about your health.

If you get a tummy bug we will ask you, or your parent or guardian to tell us straightaway. In case you forget we will contact you, your parent or guardian every week for one year to ask if you have been ill with a tummy bug.

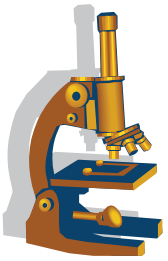
If you have <u>not</u> been ill, we will ask you again next week.

BUT

If you have been ill, we will ask you to fill in a form about your illness and to give us a sample of faeces (poo).

What will happen to the sample?

The sample will be tested for germs. The results will be sent back to your doctor. The sample and any germs that are found will be stored. These may be used in future studies, if you agree.



How will you make sure that nobody else reads the information about me?

There is a law that tells us how to keep study information safe.

We will store the information that you give us on a very safe web-based electronic database. The system has been built in the same way that is used by the high street banks for internet banking and only some members of the Study Team using special passwords will be allowed to see this. We will not give your details to anyone else. When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept secret.

How will the Tummy Bug Study help?

This study will help us to make food safer.

What if I have any more questions or have any problem after I start?

If you are not sure about any part of this study you should ask to speak to the nurse who will try to answer your questions.
If you are unhappy you could make a complaint.

What if I don't want to help anymore?

If you do not want to carry on with the study you can stop at any time. It will not change how your doctor and nurse treat you.

If you stop the information you have given will still be helpful.

What will happen when the study finishes?

We will write a report. This is for people to learn about the results. Your name and details that can identify you will not be used.

Did anyone check that the study is safe and being done properly?

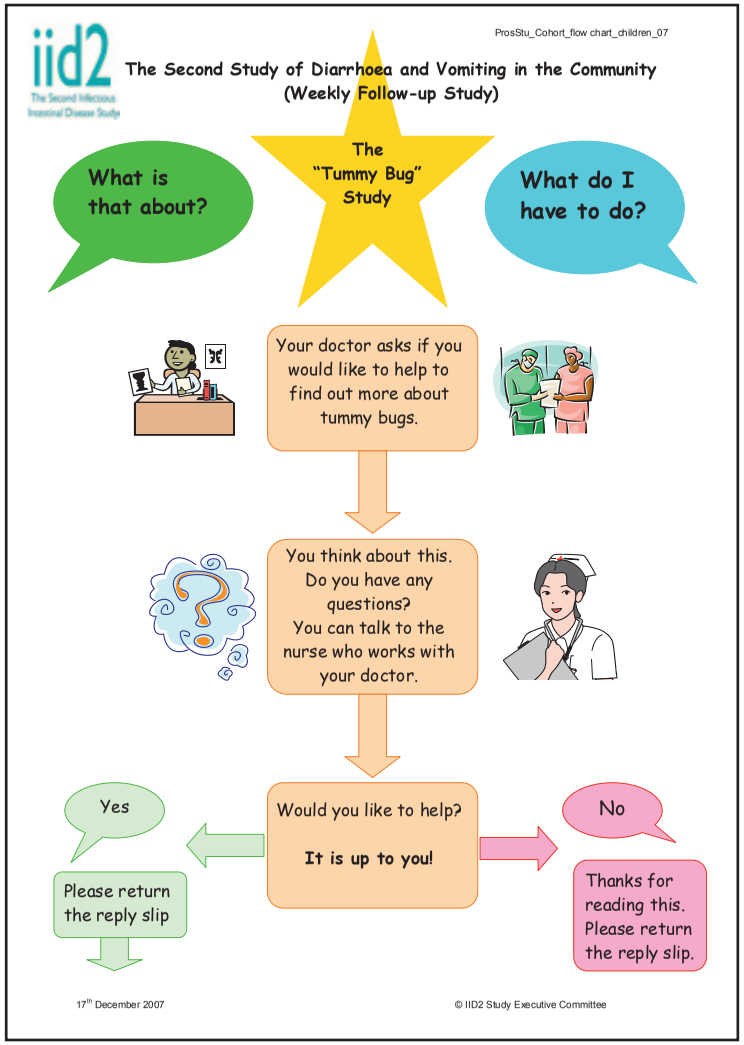
The Tummy Bug Study has been checked by the North West Research Ethics Committee.

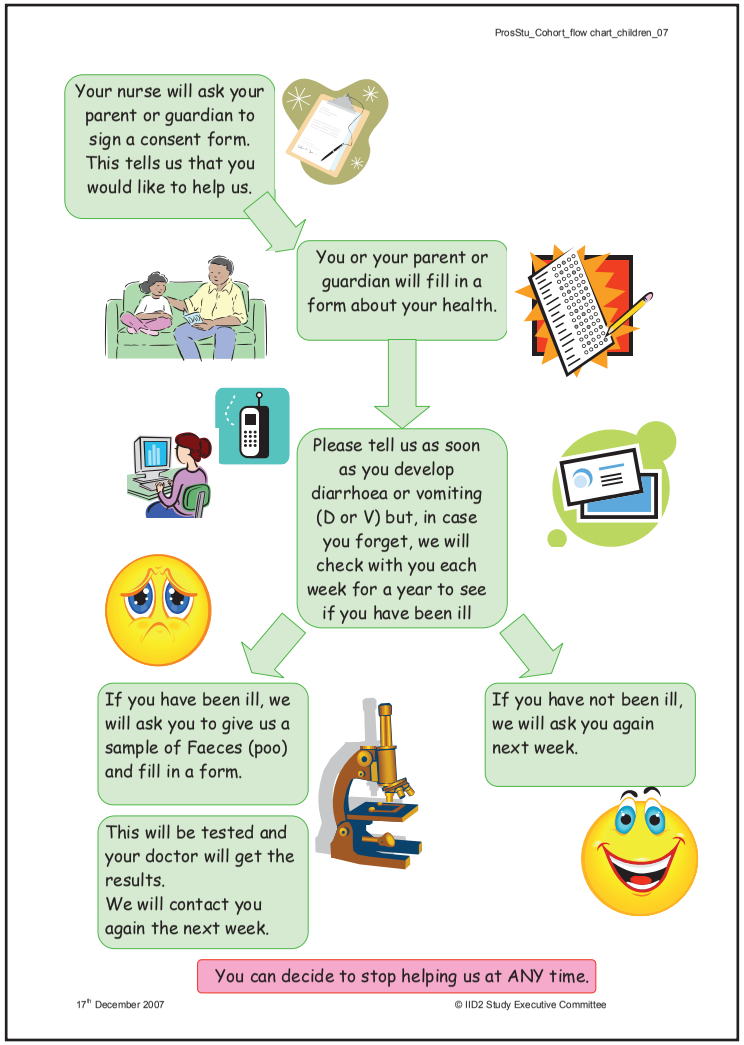
Contact details:
During office hours: *Julie Dodds* (IID2 Study Manager): *0207 670 4869* (please leave a message out of office hours)
Complaints: *Kathryn Jackson* (IID2 Project Manager): *0161 206 4394*

If you decide to join in the Tummy Bug Study, we will give you this information sheet and your parent or guardian will keep a signed copy of the form that tells us you want to join in.

Thank you for taking the time to read about the Tummy Bug Study.

App 6.2.3: Flow Chart





App 6.2.4: Reply slip

ProsStu_Cohort_ReplySlip_Child_04

iid2 The Second Infectious Intestinal Disease Study

The Second Study of Diarrhoea and Vomiting in the Community

Reply Slip

Thank you for taking the time to read the letter and information sheet about this study.

Please let us know if you want to find out more about the study or not by completing this form below and sending it back to us in the enclosed pre-paid envelope.

Your child's surname: _____ forename: _____

Your child's date of birth (dd/mm/yyyy): _____/____/____

Your child's sex: Male ☐ Female ☐

Today's date (dd/mm/yyyy): _____/____/____

YES please, I want to find out more about the study ☐

If Yes, please give best mobile and landline contact numbers:

Mobile No: _____ Landline No:_____

NO thank you, I do not want to find out more about the study ☐

If NO, please to let us know why not by ticking one of the boxes below

No time ☐ Not interested ☐

Often away ☐ Other (please state below) ☐

Other_____

17th December 2007 Page 1 of 1

Appendix 6.3: Prospective Cohort Study – Reminder Letters – Phase 1 recruitment

App 6.3.1: Reminder Letter –Adult

GP Headed Notepaper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

We wrote to you recently to let you know that our surgery is taking part in an important national study about the gut health of our communities. We are contacting you again to see whether you would be prepared to help us.

What's involved?
We simply need to ask you a few questions at the start of the study about yourself. Then, all you need to do is keep in touch with us once a week for a year. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

Who can take part?
We are looking for people of all ages.

What are we looking for?
We want to find out how often people get diarrhoea and vomiting (D&V) and, if they do, which germs are causing it. This will help us find ways of preventing the infections. YOU DO NOT NEED TO HAVE SYMPTOMS OF D&V TO GET INVOLVED WITH THE STUDY.

Can you help us?
If you think this sounds interesting, we'd really like to talk to you so we've enclosed some more details about what's involved.

How to find out more
Please spare a little time to read the enclosed information pack which explains why we're doing the study and what will happen if you agree to help us. You can take your time to decide whether to take part and also talk to other people about the study. If you have any more questions just contact xxxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you are interested please return the enclosed form in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your care in any way and we won't contact you again about this study.

Thank you for taking the time to read this letter and the information enclosed.

Yours sincerely

Signed by Patient's GP

App 6.3.2: Reminder Letter –Child

GP Headed Notepaper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

We wrote to you recently to let you know that our surgery is taking part in an important national study about the gut health of our communities. We are contacting you again to see whether you would be prepared to help us.

We are inviting your child: ……..
to take part. If your child is old enough please discuss this with them.

What's involved?
We simply need to ask you a few questions at the start of the study about your child. Then, all you need to do is keep in touch with us once a week for a year. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

Who can take part?
We are looking for people of all ages including children.

What are we looking for?
We want to find out how often people get diarrhoea and vomiting (D&V) and, if they do, which germs are causing it. This will help us find ways of preventing the infections. YOUR CHILD DOES NOT NEED TO HAVE SYMPTOMS OF D&V TO GET INVOLVED WITH THE STUDY.

Can you help us?
If you think this sounds interesting, we'd really like to talk to you so we've enclosed some more details about what's involved.

How to find out more
Please spare a little time to read the enclosed information pack which explains why we're doing the study and what will happen if you agree to help us. You can take your time to decide whether to

take part and also talk to other people about the study. If you have any more questions just contact xxxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you are interested please return the enclosed form in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your or your child's care in any way and we won't contact you again about this study.

Thank you for taking the time to read this letter and the information enclosed.

Yours sincerely

Signed by Patient's GP

Appendix 6.4: GP Presentation Study - Invitation Pack - Adults - Phase 1 recruitment

App 6.4.1: Letter of invitation

ProsStu_GP Presentation Participant Letter_04

GP Practice Headed Paper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

This surgery is taking part in a national study about diarrhoea and vomiting (D&V). We want to find out exactly how often people get D&V and what germs are causing it.

We are inviting you (or your child) to take part because you or your child have come into the surgery with symptoms of D&V. Before you decide if you would like to join in or not please take time to read the enclosed information. This tells you why we are doing the study and what will happen if you agree to join in. You can take your time to decide if you want to take part and also talk to other people about the study.

Please contact xxxxxxxx at the surgery if there is anything that is not clear or if you would like more information. The practice nurse will contact you by telephone to find out if you are interested in taking part.

If you are not interested that's fine – it won't affect your care in any way and we won't contact you again about the study.

Thank you for taking the time to read this letter and the information enclosed.

Yours Sincerely

Signed by Patient's GP

17th January 2008

App 6.4.2: Information sheet

Information Sheet (GP Presentation Study)

The Second Study of Diarrhoea and Vomiting in the Community

Protocol Reference:
Version Number: 6
Date: 31/12/07

Introduction to the Diarrhoea and Vomiting Study

Please read this information leaflet about the study before you decide whether or not to take part.

This leaflet will tell you:

- Why the study is being done.
- What you will have to do if you decide to take part in this study.

What is the Diarrhoea and Vomiting Study about?

It will find out how many people have diarrhoea or vomiting during a year. We also would like to know how many of these people go to their doctor when they have diarrhoea and what germs are causing the diarrhoea.

Other names for diarrhoea and vomiting are “infectious intestinal disease”, “food poisoning”, gastroenteritis and “gastric flu”.

Although there is some official information about how big a problem diarrhoea is, we want to find out how good this information is.

What sort of Study is this?

This is a large study that involves everyone who goes to see their doctor with diarrhoea or vomiting.

Who is organising and paying for this Study?

The study is being organised by the University of Manchester and other partners from all over the UK who are working with your doctor (Further information about our partners is available on the website: www.iid2.org.uk). The research is being funded by the Food Standards Agency (the body that is responsible for making our food safe) (see www.food.gov.uk).

Why have I been chosen and do I have to take part?

We are inviting you to take part in this study because you have come into the surgery with diarrhoea or vomiting.

It is up to you to decide whether or not you want to take part.

If you decide not to take part your health care will not be affected in any way.

What happens next if I agree to take part in this Study?

If you do agree to take part, you will be asked to:

1. Fill in a consent form. This is to show that you are happy to take part in the study.
2. Fill in a short questionnaire to tell us about yourself and your illness.
3. Give a faeces (stool) sample.

What will happen to the faeces sample?

The faeces sample that you give us will be tested for germs. The results will be sent back to your doctor. The sample and any germs that are found will be stored and these may be used in future studies, if you agree.

What kind of information will be collected about me?

We will collect information like your name, age, ethnic group, post code, job, and any relevant medical history (e.g. a history of diarrhoea problems), and details of your symptoms and any foreign travel.

We will keep a record of the results of your faeces sample.

How will this information be kept confidential?

The law called the Data Protection Act (1998) tells us how to keep the Study information secure.

We will store the information that you give us on a highly secure web-based electronic database. The system has been built to the standards used by the high street banks for internet banking and can only be accessed by authorised members of the Study Team using special passwords. We will not give your details to anyone else. When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept anonymous.

What are the benefits in taking part in this Study?

This Study will help the Food Standards Agency to decide whether current food safety measures have worked or if they need to make changes to food safety policy.

Are there any risks in taking part in this Study?

No. There are no risks in taking part in this Study.

After the Study starts, can I change my mind?

You can leave the Study at any time. If you do leave the information you have given up to that time will still be helpful.

What if I have a question or there is a problem?

If you are not sure about any aspect of this Study you should ask to speak to the research nurse who will try to answer your questions.

If you are unhappy and wish to complain you can do this through the NHS Complaints Procedure. You can get information about this from your doctor's surgery.

What happens when the Study finishes?

The results will be published as a report, in medical journals and presented at conferences. Your name and information that can identify you will not be used. If you would like us to send you a summary of the results, please tick the box on the consent form. This will be available from April 2010.

We will ask your permission to contact you in the future to find out if you are interested in taking part in related research.

Who has checked the Study?

Before a study like this goes ahead it has to be checked by an NHS Ethics Committee. This Study has been checked by the North West Research Ethics Committee.

Contact Details

During office hours: *Julie Dodds* (IID2 Study Manager): *0207 670 4869*
(Please leave a message out of office hours)

Complaints: *Kathryn Jackson* (IID2 Project Manager): *0161 206 4394*

If you decide to take part in the Study, you can keep this information sheet and a signed copy of the consent form.

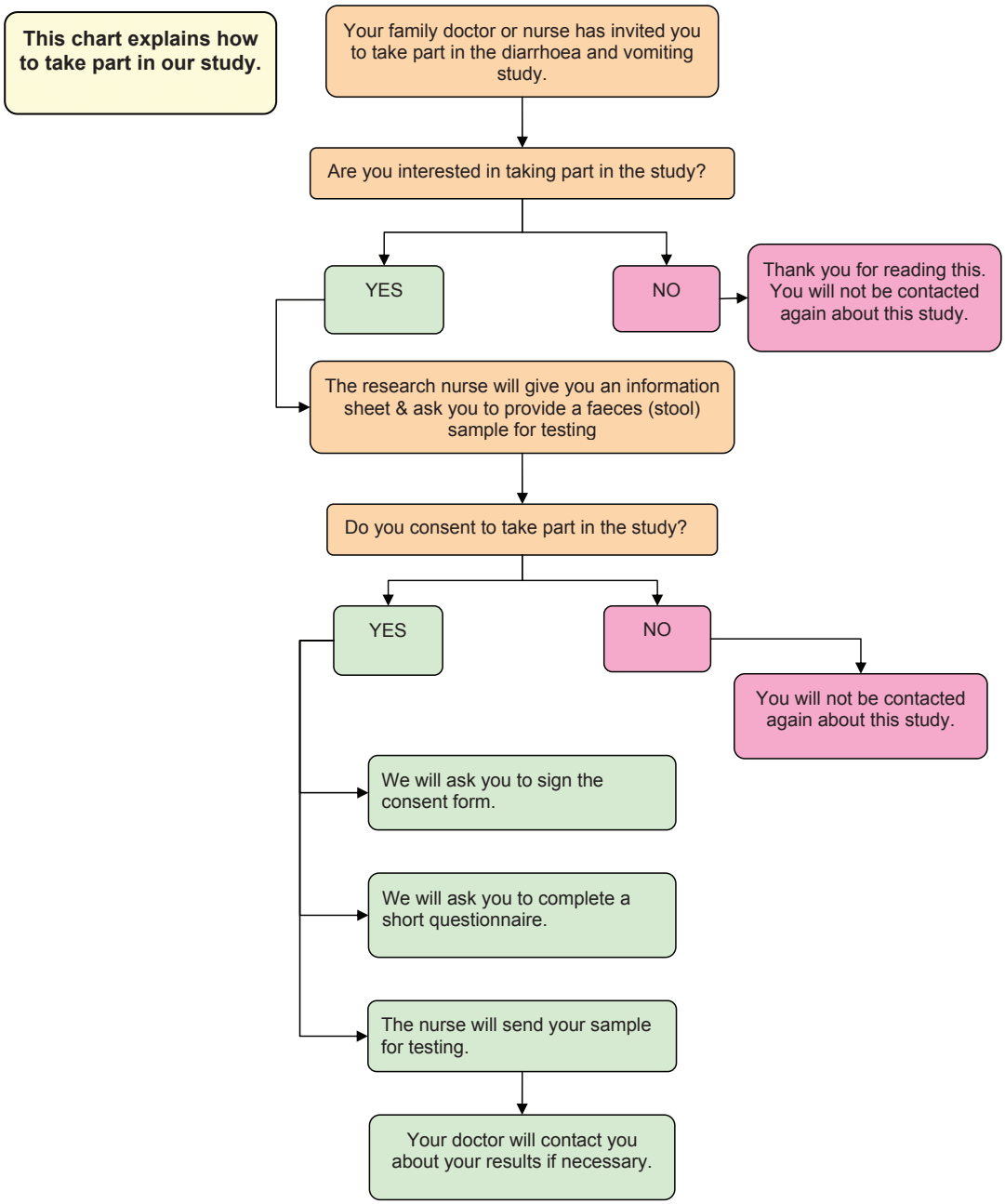
Finally, we would like to thank you for taking the time to read this information sheet.

App 6.4.3: Flow Chart

ProsStu_GP Presentation_Flowchart Adults_03

The Second Study of Diarrhoea and Vomiting (D&V) in the Community

(GP Presentation Study)



12th February 2008

App 6.4.4: Reply slip

ProsStu_GP Presentation_ReplySlip_Child_01

The Second Study of Diarrhoea and Vomiting in the Community

For Official Use only

Name of Research Nurse:

Please enter study number:

Reply Slip for Invitation to take part in the GP Presentation Study

Thank you for taking the time to read the letter and information sheet about the second study of diarrhoea and vomiting in the community.

Please let us know if you would like to find out more by completing the form below and returning it to us in the enclosed pre-paid envelope.

Today's date (dd/mm/yyyy): _____/____/____

Your child's date of birth (dd/mm/yyyy): _____/____/____

Your child's sex: Male ☐ Female ☐

YES please, I want to find out more about the study ☐

NO thank you, I do not want to find out more about the study ☐

If NO, please take a moment to let us know why not by ticking one of the boxes below

No time ☐ Not interested ☐

Often away ☐ Other (please state below) ☐

Other_____

_____

29 November 2006

Appendix 6.5: GP Presentation Study - Invitation Pack - Child - Phase 1 recruitment

App 6.5.1: Letter of invitation

ProsStu_GP Presentation Participant Letter_04

GP Practice Headed Paper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

This surgery is taking part in a national study about diarrhoea and vomiting (D&V). We want to find out exactly how often people get D&V and what germs are causing it.

We are inviting you (or your child) to take part because you or your child have come into the surgery with symptoms of D&V. Before you decide if you would like to join in or not please take time to read the enclosed information. This tells you why we are doing the study and what will happen if you agree to join in. You can take your time to decide if you want to take part and also talk to other people about the study.

Please contact xxxxxxxx at the surgery if there is anything that is not clear or if you would like more information. The practice nurse will contact you by telephone to find out if you are interested in taking part.

If you are not interested that's fine – it won't affect your care in any way and we won't contact you again about the study.

Thank you for taking the time to read this letter and the information enclosed.

Yours Sincerely

Signed by Patient's GP

17th January 2008

App 6.5.2: Information sheet

iid2
The Second Infectious Intestinal Disease Study

Information Sheet (GP Presentation Study)

"The Tummy Bug Study"

Protocol Reference:
Version Number: 5
Date: 31/12/07

Please read this information leaflet about the Tummy Bug Study also known as The Second Study of Diarrhoea and Vomiting in the Community. This will help you decide if you want to help us.

This leaflet will tell you:

Why the doctors want to find out more about tummy bugs.
What you will have to do if you decide to join in.

We would still like you to take part even if you have never had or rarely had diarrhoea or vomiting. We would also still like you to take part even if you often have these symptoms.

Why do doctors want to know more about tummy bugs?

We want to find out how many people are ill because of tummy bugs in a year. We would also like to know how many of these people go to their doctor when they are ill.

Other names for tummy bugs are "diarrhoea", "vomiting" and "food poisoning".

There is official information, about how big a problem diarrhoea or vomiting is and we want to find out how good this information is.

How many people will be helping the Tummy Bug Study?

This is a very big study. There will be around 8,400 people from England, Northern Ireland, Scotland and Wales taking part.

Why have you asked me to help?

We are asking you to join in because you have come into the surgery with a tummy bug.

Do I have to join in?

It is up to you if you want to join in. If you do not want to join in, that's no problem. It will not change how your doctor and nurse treat you.

If I join in, what will happen to me?

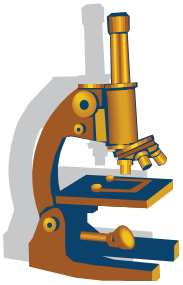
We just want you to tell us about your diarrhoea or vomiting.

Your nurse will ask your parent or guardian to sign a form. This will tell us that you agree to join in.

You, or your parent or guardian, will fill in a form about your illness.

You will give us a sample of faeces (poo).

What will happen to the sample?



The sample will be tested for germs. The results will be sent back to your doctor. The sample and any germs that are found will be stored. These may be used in future studies, if you agree.

How will you make sure that nobody else reads the information about me?

There is a law that tells us how to keep study information safe.

We will store the information that you give us on a very safe web-based electronic database. The system has been built in the same way that is used by the high street banks for internet banking and only some members of the Study Team using special passwords will be allowed to see this. We will not give your details to anyone else. When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept secret.

How will the Tummy Bug Study help?

This study will help us to make food safer.

What if I have any more questions or have any problem after I start?

If you are not sure about any part of this study you should ask to speak to the nurse who will try to answer your questions.
If you are unhappy you could make a complaint.

What if I don't want to help anymore?

If you do not want to carry on with the study you can stop at any time. It will not change how your doctor and nurse treat you.

If you stop the information you have given will still be helpful.

What will happen when the study finishes?

We will write a report. This is for people to learn about the results. Your name and details that can identify you will not be used.

Did anyone check that the study is safe and being done properly?

The Tummy Bug Study has been checked by the North West Research Ethics Committee.

Contact details:
During office hours:
Julie Dodds (IID2 Study Manager): *020 7670 4869*
(please leave a message out of hours)

Complaints: *Kathryn Jackson* (IID2 Project Manager): *0161 206 4394*

If you decide to join in the Tummy Bug Study, we will give you this information sheet and your parent or guardian will keep a signed copy of the form that tells us you want to join in.

Thank you for taking the time to read about the Tummy Bug Study.

iid2 The Second Infectious Intestinal Disease Study

The Second Study of Diarrhoea and Vomiting in the Community (GP Presentation Study)

What is that about?

The "Tummy Bug" Study

What do I have to do?

Your doctor or nurse asks if you would like to help to find out more about tummy bugs.

You think about this. Do you have any questions? You can talk to the nurse.

Would you like to help?

It is up to you!

Yes

No

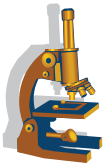
Thanks for reading this

ProsStu_GP Presentation_flow chart_children_02

Your nurse will ask your parent or guardian to sign a consent form. This tells us that you would like to help us.

You or your parent or guardian will fill in a form about your illness

We will ask you to give us a sample of Faeces (poo).



This will be tested and your doctor will tell you the results if necessary.

You can decide to stop helping us at ANY time.

App 6.5.4: Reply slip

ProsStu_GP Presentation_ReplySlip_Adult_01

The Second Study of Diarrhoea and Vomiting in the Community

For Official Use only

Name of Research Nurse:

Please enter study number:

Reply Slip for Invitation to take part in the GP Presentation Study

Thank you for taking the time to read the letter and information sheet about the second study of diarrhoea and vomiting in the community.

Please let us know if you would like to find out more by completing the form below and returning it to us in the enclosed pre-paid envelope.

Today's date (dd/mm/yyyy): _____/____/____

Your date of birth (dd/mm/yyyy): _____/____/____

Your sex: Male ☐ Female ☐

YES please, I want to find out more about the study ☐

NO thank you, I do not want to find out more about the study ☐

If NO, please take a moment to let us know why not by ticking one of the boxes below

No time ☐ Not interested ☐

Often away ☐ Other (please state below) ☐

Other_____

_____

29 November 2006

Appendix 6.6 : Prospective Cohort Study – Invitation Pack – 16-24 yr Males – Phase 2 recruitment

App 6.6.1: Letter of Invitation

ProsStu_Cohort_Participant Letter_Adult_09

Cure All Medical Practice
Clearbill Health Centre
Welling Road, Welford
WE11 YEP
Tel: 0123 456 7890
Fax: 0123 456 7891
www.cureallmedical.org.uk
Dr Dolittle
Dr Jekyl
Dr Spock
Dr Fox
Salaried Doctors
Dr Martins
Dr Kildare
Dr Legg

Mr D. Z. Spells
1 Sycamore Road
Tumbridge Swells
RUIL LEH

You are invited to take part in the UK's biggest ever gut health study

Dear Mr Spells,

Our surgery is taking part in Gut Feelings, a huge study about the gut health of the nation and we are contacting you to see whether you would be prepared to help us.

What's involved?
We simply need to ask you a few questions at the start of the study about yourself. Then, all you need to do is keep in touch with us once a week for six months. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

What are we looking for?
Gut Feelings is all about finding out how often people get diarrhoea and vomiting and which germs are causing it. We will use the results to find better ways of preventing infections.
You don't need to be ill to take part in Gut Feelings. The study needs people who don't suffer from stomach bugs as well as those who do.

Can you help us?
We are looking for people of all ages, so it would be really helpful if you could.
I've sent you some information about the study - it should tell you everything you want to know, but if you have any more questions just contact xxxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you'll take part, please return the enclosed reply slip in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your care in any way and we won't contact you again about this study. If we don't hear from you the nurse may contact you again to see if you might be interested.

Thanks for your time.

Signed by Patient's GP

P.S. Please remember you don't need to be ill to take part in Gut Feelings. **The study needs needs people who don't suffer from stomach bugs very often as well as those who do.**

1st October 2008

App 6.6.2 Information sheet – Males 16-24 years

From barfing to the squits and everything in between

Stomach bugs are a fact of life. And while we know a lot about them we don't know everything.

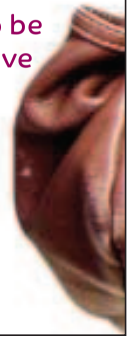
And that's where you come in.

Gut Feelings is a huge study on the gut health of the nation. The results may go on to shape government policy on food safety. And you can be a part of it.

You see, males aged between 16-24 usually can't be bothered taking part in studies. They think they're boring or too much hassle or too gross. That's why it would be really helpful if you could get involved - whether you suffer from diarrhoea or vomiting a lot, sometimes or never.

Taking part is easy - you don't even have to be ill - in fact, the chances are that all you'll have to do is answer a few questions.

Anyway, this leaflet will give you more information.



Okay, so what's Gut Feelings all about?

You may have heard of salmonella, gastroenteritis, gastric flu, or even infectious intestinal disease. These are just some of the forms of diarrhoea and vomiting we'd like to understand better.

It's important that we find out how many people suffer from them during a year, how many go to their doctor when they have a problem, and what germs are to blame.

Yes, doctors already know a lot about diarrhoea and vomiting. But we want to find out how accurate their information is.

What sort of study is this?

Gut Feelings is the biggest ever study of its kind. If you decide to take part you'll be one of thousands of people from England, Northern Ireland, Scotland and Wales helping us find out more about diarrhoea and vomiting.

Who is organising and paying for this study?

The University of Manchester is organising Gut Feelings. We also have a number of other partners who work with GPs all over the UK. And the research is being funded by the Food Standards Agency, the government body that is responsible for ensuring food safety.

Why have I been chosen, and do I have to take part?

Your name has been picked randomly from your doctor's list of males aged between 16-24. However, it is up to you whether you take part or not. If you decide not to, your healthcare will not be affected in any way.

What happens next if I agree to take part in this study?

All you have to do is:

1. Fill in a consent form. This tells us you are happy to take part in the study.
2. Complete a short questionnaire, which will help us understand a little bit more about you.
3. Tell us as soon as possible if you are ill with diarrhoea or vomiting. In case you forget we'll contact you every week for six months to find out if you've been ill with diarrhoea or vomiting. All we need is a simple yes or no.

If the answer is yes, we'll ask you to contact the nurse at your doctor's surgery, complete a symptom questionnaire and give us a faeces (poo) sample.

What happens to my sample?

We'll test the sample for germs and send the results back to your GP. And, if you agree, we'll store the sample and the germs so that they may be used in future studies.

What kind of information will be collected about me?

As well as the results of your faeces test, we'll record information like your name, age, ethnic group and any relevant medical information (for example, if you have a history of diarrhoea problems), and details of your symptoms and any foreign travel.

How will this information be kept confidential?

The law called the Data Protection Act (1998) tells us how to keep your information secure.

We'll store your information on a highly secure web-based electronic database. The system has been built to the standards used by the high street banks for internet banking and can only be accessed by authorised members of the Study Team using special passwords. We will not give your details to anyone else.

When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept anonymous.

What are the benefits of taking part in the study?

You'll be helping the Food Standards Agency decide whether current food safety measures have worked or if they need to make changes to safety policy. That's why this is an important study that could benefit everyone in the UK.

Are there any risks in taking part in this study?

No.

After the study starts, can I change my mind?

You can leave the study whenever you want. The information you have given up to that point will still be helpful to us.

What if I have a question or there is a problem?

If there is anything about the study that you're not sure about, just ask to speak to the research nurse who will try to answer your question.

If you are unhappy about an aspect of the study and you want to make a complaint, you can do this through the NHS Complaints Procedure. Your doctor's surgery will be able to give you information about how to do this.

Appendix 6.7: Prospective Cohort Study – Invitation Pack – Adult – Phase 2 recruitment

App 6.7.1: Letter of Invitation

ProsStu_Cohort_Participant Letter_Adult_09

Cure All Medical Practice
Clearbill Health Centre
Welling Road, Welford
WE11 YEP
Tel: 0123 456 7890
Fax: 0123 456 7891
www.cureallmedical.org.uk
Dr Dolittle
Dr Jekyl
Dr Spock
Dr Fox
Salaried Doctors
Dr Martins
Dr Kildare
Dr Legg

Mr D. Z. Spells
1 Sycamore Road
Tumbridge Swells
RUIL LEH

You are invited to take part in the UK's biggest ever gut health study

Dear Mr Spells,

Our surgery is taking part in Gut Feelings, a huge study about the gut health of the nation and we are contacting you to see whether you would be prepared to help us.

What's involved?
We simply need to ask you a few questions at the start of the study about yourself. Then, all you need to do is keep in touch with us once a week for six months. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

What are we looking for?
Gut Feelings is all about finding out how often people get diarrhoea and vomiting and which germs are causing it. We will use the results to find better ways of preventing infections.
You don't need to be ill to take part in Gut Feelings. The study needs people who don't suffer from stomach bugs as well as those who do.

Can you help us?
We are looking for people of all ages, so it would be really helpful if you could.
I've sent you some information about the study - it should tell you everything you want to know, but if you have any more questions just contact xxxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you'll take part, please return the enclosed reply slip in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your care in any way and we won't contact you again about this study. If we don't hear from you the nurse may contact you again to see if you might be interested.

Thanks for your time.

Signed by Patient's GP

P.S. Please remember you don't need to be ill to take part in Gut Feelings. **The study needs needs people who don't suffer from stomach bugs very often as well as those who do.**

1st October 2008

Help us reduce tummy bugs across the nation

Have you ever wondered why you occasionally get diarrhoea or suffer from vomiting? Well, that's the kind of thing we spend a lot of time thinking about.

That's why we're pleased to say that your surgery is taking part in Gut Feelings, the biggest ever study about the gut health of the nation.

And we'd love it if you could help us by getting involved - whether you suffer from diarrhoea or vomiting a lot, sometimes or never.

This leaflet will tell you about why the study's being done and what you'll be asked to do if you decide to join.

What's Gut Feelings all about?

You may have heard of salmonella, gastroenteritis, gastric flu, or even infectious intestinal disease. These are just some of the forms of diarrhoea and vomiting we'd like to understand better.

We want to find out how many people suffer from them during a year, how many go to their doctor when they have a problem, and what germs are to blame.

Of course, doctors already know a lot about how big a problem diarrhoea and vomiting is. But we'd like to find out how accurate their information is.

What sort of study is this?

Gut Feelings is the biggest ever study of its kind. If you decide to take part you'll be one of thousands of people from England, Northern Ireland, Scotland and Wales helping us find out more about diarrhoea and vomiting.

Who is organising and paying for this study?

The University of Manchester is organising Gut Feelings. We also have a number of other partners who work with GPs all over the UK. And the research is being funded by the Food Standards Agency, the government body that is responsible for ensuring food safety.

Why have I been chosen, and do I have to take part?

The reason why you're receiving this invitation is that your name is one of 800 that has been randomly picked from your doctor's list of patients.

However, it's up to you whether you take part or not. And if you decide you'd rather not take part, rest assured that your healthcare will not be affected in any way.

What happens next if I agree to take part in this study?

All you have to do is:

1. Fill in a consent form. This tells us you are happy to take part in the study.
2. Complete a short questionnaire, which will help us understand a little bit more about youself.
3. Tell us as soon as possible if you are ill with diarrhoea or vomiting. We'll contact you every week for six months to find out if you've been ill with diarrhoea or vomiting. All we need is a simple yes or no.

If the answer is yes, we'll ask you to contact the nurse at your doctor's surgery, complete a symptom questionnaire about your illness and give us a faeces (poo) sample.

What happens to my sample?

We'll test the sample for germs and send the results back to your GP. And, if you agree, we'll store the sample and the germs so that they may be used in future studies.

What kind of information will be collected about me?

As well as the results of your faeces test, we'll record information like your name, age, ethnic group and any relevant medical information (for example, if you have a history of diarrhoea problems), and details of your symptoms and any foreign travel.

How will this information be kept confidential?

The law called the Data Protection Act (1998) tells us how to keep your information secure.

We'll store your information on a highly secure web-based electronic database. The system has been built to the standards used by the high street banks for internet banking and can only be accessed by authorised members of the Study Team using special passwords. We will not give your details to anyone else.

When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept anonymous.

What are the benefits of taking part in the study?

You'll be helping the Food Standards Agency decide whether current food safety measures have worked or if they need to make changes to safety policy. So it's an important study that could benefit everyone in the UK.

Are there any risks in taking part in this study?

No.

After the study starts, can I change my mind?

You can leave the study whenever you want. The information you have given up to that point will still be helpful to us.

What if I have a question or there is a problem?

If there is anything about the study that you're not sure about, just ask to speak to the research nurse who will try to answer your question.

If you are unhappy about an aspect of the study and you want to make a complaint, you can do this through the NHS Complaints Procedure. Your doctor's surgery will be able to give you information about how to do this.

What happens when the study finishes?

The results of the study will be published after April 2010 as a report and in medical journals. It will also be presented at various medical conferences. We will not use your name or any information that might be used to identify you.

If you'd like to see the results of the study we can send you a summary. Just tick the box on the consent form. We will also ask you for permission to contact you in the future to see if you'd be interested in taking part in related studies.

Who has checked the study?

All studies like this one have to be checked by an NHS Ethics Committee. This one has been checked by the North West Research Ethics Committee.

To find out more about Gut Feelings, after having spoken to your practice nurse, please call **Julie Dodds (IID2 Study Manager) on 0207 670 4869**. If you'd like to make a complaint, please call **Kathryn Jackson (IID2 Project Manager) on 0161 206 4394**.

To help us reduce tummy bugs across the nation

Please contact your doctor's surgery today by returning the reply slip and tell them you'd like to take part in Gut Feelings.

The Second Study of Diarrhoea and Vomiting in the Community

REPLY SLIP

Thank you for taking the time to read the letter and information sheet about this study.
Please let us know if you want to find out more about the study or not by completing this form below and sending it back to us in the enclosed pre-paid envelope.

Your surname: .....

Forename: .....

Your date of birth (dd/mm/yyyy): .....

Your Sex: Male ☐ Female ☐

Today's date (dd/mm/yyyy): .....

Yes please, I want to find out more about the study ☐

If Yes, please give best mobile and landline contact numbers:

Mobile No: .....

Landline No: .....

No thank you, I do not want to find out more about the study ☐

If no, please let us know why not by ticking one of the boxes below

No time ☐ Not interested ☐

Often away ☐ Other (please state below) ☐

Other: .....

Appendix 6.8: GP Presentation Study – Information Pack – Adult – Phase 2 recruitment

App 6.8.1: Letter of Invitation

ProsStu_GP Presentation Participant Letter_04

GP Practice Headed Paper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

This surgery is taking part in a national study about diarrhoea and vomiting (D&V). We want to find out exactly how often people get D&V and what germs are causing it.

We are inviting you (or your child) to take part because you or your child have come into the surgery with symptoms of D&V. Before you decide if you would like to join in or not please take time to read the enclosed information. This tells you why we are doing the study and what will happen if you agree to join in. You can take your time to decide if you want to take part and also talk to other people about the study.

Please contact xxxxxxxx at the surgery if there is anything that is not clear or if you would like more information. The practice nurse will contact you by telephone to find out if you are interested in taking part.

If you are not interested that's fine – it won't affect your care in any way and we won't contact you again about the study.

Thank you for taking the time to read this letter and the information enclosed.

Yours Sincerely

Signed by Patient's GP

17th January 2008

Help us reduce tummy bugs across the nation

Have you ever wondered why you occasionally get diarrhoea or suffer from vomiting? Well, that's the kind of thing we spend a lot of time thinking about.

That's why we're pleased to say that your surgery is taking part in Gut Feelings, the biggest ever study about the gut health of the nation.

This leaflet will tell you all about why the study's being done and what you'll be asked to do if you decide to join.

What's Gut Feelings all about?

You may have heard of salmonella, gastroenteritis, gastric flu, or even infectious intestinal disease. These are just some of the forms of diarrhoea and vomiting we'd like to understand better.

We want to find out how many people suffer from them during a year, how many go to their doctor when they have a problem, and what germs are to blame.

Of course, doctors already know a lot about how big a problem diarrhoea and vomiting is. But we'd like to find out how good their information is.

What sort of study is this?

Gut Feelings is the biggest ever study of its kind. If you decide to take part you'll be one of thousands of people from England, Northern Ireland, Scotland and Wales helping us find out more about diarrhoea and vomiting.

Who is organising and paying for this study?

The University of Manchester is organising Gut Feelings. We also have a number of other partners who work with GPs all over the UK. And the research is being funded by the Food Standards Agency, the government body that is responsible for ensuring food safety.

Why have I been chosen, and do I have to take part?

As you have come to the surgery with either diarrhoea or vomiting we are asking you to take part. However, it is up to you whether you do or not. And if you decide you'd rather not take part, rest assured that your healthcare will not be affected in any way.

What happens next if I agree to take part in this study?

If you do agree to take part you will be asked to:

1. Fill in a consent form. This tells us you are happy to take part in the study.
2. Complete a short questionnaire, which will help us understand a little bit more about you and your illness.
3. Give a faeces (poo) sample.

What happens to my sample?

We'll test the sample for germs and send the results back to your GP. And, if you agree, we'll store the sample and the germs so that they may be used in future studies.

What kind of information will be collected about me?

As well as the results of your faeces test, we'll record information like your name, age, ethnic group and any relevant medical information (for example, if you have a history of diarrhoea problems), and details of your symptoms and any foreign travel.

How will this information be kept confidential?

The law called the Data Protection Act (1998) tells us how to keep your information secure.

We'll store your information on a highly secure web-based electronic database. The system has been built to the standards used by the high street banks for internet banking and can only be accessed by authorised members of the Study Team using special passwords. We will not give your details to anyone else.

When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept anonymous.

What are the benefits of taking part in the study?

You'll be helping the Food Standards Agency decide whether current food safety measures have worked or if they need to make changes to safety policy. So it's an important study that could benefit everyone in the UK.

Are there any risks in taking part in this study?

No.

After the study starts, can I change my mind?

You can leave the study whenever you want. The information you have given up to that point will still be helpful to us.

What if I have a question or there is a problem?

If there is anything about the study that you're not sure about, just ask to speak to the research nurse who will try to answer your question.

If you are unhappy about any aspect of the study and you want to make a complaint, you can do this through the NHS Complaints Procedure. Your doctor's surgery will be able to give you information about how to do this.

What happens when the study finishes?

The results of the study will be published after April 2010 as a report and in medical journals. It will also be presented at various medical conferences. We will not use your name or any information that might be used to identify you.

If you'd like to see the results of the study we can send you a summary. Just tick the box on the consent form. We will also ask you for permission to contact you in the future to see if you'd be interested in taking part in related studies.

Who has checked the study?

All studies like this one have to be checked by an NHS Ethics Committee. This one has been checked by the North West Research Ethics Committee.

To find out more about Gut Feelings, after having spoken to your practice nurse, please call **Julie Dodds (IID2 Study Manager) on 0207 670 4869**. If you'd like to make a complaint, please call **Kathryn Jackson (IID2 Project Manager) on 0161 206 4394**.

More information:

Gut Feelings

www.gutfeelings.org.uk

Useful links:

FOOD STANDARDS AGENCY

www.food.gov.uk

MRC General Practice Research Framework

www.gprf.mrc.ac.uk

MANCHESTER 1824 The University of Manchester

www.manchester.ac.uk

NHS

www.nhs.uk

To take part in the Gut Feelings study just tell your GP or the practice nurse.

Version.10_1/10/08

Appendix 6.9: GP Presentation Study – Information Pack – Child – Phase 2 recruitment

App 6.9.1: Letter of Invitation

ProsStu_GP Presentation Participant Letter_04

GP Practice Headed Paper

The Second Study of Diarrhoea and Vomiting in the Community

Dear

This surgery is taking part in a national study about diarrhoea and vomiting (D&V). We want to find out exactly how often people get D&V and what germs are causing it.

We are inviting you (or your child) to take part because you or your child have come into the surgery with symptoms of D&V. Before you decide if you would like to join in or not please take time to read the enclosed information. This tells you why we are doing the study and what will happen if you agree to join in. You can take your time to decide if you want to take part and also talk to other people about the study.

Please contact xxxxxxxx at the surgery if there is anything that is not clear or if you would like more information. The practice nurse will contact you by telephone to find out if you are interested in taking part.

If you are not interested that's fine – it won't affect your care in any way and we won't contact you again about the study.

Thank you for taking the time to read this letter and the information enclosed.

Yours Sincerely

Signed by Patient's GP

17th January 2008

Appendix 6.9.2: Information sheet

We're on a tummy bug hunt!

Gut Feelings

THE UK'S LARGEST EVER NATIONAL RESEARCH STUDY OF INTESTINAL HEALTH

We're on the biggest ever tummy bug hunt.

Want to join us?

Tummy bugs are tiny things that make us ill sometimes. When you have an upset tummy, it's usually these bugs up to their old tricks.

This year, thousands of people from across the country are going to help us find out more about tummy bugs - the results will help us to make food safer.

That's why we'd like you to join us on our huge hunt for tummy bugs.

Why me?

We are asking you to join in because you have come to the surgery with a tummy bug!

But you don't have to take part. It's up to you. It will not change how your doctor or nurse treats you.

How do we hunt for tummy bugs?

1. First, we'll ask your parent or guardian to complete and sign a form that tells us that you agree to join in. Then they'll answer some questions about your illness.
2. We'll then ask you to give us a sample of your poo (because that's where the tummy bugs end up!)
3. We'll have a good look at your sample in a laboratory and tell your doctor what we find. If we come across any tummy bugs we'll keep them if you don't mind.

If you want to leave The Tummy Bug Hunt that's fine. Just let us know. It will not change how your doctor or nurse treats you. If you stop, the information you have given will still be useful.

Or if you have any questions or you want to make a complaint, just speak to the nurse.

What happens to my information?

There is a law that tells us how to keep study information safe.

We will store the information that you give us on a very safe web-based electronic database. The system has been built in the same way that is used by the high street banks for internet banking and only some members of the Study Team using special passwords will be allowed to see this. We will not give your details to anyone else. When we publish the results of the study we will group together all the information that we have collected from everyone taking part in the study and your name will be kept secret.

The Tummy Bug Hunt has been checked by the North West Research Ethics Committee.

At the end of The Tummy Bug Hunt we will write a report. This is for people to learn about the results. Your name and details that can identify you will not be used.

To find out more about The Tummy Bug Hunt, please speak to your practice nurse and then call **Julie Dodds (IID2 Study Manager) on 0207 670 4869**. If you'd like to make a complaint, please call **Kathryn Jackson (IID2 Project Manager) on 0161 206 4394**

To take part in The Tummy Bug Hunt study ask your parent or guardian to tell your GP or the practice nurse.

More information:

Gut Feelings

www.gutfeelings.org.uk

Useful links:

FOOD STANDARDS AGENCY

www.food.gov.uk

MRC General Practice Research Framework

www.gprf.mrc.ac.uk

MANCHESTER 1824
The University of Manchester

www.manchester.ac.uk

NHS

www.nhs.uk

To take part in the Gut Feelings study just tell your GP or the practice nurse.

Version.10_1/10/08

Appendix 6.10: Prospective Cohort Study Reminder Letter - Phase 2 recruitment

App 6.10.1: Reminder letter – Adult

GP Practice Headed Paper

You are invited to take part in the UK's biggest ever gut health study

Dear

We wrote to you recently to let you know that our surgery is taking part in Gut Feelings, a huge study about the gut health of the nation. I am contacting you again to see whether you would be prepared to help us.

What's involved?
We simply need to ask you a few questions at the start of the study about yourself. Then, all you need to do is keep in touch with us once a week for six months. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

What are we looking for?
Gut Feelings is all about finding out how often people get diarrhoea and vomiting and which germs are causing it. We will use the results to find better ways of preventing infections.

You don't need to be ill to take part in Gut Feelings. The study needs people who don't suffer from stomach bugs as well as those who do.

Can you help us?
We are looking for people of all ages, so it would be really helpful if you could.

I've sent you some information about the study - it should tell you everything you want to know, but if you have any more questions just contact xxxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you are interested, please return the enclosed reply slip in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your care in any way and we won't contact you again about this study.

Thanks for your time.

Signed by Patient's GP

P.S. Please remember that you don't need to be ill to take part in Gut Feelings. **The study needs people who don't suffer from stomach bugs as well as those who do.**

App 6.10.2: Reminder letter – Child

GP Practice Headed Paper

Your child is invited to take part in the UK's biggest ever gut health study

Dear

We wrote to you recently to let you know that our surgery is taking part in Gut Feelings, a huge study about the gut health of the nation. I am contacting you again to see whether you would be prepared to help us.

I am inviting your child: ……..
to take part. If your child is old enough please discuss this with them.

What's involved?
We simply need to ask you a few questions at the start of the study about your child. Then, all you need to do is keep in touch with us once a week for six months. If you forget, that doesn't matter because we'll contact you to remind you. In all, we will need no more than about 10 minutes of your time every week.

What are we looking for?
Gut Feelings is all about finding out how often people get diarrhoea and vomiting and which germs are causing it. We will use the results to find better ways of preventing infections.

Your child doesn't need to be ill to take part in Gut Feelings. The study needs people who don't suffer from stomach bugs as well as those who do.

Can you help us?
We are looking for people of all ages, so it would be really helpful if you could.

I've sent you some information about the study - it should tell you everything you want to know, but if you have any more questions just contact xxxxxxxxxx at the surgery for more information.

What to do now
Once you have decided whether or not you are interested, please return the enclosed reply slip in the stamped addressed envelope provided.

If you are interested, or just want to know more, a nurse from the practice will contact you by telephone to discuss the study. If you reply that you are not interested that's fine – it won't affect your child's care in any way and we won't contact you again about this study.

Thanks for your time.

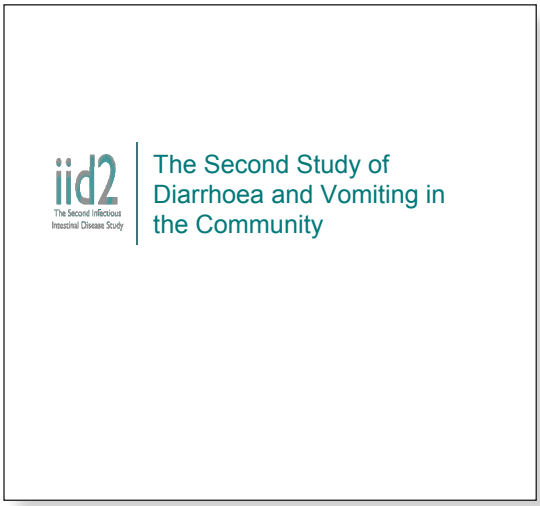
Signed by Patient's GP

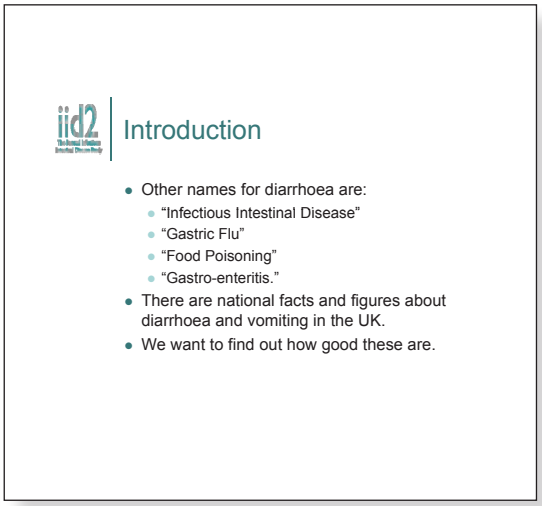
P.S. Please remember that your child doesn't need to be ill to take part in Gut Feelings. **The study needs people who don't suffer from stomach bugs as well as those who do.**

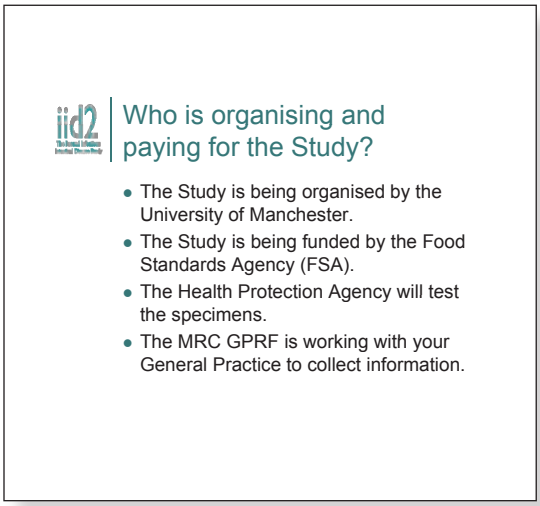
Appendix 7: Baseline interview PowerPoint™ presentations

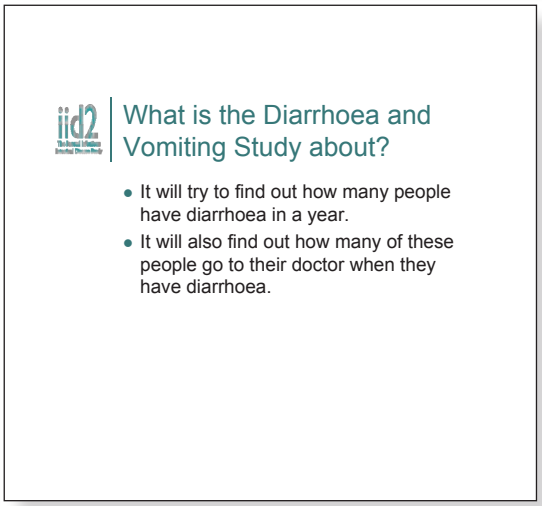
Appendix 7: Baseline interview PowerPoint™ presentations

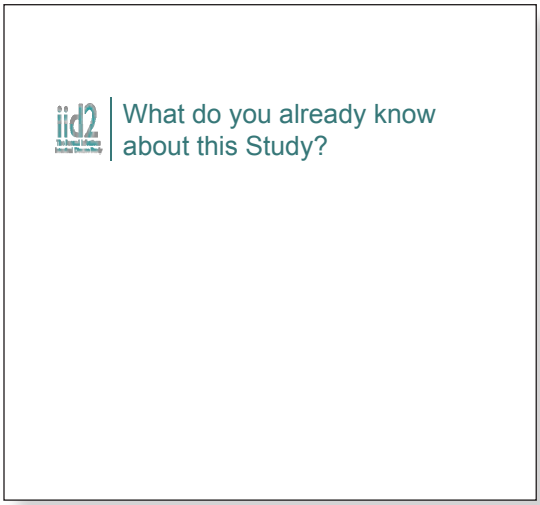
App 7.1: Prospective Cohort Study – Adult (Phase 1 recruitment)

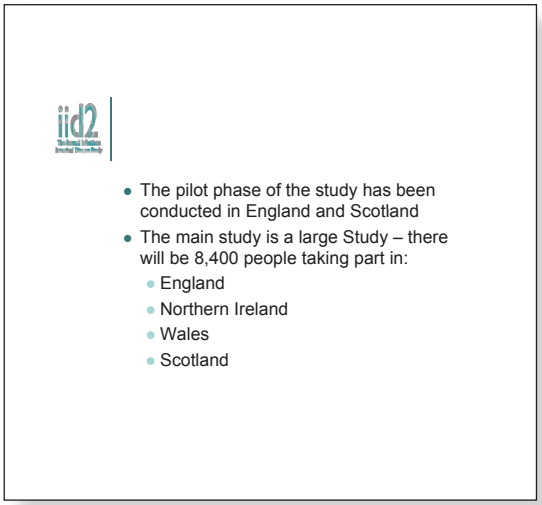












Why is this Study important?

- In the mid 1990s, diarrhoea and vomiting affected one in five people in England.
- Because this was a large number of people becoming ill, new rules and laws were made to improve food safety.
- This Study will find out if these rules and laws mean that less people now become ill.

Why have you been chosen?

- Your doctor randomly picked people (from their practice list) who could be asked if they wanted to take part.
- This Study is inviting people from across the UK.

What will happen to you during this Study?

- We have invited a large number of people to take part in this Study.
- Over one year we will:
  - Ask you to tell us if you have been well or ill.
  - If you have been ill with diarrhoea, we will ask you to send a sample of faeces/stool to a laboratory so that we can test it for germs.
- Your doctor or nurse will tell you if you need treatment for diarrhoea and vomiting if you become ill.

Do you have to take part in this Study?

- No. It is up to you.
- If you do, we will ask you to sign a consent form to show that you agree.
- You can still decide to leave the Study at any time if you change your mind.
- Your healthcare will not be affected if you decide to leave.

What happens next if you do agree to take part?

- If you do decide to take part, you will be asked to do three things:
  - Fill in a consent form.
  - Fill in a short questionnaire.
  - To complete a post card **or** reply to an email we send to you each week.

Consent Form

- The consent form shows that you are happy to take part in the Study. It says that:
  - You have been given a full description of this Study.
  - You have had a chance to ask any questions.
  - You have received an information pack.

Short Questionnaire

- The questionnaire will tell us about yourself:
  - E.g. age, sex, postcode, job
- We will then contact you once a week, over the next twelve months to see if you are well or if you have been ill.

If you are well…

- We will contact you every week until:
  - The study ends
- If you are not ill, it is still important that you keep telling us this so that we can work out how many people become ill with diarrhoea and vomiting.
- There is no need for you to change your lifestyle while taking part in this Study

If you are ill…

- Please contact the nurse at your doctor's surgery as soon as you become ill.
- We will ask you to complete a short questionnaire about your illness:
  - E.g. How long were you ill?
- Give us a faeces/stool sample so we can test for germs. You will be given a sample pot at the start of the Study.

What will happen to the faeces/stool sample?

- The faeces/stool samples will be tested for germs at the Health Protection Agency Laboratory in Manchester.
- The results will be sent back to your doctor.
- The sample and any germs found will then be stored at the Centre for Infections at Colindale in North London. More tests will be done to find out more about the germs. The germs will be stored and may be used in future studies.
- If your sample grows germs for e.g. Salmonella you may be contacted by an environmental health officer.

What will happen if you do not give a faeces/stool sample?

- We would prefer it if you did provide a faeces sample.
- If you do not, you can still stay in the Study.
- Continue to send back the post cards or emails to us.
- Send back the questionnaire to the nurse.

What kind of information will be collected?

- Name; Age; Postcode; Job.
- Relevant medical history e.g. a history of diarrhoea problems
- Any symptoms of diarrhoea and vomiting
- Results of test on the faeces/stool

This information will actually be kept anonymous and will all be stored securely – working with the guidelines of the Data Protection Act (1998).

Appendix 7.2: Prospective Cohort Study – Child (Phase 1 recruitment)

The Tummy Bug Study

Introduction

- Other names for tummy bugs are:
  - "Diarrhoea"
  - "Food poisoning"
- We want to find out how many people get tummy bugs in a year.
- We would also like to know how many of these people go to their doctor in a year.

Why have you asked me to help?

- We asked your doctor to choose people from the list of people who go to see them when they are ill.
- Your name was picked.

Do I have to help?

- No. It is up to you.
- If you do, we will ask you to sign a consent form to show that you agree.
- You can still decide to leave the Study at any time if you change your mind.

If I decide to help you, what will happen?

- Your nurse will ask you to sign a consent form. This will tell us that you would like to help us.
- You, or your mum or dad or anyone who looks after you, will fill in a questionnaire about your health.

Then what happens?

- Every week we will ask you, or the person who looks after you, if you have been ill with a tummy bug.
  - If you have not been ill, we will ask you again next week.

- But
  - If you have been ill, we will ask for a sample of faeces/stool.

What will happen to the faeces/stool sample?

- The faeces sample will be tested for germs.
- The results will be sent back to your doctor.
- The sample and any germs that are found will be stored. These may be used in future studies to find out more about germs.

How will the Tummy Bug Study help me?

- The Study will tell us if we need to have more rules to make food safer to help stop people being ill.
- So, if you decide to take part, you may not get anything, but you could be helping the people who live in this country.

What if I don't want to help anymore?

- It is up to you decide if you want to take part. You can refuse.
- You can stop taking part whenever you want. It will not change how your doctor and nurse treat you.

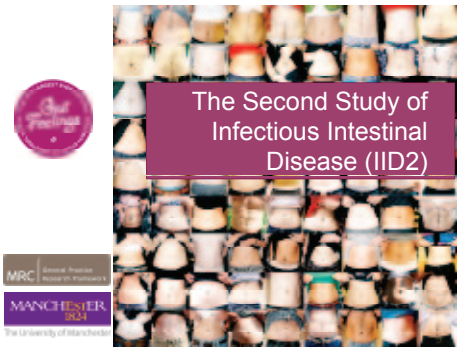
What if I have a question or there is a problem?

- If you are worried about any aspect of this Study you should ask to speak to the researchers who will do their best to answer your questions.

What will happen when the Tummy Bug Study finishes?

- The results will be published as a report, for people to read and it will be talked about at conferences. Your name will not be used.
- We will give you a short report of the results if you would like one.
- You can tell us if you would like this by ticking a box on the consent form.

Appendix 7.3: GP Presentation Study – Adult (Phase 2 recruitment)



What is the Diarrhoea and Vomiting Study about?

- It will try to find out how many people have diarrhoea or vomiting in a year.
- It will also find out how many of these people go to their doctor when they have diarrhoea or vomiting.
- Other names for diarrhoea or vomiting are:
  - "infectious intestinal disease"
  - "food poisoning"
  - "gastric flu"

What sort of Study is this?

- This is a large Study that involves everyone who goes to see their doctor with diarrhoea and/or vomiting.

Who is organising and paying for the Study?

- The Study is being organised by the University of Manchester and other partners from all over the UK.
- They are working with your doctor.
- The Study is being funded by the Food Standards Agency (FSA).

Why have you been chosen?

- We are inviting you to take part, because you have come into the surgery with diarrhoea or vomiting.
- It is up to you to decide whether you want to take part.
- If you decide not to take part your health care will not be affected in any way.

What happens next if you do agree to take part?

- If you do decide to take part, you will be asked to do three things:
  - Fill in a consent form.
  - Fill in a short questionnaire to tell us about yourself and your illness.
  - Give a faeces/stool sample.

What will happen to the faeces/stool sample?

- The faeces/stool samples will be tested for germs at the Health Protection Agency Laboratory in Manchester.
- The results will be sent back to your doctor.
- The sample and any germs found will then be stored at the Centre for Infections at Colindale in North London. More tests will be done to find out more about the germs. The germs will be stored and may be used in future studies.
- If your sample grows germs for e.g. Salmonella you may be contacted by an environmental health officer.

What kind of information will be collected about me?

- Name; Age; Postcode; Job; Ethnic Group
- Relevant medical history e.g. a history of diarrhoea problems
- Any symptoms of diarrhoea and vomiting
- Details of any travel abroad
- Results of test on the faeces/stool

This information will be kept anonymous and will all be stored securely – working within the guidelines of the Data Protection Act (1998).

What are the benefits of taking part in this Study?

- The Study will help the Food Standards Agency to decide whether current rules about food safety have worked.
- It will help them see if they need to make changes to food safety regulations.

Are there any risks in taking part in this Study?

- No. There are no risks in taking part in this Study.

After the Study starts , can I change my mind?

- You can leave the Study at any time.
- If you do leave the information you have given up to that time will still be helpful.

What if I have a question or there is a problem?

- If you are not sure about any aspect of this Study, talk to the Research Nurse who will try to answer your questions.
- If you are unhappy with the study and we are unable to resolve the issue you may wish to complain. You can do this through the NHS Complaints Procedure. You can get information about this from the Surgery.

What happens when the Study finishes?

- The results will be published as a report.
- Your name and any information that can identify you will not be used.
- We will give you a short copy of the results if you would like one. (Please tick the box on the consent form).

Appendix 7.4: GP Presentation Study – Child (Phase 2 recruitment)

The Tummy Bug Study

Introduction

- Other names for tummy bugs are:
  - "Diarrhoea"
  - "Food poisoning"
- We want to find out how many people get tummy bugs in a year.
- We would also like to know how many of these people go to their doctor in a year.

What sort of Study is this?

- This is a large Study that involves everyone who goes to see their doctor with diarrhoea and/or vomiting.

Why have you asked me to help?

- We're asking you to join in because you have come into the Surgery with a tummy bug.

Do I have to join in?

- No. It is up to you.
- If you do not want to join in, that's no problem. It will not change how your doctor and nurse treat you.

If I join in, what will happen to me?

- We want you to tell us about your diarrhoea or vomiting.
- Your nurse will ask your mum or dad or guardian to sign a form. This will tell us that you agree to join.
- You, or your parent or guardian will fill in a form about your illness.
- You will give us a sample of faeces/stool.

What will happen to the faeces/stool sample?

- The faeces/stool sample will be tested for germs.
- The results will be sent back to your doctor.
- The sample and any germs that are found will be stored. These may be used in future studies to find out more about germs.

How will the Tummy Bug Study help me?

- The Study will tell us if we need to have more rules to make food safer to help stop people being ill.
- So, if you decide to take part, you may not get anything, but you could be helping the people who live in this country.

What if I have a question or there is a problem?

- If you are worried about any aspect of this Study ask to speak to the nurse who will try to answer your questions.
- If you are unhappy with the study and we are unable to resolve the issue you could make a complaint.

What if I don't want to help anymore?

- If you do not want to carry on with the Study, you can stop at any time.
- It will not change how your doctor and nurse treat you.
- If you stop, the information you have given will still be helpful.

What will happen when the Tummy Bug Study finishes?

- We will write a report for people to read and it will be talked about at conferences.
- Your name will not be used.

Appendix 8: Informed Consent/Assent

Appendix 8.1: Prospective Cohort Study – Adult Consent

iid2
The Second Infectious Intestinal Disease Study

ProsStu_Cohort_Consent_Adults_10

Centre Number: *For official use only*
Participants Study Number:

Consent Form
The Second Study of Diarrhoea and Vomiting in the Community
(Weekly Follow Up Study)

Name of Local Researcher:

I consent (agree) to take part in this Study, which means that:

(Please initial on the lines if you agree with each of these statements)

- I have read and understand the information pack (01/10/08 Version 16) for this Study and
  - I have been given a copy to keep.
  - I have been able to ask questions,
  - These questions have been answered satisfactorily. ----------
- I understand that taking part in this Study is voluntary and that I can leave the Study at any time. ----------
- I give my permission for someone from the Study team to look at my medical records to get relevant information about my medical history. ----------
- I understand that all information will be kept confidential. ----------
- I agree to give a faeces (poo) sample if I become ill with diarrhoea or vomiting
  - I understand that giving a sample is voluntary.
  - I understand that my doctor will be given the results.
  - I understand that I am free to withdraw my agreement for the use of this sample without giving a reason and without my medical treatment or legal rights being affected. ----------
- I agree that the faeces sample I have given can be stored for possible use in future research projects.
  - I understand that some of these projects may be carried out by researchers other than this Study team. ----------
- I agree that the Study team can contact me in the future to find out if I am interested in future research. ----------

Name of Participant (BLOCK CAPITALS)	Date	Signature
Name of Researcher taking consent	Date	Signature

Would you like us to send you the results of this project? Yes ☐ No ☐

Thank you for agreeing to take part in this research

When completed, please send the top copy to the research team; and give 1 copy to the participant and keep 1 copy in the GP medical notes

1st October 2008

Appendix 8.2: Prospective Cohort Study – Child Assent

ProsStu_Cohort_Assent_Child_11

Centre Number: *For official use only*
Participants Study Number:

Assent Form
The Second Study of Diarrhoea and Vomiting in the Community
(Weekly Follow Up Study)

Name of Local Researcher:

I assent (agree) to my child taking part in this Study, which means that:

(Please initial the boxes if you agree with each of these statements)

- I have read and understand the information pack (01/10/08 Version *13*) for this Study and
  - I have been given a copy to keep.
  - I have been able to ask questions,
  - These questions have been answered satisfactorily. ----------
- I understand that taking part in this Study is voluntary for my child and that they can leave the Study at any time. ----------
- I give my permission for someone from the Study team to look at my child's medical records to get relevant information about their medical history. ----------
- I understand that all information will be kept confidential. ----------
- I agree that my child can give a faeces (poo) sample if they become ill with diarrhoea or vomiting.
  - I understand that giving a sample is voluntary.
  - I understand that my doctor will be given the results.
  - I understand that I am free to withdraw my agreement for the use of this sample without giving a reason and without my medical treatment or legal rights being affected. ----------
- I agree that the faeces sample my child has given can be stored for possible use in future research projects.
  - I understand that some of these projects may be carried out by researchers other than this Study team. ----------
- I agree that the Study team can contact me in the future to find out if I am interested in related research. ----------

_____
Name of Participant (BLOCK CAPITALS)

_____ _____ _____
Name of parent/guardian (BLOCK CAPITALS) Date Signature

_____ _____ _____
Name of Researcher taking consent Date Signature

Would you like us to send you the results of this project? Yes ☐ No ☐

Thank you for agreeing to take part in this research.

When completed, please send the top copy to the research team; and give 1 copy to the participant and keep 1 copy in the GP medical notes

5th November 2008

Appendix 8.3: GP Presentation Study – Adult Consent

ProsStu_GP Presentation_Consent_Adults_06

Centre Number: *For official use only*
Participants Study Number:

Consent Form
The Second Study of Diarrhoea and Vomiting in the Community
(GP Presentation Study)

Name of Local Researcher:

I consent (agree) to take part in this Study, which means that:

(Please initial on the lines if you agree with each of these statements)

- I have read and understand the information pack (01/10/08 Version 10) for this Study and
  - I have been given a copy to keep.
  - I have been able to ask questions,
  - These questions have been answered satisfactorily. ----------
- I understand that taking part in this Study is voluntary and that I can leave the Study at any time. ----------
- I give my permission for someone from the Study team to look at my medical records to get relevant information about my medical history. ----------
- I understand that all information will be kept confidential. ----------
- I agree to give a faeces (poo) sample.
  - I understand that giving a sample is voluntary.
  - I understand that my doctor will be given the results.
  - I understand that I am free to withdraw my agreement for the use of this sample without giving a reason and without my medical treatment or legal rights being affected. ----------
- I agree that the faeces sample I have given can be stored for possible use in future research projects.
  - I understand that some of these projects may be carried out by researchers other than this Study team. ----------
- I agree that the Study team can contact me in the future to find out if I am interested in future research. ----------

Name of Participant (BLOCK CAPITALS)	Date	Signature
Name of Researcher taking consent	Date	Signature

Would you like us to send you the results of this project? Yes ☐ No ☐

Thank you for agreeing to take part in this research

When completed, please send the top copy to the research team; and give 1 copy to the participant and keep 1 copy in the GP medical notes

1st October 2008

Appendix 8.4: GP Presentation Study – Child Assent

ProsStu_GP Presentation_Assent_Child_06

For official use only

Centre Number:
Participants Study Number:

Assent Form
The Second Study of Diarrhoea and Vomiting in the Community
(GP Presentation Study)

Name of Local Researcher:

I assent (agree) to my child taking part in this Study, which means that:

(Please initial the boxes if you agree with each of these statements)

- I have read and understand the information pack (01/10/08 Version 10) for this Study and
  - I have been given a copy to keep.
  - I have been able to ask questions,
  - These questions have been answered satisfactorily. ----------
- I understand that taking part in this Study is voluntary for my child and that they can leave the Study at any time. ----------
- I give my permission for someone from the Study team to look at my child's medical records to get relevant information about their medical history. ----------
- I understand that all information will be kept confidential. ----------
- I agree that my child can give a faeces (poo) sample.
  - I understand that giving a sample is voluntary.
  - I understand that my doctor will be given the results.
  - I understand that I am free to withdraw my agreement for the use of this sample without giving a reason and without my medical treatment or legal rights being affected. ----------
- I agree that the faeces sample my child has given can be stored for possible use in future research projects.
  - I understand that some of these projects may be carried out by researchers other than this Study team. ----------
- I agree that the Study team can contact me in the future to find out if I am interested in related research. ----------

_____
Name of Participant (BLOCK CAPITALS)

_____ _____ _____
Name of parent/guardian (BLOCK CAPITALS) Date Signature

_____ _____ _____
Name of Researcher taking consent Date Signature

Would you like us to send you the results of this project? Yes ☐ No ☐

Thank you for agreeing to take part in this research.

When completed, please send the top copy to the research team; and give 1 copy to the participant and keep 1 copy in the GP medical notes

1st October 2008

Appendix 9: Questionnaires

Appendix 9.1: Prospective Cohort Study – Baseline Questionnaire - Adult

ProsStu_Cohort_Base Questionnaire_Adult_06

Baseline Questionnaire (Weekly Follow-up Study)

The Second Study of Diarrhoea and Vomiting in the Community

Name of Research Nurse:	*For office use only*
Participant's study number:	
Mode of Contact:	

We want to know how often people in the UK suffer from diarrhoea or vomiting and the germs that cause this.

We need to collect some basic information before you take part in the Study.
The information that you give us will be treated in strict confidence

1. What is your surname: ……

   forename(s): ……

2. What is your date of birth (dd/mm/yyyy)? ____/____/____

3. Are you? Male ☐ Female ☐

4. Please give your address: ……

   ……

   ……

5. What is your postcode? ☐☐☐☐ ☐☐☐

6. What is your email address? ……

7. Which ethnic group do you belong to?

Please tick one

White	British or Irish	
	Other	
Mixed	White & Black Caribbean	
	White and Black African	
	White and Asian	
	Other Mixed	
Asian or Asian British	Indian	
	Pakistani	
	Bangladeshi	
	Other Asian	
Black or Black British	Black Caribbean	
	Black African	
	Other Black	
Another Group	Chinese	
	Other ethnic group	

PLEASE TURN OVER

8. Please tell us what the job title is of the **main earner** in your household:……

9. Please tick one box to show which **best** describes the sort of work the **main earner** in your household does. (If the main earner is not working now, please tick a box to show what they did in their last job).

Please tick one box.

Modern professional occupations *such as:* teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer	
Clerical and intermediate occupations *such as:* secretary - personal assistant - clerical worker - office clerk - call centre agent - nursing auxiliary - nursery nurse	
Senior managers or administrators (usually responsible for planning, organising and co-ordinating work and for finance) *such as:* finance manager - chief executive	
Technical and craft occupations *such as:* motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver	
Semi-routine manual and service occupations *such as:* postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant	
Routine manual and service occupations *such as:* HGV driver - van driver - cleaner - porter - packer - sewing machinist - messenger - labourer - waiter / waitress - bar staff	
Middle or junior managers *such as:* office manager - retail manager - bank manager, restaurant manager - warehouse manager - publican	
Traditional professional occupations *such as:* accountant - solicitor - medical practitioner - scientist - civil / mechanical engineer	

10. Last week, was the **main earner** in your home any of the following?

Please tick one box.

Retired	
Student	
Looking after home/family	
Currently sick/disabled	
None of the above	

11. Does (did) the **main earner** work as an employee or are (were) they self-employed?

Please tick one box.

Employee	
Self-employed with employees	
Self-employed/freelance without employees (please skip questions 12 and 13)	

12. **For employees**: indicate below how many people work (worked) for the **main earner's** employer at the place where they work (worked).
For self-employed: indicate below how many people the main earner employs (employed).

Please tick one box.

1 to 24	
25 or more	

13. Does (did) the **main earner** supervise any other employees?
A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis

Please tick one box.

Yes	
No	

14. The nurse may need to contact you at some time during the study.
What is the best telephone number to contact you on?

.....

15. Do you have a landline at your home? Yes ☐ No ☐

Thank you for agreeing to fill in this questionnaire.

Appendix 9.2: Prospective Cohort Study – Baseline Questionnaire - Child

ProsStu_Cohort_Base Questionnaire_Child_06

Baseline Questionnaire (Weekly Follow-up Study)

The Second Study of Diarrhoea and Vomiting in the Community

Name of Research Nurse:	*For office use only*
Participant's Study Number:	
Mode of Contact:	

We want to know how often people in the UK suffer from diarrhoea or vomiting and the germs that cause this.

We need to collect some basic information about your child before they take part in the Study.
The information that you give us will be treated in strict confidence

1. What is your child's surname: ……..……
   child's forename(s): ……
2. What is your child's date of birth (dd/mm/yyyy)? ____/____/____
3. Are they? Male ☐ Female ☐
4. Please give your child's address: ……
   ……
   ……
5. What is your child's postcode? ☐☐☐☐ ☐☐☐
6. What is your email address? ……
7. Which ethnic group does your child belong to?

Please tick one box.

White	British or Irish	
	Other	
Mixed	White & Black Caribbean	
	White and Black African	
	White and Asian	
	Other Mixed	
Asian or Asian British	Indian	
	Pakistani	
	Bangladeshi	
	Other Asian	
Black or Black British	Black Caribbean	
	Black African	
	Other Black	
Another Group	Chinese	
	Other ethnic group	

8. Please tell us what the job title is of the **main earner** in your child's household:……

9. Please tick one box to show which **best** describes the sort of work the **main earner** in your child's household does. (If the main earner is not working now, please tick a box to show what they did in their last job).

Please tick one box.

Modern professional occupations *such as:* teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer	
Clerical and intermediate occupations *such as:* secretary - personal assistant - clerical worker - office clerk - call centre agent - nursing auxiliary - nursery nurse	
Senior managers or administrators (usually responsible for planning, organising and co-ordinating work and for finance) *such as:* finance manager - chief executive	
Technical and craft occupations *such as:* motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver	
Semi-routine manual and service occupations *such as:* postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant	
Routine manual and service occupations *such as:* HGV driver - van driver - cleaner - porter - packer - sewing machinist - messenger - labourer - waiter / waitress - bar staff	
Middle or junior managers *such as:* office manager - retail manager - bank manager, restaurant manager - warehouse manager - publican	
Traditional professional occupations *such as:* accountant - solicitor - medical practitioner - scientist - civil / mechanical engineer	

10. Last week, was the **main earner** in your home any of the following?

Please tick one box.

Retired	
Student	
Looking after home/family	
Currently sick/disabled	
None of the above	

11. Does (did) the **main earner** work as an employee or are (were) they self-employed?

Please tick one box.

Employee	
Self-employed with employees	
Self-employed/freelance without employees (please skip questions 12 and 13)	

12. **For employees**: indicate below how many people work (worked) for the **main earner's** employer at the place where they work (worked).
For self-employed: indicate below how many people the main earner employs (employed).

Please tick one box.

1 to 24	
25 or more	

13. Does (did) the **main earner** supervise any other employees?
A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis

Please tick one box.

Yes	
No	

14. The nurse may need to contact you at some time during the study.
What is the best telephone number to contact you on?

.....

15. Do you have a landline at your home? Yes ☐ No ☐

Thank you for agreeing to fill in this questionnaire.

Appendix 9.3: Prospective Cohort Study – Symptom Questionnaire - Adult

ProsStu_Cohort Study_Questionnaire_Adult__09

iid2 The Second Infectious Intestinal Disease Study

Questionnaire (Weekly Follow-up Study)

The Second Study of Diarrhoea and Vomiting in the Community

Name of Research Nurse:	*For Official Use Only*
Participant's Study Number:	

We want to know how often people in the UK suffer from diarrhoea or vomiting and the germs that cause this.

Thank you for agreeing to fill in this questionnaire.

Please read each question carefully before you answer it, and try to answer every question. Please either tick the appropriate box or write your answer in the space provided.

The information that you give us will be treated in strict confidence.

Part 1: This section asks about your age and sex

Please tell us:

1.1 Today's date (dd/mm/yyyy): _____/_____/_____

1.2 Your date of birth (dd/mm/yyyy): _____/_____/_____

1.3 Your sex: Male ☐ Female ☐

Part 2: This section asks about the symptoms you had during your recent illness

2.1 Do you have any of the following symptoms? For EACH symptom please tick Yes, No or Not sure.

Diarrhoea: (loose watery bowel movements)

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Diarrhoea with blood in it:

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Nausea (feeling sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Vomiting (being sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Abdominal cramps (colic):

Yes ☐ No ☐ Not sure ☐

Loss of appetite:

Yes ☐ No ☐ Not sure ☐

Fever (high temperature):

Yes ☐ No ☐ Not sure ☐

Cough or runny/blocked nose or sore throat:

Yes ☐ No ☐ Not sure ☐

Headache:

Yes ☐ No ☐ Not sure ☐

2.2 What was the date (dd/mm/yyyy) on which you first had diarrhoea and/or vomiting?

____/____/____

2.3 If you answered “yes” to having diarrhoea, roughly how many times did you go to the toilet on the worst day (24 hours) of your illness?

Number of times ☐☐

2.4 If you answered “yes” to vomiting, roughly how many times did you vomit on the worst day (24 hours) of your illness?

Number of times ☐☐

2.5 Have you phoned NHS Direct/NHS 24 about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone NHS Direct/NHS 24 about these symptoms?

____/____/____

2.6 Have you contacted the out-of-hours doctor service about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the out-of-hours doctor service about these symptoms?

____/____/____

2.7 Have you visited a Walk-in centre about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the walk-in-centre about these symptoms?

____/____/____

2.8 Have you spoken to your nurse or doctor on the 'phone for advice about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone for advice about these symptoms?

____/____/____

2.9 Have you been to see a doctor or nurse in your practice about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first see your doctor about these symptoms?

____/____/____

2.10 Did you go to hospital, Accident and Emergency (A&E) or casualty with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you go to hospital, Accident and Emergency (A&E) or casualty about these symptoms?

____/____/____

PLEASE TURN OVER

2.11 Were you admitted to hospital overnight or longer with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) were you admitted to hospital with this illness?

____/____/____

If "yes", how many nights did you spend in hospital with this illness?

☐☐

2.12 Did your illness stop you from going to work or to school or carrying out your daily activities?

Yes ☐ No ☐ Not sure ☐

If "yes", how many days? ☐☐

Part 3: This section asks about your travel in the ten days before you became ill.

3.1 Did you travel outside the UK in the ten days before you became ill?

Yes ☐ No ☐ Not sure ☐

3.2 If you answered "yes", what dates (dd/mm/yy) were you away?

From: ____/____/____ To: ____/____/____

3.3 If you were abroad, please tell us which country or countries you visited:

_____

Have you sent a faeces (stool) specimen?

Yes ☐ No ☐

If no, please do so as soon as possible, as this is really important for the study. You can get another specimen pot from your practice nurse if you do not have one.

Thank you for taking the time to fill in this questionnaire.
Please return this questionnaire to the research nurse at your doctor's surgery using the reply paid envelope

Appendix 9.4: Prospective Cohort Study – Symptom Questionnaire - Child

ProsStu_Cohort Study_Questionnaire_Child__09

iid2 The Second Infectious Intestinal Disease Study

Questionnaire (Weekly Follow-up Study)

The Second Study of Diarrhoea and Vomiting in the Community

The "Tummy Bug" Study

Name of Research Nurse:	***For Official Use Only***
Participant's Study Number:	

We want to know how often people in the UK suffer from diarrhoea or vomiting and the germs that cause this.

Thank you for agreeing to fill in this questionnaire.

Please read each question carefully before you answer it, and try to answer every question. Please either tick the appropriate box or write your answer in the space provided.

The information that you give us will be treated in strict confidence.

Part 1: This section asks about your child's age and sex

Please tell us:

1.1 Today's date (dd/mm/yyyy): ____/____/____

1.2 Child's date of birth (dd/mm/yyyy): ____/____/____

1.3 Child's sex: Male ☐ Female ☐

Part 2: This section asks about the symptoms your child had during your recent illness

2.1 Did they have any of the following symptoms? For EACH symptom please tick Yes, No or Not sure.

Diarrhoea: (loose watery bowel movements)

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Diarrhoea with blood in it:

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

PLEASE TURN OVER

Nausea (feeling sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Vomiting (being sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Abdominal cramps (colic):

Yes ☐ No ☐ Not sure ☐

Loss of appetite:

Yes ☐ No ☐ Not sure ☐

Fever (high temperature):

Yes ☐ No ☐ Not sure ☐

Cough or runny/blocked nose or sore throat:

Yes ☐ No ☐ Not sure ☐

Headache:

Yes ☐ No ☐ Not sure ☐

2.2 What was the date (dd/mm/yyyy) on which your child first had diarrhoea and/or vomiting?

____/____/____

2.3 If you answered "yes" to having diarrhoea, roughly how many times did your child go to the toilet on the worst day (24 hours) of their illness?

Number of times ☐☐

2.4 If you answered "yes" to having vomiting, roughly how many times did your child go to the toilet on the worst day (24 hours) of their illness?

Number of times ☐☐

2.5 Have you phoned NHS Direct/NHS 24 about your child's illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone NHS Direct/NHS 24 about your child's symptoms?

____/____/____

2.6 Have you contacted the out-of-hours doctor service about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the out-of-hours doctor service about your child's symptoms?

____/____/____

2.7 Have you visited a Walk-in centre about your child's illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the walk-in-centre about your child's symptoms?

____/____/____

2.8 Have you spoken to your child's nurse or doctor on the 'phone for advice about their illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone for advice about these symptoms?

____/____/____

2.9 Have you been to your child's doctor or nurse in your practice about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did your child first see their doctor about these symptoms?

____/____/____

2.10 Did you take your child to hospital, Accident and Emergency (A&E) or casualty with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you go to hospital, Accident and Emergency (A&E) or casualty about these symptoms?

_____/____/____

PLEASE TURN OVER

2.11 Was your child admitted to hospital overnight or longer with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) was your child admitted to hospital with this illness? ____/____/____

If "yes", how many nights did your child spend in hospital with this illness? ☐☐

2.12 Did your child's illness stop them from going to school or day care?

Yes ☐ No ☐ Not sure ☐

If "yes", how many days? ☐☐

Part 3: This section asks about your travel in the ten days before your child became ill.

3.1 Did your child travel outside the UK in the ten days before they became ill?

Yes ☐ No ☐ Not sure ☐

3.2 If you answered "yes", what dates (dd/mm/yy) were you away?

From: ____/____/____ To: ____/____/____

3.3 If you were abroad, please tell us which country or countries your child visited:

_____

Have you sent a faeces (stool) specimen?

Yes ☐ No ☐

If no, please do so as soon as possible, as this is really important for the study. You can get another specimen pot from your practice nurse if you do not have one.

Thank you for taking the time to fill in this questionnaire.
Please return this questionnaire to the research nurse at your doctor's surgery using the reply paid envelope

Appendix 9.5: GP Presentation Study Questionnaire – Adult

Questionnaire (GP Presentation Study)

The Second Study of Diarrhoea and Vomiting in the Community

Name of Research Nurse:	***For office use only***
Participant's study number:	
Date of consultation that lead to study entry:	

We want to know how often people in the UK suffer from diarrhoea or vomiting and the germs that cause this.

Please read each question carefully before you answer it, and try to answer each question. Please either tick the appropriate box or write your answer in the space provided.
The information that you give us will be treated in strict confidence.

Part 1: This section asks for some background information about you.

1. What is your surname: …….
   forename(s): …….
2. What is your date of birth (dd/mm/yyyy)? ____/____/____
3. Are you? Male ☐ Female ☐
4. Please give your address: ……
   ……
   ……
5. What is your postcode? ☐☐☐☐ ☐☐☐
6. What is your email address? ……
7. Which ethnic group do you belong to? Please tick one

White	British or Irish	
	Other	
Mixed	White & Black Caribbean	
	White and Black African	
	White and Asian	
	Other Mixed	
Asian or Asian British	Indian	
	Pakistani	
	Bangladeshi	
	Other Asian	
Black or Black British	Black Caribbean	
	Black African	
	Other Black	
Another Group	Chinese	
	Other ethnic group	

PLEASE TURN OVER

8. Please tell us what the job title is of the **main earner** in your household:……

9. Please tick one box to show which **best** describes the sort of work the **main earner** in your household does. (If the main earner is not working now, please tick a box to show what they did in their last job).

Please tick one box.

Modern professional occupations *such as:* teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer	
Clerical and intermediate occupations *such as:* secretary - personal assistant - clerical worker - office clerk - call centre agent - nursing auxiliary - nursery nurse	
Senior managers or administrators (usually responsible for planning, organising and co-ordinating work and for finance) *such as:* finance manager - chief executive	
Technical and craft occupations *such as:* motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver	
Semi-routine manual and service occupations *such as:* postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant	
Routine manual and service occupations *such as:* HGV driver - van driver - cleaner - porter - packer - sewing machinist - messenger - labourer - waiter / waitress - bar staff	
Middle or junior managers *such as:* office manager - retail manager - bank manager, restaurant manager - warehouse manager - publican	
Traditional professional occupations *such as:* accountant - solicitor - medical practitioner - scientist - civil / mechanical engineer	

10. Last week, was the **main earner** in your home any of the following?

Please tick one box.

Retired	
Student	
Looking after home/family	
Currently sick/disabled	
None of the above	

11. Does (did) the **main earner** work as an employee or are (were) they self-employed?

Please tick one box.

Employee	
Self-employed with employees	
Self-employed/freelance without employees (please skip questions 12 and 13)	

12. **For employees**: indicate below how many people work (worked) for the **main earner's** employer at the place where they work (worked).
For self-employed: indicate below how many people the main earner employs (employed).

Please tick one box.

1 to 24	
25 or more	

13. Does (did) the **main earner** supervise any other employees?
A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis

Please tick one box.

Yes	
No	

14. The nurse may need to contact you at some time during the study. What is the best telephone number to contact you on?

.....

15. Do you have a landline at your home? Yes ☐ No ☐

PLEASE TURN OVER

Part 2: This section asks about the symptoms you had during your recent illness

2.1 Do you have any of the following symptoms? For EACH symptom please tick Yes, No or Not sure.

Diarrhoea: (loose watery bowel movements)

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Diarrhoea with blood in it:

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Nausea (feeling sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Vomiting (being sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Abdominal cramps (colic):

Yes ☐ No ☐ Not sure ☐

Loss of appetite:

Yes ☐ No ☐ Not sure ☐

Fever (high temperature):

Yes ☐ No ☐ Not sure ☐

Cough or runny/blocked nose or sore throat:

Yes ☐ No ☐ Not sure ☐

Headache: Yes ☐ No ☐ Not sure ☐

2.2 What was the date (dd/mm/yyyy) on which you first had diarrhoea and/or vomiting?

____/____/____

2.3 If you answered "yes" to having diarrhoea, roughly how many times did you go to the toilet on the worst day (24 hours) of your illness?

Number of times ☐☐

2.4 If you answered "yes" to vomiting, roughly how many times did you vomit on the worst day (24 hours) of your illness?

Number of times ☐☐

2.5 Have you phoned NHS Direct/NHS 24 about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone NHS Direct/NHS 24 about these symptoms?

____/____/____

2.6 Have you contacted the out-of-hours doctor service about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the out-of-hours doctor service about these symptoms?

____/____/____

2.7 Have you visited a Walk-in centre about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the walk-in-centre about these symptoms?

____/____/____

PLEASE TURN OVER

2.8 Have you spoken to your nurse or doctor on the 'phone for advice about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone for advice about these symptoms?

____/____/____

2.9 Have you been to see a doctor or nurse in your practice about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first see your doctor about these symptoms?

____/____/____

2.10 Did you go to hospital, Accident and Emergency (A&E) or casualty with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you go to hospital, Accident and Emergency (A&E) or casualty about these symptoms?

____/____/____

2.11 Were you admitted to hospital overnight or longer with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) were you admitted to hospital with this illness?

____/____/____

If "yes", how many nights did you spend in hospital with this illness?

☐☐

2.12 Did your illness stop you from going to work or to school or carrying out your daily activities?

Yes ☐ No ☐ Not sure ☐

If "yes", how many days? ☐☐

Part 3: This section asks about your travel in the ten days before you became ill.

3.1 Did you travel outside the UK in the ten days before you became ill?

Yes ☐ No ☐ Not sure ☐

3.2 If you answered "yes", what dates (dd/mm/yy) were you away?

From: ____/____/____ To: ____/____/____

3.3 If you were abroad, please tell us which country or countries you visited:

_____

Have you sent a faeces (stool) specimen?

Yes ☐ No ☐

If no, please do so as soon as possible, as this is really important for the study. You can get another specimen pot from your practice nurse if you do not have one.

Thank you for taking the time to fill in this questionnaire.
Please return this questionnaire to the research nurse at your doctor's surgery using the reply paid envelope

Appendix 9.6: GP Presentation Study Questionnaire – Child

iid2 The Second Infectious Intestinal Disease Study

Questionnaire (GP Presentation Study)

The Second Study of Diarrhoea and Vomiting in the Community

Name of Research Nurse: Participant's study number: Date of consultation that lead to study entry:	***For office use only***

We want to know how often people in the UK suffer from diarrhoea or vomiting and the germs that cause this.

Please read each question carefully before you answer it, and try to answer each question. Please either tick the appropriate box or write your answer in the space provided.
The information that you give us will be treated in strict confidence.

Part 1: This section asks for some background information about your child.

1. What is your child's surname: ……
   forename(s): ……
2. What is your child's date of birth (dd/mm/yyyy)? ____/____/____
3. Is your child? Male ☐ Female ☐
4. Please give your child's address: ……
   ……
   ……
5. What is your child's postcode? ☐☐☐☐ ☐☐☐
6. What is your email address? ……
7. Which ethnic group does your child belong to? Please tick one

White	British or Irish	
	Other	
Mixed	White & Black Caribbean	
	White and Black African	
	White and Asian	
	Other Mixed	
Asian or Asian British	Indian	
	Pakistani	
	Bangladeshi	
	Other Asian	
Black or Black British	Black Caribbean	
	Black African	
	Other Black	
Another Group	Chinese	
	Other ethnic group	

PLEASE TURN OVER

8. Please tell us what the job title is of the **main earner** in your child's household:……

9. Please tick one box to show which **best** describes the sort of work the **main earner** in your child's household does. (If the main earner is not working now, please tick a box to show what they did in their last job).

Please tick one box.

Modern professional occupations *such as:* teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer	
Clerical and intermediate occupations *such as:* secretary - personal assistant - clerical worker - office clerk - call centre agent - nursing auxiliary - nursery nurse	
Senior managers or administrators (usually responsible for planning, organising and co-ordinating work and for finance) *such as:* finance manager - chief executive	
Technical and craft occupations *such as:* motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver	
Semi-routine manual and service occupations *such as:* postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant	
Routine manual and service occupations *such as:* HGV driver - van driver - cleaner - porter - packer - sewing machinist - messenger - labourer - waiter / waitress - bar staff	
Middle or junior managers *such as:* office manager - retail manager - bank manager, restaurant manager - warehouse manager - publican	
Traditional professional occupations *such as:* accountant - solicitor - medical practitioner - scientist - civil / mechanical engineer	

10. Last week, was the **main earner** in your child's home any of the following?

Please tick one box.

Retired	
Student	
Looking after home/family	
Currently sick/disabled	
None of the above	

11. Does (did) the **main earner** work as an employee or are (were) they self-employed?

Please tick one box.

Employee	
Self-employed with employees	
Self-employed/freelance without employees (please skip questions 12 and 13)	

12. **For employees**: indicate below how many people work (worked) for the **main earner's** employer at the place where they work (worked).
For self-employed: indicate below how many people the main earner employs (employed).

Please tick one box.

1 to 24	
25 or more	

13. Does (did) the **main earner** supervise any other employees?
A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis

Please tick one box.

Yes	
No	

14. The nurse may need to contact you at some time during the study.
What is the best telephone number to contact you on?

.....

15. Do you have a landline at your home? Yes ☐ No ☐

PLEASE TURN OVER

Part 2: This section asks about the symptoms your child had during their recent illness

2.1 Did they have any of the following symptoms? For EACH symptom please tick Yes, No or Not sure.

Diarrhoea: (loose watery bowel movements)

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Diarrhoea with blood in it:

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Nausea (feeling sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Vomiting (being sick):

Yes ☐ No ☐ Not sure ☐

Number of days: ☐☐

Still Present: Yes ☐ No ☐ Not sure ☐

Abdominal cramps (colic):

Yes ☐ No ☐ Not sure ☐

Loss of appetite:

Yes ☐ No ☐ Not sure ☐

Fever (high temperature):

Yes ☐ No ☐ Not sure ☐

Cough or runny/blocked nose or sore throat:

Yes ☐ No ☐ Not sure ☐

Headache: Yes ☐ No ☐ Not sure ☐

2.2 What was the date (dd/mm/yyyy) on which your child first had diarrhoea and/or vomiting?

____/____/____

2.3 If you answered "yes" to having diarrhoea, roughly how many times did your child go to the toilet on the worst day (24 hours) of their illness?

Number of times ☐☐

2.4 If you answered "yes" to vomiting, roughly how many times did your child vomit on the worst day (24 hours) of their illness?

Number of times ☐☐

2.5 Have you phoned NHS Direct/NHS 24 about your child's illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone NHS Direct/NHS 24 about your child's symptoms?

____/____/____

2.6 Have you contacted the out-of-hours doctor service about your child's illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the out-of-hours doctor service about your child's symptoms?

____/____/____

2.7 Have you visited a Walk-in centre about your child's illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first contact the walk-in-centre about your child's symptoms?

____/____/____

PLEASE TURN OVER

2.8 Have you spoken to your nurse or doctor on the 'phone for advice about their illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first phone for advice about their symptoms?

____/____/____

2.9 Have you been to see a doctor or nurse in your practice about this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you first see your doctor about these symptoms?

____/____/____

2.10 Did you take your child to hospital, Accident and Emergency (A&E) or casualty with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) did you take your child to hospital, Accident and Emergency (A&E) or casualty about these symptoms?

____/____/____

2.11 Was your child admitted to hospital overnight or longer with this illness?

Yes ☐ No ☐ Not sure ☐

If "yes", on what date (dd/mm/yyyy) was your child admitted to hospital with this illness?

____/____/____

If "yes", how many nights did your child spend in hospital with this illness?

☐☐

2.12 Did your child's illness stop them from going to work or to school or carrying out your daily activities?

Yes ☐ No ☐ Not sure ☐

If "yes", how many days? ☐☐

Part 3: This section asks about your travel in the ten days before you became ill.

3.1 Did you travel outside the UK in the ten days before you became ill?

Yes ☐ No ☐ Not sure ☐

3.2 If you answered "yes", what dates (dd/mm/yy) were you away?

From: ____/____/____ To: ____/____/____

3.3 If you were abroad, please tell us which country or countries you visited:

_____

Have you sent a faeces (stool) specimen?

Yes ☐ No ☐

If no, please do so as soon as possible, as this is really important for the study. You can get another specimen pot from your practice nurse if you do not have one.

Thank you for taking the time to fill in this questionnaire.
Please return this questionnaire to the research nurse at your doctor's surgery using the reply paid envelope

Appendix 9.7: GP Validation Study Questionnaire

iid2
The Second Infectious Intestinal Disease Study

VALIDATION STUDY

Please extract the following information from the patient practice records (using the selected read codes):

(Please **circle** one option only for each question)
(Yes [Y], No [N], Not Recorded [NR])

Clinic ID:……

Validation study ID (as in study register, i.e. 1-N)):
……

Age: ……

Sex: M F

Problem title (read code):……..

CONTACT:
Contacted out-of-hours doctor service? Y NR

Date of 1st out-of-hours doctor service contact (dd/mm/yyyy):

……

Spoke to a nurse or doctor on the telephone? Y NR

Date 1st spoke to doctor or nurse on the telephone (dd/mm/yyyy):

……

Been to see doctor or nurse in surgery? Y NR

Date of 1st visit to surgery (dd/mm/yyyy): ……

DID THE PATIENT HAVE ANY OF THE FOLLOWING SYMPTOMS:

Diarrhoea? Y N NR
Number of days with diarrhoea: …….

Diarrhoea with blood? Y N NR
Number of days with diarrhoea with blood: …….

Nausea? Y N NR
Number of days with nausea: …….

Vomiting?	Y	N	NR
Number of days with vomiting: …….			
Abdominal pain?	Y	N	NR
Loss of appetite?	Y	N	NR
Fever?	Y	N	NR
Cough or runny blocked nose or sore throat?	Y	N	NR
Headache?	Y	N	NR

TRAVEL:

Travel outside UK in 10 days before illness?	Y	N	NR

If yes, please give place & dates of travel:

(dd/mm/yyyy): From……. to…….

Country/Countries……

HOSPITALISED:

Hospital admission?	Y	N	NR

If yes, date of admission (dd/mm/yyyy):……..

Number of nights in hospital:……..

STOOL SAMPLE:

Was a faeces sample requested?	Y	N	NR

If yes, what was the result of the faeces test: …….

Appendix 9.8: GP Enumeration Study Questionnaire

ProsStu_IID2_Enumeration Study Form_08 August_04

iid2
The Second Infectious Intestinal Disease Study

ENUMERATION STUDY

Please extract the following information from the patient practice records (using the selected read codes) and transfer the data onto the web-based system:

(Please **circle** one option only for each question)
(Yes [Y], No [N], Not Recorded [NR])

Enumeration study ID:……..

Name : ……..

Age: ……

Sex: M F

Problem title (read code):……..

CONTACT:
Contacted out-of-hours doctor service? Y NR

Date of 1st out-of-hours doctor service contact (dd/mm/yyyy): ……

Spoke to a nurse or doctor on the telephone? Y NR

Date 1st spoke to doctor or nurse on the telephone (dd/mm/yyyy):

……..

Been to see doctor or nurse in surgery? Y NR

Date of 1st visit to surgery (dd/mm/yyyy): ……

DID THE PATIENT HAVE ANY OF THE FOLLOWING SYMPTOMS:

Diarrhoea? Y N NR
Number of days with diarrhoea: …….

Diarrhoea with blood? Y N NR
Number of days with diarrhoea with blood: …….

Nausea? Y N NR
Number of days with nausea: …….

Vomiting? Y N NR
Number of days with vomiting: …….

Abdominal pain?	Y	N	NR
Loss of appetite?	Y	N	NR
Fever?	Y	N	NR
Cough or runny blocked nose or sore throat?	Y	N	NR
Headache?	Y	N	NR

TRAVEL:

Travel outside UK in 10 days before illness? Y N NR
If yes, please give place & dates of travel:

(dd/mm/yyyy): From……. to…….

Country/Countries……

HOSPITALISED:
Hospital admission? Y N NR

If yes, date of admission (dd/mm/yyyy):……..

Number of nights in hospital:……..

STOOL SAMPLE:
Was a faeces sample requested? Y N NR

If yes, what was the result of the faeces test: …….

Appendix 10: Sample collection

Appendix 10.1: Sample collection instructions

NATIONAL GASTROENTERITIS STUDY

How to collect and send a stool sample for laboratory tests

The sample container (blue top) has a small plastic spoon fitted to the underside of the lid and can be found inside the transport box.

Write your full name (or your child's), date of birth, the date and time the sample was collected on the label on the sample container and complete the details on the laboratory request form.

Use a clean toilet which has been well flushed.

Do not allow toilet cleaner or disinfectant to come into contact with the stool sample

1. ***In case of diarrhoea (loose stools/motions)***
   Line the inside of the toilet bowl with toilet roll. Pass the stool sample onto the paper. Use the plastic spoon fitted to the container lid to scoop enough to fill the sample container to the 10ml marker (see overleaf). Dispose of the paper by flushing the toilet.

2. ***If the motion is not loose***
   It may be simpler to sit on the toilet and collect a piece of formed stool as it is passed, or collect as above. Use the plastic spoon fitted to the lid to fill the sample container to the 10ml marker (see overleaf).

3. ***From a nappy***
   With the spoon provided scoop enough stool sample directly from the nappy to fill the sample container to the 10ml marker (see overleaf).

Once the sample has been taken, make sure the cap is screwed tightly onto the container.

Put the sample container into the strong screw top plastic container, then into the transit box and then into the prepaid postal bag, along with the laboratory request form. Please ensure that the postal bag is securely closed.

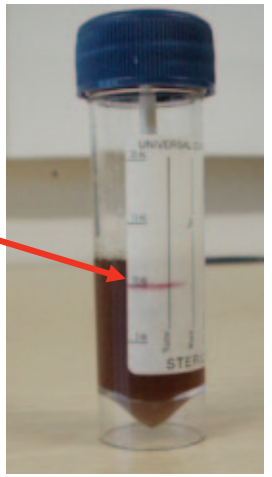
Wash your hands thoroughly, using soap and running water, then dry well.

Post the sample as soon as possible on the same day. If you are unable to do this, keep the package in a cool place (but not your fridge) and post as soon as possible the next day

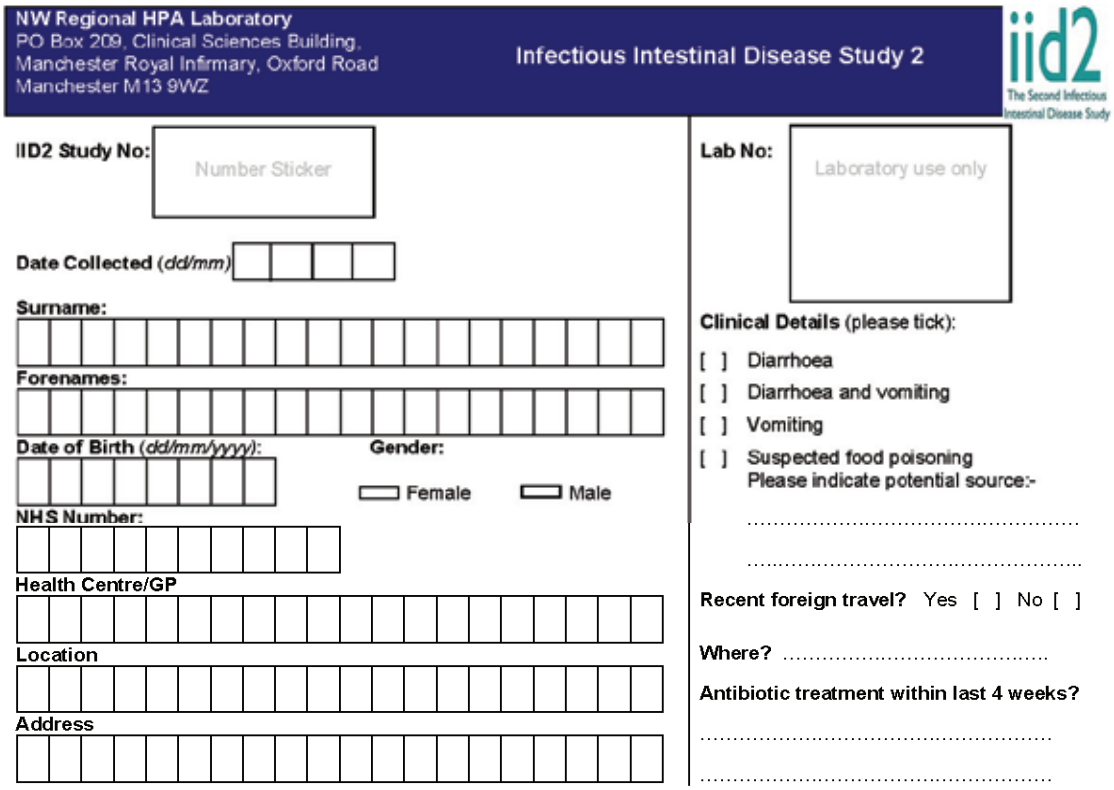
Thank you for your co-operation in the study

Micro_Specimen collection instructions_03

Fill the sample container to the 10ml mark



Appendix 10.2: Microbiology sample request card



NW Regional HPA Laboratory
PO Box 209, Clinical Sciences Building,
Manchester Royal Infirmary, Oxford Road
Manchester M13 9WZ

Infectious Intestinal Disease Study 2

iid2 The Second Infectious Intestinal Disease Study

IID2 Study No: Number Sticker

Date Collected (*dd/mm*)

Surname:

Forenames:

Date of Birth (*dd/mm/yyyy*): **Gender:** Female Male

NHS Number:

Health Centre/GP

Location

Address

Lab No: Laboratory use only

Clinical Details (please tick):

[ ] Diarrhoea
[ ] Diarrhoea and vomiting
[ ] Vomiting
[ ] Suspected food poisoning
Please indicate potential source:-

.....

.....

Recent foreign travel? Yes [ ] No [ ]

Where? .....

Antibiotic treatment within last 4 weeks?

.....

.....

Appendix 11: Study Registers

Appendix 11.1: Prospective Cohort Study Register

	A	B	C	D	E	F	G	H	I	J	K
1	**DELETE THESE TWO COLUMNS BEFORE SENDING TO GPRF					COHORT STUDY					
2											
3			Date:			Practice ID:			Nurse's Name:		
4											
5								1st Invite			
6	Participant Name	Participant phone number	Number (1 to N)	Age	Gender (M/F)	Eligible (see attached code list)	Eligible: If 'Other', please specify	Date 1st invite letter sent (dd/mm/yyyy)	1st invite letter Response: Positive (P) Negative (N) No Response (NR)	Interview date (dd/mm/yyyy)	Attended 1st invite interview (Y/N)
7			1	34	M						
8			2								
9			3								
10			4								
11			5								
12			6								
13			7								
14			8								
15			9								
16			10								
17			11								
18			12								
19			13								
20			14								
21			15								

	A	B	C	L	M	N	O	P	Q	R	S
1	**DELETE THESE TWO COLUMNS BEFORE SENDING TO GPRF										
2											
3			Date:								
4											
5				FOR NEGATIVE RESPONDERS		Reminders				FOR CONSENT	
6	Participant Name	Participant phone number	Number (1 to N)	If negative response reason declined to take part in study (see attached code list)	Negative response: If 'Other' please specify	Date reminder letter sent (dd/mm/yyyy)	Reminder invite letter Response: Positive (P) Negative (N) No Response (NR)	Re-invite for interview date (dd/mm/yyyy)	Attended 2nd invite interview (Y/N)	Consent form signed (Y/N)	Study number
7			1								
8			2								
9			3								
10			4								
11			5								
12			6								
13			7								
14			8								
15			9								
16			10								
17			11								
18			12								
19			13								
20			14								
21			15								

Appendix 11.2: GP Presentation Study Register

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	**DELETE THIS COLUMN BEFORE SENDING TO GPRF				GP PRESENTATION STUDY											
2																
3		Date:			Practice Number:			Nurse's Name:								
4																
5																
6	Participant Name	Number (1 to N)	Age	Gender (M/F)	Name of Doctor/Nurse seen	Date Seen by Doctor/Nurse (dd/mm/yyyy)	Date Patient contacted by nurse (dd/mm/yyyy)	Patient response Positive (P) Negative (N) No Response (NR)	If negative response reason declined to take part (see attached code list)	Negative response: If "Other", please specify	Eligible (see attached code list)	Eligible: If "Other", please specify	Interview date (dd/mm/yyyy)	Attended interview (Y/N)	Consent form signed (Y/N)	Study numbe
7		1														
8		2														
9		3														
10		4														
11		5														
12		6														
13		7														
14		8														
15		9														
16		10														
17		11														
18		12														
19		13														
20		14														
21		15														
22		16														
23		17														
24		18														

Appendix 11.3: GP Validation Study Register

	A	B	C	D	E	F
1	DELETE THIS					
2	COLUMN BEFORE	Validation Study				
3	SENDING TO					
4	GPRF	Date:		Nurse Name:		
5		Practice ID:				
6						
7	Participant Name	Age	Sex (M/F)	Number (1 to N)	AT THIS POINT PLEASE FILL IN THE VALIDATION QUESTIONNAIRE	GP Presentation Study ID Number (if applicable)
8						
9						
10						
11						
12						
13						
14						
15						

Appendix 12: Prospective Cohort Study Weekly Follow-up information

Appendix 12.1: Email follow-up instructions

EMAIL FOLLOW-UP

You have chosen the email follow up option.
Each week you will be sent an email to your chosen email address. This email will ask you if you have had diarrhoea or vomiting in the last week.

The email will be sent from the following email addresses:

Welcome email: welcome@iid2-research-study.org
Subsequent follow up emails: follow-ups@iid2-research-study.org

Please add these email addresses to your address book and check that emails from the study are not being sent to your spam/junk mail box.

The welcome email will read as follows:

Dear *your name*,

Thank you for agreeing to take part in the IID2 study.

We will be sending you weekly emails to check whether you have had any symptoms of diarrhoea or vomiting in the last week.

If this email has arrived in your junk/spam folder, please add the email address to your safe list in your address book.

If you have any questions about the study, please contact your practice nurse.

Thank you once again for agreeing to take part in this important study.

PLEASE TURN OVER

The weekly emails will read as follows:

Dear *your name*,
Thank you for taking part in the IID2 study.

Have you had diarrhoea or vomiting in the last week (the week runs from Monday to Sunday):

Please **click** one of the links below:
Diarrhoea only
Vomiting only
Diarrhoea and Vomiting
Neither

PLEASE NOTE – YOU MUST CLICK ON THE LINK WITHIN THE EMAIL TO RESPOND

If you have had diarrhoea or vomiting, please collect a stool sample using the packaging provided and post it as soon as possible to the Health Protection Agency laboratory in Manchester.

Please send the questionnaire to the nurse in the pre-paid envelope addressed to your GP practice.

Frequently asked questions:

What if I don't receive any IID2 emails?
Please check in your spam/junk mail box. If the emails are not there please contact the research nurse.

What if the email won't send?
Please make sure you are clicking on the link within the email and are not trying to reply using the reply button. If you are still having problems please contact the research nurse.

What if I forget to respond?
You will be sent a reminder email 3 days after your follow up email.

What if I go on holiday?
Please inform the research nurse.

THANK YOU FOR TAKING PART IN THE IID2 STUDY

Appendix 12.2: Postcard Follow-up – Weekly reply cards

ProsStu_Cohort_ Symptoms reply cards_07.doc

iid2
The Second Infectious Intestinal Disease Study

The Second Study of Diarrhoea and Vomiting in the Community

Study Number	Week Number

Please tick the appropriate box below and post the card in the stamped, addressed envelope on:

Monday ……

Have you had diarrhoea or vomiting in the last week (the week runs from Monday to Sunday):
Please **circle one** of the following options:

Diarrhoea only **Vomiting only** **Diarrhoea and Vomiting** **Neither**

If you have had symptoms of diarrhoea and/or vomiting, please collect a stool sample using the packaging provided and post it as soon as possible to the Health Protection Agency laboratory in Manchester. Please send the questionnaire to the nurse in the pre-paid envelope addressed to your GP practice.

If you do not have a questionnaire or sample pot, please let the nurse know and they will send it to you.

Please let the nurse at your practice know if you are going to be away from home (dd/mm/yyyy):

From …… to ……..

Appendix 13.1: Adenovirus

iid2
The Second Infectious Intestinal Disease Study

Micro_IID2_Adenovirus_03

FACT SHEET

Adenovirus

Common clinical features

Watery diarrhoea with vomiting with most infections occurring in children aged under five. Duration of illness can be up to 5 days.

Incubation period

1 – 3 days.

Where is it found?

In gastrointestinal tract of man, sewage and contaminated water.

How is it acquired by affected individuals?

Usually by person to person spread by the faecal oral route.

How does the laboratory confirm the diagnosis?

An immunoassay test can be used to detect virus antigens in a faecal sample but not many laboratories test for this organism.

How is it treated?

Symptomatic treatment and rehydration.

11th January 2008

Appendix 13.2: Astrovirus

Micro_IID2_Astrovirus_05

FACT SHEET

Astrovirus

Common clinical features

Mild self limiting diarrhoea that lasts 2-3 days occasionally associated with fever and vomiting.

Incubation period

1-3 days.

Where is it found?

Human gastrointestinal tract, sewage and contaminated water.

How is it acquired by affected individuals?

Person to person by the faecal oral route. Contaminated surfaces in nurseries may be an environmental source. Shellfish have occasionally been implicated as sources of infection.

How does the laboratory confirm the diagnosis?

There is no test available in routine hospital laboratories but specialist virology laboratories can use a molecular test to detect the virus.

How is it treated?

Symptomatic treatment and rehydration.

Appendix 13.3: *Bacillus* spp.

Micro_IID2_Bacillus spp_04

FACT SHEET

Bacillus

Common clinical features

Some cases have a sudden onset of nausea and vomiting and others have colicky pain and diarrhoea. The illness generally lasts for no longer than one day.

Incubation period

B. cereus – emetic syndrome: 1 – 5 hours; diarrhoeal syndrome: 8 to 16 hours
B. subtilis – 10 minutes to 4 hours
B. licheniformis – 2 to 14 hours

Where is it found?

Widespread in the environment: soil, dust, vegetation. A variety of food products can be contaminated. There are no human or animal sources.

How is it acquired by affected individuals?

From contaminated foods subjected to inadequate post-cooking temperature control during cooling and storage. A wide variety of food products can act as sources but *B. cereus* is particularly associated with rice dishes. It is not passed from person-to-person.

How does the laboratory confirm the diagnosis?

The bacteria are cultured from faeces and suspected foods, and the results are usually available in 2 to 3 days. This test will only be carried out if food poisoning with Bacillus is strongly suspected.

How is it treated?

Symptomatic treatment only.

11th January 2008

Appendix 13.4: *Campylobacter* spp.

Micro_IID2_Campylobacter_06

FACT SHEET

Campylobacter

Common clinical features

Diarrhoea, abdominal pain, malaise, fever, nausea and vomiting are the common symptoms with varying severity. The illness is frequently over within 2 – 5 days and usually lasts no more than 10 days. Blood and mucus may be present in liquid stools. Some people infected have no symptoms. Uncommon complications include joint pains (arthritis) and Guillain-Barré (a disease of the nervous system that can lead to temporary paralysis).

Incubation period

1 – 11 days (usually 2 to 5 days)

Where is it found?

Gastrointestinal tract of farm livestock and poultry, wildlife including birds, and domestic pets.

How is it acquired by affected individuals?

From raw or undercooked meat (especially poultry), unpasteurised milk, bird-pecked milk on doorsteps, untreated water, and domestic pets with diarrhoea. It is rare for Campylobacter to be passed from person to person, only if personal hygiene is very poor.

How does the laboratory confirm the diagnosis?

The bacteria are cultured on selective media from faeces samples and results are usually available in 2 – 3 days.

How is it treated?

Symptomatic treatment and rehydration. Antibiotics are required only in severe cases.

10th January 2008

Appendix 13.5: *Clostridium difficile*

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The Second Infectious Intestinal Disease Study

Micro_IID2_Clostridium difficile_05

FACT SHEET

Clostridium difficile

Common clinical features

Clostridium difficile is the most commonly identified cause of clinically significant antibiotic-associated diarrhoea. Many antibiotics cause loose stools but *C.difficile* associated diarrhoea (CDAD) may be mild or severe and there is often fever and abdominal pain. In severe cases colitis may develop. There may be relapses after treatment. The incubation period is variable within one day of starting or several weeks after finishing a course of antibiotics.

Where is it found?

C.difficile is a spore forming bacterium that is found in the faeces of humans and other animals, in soil and water, and on environmental surfaces in homes and hospitals. Carriage rates are low (less than 3%) in healthy adults with no diarrhoea. Rates are high (greater than 50%) in children up to the age of 2 years and moderate rates (greater than 10%) are found in the elderly, with higher rates in those in hospital and in residential care.

How is it acquired by affected individuals?

Spores may be ingested from the environment. Colonisation rates are higher in the elderly, particularly in hospitals and residential homes where antibiotic use is common. The environment is more heavily contaminated around individuals who have diarrhoea. Antibiotics kill some of the normal "healthy" gut bacteria and allow *C.difficile* to multiply, producing toxins that cause ulceration and diarrhoea.

How does the laboratory confirm the diagnosis?

A faeces sample is tested for the presence of *C.difficile* toxins using an immunoassay test. Results will usually be available in two days. Toxins can be detected in the faeces of healthy, asymptomatic children up to the age of 2 years, and a positive test result is not clinically significant in this age group. Studies have shown that toxins are rarely detected in asymptomatic older children or adults living in the community. However, toxins may be detected in the faeces of individuals who have received antibiotics recently, but who do not have diarrhoea.

How is it treated?

C.difficile associated disease can be severe (colitis) and even life threatening. If a patient has significant diarrhoea while on antibiotics or has a positive *C.difficile* toxin test, the causative antibiotics should be discontinued. If the patient requires continuing treatment for their initial infection a Consultant Microbiologist should be consulted. Fluid and electrolyte losses should be replaced and the use of anti-motility agents should be avoided. If symptoms
are moderate to severe or measures above are ineffective, oral metronidazole 400 mg three times daily should be given for ten days.

12th January 2008

Appendix 13.6: *Clostridium perfringens*

Micro_IID2_Clostridium perfringens_07

FACT SHEET

Clostridium perfringens

Common clinical features

An intoxication which causes a sudden onset of colicky pain followed by diarrhoea. Nausea is common but vomiting and fever are usually absent. Generally a mild disease of short duration.

Incubation period

8 to 22 hours (usually 12 to 18 hours)

Where is it found?

Gastrointestinal tract of animals, soil and dust.

How is it acquired by affected individuals?

From contaminated cooked meat and poultry dishes subjected to inadequate temperature control after cooking, during cooling, and storage. It is only acquired from food and not passed from person to person.

How does the laboratory confirm the diagnosis?

Low numbers of this organism are present in normal faeces samples but high counts are present when it is causing illness. An immunoassay test can be used to detect the toxin in faeces and the organism can be grown from suspected food. Results will usually be available in 2 days. The tests will only be carried out if food poisoning with *Clostridium perfringens* is strongly suspected.

How is it treated?

Symptomatic treatment only.

Appendix 13.7: *Cryptosporidium*

iid2
The Second Infectious Intestinal Disease Study

Micro_IID2_Cryptosporidium_05

FACT SHEET

Cryptosporidium

Common clinical features

Watery or mucoid diarrhoea, accompanied by cramping abdominal pain. Symptoms commonly last for several days, up to 4 weeks. Asymptomatic infection is common. Prolonged and severe infection occurs in individuals with severe immunodeficiency.

Incubation period

Average 7 - 10 days, range 1 – 28 days.

Where is it found?

Gastrointestinal tract of man and animals, particularly farm and other domesticated animals. Drinking and recreational water contaminated with faeces or sewage.

How is it acquired by affected individuals?

Contact with infected animals or animal faeces. Outbreaks have been associated with drinking water supplies and rarely contaminated food. Seasonal outbreaks are associated with farm visits (open farms). Infection has been reported following contamination of swimming and paddling pools. Person to person spread does occur particularly in households and nurseries. The cysts are not killed by the levels of chlorine used to disinfect drinking water supplies.

How does the laboratory confirm the diagnosis?

The cysts are detected by microscopy or using an immunoassay test on the faeces. Results are usually available within 2 days of receipt in the laboratory.

How is it treated?

Rehydration and symptomatic treatment. There is no specific treatment although several anti-cryptosporidial agents are under investigation for treatment of immunodeficient patients.

Appendix 13.8: *Cyclospora cayetanesis*

Micro_IID2_Cyclospora cayetanensis_03

FACT SHEET

Cyclospora cayetanensis

Common clinical features

Watery diarrhoea, loss of weight, loss of appetite, bloating, nausea, vomiting, muscle aches and persistent fatigue. Illness may last from a week to a month or longer if untreated.

Incubation period

1 – 11 days, on average one week.

Where is it found?

The gastrointestinal tract of humans, no known animal reservoir. Once excreted the oocysts sporulate in the environment before becoming infectious and this process occurs over several days to weeks.

How is it acquired by affected individuals?

From drinking or swimming in contaminated water and eating contaminated food, particularly fresh produce such as salad vegetables and fruit. Direct person to person spread (faecal oral) is unlikely as the oocysts are not infectious when first excreted in faeces. Although infection may be acquired worldwide, it is more common in developing countries and travellers are at increased risk.

How does the laboratory confirm the diagnosis?

Oocysts are detected in faeces samples examined by microscopy. Results are usually available within 2 days of receipt in the laboratory.

How is it treated?

One of the few gastrointestinal infections for which there is a specific antibiotic treatment, Trimethoprim/Sulfamethoxazole.

Appendix 13.9: Enteroaggregative *E. coli* (EaggEC)

Micro_IID2_Enteroaggregative Escherichia coli (EAggEC)_03

FACT SHEET

Enteroaggregative Escherichia coli (EAggEC)

Common clinical features

Variable. EAggEC can cause either an acute or chronic (greater than 14 days) diarrhoeal illness. The most commonly reported symptoms are watery diarrhoea with or without blood and mucus, abdominal pain, nausea, vomiting and low grade fever.

Incubation period

Generally 8 – 18 hours

Where is it found?

The gastrointestinal tract of humans, cattle, sheep, pigs and dogs.

How is it acquired by affected individuals?

EAggEC is described as a cause of large outbreaks of diarrhoeal disease across the world probably through ingestion of contaminated food and water. EAggEC is a common bacterial cause of diarrhoea among travellers to developing countries and among children and HIV-infected persons living in both developing and developed regions of the world. Direct person to person spread (faecal oral) is unlikely unless hygiene is very poor.

How does the laboratory confirm the diagnosis?

There is no test in routine use in clinical diagnostic laboratories. In the **IId2** Study a research molecular test is being used to identify EAggEC at the reference laboratory and the result will be available within seven days.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Antibiotic treatment is only recommended for persistent diarrhoea. Advice on antibiotic treatment should be sought from your local microbiology laboratory.

12th January 2008

Appendix 13.10: Enterotoxigenic *E. coli* (ETEC)

Micro_IID2_Enterotoxigenic E.coli_ ETEC_03

FACT SHEET

Enterotoxigenic Escherichia coli (ETEC)

Common clinical features

Diarrhoea which may be mild to severe, typically profuse and watery without blood or mucus. Abdominal pains, vomiting and low grade fever may be present. Usually the symptoms last for less than 5 days.

Incubation period

12 – 72 hours.

Where is it found?

The gastrointestinal tract of humans, no known animal reservoir.

How is it acquired by affected individuals?

From ingestion of contaminated food and, less often, contaminated water. Direct person to person spread (faecal oral) is unlikely unless hygiene is very poor. ETEC is the major cause of travellers diarrhoea particularly among travellers to developing countries. ETEC is also the major cause of severe diarrhoea and dehydration in young children in developing countries.

How does the laboratory confirm the diagnosis?

There is no test in routine use in clinical diagnostic laboratories. In the **iid2** study a research molecular test is being used to identify ETEC at the reference laboratory and the result will be available within seven days.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Antibiotic treatment is only recommended for severe and continuing diarrhoea. Advice on antibiotic treatment should be sought from your local microbiology laboratory.

12th January 2008

Appendix 13.11: Vero cytotoxin-producing *E. coli* (VTEC) O157

FACT SHEET

Vero cytotoxin-producing Escherichia coli (VTEC) O157

Common clinical features

Diarrhoea which may be mild to severe and can contain a large amount of blood (haemorrhagic colitis). In severe cases haemolytic uraemic syndrome (HUS) may occur leading to renal failure, particularly in the very young and very old.

Incubation period

Generally 1 – 6 days

Where is it found?

The gastrointestinal tract of cattle, sheep, pigs and some wild animals e.g. rabbits.

How is it acquired by affected individuals?

From contaminated food generally animal products – meat, particularly undercooked beef, milk, cheese and occasionally contaminated vegetables. Direct contact with infected animals on farms or animal sanctuaries, or contaminated land. Person to person spread can occur by direct contact (faecal oral), particularly in households, nurseries and infant schools.

How does the laboratory confirm the diagnosis?

E.coli are cultured from faeces on selective media and the O157 strain has special biochemical characteristics. Presumptive results are usually available within 2 days. Other VTEC (non-O157) are a much less common cause of illness. Suspected *E.coli* strains are confirmed at the Reference Laboratory and tested for toxin production. Suspected foods are tested when outbreaks occur.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Some reports suggest that antibiotics may be harmful rather than beneficial (killing the bacteria and releasing more toxins into the bloodstream). Hospital treatment is required for severe cases. HUS is one of the most common causes of acute renal failure in children.

Appendix 13.12: Vero cytotoxin-producing *E. coli* (VTEC) non-O157

Micro_IID2_Vero cytotoxin-producing Eschericia coli (VTEC) non-0157_07

FACT SHEET

Vero cytotoxin-producing Escherichia coli (VTEC) [non- O157]

Common clinical features

Variable, from asymptomatic to diarrhoea, which may be mild to severe and can contain a large amount of blood (haemorrhagic colitis). In severe cases (which are rare) haemolytic uraemic syndrome (HUS) may occur leading to renal failure, particularly in the very young and very old. Outbreaks and individual cases of severe diarrhoea caused by VTEC (producing VT1 and/or VT2 toxins) that belong to serogroups other than O157 are very rarely identified in the UK, but reported more frequently from mainland Europe and the rest of the world. It is not clear whether all non-O157 VTEC are capable of causing human illness.

Incubation period

Generally 1 – 6 days.

Where is it found?

The gastrointestinal tract of humans, cattle, sheep, pigs and some wild animals. Some of the animal strains are known to be non-pathogenic in humans and the source of most human infections is not identified.

How is it acquired by affected individuals?

Presumed to be similar sources or vehicles to *E.coli* O157. Potentially, therefore:

- From contaminated food, generally animal products – meat, particularly undercooked beef, gravy, milk, cheese and occasionally contaminated vegetables.
- Direct contact with infected animals on farms or animal sanctuaries, or contaminated land.
- Person to person spread by direct contact (faecal oral), particularly in households, nurseries and infant schools.

How does the laboratory confirm the diagnosis?

In the UK, *E.coli* producing VT1 and VT2 toxins that cause disease are most commonly the O157 serogroup. Less is known about the other serotypes and there is no test available to identify them in routine diagnostic laboratories. A molecular test is used in the IID2 Study at the reference laboratory to directly identify the toxin genes in the faeces specimen. Where possible this test is followed by culture of the suspected *E.coli* strains from the faeces for confirmatory tests, typing and testing for other properties associated with the capacity to cause illness. Suspected foods and other potential sources are tested when outbreaks occur.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Some reports suggest that antibiotics may be harmful rather than beneficial (killing the bacteria and releasing more toxins into the bloodstream). Hospital treatment is required for severe cases. HUS, although rare, is one of the most common causes of acute renal failure in children. Treatment for bloody diarrhoea and HUS is related to clinical need and the same approach is required irrespective of whether an O157 or non-O157 strain of *E. coli* is the causative infective agent.

17th October 2008

Appendix 13.13: *Giardia*

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Micro_IID2_Giardia_04

FACT SHEET

Giardia

Common clinical features

Variety of intestinal symptoms including chronic diarrhoea, abdominal cramps, flatulence, leading to weight loss and fatigue. Duration can extend to months or years if undiagnosed. Often asymptomatic.

Incubation period

5 – 25 days

Where is it found?

Gastrointestinal tracts of people and animals.

How is it acquired by affected individuals?

Either by person to person spread or from faecally contaminated food or water. Food borne transmission is rare. Spread within families and nurseries is well documented. Cysts are resistant to chlorine levels in drinking water, so deficiencies in filtration or sewage contamination can result in outbreaks.

How does the laboratory confirm the diagnosis?

Faeces samples are examined by microscopy for cysts or tested with an immunoassay test. Results are usually available within 2 days of receipt in the laboratory.

How is it treated?

One of the few gastrointestinal infections for which there is a specific antibiotic treatment, Metronidazole.

Appendix 13.14: *Listeria*

Micro_IID2_Listeria_04

FACT SHEET

Listeria

Common clinical features

Infection may cause a mild acute illness with fever and may be associated with diarrhoea. Asymptomatic systemic infection can occur. In pregnant women the infection can be transmitted to the foetus and cause septicaemia and meningitis and spontaneous abortion. Septicaemia and meningitis also occur in adults, usually in older people or the immunocompromised.

Incubation period

Variable 3 – 70 days

Where is it found?

Environment, cattle, sheep, soil, silage. The bacterium has been isolated from a range of raw foods including vegetables and uncooked meats as well as processed foods. A wide range of food products have been implicated in outbreaks including soft cheeses and meat based patés. It is commonly carried in the human gut.

How is it acquired by affected individuals?

The majority of cases are believed to be food borne, from foods where the counts are very high because of contamination or poor storage. Some cases are from direct contact with animals. The organism can be transmitted from mother to foetus in utero or at delivery. Infants may acquire infection from person to person spread shortly after delivery.

How does the laboratory confirm the diagnosis?

Culture of blood and cerebrospinal fluid for cases of systemic infection. Culture of faecal specimens in cases with diarrhoea as the main symptom. Results are usually available within 2 days. This test would only be carried out if infection with Listeria was strongly suspected.

How is it treated?

No specific treatment for diarrhoeal illness. Antibiotics are required for treatment of systemic illness.

Appendix 13.15: Clinical significance of *Listeria monocytogenes*

CLINICAL SIGNIFICANCE OF LISTERIA MONOCYTOGENES IN HUMAN FAECES

Distribution

Listeria monocytogenes is very widely distributed in nature in soil, water, sewage, plant material and numerous species of birds and mammals. Approximately 5% of healthy humans carry *Listeria monocytogenes* in the gut.

Food

Listeriosis is a serious but rare food-borne disease. Many foods can contain *Listeria monocytogenes*, albeit usually at low levels which are considered to be of very low risk for health.

Febrile Gastroenteritis and significance of *Listeria monocytogenes*

Outbreaks of gastroenteritis caused by *Listeria monocytogenes* have been described with cases having fever, malaise, headache, vomiting and diarrhoea. As noted above, 5% of humans carry in the gut and it is not known how frequently *Listeria monocytogenes* causes sporadic cases of gastroenteritis. Hence, finding *Listeria monocytogenes* in a faecal sample may be incidental and not related to the actual cause of the diarrhoea. Diagnosis of Listeriosis in these cases is achieved by culturing the patient's blood.

Invasive Disease, Septicaemia and Meningitis

Septicaemia and meningitis can be caused by *Listeria monocytogenes*, particularly in elderly patients, and those who are severely immunocompromised or on immunosuppressive drugs. Septicaemia in patients over 60 years of age is the most common presentation of the disease.

Pregnancy Associated Disease

Listeriosis can occur when the bacterium infects the unborn infant and is most often diagnosed during the third trimester of pregnancy. The mother may be asymptomatic or have a mild 'flu-like illness and a diagnosis can be made by culturing *Listeria monocytogenes* from maternal blood. Trans-placental spread can occur and the foetus can develop severe infection. Pregnant women (as well as the immunocompromised) are advised to avoid mould ripened soft cheese (such as camembert and brie) and pâté, as well as to re-heat cook chill food until piping hot. Routine screening of healthy pregnant women for *Listeria monocytogenes* is not recommended.

Antibiotic Treatment

If *Listeria monocytogenes* is isolated from a high risk patient, e.g. elderly (>60y), pregnant woman or immunocompromised person, and there is evidence of systemic symptoms, e.g. pyrexia then antibiotic treatment may be considered. Advice on antibiotic treatment should be sought from your local microbiology laboratory.

12th December 2007

Appendix 13.16: Norovirus

Micro_IID2_Norovirus_04

FACT SHEET

Norovirus

Common clinical features

Vomiting, diarrhoea, fever, nausea, headache, malaise for 24 – 48 hours. All age groups affected.

Incubation period

Usually 24 – 48 hours

Where is it found?

Gastrointestinal tract of man

How is it acquired by affected individuals?

Very easily transmitted from person to person by the faecal oral route. Easily acquired by persons in the vicinity of vomiting individuals, when aerosolised particles are ingested. Infection may also be acquired from the contaminated environment. Food may be contaminated by affected individuals, including those who are asymptomatic or incubating or convalescing from illness (for 48 hours after symptoms cease). Shellfish (bivalve molluscs) filter the virus particles from sewage in sea water and can be the source of infection if eaten raw. Large outbreaks occur in hospitals, nursing homes, schools and other semi-closed communities such as cruise ships.

How does the laboratory confirm the diagnosis?

An immunoassay test to detect virus antigens in faeces may be available locally and molecular tests are available in specialist laboratories. Results are usually available within 1 day of the laboratory receiving the specimen. When a large outbreak has been confirmed later cases with similar symptoms will not be tested.

How is it treated?

Symptomatic treatment only required, no specific treatment.

Appendix 13.17: Rotavirus

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Micro_IID2_Rotavirus_03

FACT SHEET

Rotavirus

Common clinical features

Diarrhoea and vomiting with a duration of up to 5 days. Can be severe watery diarrhoea leading to dehydration in young children. Major cause of hospital admission for diarrhoea in young children. Infection in adults can be mild but outbreaks can occur in elderly hospital patients and nursing home residents.

Incubation period

Usually 2 days.

Where is it found?

Gastrointestinal tract of man. Rarely, infections are caused by animal strains.

How is it acquired by affected individuals?

Transmitted directly from person to person by faecal oral route and sometimes from environmental contamination. More common in cooler months of year.

How does the laboratory confirm the diagnosis?

Rotavirus antigens are detected in faeces using an immunoassay test. The result is usually available within 1 day of receipt of the sample.

How is it treated?

Symptomatic treatment and rehydration.

Appendix 13.18: *Salmonella* spp.

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Micro_IID2_Salmonella_04

FACT SHEET

Salmonella

Common clinical features

Diarrhoea, vomiting and abdominal pain. Malaise and fever almost always present. Dehydration may occur, particularly in infants and the elderly. Septicaemia with abscess formation in virtually any organ is an uncommon complication. Diarrhoea and fever often persist for several days. Blood may be present in the stool in 20% of cases.

Incubation period

12 hours to 3 days.

Where is it found?

Gastrointestinal tract of wild and domestic animals, birds (especially poultry) reptiles, amphibians (for example terrapins) and occasionally humans become long term carriers.

How is it acquired by affected individuals?

Predominantly from food (most commonly red and white meats, raw and undercooked eggs, milk and dairy products) following contamination of cooked food by raw food or failing to achieve adequate cooking temperatures. Contact with infected animals or animal faeces. Person to person spread from the case by close contact, usually when the case has diarrhoea. These so-called “secondary” cases are common in outbreaks.

How does the laboratory confirm the diagnosis?

The bacteria are cultured on selective media from faeces samples. Foods may be tested for the bacteria in outbreaks. A result will usually be available within 2 to 3 days but it may take several days to confirm the particular type of Salmonella.

How is it treated?

Symptomatic treatment and rehydration. Generally, antibiotics are not required for adults who are otherwise healthy and have mild to moderate disease. Antibiotics may be required for more severe cases.

Appendix 13.19: Sapovirus

Micro_IID2_Sapovirus_02

FACT SHEET

Sapovirus

Common clinical features

Mild self limiting diarrhoea that lasts 2-3 days occasionally associated with fever and vomiting.

Incubation period

1-3 days.

Where is it found?

Human gastrointestinal tract, sewage and contaminated water.

How is it acquired by affected individuals?

Sapovirus is predominantly an infection in children under 5 years of age and occurs as sporadic cases or outbreaks of diarrhoea and vomiting in child day care centres and schools. Transmission is by person to person by the faecal oral route or through contact with contaminated surfaces in nurseries.

How does the laboratory confirm the diagnosis?

There is no test available in routine hospital laboratories but specialist virology laboratories can use a molecular test to detect the virus.

How is it treated?

Symptomatic treatment and rehydration.

12th January 2008

Appendix 13.20: *Shigella* spp.

Micro_IID2_Shigella_04

FACT SHEET

Shigella

Common clinical features

Typically causes bloody diarrhoea, but the most common species found in the UK (*Shigella sonnei*) causes a mild illness. Species found outside the UK, particularly in the tropics, can cause severe dysentery with blood mucus and pus in the stool sample. Gastrointestinal complications may occur and occasionally haemolytic uraemic syndrome.

Incubation period

1 - 7 days.

Where is it found?

Human gastrointestinal tract, sewage and contaminated water.

How is it acquired by affected individuals?

Usually transmitted by the faecal oral route from cases with diarrhoea, in households and institutions, mainly those containing young children. Occasionally spread by sewage contamination of food or water.

How does the laboratory confirm the diagnosis?

Culture of the bacteria from a faecal sample on selective media. Results are usually available in 2 days but confirmation of the particular type of Shigella may take several days.

How is it treated?

Rehydration and antibiotics.

Appendix 13.21: *Staphylococcus aureus*

Micro_IID2_Staphylococcus_aureus_04

FACT SHEET

Staphylococcus aureus

Common clinical features

Typically, an abrupt onset of nausea, vomiting and prostration often accompanied by diarrhoea. Illness lasts for 1-2 days.

Incubation period

30 minutes to 8 hours, usually 2 – 4 hours.

Where is it found?

Human skin – carried by 25–30% of individuals. Rarely, infected cow udders lead to contaminated milk.

How is it acquired by affected individuals?

Food handlers contaminate food that is left at room temperature for several hours, so that the bacteria multiply and produce the toxin in the food. Food handlers with infected skin lesions such as boils are a particular risk.

How does the laboratory confirm the diagnosis?

Toxin of the bacteria may be detected in food. High counts of *Staphylococcus aureus* may be found in faeces of affected individuals but occasionally high counts are present in faeces of individuals with no symptoms. The test results will usually be available in 2 days, but tests will only be carried out if *Staphylococcus aureus* is strongly suspected as the cause of illness.

How is it treated?

Rehydration and symptomatic treatment.

Appendix 13.22: *Vibrio*

Micro_IID2_Vibrio_03

FACT SHEET

Vibrio

Common clinical features

Vibrio species are uncommon causes of infectious intestinal disease in the UK. One species, *Vibrio cholerae* is the cause of cholera, a severe diarrhoeal disease. *Vibrio parahaemolyticus* is the most common species causing food poisoning in the UK. This causes watery diarrhoea and abdominal cramps in the majority of cases, occasionally with nausea, vomiting fever and headache. Occasionally a dysentery like illness is seen with blood and mucus in the stools and a high fever. More commonly it is a disease of moderate severity lasting 1-7 days.

Incubation period

Usually 12-24 hours.

Where is it found?

In fish or shellfish.

How is it acquired by affected individuals?

By eating raw or inadequately cooked seafood.

How does the laboratory confirm the diagnosis?

The bacteria can be cultured from faeces on selective media. Results are usually available within 2 or 3 days. The tests will be carried out only if the history and symptoms strongly suggest infection with Vibrio.

How is it treated?

Symptomatic treatment and rehydration with antibiotics for the more severe cases.

Appendix 13.23: *Yersinia*

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Micro_IID2_Yersinia_03

FACT SHEET

Yersinia

Common clinical features

Watery diarrhoea, abdominal pain and fever. Abdominal pain is often severe and may mimic appendicitis particularly in children. An immune reaction may occur after infection with *Yersina* leading to arthritis particularly in adolescents and adults. Septicaemia occasionally occurs in the immuno compromised.

Incubation period

3-7 days.

Where is it found?

Gastrointestinal tracts of many species of wild and domestic animals and birds.

How is it acquired by affected individuals?

From eating contaminated food and drinking contaminated water. It is particularly associated with pork. Direct contact with infected animals and person to person spread are also possible routes of transmission.

How does the laboratory confirm the diagnosis?

The bacteria are cultured from faeces samples on selective media. Results will usually be available after 2 to 3 days. Tests will be set up only if symptoms strongly suggest infection with Yersinia.

How is it treated?

Symptomatic treatment and rehydration. Antibiotics may be required for more severe disease.

Appendix 13.24: Reports with multiple pathogens

Micro_IID2_reports with multiple pathogens_03

FACT SHEET

iid2 MICROBIOLOGY REPORTS

Why might the laboratory reports be more complex than the reports from local diagnostic laboratories?

Around 500 different species of micro-organism (bacteria, viruses, fungi, protozoa) have been detected in the human intestinal tract. Most of these have no known harmful effects and, on the contrary, help to keep the gut lining healthy. A small minority of species are known to be present in cases of infectious intestinal disease (IID). Usually, these micro-organisms are present in very large numbers in the gut when they are associated with illness.

In this study we are trying to detect all the major micro-organisms known to cause IID, and toxins made by some of the harmful micro-organisms. This range of tests is more extensive than that carried out in hospital laboratories that routinely investigate gastroenteritis. So we expect to find a wide range of "suspect" micro-organisms. We are also carrying out some very sensitive research tests which will detect small numbers of suspect micro-organisms when present among the many millions of harmless ones.

In routine investigation of cases or outbreaks of IID only one micro-organism is identified as the "cause" of the illness in most cases. Occasionally we find more than one suspected cause is present in the stool specimen. In this study, because of the wide range of tests and the use of super-sensitive research tests we expect to find a lot of cases with more than one potentially causative micro-organism.

Interpretation of laboratory tests

So how can we interpret the investigations of a case when we find more than one potentially harmful micro-organism present in the specimen? There are a number of different interpretations.

1. The person with IID ate food or drank water contaminated with, or was otherwise exposed to, a wide range of micro-organisms and more than one is producing harmful effects in the body causing the symptoms.
2. One (or more) of the micro-organisms is causing the disease and the others, although detected, are not causing harm on this occasion:
   - because they are similar to but missing some key properties of the disease-causing species.
   - because they are in very low numbers and greater numbers are needed to give a harmful effect.
   - because they caused illness some weeks or months previously, and the person is now immune to their effects, but they are still present in small numbers of the intestinal tract.

Most cases of IID will only require supportive therapy such as fluids. Few cases of IID require specific antimicrobial therapy. If micro-organisms are detected that are of particular clinical or significance requiring specific therapy these will be reported by telephone to the practice concerned. There will also be urgent reporting of organisms that are of a serious public health concern. So, important results will be highlighted by the laboratory. However there will be many cases where it will not be possible or necessary to differentiate the disease producing micro-organisms from those present but not producing the symptoms in the patient.

Appendix 14: Newsletters

Appendix 14.1: Participant Newsletter

Insider

IID2 Newsletter April 2009

Thank you for all your help!

We are now almost half way through the IID 2 Study (the Second Study of Infectious Intestinal Disease in the community) and things are going really well!

There are now 88 general practices across England, Wales, Scotland and Northern Ireland who are involved and over 7,500 people who are taking part in the study!

We would like to thank you all for your help and support in making this the biggest ever study into the gut health of the nation.

The information we have collected so far has been very interesting and we are all getting excited to see the final results. These results may be used to shape government policy on food safety to try and reduce tummy bugs.

If you have said that you would like a summary of the results you will receive this when the results are ready after May 2010. If you didn't tick this box on the consent form but have decided you would like a summary then just tell the research nurse at your GP surgery and we'll be happy to send you one.

Further information about the study can be found at www.iid2.org.uk and if you have any other questions then just ask to speak to your research nurse.

Remember to send in your questionnaires!

Remember, if you do have any episodes of diarrhoea and/ or vomiting then please tell us ASAP and send in the questionnaire and stool sample. These are both really important for us to find out about how much gut infection happens in the community and what bugs are causing it. For those of you using e mails to keep in touch, if you are having any problems please let your research nurse know.

Even if you can't get a stool sample please still send the questionnaire/ e mail as this provides us with very useful information!

Helping us to reduce tummy bugs across the nation!

Do I need to send a sample if...

I have just been vomiting and not had diarrhoea?

Yes: Even if you have just been sick there may still be bugs in the stool that we can detect in the lab.

I forgot to send a sample straight away and feel better now?

Yes: With the specialised techniques our labs use we can detect bugs up to 10 days after you have been ill so it is still very useful for us to have a sample.

NHS · MANCHESTER 1824 The University of Manchester · MRC General Practice Research Framework · FOOD STANDARDS AGENCY · Gut Feelings – The UK's largest ever national research study of intestinal health

It's what's on the inside that counts!

Appendix 14.2: General Practice Newsletter

Insider

New Website

Welcome to the third IID2 newsletter. This month's newsletter focuses on the website, study updates from both the cohort and GP Presentation study and an article from our study administrator Hansa Shah, based on her own experiences of working on the IID2 study.

We are pleased to announce that the new 'Gut Feelings' website is now up and running and can be found at www.gutfeelings.org.uk (if you type in the old IID2 web page link you will be automatically re-directed to the new site). The site contains links to all of the new study material.

'Gut Feelings' website - front page

Cohort study update

We currently have over 6,700 participants recruited into the cohort study which is an incredible achievement! Thank you to all of the nurses and administrative staff for your incredibly hard work enabling us to achieve this.

We are also starting to see some younger participants joining in those practices that have started the re-recruitment phase, which is very encouraging. We have a few more months to go on the study and are keen to recruit as many participants as possible, as soon as possible. Every person and every follow up week counts!

We know that younger people are notoriously hard to recruit to any research study, so don't be disappointed if the recruitment rate is lower than before, every patient recruited to the study in this age group is crucial.

For those participants that become ill with diarrhoea and/or vomiting it is really important for us to obtain a sample and questionnaire so that we can identify what has caused the illness. Please remember to run the web reports on a weekly basis and follow up all participants who have reported symptoms to ensure they return a questionnaire and sample.

Administrative challenges on the Gut Feelings study

The IID2, Gut Feelings Study has been a very challenging and enjoyable study to work on.

It has been a pleasure to work with some of the nurses that I know from previous studies. This has helped me to build very good working relationships with all the nurses I am in contact with during my day to day tasks.

A lot of my time is involved around answering queries and training the nurses over the phone, on how to change and transfer information onto the study register. I get a real sense of achievement when the nurses get really happy and excited, "I've done it, I've done it!', as they manage to complete the task using an Excel spreadsheet, which many of them have not used before. To find a solution to a problem on Excel and then explain it over the phone can be quite difficult but together we always get there in the end!

It makes me really happy when I receive appreciative comments as it further highlights the fact that I can help the nurses and that we are all one big happy team working together on this study.

Other duties also include checking and logging consent forms and validation study forms received from the practices. If there are any discrepancies I have to pass them back to the nurses to correct. I must say that these discrepancies are usually sorted out very quickly and efficiently by the nurses which is great.

Another part of my job involves obtaining approvals and sending amendments to the local PCT's for the study to commence in the practices. This can be quite a challenging job as the staff may have changed or their contact details may not be correct as previously published. This can sometimes be like trying to find a needle in a haystack!

My job keeps me very busy and is also interesting and challenging, and keeps me out of mischief!

Thank you to all the nurses and the whole team on this study for making it very enjoyable and somewhere we can all work to the best of our abilities and beyond to help others.

Hansa Shah

IID2 Study Administrator

GP Presentation practice visits and study update

Over the last four months the IID2 study team have been on the road visiting the GP Presentation practices to feedback on the progress of the study to the doctors and nurses and introduce the new study material. The study team have really enjoyed visiting the practices, meeting the staff and viewing the setup at each practice. The new materials have been well received both by the practice staff and patients.

Since the beginning of April we have been sending fortnightly feedback graphs to all the GP Presentation practices so that you can monitor your own progress and the progress of the study in general. Please ensure the doctors and nurses are kept informed of study progress and continue to offer them friendly encouragement!

Please encourage all doctors and nurses to ask all patients with diarrhoea and/or vomiting to speak to the IID2 study nurse about the possibility of participating in the study. Please stress to your doctors and nurses the importance of giving patients the opportunity to participate.

Finally, thank you for your commitment to this study and to all the GPs and nurses that have referred patients. We really value your practice's participation and your continued enthusiasm for the study. If you would like to discuss any aspect of the study, please do not hesitate to contact a member of the IID2 study team.

GP PRESENTATION STUDY TARGET RECRUITMENT: 4-5 PARTICIPANTS PER PRACTICE PER WEEK

Contacts at GPRF

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Appendix 15: Web-based data system: Data Security and Access

Appendix 15.1: Access Levels

Only the system administrator was permitted to set up new individual user accounts. Different levels of access to the website were assigned to each authorised user and restricted to information necessary for the performance of their own particular role within the study team. Levels of access to the web based data system were assigned as follows;

App 15.1.1: GP Practice Research nurse.

Individual general practices had ownership of all records for participants from within their own practice. The nurses only had access to data from their own practice and were unable to view any other records. The authorised user within the practice was the research nurse and s/he was able to add new participants to the system and update information e.g. weekly follow-up responses, episode details. It was also possible to view laboratory results on their own practice participants.

Once a record had been generated edit facilities were not available at practice level however the system incorporated a record amendment notification field. This field which was within the individual participant record enabled the nurses to notify any errors or changes to participant information and this was automatically flagged at the GPRF co-ordinating centre.

App 15.1.2: GPRF Co-ordinating Centre

The co-ordinating centre had access to practice information from all participating practices in order to permit real-time monitoring of the study. The study manager was assigned edit facilities should any changes be required to participant record be required.

N.B. the co-ordinating centre did not have access to edit any of the microbiology data.

App 15.1.3: Diagnostic Microbiology - Manchester HPA Microbiology laboratory.

Assigned users at the diagnostic laboratory had the ability to view (but not edit) participant information and research microbiology results and were able to record receipt of samples and add results, both manually and by batch upload. They were also able to view results uploaded at the research laboratory.

The system also permitted tracking of specimens being transferred between the laboratories, with fields being available to record the date and time of transfer and the courier log number. Within the laboratory one super-user was assigned additional functionality to permit editing of results.

App 15.1.4: Research Microbiology - HPA Centre for Infections

Assigned users at the laboratory had the ability to view (but not edit) participant information and Manchester laboratory results. They were able to record receipt of samples thereby ensuring full tracking of specimens between laboratories. They were able to add results of research and reference tests to the system via both manual and batch upload. Within the laboratory one super-user was assigned additional functionality to permit editing of results.

App 15.1.5: London School of Hygiene and Tropical Medicine

Authorised users at the LSHTM were not given access to any patient identifiable information but were able to view and download all data from pseudonomysed records. They were not able to amend or edit any records.

App 15.1.6: The University of Manchester IID2 Study Group-

Authorised users had access to anonymised data only in order to monitor recruitment and follow-up and generate reports, but were not be able to amend the data in any fields.

Appendix 15.2: Data security measures

Access to the server was assigned through a secure shell (SSH) via unique user names and passwords. All information was encrypted prior to transfer using secure socket layer certificates (SSLs) providing 128 bit encryption. The range of Internet Protocol (IP) addresses were restricted to national IP ranges.

Levels of access for individual authorised users; Practice Staff, MRC GPRF co-ordinating centre, Microbiology laboratories, LSHTM and University of Manchester was provided by the assignment of a bit flag – a number unique to that access level. Each page and operation in the system was assigned a number which consisted of a sum of bit flags, representing the groups who are able to use the page/perform the operation. When a user tried to access a page/perform an operation the page's security number was first checked against the user's bit flag using bitwise operations. Anyone attempting to access a page from which they were excluded was returned to their home page and their session cleared.

Participant weekly follow-up - Automated emails were sent on a weekly basis to all cohort participants. Emails sent out to participants did not contain any sensitive information. Contained within the body of the email was a specific response link to notify the presence or absence of diarrhoea and/or vomiting in the previous week. The reply was encrypted using SSL, and additional security measures were in place to minimize the probability of a brute force attack. This involved the generation of a random hexadecimal number for each participant in each follow-up (with 16^32 permutations) which was passed back in the response. Any tampering (attempting to provide a response without the correct hash) was flagged in the database and any response for that participant blocked.

Appendix 15.3: Hardware

App 15.3.1: Server

The data were stored on a study specific server housed behind a dedicated Cisco firewall. A Redundant Array of Independent Disks (RAID 5 array) was employed for the server to provide additional fault tolerance and hence security of the data.

App 15.3.2: Network

The system was hosted by a managed hosting company (Rackspace™) which provided 24x7x365 staffed security and the monitoring of both internal devices and external threats. Due to its high integrity only Cisco certified equipment was used throughout the network. This Cisco certified network, built on hardened routers was audited every quarter to ensure its security.

Rackspace™ constantly monitored the server to ensure network connectivity. These monitoring tests assessed both the performance of the server and the individual ports every few minutes. This level of support ensured that failure of any signal tests would be highlighted within minutes and an authorised engineer to provide a rapid response.

Appendix 15.4: Infrastructure

The data centre employed multiple levels of security (in SAS 70 certified buildings) to ensure that only data centre operations engineers are physically allowed near to the routers, switches and servers e. g. no public access; live video surveillance; on-site security personnel 24/7; biometric security and pass cards e.g. access to the data centre where the server is held, requires a specific security card linked to a palm print. Since this is an automated service requiring two identical matches any discrepancy would not permit access. In addition the company use background checks and certifications to ensure the integrity of all data centre personnel.

Appendix 15.5: System administration

Uploading new information e. g. software patches from the developers of the system, was managed using the secure shell (SSH) thereby providing a higher level of security to the standard file transfer protocol (FTP).

Appendix 15.6: Data Back-up

There was managed back-up of the data with daily incremental and full weekly back-up with 2 weeks retention.

Appendix 16: Quality control/Audit procedures

Appendix 16.1 Study nurse – Quality control visit form

MRC General Practice Research Framework

IID2

Quality Control Form

Clinic Number_____ **Nurse**_____

Regional Nurse_____

Date of Visit _ _/_ _/_ _

Follow up visit required
In line with GPRF SOP for QC

YES ☐ NO ☐

Please return to Louise Letley, Senior Nurse Manager, Stephenson House, 158-160 North Gower Street, London NW1 2ND

	GENERAL (Cohort Study)	YES	NO
	Do you consider that the nurse understands:		
	. The aims of the IID2 Cohort study?		
	. The importance of and types of weekly follow-up for the Cohort Study?		
	. The inclusion and exclusion criteria?		
	. The cohort study case definition		
	Is the nurse able to identify the following cohort study documents: • Information sheets (adult and child) • Flow charts (adult and child) • Consent and Assent forms • Baseline questionnaires (adult and child) • Symptom questionnaires (adult and child) • Post cards and explain when and how these are to be used?		
	Does the nurse know the correct procedures for recruiting patients into the Cohort study?		
	Is the nurse maintaining the Cohort study log/register?		
	Is the nurse sending a copy of the study register to the GPRF each week?		
	Is the nurse adhering to the estimated timings for the study?		
	Does the nurse know who to contact to order general study supplies?		
	Is the MRC research notice displayed in the waiting room? (if not, please ask nurse to inform practice manager)		
	Does the practice leaflet contain information about MRC research? (if not, please ask nurse to inform practice manager)		

	Informed consent (Cohort and GP Presentation Studies)		
		YES	**NO**
	Does the nurse give every patient: • A clear correct explanation of each study including info about • Faeces samples • Baseline questionnaire • Symptoms questionnaires (Cohort study only) • Weekly follow up by email or post card (Cohort study only) • An opportunity to ask questions?		
	Does the nurse ask the patient to complete, initial & sign appropriate consent/assent forms for each study?		
	Does the nurse check that the consent forms have been completed correctly?		
	Does the nurse do the following once the consent form is complete • Send the original consent form to the study manager at the GPRF? • Give a copy to the patient? • File a copy in the patient's research record?		

	First patient interview (Cohort study)		
		YES	**NO**
	Does the nurse explain correctly to the participant the follow-up procedures for • email and postcard follow-up?		
	Does the nurse know the correct procedures for • Attaching pt ID labels to postcards? • Entering week dates on post cards? • Completing week numbers on postcards?		
	Does the nurse explain correctly to the participant • how and when to complete the symptom questionnaire?		
	Does the nurse explain the importance of obtaining faeces samples?		
	Does the nurse complete the correct details on the specimen pot and specimen request form?		
	Does the nurse explain correctly the procedures for returning • specimens and • symptom questionnaires?		
	Does the nurse give the patient her contact details at the surgery?		
	Does the nurse explain the importance of informing him/her if the patient changes home address or email address?		
	Does the nurse ensure s/he has up to date contact details for the patient?		
	Does the nurse enter the baseline data on the web based system?		

	Cohort study follow-up (email)		
		YES	**NO**
	Does the nurse check weekly emails not returned on the web based system?		
	Does the nurse contact the participants who have **not** replied to the weekly email?		
	If the participant does not return emails for 6 weeks does the nurse enter **withdrawn** on the database?		
	Does the nurse check the list of emails bounced back on the web based system on a weekly basis? *(If the answer is" yes" to this question)* Does the nurse then do the following:		

	• Check each bounced back email address with each participant? • Record the new email address in the database? • Resend the email to the new email address?		
	Cohort study follow-up (postcard)		
		YES	**NO**
	Each week does the nurse enter the data from returned postcards in the web based data collection system?		
	If the participant does not return postcards does the nurse enter withdrawn on the database after 6 weeks?		
	Each week does the nurse check postcard non responders on the web based system?		
	Does the nurse call participants who have not returned their postcards (**by Thursday of each week**) to remind them to send their postcard for the previous week to the practice?		
	Cohort study follow-up symptom questionnaires		
	Does the nurse enter data from the returned symptom questionnaires in the web based data collection system each week?		
	Does the nurse post **a symptom questionnaire and specimen pot** to participants who report subsequent episodes of IID symptoms 3 weeks after the previous episode?		
	Each week does the nurse check the web based data collection system to identify participants with symptoms who have **not returned** their symptom questionnaire?		
	Does the nurse contact the participants who have **not returned** their symptom questionnaire within 7 days?		

	GENERAL (GP presentation study) ***For discussion in relevant practices if interview not attended***		
		YES	**NO**
	Do you consider that the nurse understands:		
	The aims of the GP presentation study?		
	The inclusion and exclusion criteria?		
	The study case definition		
	Is the nurse able to identify the following study documents; • Information sheets (adult and child). • Flow charts (adult and child). • Baseline questionnaires. • GP referral notepad. and explain when and why these are to be used?		
	Does the nurse check out of hours faxes, emails and letters on a daily basis to see if patients with IID2 have presented?		
	Does the nurse know the correct procedures for recruiting patients into the GP presentation study?		
	Is the nurse maintaining the GP presentation study log/register?		
	Does the nurse know who to contact to order general study supplies for the GP presentation study?		

	First patient interview (GP Presentation study) *where applicable*		
		YES	**NO**
	Is the nurse reminding GP's and practice nurses to refer patients for the GP presentation study?		
	Are patients being referred through the note pad system? If **no**, how are patients being referred? *(Please write here)*		
	Does the nurse explain the procedure for returning specimens if the patient does not bring a specimen to the interview?		

	Enumeration and Validation study *(as applicable)* ***For discussion***		
		YES	**NO**
	Does the nurse understand the procedures for the Enumeration Study?		
	Does the nurse understand the procedures for the Validation study?		

	Web Based data collection		
		YES	**NO**
	Can the nurse log into the web-based data collection system?		
	Can the nurse create new participants on the web-based system?		
	Can the nurse find existing participants on the web-based system?		
	Can the nurse generate the following reports on the web based data collection system? • Emails bounced back • Phone calls to non responders of email follow up • Phone calls to non responders of postcard follow up • Symptoms questionnaires not received at the practice • Samples over due at the lab (*Cohort and GP presentation studies)* • Replacement sample posts and questionnaires required • Numbers withdrawn from the study		

Recruitment

Number of participants recruited to the Cohort Study:_____

Number of participants recruited to the GP Presentation Study:_____

Regional Nurse comments *(to be completed before the nurse signs form)*

Signature of Regional Nurse .....

Study Nurse comments

Study nurse signature .....

Appendix 16.2: Telephonist QC checklist

TeleSurv_IID2_Quality checklist for telephonists_05.xls

Call details												
Telephonist interviewing												
Date & Time of call												
Call ID (if available)												

Quality checklist for completed calls												
Opening statement read exactly as on page												
Request for consent/assent clear												
Asks same questions, in same order												
Avoids adding own words & so changing the question meaning												
Follows script but doesn't appear too mechanical												
Asks questions slowly, clearly & at a reasonable volume												
Randomisation done or explains why not.												
Access file labelled as expected & saved properly.												
Audio file saved and labelled correctly w Call ID added to tape.												
Comments												

Appendix 16.3: Internal audit form – Telephone Survey

ProjMan_QC Site Visit_UEA_02

IID2 Study Quality Control Site Visit

Site:

Date of visit:

Research Staff present:

Auditor(s):

Item	Yes	No	No Evidence	Document title/Filename
Staff				
Is there a documented organisational structure showing line management responsibility				
Is there a list of personnel associated with the project?				
Are there up to date CVs (and job descriptions) available for all staff involved in the project?				
Are there signed confidentiality agreements for all staff?				
Are there Induction and Training portfolios for all staff?				
Training manual – Is there an up to date validated version of the training manual?				
Is there a Safety manual available?				
Is there a Work alone procedure?				
Worksheets/worklists for telephonists				
Work Area:				
Telephone booths Clean and tidy, Suitable for purpose				
Instructions available in the telephone booths?				

Item	Yes	No	No Evidence	Document title/Filename
Copy Call software – Is there an up to date license for this software				
Are there documented procedures for any statistical analyses performed at UEA				
Are there approved and documented procedures for data collection				
Is there an approved questionnaire?				
Does the database follow the same flow as the paper questionnaire?				
Risk assessments for all procedures?				
Database and data quality:				
Database – description of structure and security. • where is the data stored, what security is in place for access to the server where data is stored? • data security encryption?				
Standard Operating Procedure - Data quality control procedure				

Item	Yes	No	No Evidence	Document title/Filename
Standard Operating Procedure - Data archive procedure				
Standard Operating Procedure - Downloading data for transfer to LSHTM				
Is it possible to conduct a full audit trail from the retained record?				
Standard Operating Procedure- Requests for further information • Evidence that the SOP is being followed				
Forms for telephonists to request written information • Does this log the filename of the call?				
Standard Operating Procedure- What is the procedure for telephonists to record any problems encountered during telephone calls? • Abusive or threatening calls • Child alone • Domestic violence procedures				
Telephonist QC:				
Standard Operating Procedure for QC of telephonists • Evidence that the SOP is being followed				

Item	Yes	No	No Evidence	Document title/Filename
Monitoring calls *Select a number of records at random for each telephonist*				
Did the telephonist introduce the study in a friendly and professional manner?				
Did the telephonist check to ensure that the respondent consented to take part?				
If this is a child or teenager, did the parent consent for them to take part the study?				
Did the telephonist inform participant that the call would be recorded for monitoring purposes?				
Did the telephonist follow the script?				
Requests for additional information:				
Did the participant request further information about the study?				
Did the telephonist refer the potential participant to the iid2 website?				
If the participant asks for written information, did the telephonist explain that they needed to pause the recording of the call? Did the telephonist pause the recording so that no record of PII was made?				

Item	Yes	No	No Evidence	Document title/Filename
Double Data Entry				
Standard Operating Procedure for DDE • Evidence that the SOP is being followed				
How are discrepancies highlighted? • Evidence that discrepancies are highlighted				
Standard Operating Procedure for correction of discrepancies • Evidence that the SOP is being followed				
Select a number of records at random where discrepancies have been highlighted				
Were discrepancies highlighted appropriately?				
Were discrepancies recorded correctly?				

Is a further visit required? Yes ☐ No ☐

Auditor Comments (*to be completed before the auditor signs the form*)

Signature of auditor(s)

…… **Date:**……

…….... **Date:**……

Site Researcher Comments (*to be completed before the auditor signs the form*)

Signature of site researcher(s)

…….... **Date:**……

…….... **Date:**……

Appendix 16.4: Internal audit form – Diagnostic Microbiology

IID2 Study Quality Control Site Visit

Site: Manchester Regional Laboratory

Date of visit:

Research Staff present:

Auditor(s):

Item	Yes	No	No Evidence	Document title/Filename
Staff				
Is there a documented organisational structure showing line management responsibility?				
Is there a list of personnel associated with the project?				
Are there up to date CVs (and job descriptions) available for all staff involved in the project?				
Are there Induction and Training portfolios for all staff?				
Health and Safety				
Is there a documented safety manual? Are staff made aware of it? Is it the latest version? Is this documented in staff training portfolios?				
Are there COSHH and risk assessments in place for all the procedures used in the project? Are they in date? Are they readily available? Are staff aware of these and been signed off against them?				

Item	Yes	No	No Evidence	Document title/Filename
Are there procedures for breakages and spillages?				
Are work areas suitable for purpose?				
Handling of samples and materials				
Are there SOPs in place for sample receipt, labelling and tracking, retention and disposal?				
Is there evidence of who enters samples on to Telepath?				
Documentation of procedures and methods				
Are there SOP's/protocols in place for the tests undertaken?				
Is there evidence of regular review and document control?				
Are the SOPs authorised versions and have these been reviewed?				
Quality Assurance				
Is there participation in all relevant EQA schemes? Is performance good and monitored?				

Item	Yes	No	No Evidence	Document title/Filename
Is there appropriate IQA? Is there replicate testing (IQC)? Are internal controls used on all tests? Is there QC of media used?				
Work methods/audit				
Are work books used to record experimental details and results e.g. machine readouts, batch details, printed data or photographic records obtained of all work performed?				
Are all records archived and recoverable?				
Is it possible to construct a full audit trail from the retained records?				
Vertical Audit				
Request Form				
Is the request form easily located? Has the request form been correctly completed? Are there any transcription errors to LIMS?				
Specimen receipt				
Is there a specimen reception policy?				

Item	Yes	No	No Evidence	Document title/Filename
Is there a rejection policy for				
a) inadequate identification?				
b) broken/leaking specimen?				
c) inadequate specimen?				
Are reception staff aware of study policies?				
Are reception staff aware of safety policies?				
Specimen				
Has any material been stored and is it easily located?				
Is storage adequate and appropriate?				
Is all material adequately labelled and uniquely identifiable?				
Is all material logged?				

Item	Yes	No	No Evidence	Document title/Filename
Tests				
Are there procedures for all tests on this specimen?				
Were all appropriate tests carried out?				
Can an audit trail be constructed for all tests on this sample?				
Report				
Is a copy report able to be generated?				
Are there any transcription errors?				
Is there a procedure for interpretive comments?				
Is there a telephone procedure and was this followed?				
Is there an amended report procedure and was this followed?				
Was the specimen reported within the appropriate turn around time?				

Item	Yes	No	No Evidence	Document title/Filename
Staff				
Are there staff competency/training records for those processing this sample?				
Equipment				
Does equipment used (list) have				
- Routine maintenance?				
- Calibration checks?				
Reagents				
Check media used (if applicable), are the use by dates and media batch numbers recorded for traceability? Document what media is used (if a vast amount of media has been used for this sample, only pick a few and document below).				
Check kits/reagents used. Are the use by dates and batch numbers recorded for traceability either in work books or on works sheets? Document which kits/reagents are used.				

Item	Yes	No	No Evidence	Document title/Filename
Check the storage facilities for the current media, kits and/or reagents. Are these all stored at the correct temperature? Are fridges and freezers monitored?				
Is the storage area clean and tidy?				
Check the worksheets/work books /work instructions for the sample/tests. Are these controlled documents?				
Is there an inventory for the contents held in the fridge/freezer/room storage? Who maintains this?				
Who is responsible for monitoring stock? Is there a first in, first out stock rotation system in place?				

Is a further visit required? Yes ☐ No ☐

Auditor Comments (*to be completed before the auditor signs the form*)

Signature of auditor(s)

…… **Date:**……

…… **Date:**……

Site Researcher Comments (*to be completed before the researcher signs the form*)

Signature of site researcher(s)

…… **Date:**……

…… **Date:**……

Appendix 16.5: Internal audit improvement actions

iid2 The Second Infectious Intestinal Disease Study

IID2 Study Quality Control Site Visit
Improvement Actions and Recommendations

Site:
Date of Audit Visit:
Research Staff present:
Auditor(s):

Finding No.	Description of Finding	Suggested improvement action	Agreed timescale	Date Completed	Improvement action reviewed by

Appendix 16.6: External audit – Research Management and Governance

NHS
Halton and St Helens

Audit Report

Audit of Research Study 12/09

Audit Team: Kirsty Pine, Research and Development Manager
Paul O'Connor, Research and Development Officer

Issued to Professor Sarah O'Brien – Chief Investigator
Kathryn Jackson – Study Project Manager

Research and Development
Suite 1 Unit 1H
Midwood House
Midwood Street
Widnes, WA8 6BH
0151 495 5480

NHS
Halton and St Helens

Project Title: The second study of infectious intestinal disease in the community determining disease burden and calibrating national surveillance systems in the UK.

1. Trust R&D Office Research Project Approval:

(i) Does the project have a research sponsor? (All studies started after May 2004 should have a recognised sponsor, usually the Chief Investigator's employer or project funder.) YES – University of Manchester
(ii) Does the project have R&D Office Project approval? YES – Halton and St Helens, Warrington and Knowsley.
(iii) If Trust approval was subject to modifications being made to the research design and protocol, were these amendments made prior to the study commencing? *N/A*
(iv) Do you have indemnity provided by the Trust and/or commercial funder? *YES – University of Manchester*

2. Scientific Requirements:
(i) Is this project a clinical trial undertaken to ascertain the efficacy or safety of a medicine? *NO*
(ii) Does this project involve an investigative medical device or device not usually used for treatment? NO
(iii) Has the project been peer reviewed? *YES – Project has been scientifically peer reviewed which has been accepted by the main funder, the Food Standards Agency.*
(iv) Are there copies of all correspondence relating to an external funder's scientific review? *YES*
(v) If applicable, have all recommendations made during the scientific review been addressed? *YES*

3. Ethical Requirements:
(i) Is there a record of full approval from the relevant Research Ethics Committee (REC)? *YES – North West Research Ethics Committee*
(ii) If the study is Multi-centred is there a record of local Site Specific Assessment (SSA) approval? *SSA Exempt*
(iii) If the research protocol has been amended in any way since full ethics approval was obtained has the research ethics committee approved any substantial amendments? *YES*
(iv) Have procedures been put in place to ensure confidentiality of patient identifiable data? *YES – The details of the participant are kept at the G.P Practice. The data is then sent to the co-ordinating centre anonymised. This information is kept on a secure password protected, encrypted web based tool. The researcher has limited access to the data respective of where they are based. Hard data is kept in locked filing cabinets in a locked office. The study data will be kept in G.P Practices for 25 years.*
(v) Is there a system for the recording of all research participants' written informed consent and/or where appropriate written carer assent? *YES – The participant has to initial the specific sections of the research they agree to take part in, the*

consent form includes signature and dates. The participant is given a study I.D number.

(vi) If the research involves Trust patients in research on interventions/therapies, is there a copy of patients' written informed consent and/or written carer assent, included in patients' medical notes? *N/A*

(vii) And details of the research project? *N/A*

(vii) Is there a system for the recording of all research participants (clients, staff or healthy volunteers)? *YES – Quality control audits are completed on the research nurses involved in the study. These audits are recorded and kept with document files.*

4. Health and Safety Requirements:

(i) Is there a system for the recording of all adverse events (clinical and non-clinical including any not specified in the protocol) that may have resulted from participation in the research? *YES – No adverse events occurred within the study. If they did occur the event would be logged at the coordinating centre*.

(ii) Will all serious adverse events been reported to the appropriate:

Research Ethics Committee	*YES*
Research Sponsor	*YES*
Host Trust	*YES*

(iii) Do all members of the research team who have access to patients, their organs, tissues, data or access to NHS staff, information and facilities hold an in date Trust employment contract/NHS honorary contract? *YES – NHS Staff members and honorary contracts for Non NHS Staff members.*

5. Information Requirements:

(i) Are there any arrangements in place to disseminate the research findings, to the research participants and other users/carers? *YES – Presentations of the final report will be given to the Food Standards Agency May 2010. R&D Departments and REC will be given a summary report of the findings.*

(ii) Are there plans to publish research findings in professional and where appropriate in peer reviewed journals? *YES*

6. Finance and Intellectual Property Rights (IPR) requirements:

(i) Has the Trust Finance Department approved all agreements/contracts made with external funders? *N/A*

(ii) Have the Trust Finance Department and the Trust R&D Office given approval for all Treatment Costs and Service Support Costs incurred during the course of the research? *N/A*

(iii) As Chief / Principal Investigator, are you taking responsibility for the project being conducted according to strict financial probity, and compliance with the law and rules laid down by H. M. Treasury and the Trust, for the use of public funds? *YES*

(iv) Are there agreements covering intellectual property rights (IPR) with any third party researchers/organisations/companies?
If yes have these been approved by the Trust Finance Department, and by R&D Office? (This may include sharing of data/materials etc with any parties outside the Trust.) *N/A*

Conclusions, recommendations and actions required.

The standard of the research management was excellent. The Chief Investigator and research team have endeavoured to conduct this project to a high standard and safeguard participant data throughout the research, which is ongoing. From the study files reviewed no issues were highlighted with regards to protocol compliance. Documentation to demonstrate adherence, in accordance with the above criteria was evidenced.

To further emphasise the standard of research management for this study, there is evidence in the documentation of the project being extensively and regularly reviewed at Executive Committees. These meetings are well documented and the actions agreed are effectively monitored.

The following points requiring consideration were highlighted during the course of the audit:

No actions required.

Appendix 16.7: External audit- UK Accreditation Service

United Kingdom Accreditation Service

Commercial in confidence

[redacted]

ASSESSMENT REPORT

Name & Address of Research Contractor	University of Manchester Department of Health Science and Epidemiology Division of Medicine & Neurosciences Clinical Sciences Building Hope Hospital Salford Manchester M6 8HD	**Date of Assessment**	26th March 2008
		Date of Assessment Plan	18 March 2008
		Funding Body	FSA
Assessment Location	As above	**Contact**	Prof S. O'Brien
Assessment Criteria	Joint Code of Practise for Research (JCoPR)	**UKAS Assessor**	Rachel Oakley
Research Contractor Representatives	**Project Representatives** Prof Sarah O'Brien Kathryn Jackson	**Project Number**	B18021
		Project Reference	IID2 Study
Report Issued by	Rachel Oakley	**Recommendations**	2
Report Issued Date	28/3/08	**Report Acknowledged Method**	Email

1. Executive Summary
The project is being conducted to a very high standard. It is evident that the requirements of the Joint Code of Practise have been carefully considered and the systems in place have been very well thought through and are being effectively implemented.

The project has been meticulously planned and the project team at Manchester has all aspects under effective control. The staff are knowledgeable and enthusiastic and cooperated fully through this audit. The level of detail of the documentation is excellent and the records relating to the project are well-organised and maintained to a very high level.

Only two recommendations were made for potential improvements and this low number is indicative of the standard to which the project is being managed. The audit provides assurance that the project is progressing well and shows a high level of compliance with the requirements of the Joint of Practise For Research.

2. Scope
The purpose of this visit was to conduct an assessment of the laboratory's project (Project number B18021) in order to assess compliance with the Joint Code of Practise for Research. The audit took place at the University of Manchester's Department of Health Science and Epidemiology at the Hope Hospital where the project is being coordinated.

The audit included a discussion regarding the current status of the project and future work followed by assessment of project documentation, collaborators' records including CVs and collaborator agreements, personnel records, review meeting records, training procedures, ethical approvals, audit procedures and records, data collection processes.

The project started in 2006 and to date the pilot study has been completed. The main study is due to start from the beginning of April and the anticipated completion date for the project including reporting of results to the FSA is March 2010.

3. Overview of Research Contractor
The project is being managed and coordinated by the staff working at the University of Manchester. The Project Coordinator (Sarah O'Brien) has been working at the University since August 2004 and has experience of managing other research projects including other FSA funded projects. Kathryn Jackson (Project Manager) and Emma Dixon (Administrative Assistant) have been employed specifically to work on this project.

4. Observations & Assessment Findings

4.1 Responsibilities
The responsibilities of all personnel working on this project are clearly defined. In addition there is been close communication between all participants throughout the project, which is ensuring that requirements are clearly understood by all parties.

The level of experience and expertise of personnel working on this project is extensive. The project is being managed by staff at the University of Manchester, however there are a large number of collaborators also working on this project as follows:

HPA Centre for Infections (CfI) – responsible for microbiological analysis of stool samples using molecular methods – CPA accredited
HPA North West Regional Laboratory – responsible for microbiological analysis of stool samples using traditional methods – CPA accredited

London School of Hygiene and Tropical Medicine - statistical input including analysis of patient data to ensure representative data is produced.

MRC General Practice Framework (GPRF) – Studies in Primary Care e.g. Cohort studies/GP Presentation, Enumeration Study – coordination of the research nurse training.

University of East Anglia (UEA) – design and conduct of the telephone survey work

Provision of scientific Advice
University of Nottingham
CDSC Northern Ireland
Cardiff University (formerly University of Wales College of Medicine)
University of Glasgow
NHS Direct/HPA Collaborative Group

Collaborator agreements are held for each participant and this provides details of the terms and conditions for this involvement on this project, including a requirement to comply with the JCoPR.

4.1.1 Project Personnel
The University of Manchester personnel are well-qualified and have appropriate experience.

4.1.2 Subcontractors
One subcontractor has been used to develop the web-based data collection system. The subcontractor was assessed and appointed using the University's procurement procedure. Records show that a thorough evaluation was done of a number of potential suppliers before the chosen provider was selected.

4.2 Competence

4.2.1 CVs of Project Personnel
CVs for University of Manchester staff and for all personnel working for the collaborators are held and indicate appropriate experience and support the selection of the relevant participants. These records are well-maintained in an ordered manner.

Roles are also defined through job descriptions and these were checked for University of Manchester staff. The records are well-documented and clearly define responsibilities for individuals relevant to their position in the project team.

4.2.2 Training Records
University of Manchester staff have had to complete an induction programme including health and safety training and records of these are maintained, although it was noted that Kathryn's record had not been signed off by the relevant training manager and the records need to be completed.

Whilst most training is the responsibility of individual collaborators to ensure staff are up-to-date and competent, the training involving practice nurses has involved the University of Manchester staff and other project members. The training agenda appears comprehensive and the training material supplied is clearly documented and easy to follow. As a result of the pilot study some changes have been made to procedures and further training has been conducted with nursing staff to ensure they are up-to-date. This will continue into the main study as other practices become involved with the project. There is a very good system in place using QC audits, which enables the effectiveness of these training sessions to be monitored in order to ensure that nurses are following procedures correctly particularly as this is a critical part of the project. This will continue to be done during the main study, although the audits will be delegated to research nurses located in the regions. Training of the research nurses to do these audits is already planned and it is expected that records of this training and assessment of competence will be documented.

4.3 Project Planning

4.3.1 Risk Assessment
There has been on-going assessment of risks since the start of the project, which are documented

using the risk register (currently at version 16). The system is ensuring that risks are reviewed and addressed, where possible, as and when they are identified. The register is under constant review and this aspect appears under effective control.

4.3.2 Project Plan
The key document, which details the requirements for each stage of the project, is the project proposal, which provides clear details regarding the delivery of the project. In the main milestones have been achieved and where delays have occurred these have been communicated to the FSA. Whilst the project proposal is the key point of reference, further planning and development is done through regular review meetings, which involve all project personnel. The decision to generate sub-groups is very good because it is enabling regular reviews on a quarterly, monthly and weekly basis to be conducted by relevant project personnel. There is a good and effective system in use for monitoring actions identified at these meetings to ensure that they are progressed effectively and within agreed timescales.

4.3.3 Approved Procedures for Sampling Materials
This is not applicable to the work being done at the University of Manchester location, but would be relevant e.g. to the laboratories, research nurses. Whilst this could not be assessed directly, protocols were seen detailing sampling requirements and these appeared to be adequate.

4.3.4 Ethical Approval
Due to the nature of this project it has been necessary to obtain the relevant ethical approvals from the Multi Centre Research Ethics Committee and from the NHS R&D organisations. These initial approvals were obtained to enable the pilot study to proceed. Since then some amendments have been made to the study and these changes have been re-submitted for further approval by the relevant committees and these have been completed successfully.

Some approvals are still awaited from the local Research Management and Governance committees to permit the involvement of individual practices in the study, but there are a sufficient number of practices where approval has been obtained to enable the main study to commence.

4.4 Quality Control
Whilst individual collaborators are responsible for the quality of the data being generated, some additional QC checks have been instigated to verify the data being collected. This is done in a variety of ways, e.g. through QC audits which are working well. Telephone survey data is subject to double-checking, by comparing conversations recorded on tape against the records/notes made by telephonist when making the call. University staff will be responsible for reviewing this data and following up any significant discrepancies.

4.4.1 Auditing & Assessment Procedures
An audit programme is in place, which ensures that at least one aspect of the IID2 study is audited quarterly. An audit has already been done of the telephone survey work being coordinated by the University of East Anglia and the record of this audit is well-documented. A few relatively minor non-conformities were raised, which had reportedly been addressed, but it would be useful for the record to indicate this and in particular to show that someone (i.e. the auditor) has followed this up.

Further audits are scheduled and will ensure that each area of the project is audited within the set timescales. It will be important to ensure that these audits cover the requirements of the Joint Code of Practise for Research to verify collaborators' compliance with those requirements. Auditors appear to have been allocated an audit area that they are not directly involved in enuring a degree of independence, which should enable a thorough and objective assessment.

The QC audits done on nurses participating in the Cohort and GP Presentation studies were done as scheduled during the pilot study. The process also enabled nurses to provide feedback and this has been effectively collated enabling further correction/improvement actions to be taken e.g. further training, amendment of the forms used in the data collection.

The breach of contract that was identified was handled very well and records indicated that all relevant parties were notified at the time. Corrective/preventive actions taken were appropriate. The recent audit at UEA involved a check of this aspect, however no such incidents had occurred since the breach so this could not be audited fully. The project team could consider another follow-up audit at a later time to verify that correct procedures are being used, if they felt this to be a particular issue.

4.4.2 Internal Project Reviews
The project is being extensively and regularly reviewed, which is critical for a project of this size and the project team has recognised this. The Executive Committee meetings are held quarterly and are attended by all project personnel where possible and provide a good overall review of the project. A number of sub-groups have been set up who meet more regularly and enable the day-to-day issues to be reviewed and actions agreed which ensures continued focus and timely follow-up of any issues where needed. The team is making effective use of the expertise of the collaborators on this project and the meetings are proving to be an effective management tool. Records from the meetings are well-documented and actions agreed are being effectively monitored.

4.4.3 Publication Policy & Authorisation Procedures
The project personnel are aware of the need to notify and agree with the Funding Body any publications of material associated with this project. A publications policy is documented, although this is still currently in draft and now needs to undergo a final review before being issued. It is expected that all project personnel including collaborators will follow this procedure.

4.5 Health & Safety
There are no specific requirements relating to the work being done at the University of Manchester. It is expected that individual collaborators will have their own health and safety systems in place, which comply with the JCoPR.

4.6 Handling of Samples & Materials
There are no specific requirements relating to the work being done at the University of Manchester. It is expected that individual collaborators will have their own systems in place to deal with this aspect, which comply with the JCoPR.

4.7 Facilities & Equipment
There are no specific requirements relating to the work being done at the University of Manchester. It is expected that individual collaborators will have their own systems in place to deal with this aspect, which comply with the JCoPR.

4.8 Documentation of Procedures & Methods
Documentation relating to this project is of a very high standard. Standard Operating Procedures have been produced specific to the project and are expected to be followed by all project personnel. These are readily accessible via the intranet, which each collaborator is able to access using a username and password. Most documents are prepared under the responsibility of the project manager. These are being effectively reviewed and input is provided by the other collaborators.

SOPs specific to collaborators are their responsibility to maintain, however copies of all protocols are held centrally by the University of Manchester team. The documentation is comprehensive and very well-maintained although due to the size and variety of documents held it would be useful to hold a masterlist which details all the documents held and their current revision status to make using the system and locating documents easier.

4.8.1 Validated Standard Operating Procedures
A web-based data collection system is being used to collect data generated from this project. It is key to ensure that the system is operating effectively and much work has been done to trial this throughout the pilot study. Further validation is planned at the start of the main study to give assurance that the system is operating effectively and the proposed plan has been well thought out and should ensure all aspects of the system are appropriately verified.

United Kingdom Accreditation Service – Assessment Report – Continuation Sheet
Research Contractor: Manchester

4.8.2 Document Control Procedures
The system for preparing, reviewing and issuing documents is excellent and ensures that these aspects are done effectively. There were a few occasions when the document control procedure did not appear to have been followed in its entirety, e.g. issued documents not always marked as final when required, although the overall impact of this is small. It would be useful to remind project staff of the procedure and ensure it is followed. Document changes are communicated effectively and documents are easily accessed by project personnel via the intranet.

4.9 Research/Work Records

4.9.1 Experimental Records, Sampling records, Project related records
Records held by the University of Manchester department are comprehensive and very well-maintained.

4.9.2 Data Management & Archiving Procedures
Most records relating to the project are stored on the web-based data collection system. This can be accessed by different members of the project team, but access is restricted depending on level of participation and this arrangement appears to ensure appropriate security and to ensure patient confidentiality where necessary.

There are procedures in place, which describe the arrangements for data security, firewall, back-up systems, archiving etc and these are satisfactory and demonstrate adequately that appropriate measures are in place.

5. References
Joint Code of Practice for Research

6. Appendices
Improvement Action Report & Recommendations prepared by Rachel Oakley

Commercial in confidence	**IMPROVEMENT ACTION REPORT & RECOMMENDATIONS**	**REF NO: RMO/MAN**	[redacted]

Name of Research Contractor	University of Manchester	**Project Reference**	**B18021**
Assessment Location	Department of Health Science and Epidemiology Division of Medicine & Neurosciences Clinical Sciences Building Hope Hospital Salford Manchester M6 8HD	**Research Contractor Representatives**	Prof Sarah O'Brien Kathryn Jackson

Finding No.	**UKAS Assessor**	Rachel Oakley	**Date of issue: 26/3/08**	**Please read in context with the Assessment Report**
	Description of Finding (including reference to the Joint Code of Practise for Research)		**Suggested Improvement Action** (discussed with the Research Contractor)	
1	**JCoPR, Section 8** There are a significant number of documents in use for this project and it would be useful to implement a system, which enables these documents to be quickly and easily identified e.g. through use of a masterlist, which includes their current revision status. This would be particularly beneficial due to the number of documents and would assist collaborators in their use and application.		Generate an up-to-date list of documents to include current revision status for use by all members of the project team.	
2	**JCoPR, Section 8** Audit records do not indicate timescales for completing corrective actions in order to demonstrate that appropriate timescales have been agreed with the person designated to take the action. In addition whilst corrective actions raised during internal audits are verified when complete, no record of this is currently held to show when and who completed this check. This is important to show that appropriate follow-up has been taken and actions identified as agreed.		Audit record was amended during the audit to enable timescale/follow-up etc to be recorded. The updated record needs to be formally issued.	

END

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Appendix 13: Microbiology Fact Sheets

Appendix 13.1: Adenovirus

iid2
The Second Infectious Intestinal Disease Study

Micro_IID2_Adenovirus_03

FACT SHEET

Adenovirus

Common clinical features

Watery diarrhoea with vomiting with most infections occurring in children aged under five. Duration of illness can be up to 5 days.

Incubation period

1 – 3 days.

Where is it found?

In gastrointestinal tract of man, sewage and contaminated water.

How is it acquired by affected individuals?

Usually by person to person spread by the faecal oral route.

How does the laboratory confirm the diagnosis?

An immunoassay test can be used to detect virus antigens in a faecal sample but not many laboratories test for this organism.

How is it treated?

Symptomatic treatment and rehydration.

11th January 2008

Appendix 13.2: Astrovirus

Micro_IID2_Astrovirus_05

FACT SHEET

Astrovirus

Common clinical features

Mild self limiting diarrhoea that lasts 2-3 days occasionally associated with fever and vomiting.

Incubation period

1-3 days.

Where is it found?

Human gastrointestinal tract, sewage and contaminated water.

How is it acquired by affected individuals?

Person to person by the faecal oral route. Contaminated surfaces in nurseries may be an environmental source. Shellfish have occasionally been implicated as sources of infection.

How does the laboratory confirm the diagnosis?

There is no test available in routine hospital laboratories but specialist virology laboratories can use a molecular test to detect the virus.

How is it treated?

Symptomatic treatment and rehydration.

Appendix 13.3: *Bacillus* spp.

Micro_IID2_Bacillus spp_04

FACT SHEET

Bacillus

Common clinical features

Some cases have a sudden onset of nausea and vomiting and others have colicky pain and diarrhoea. The illness generally lasts for no longer than one day.

Incubation period

B. cereus – emetic syndrome: 1 – 5 hours; diarrhoeal syndrome: 8 to 16 hours
B. subtilis – 10 minutes to 4 hours
B. licheniformis – 2 to 14 hours

Where is it found?

Widespread in the environment: soil, dust, vegetation. A variety of food products can be contaminated. There are no human or animal sources.

How is it acquired by affected individuals?

From contaminated foods subjected to inadequate post-cooking temperature control during cooling and storage. A wide variety of food products can act as sources but *B. cereus* is particularly associated with rice dishes. It is not passed from person-to-person.

How does the laboratory confirm the diagnosis?

The bacteria are cultured from faeces and suspected foods, and the results are usually available in 2 to 3 days. This test will only be carried out if food poisoning with Bacillus is strongly suspected.

How is it treated?

Symptomatic treatment only.

11th January 2008

Appendix 13.4: *Campylobacter* spp.

Micro_IID2_Campylobacter_06

FACT SHEET

Campylobacter

Common clinical features

Diarrhoea, abdominal pain, malaise, fever, nausea and vomiting are the common symptoms with varying severity. The illness is frequently over within 2 – 5 days and usually lasts no more than 10 days. Blood and mucus may be present in liquid stools. Some people infected have no symptoms. Uncommon complications include joint pains (arthritis) and Guillain-Barré (a disease of the nervous system that can lead to temporary paralysis).

Incubation period

1 – 11 days (usually 2 to 5 days)

Where is it found?

Gastrointestinal tract of farm livestock and poultry, wildlife including birds, and domestic pets.

How is it acquired by affected individuals?

From raw or undercooked meat (especially poultry), unpasteurised milk, bird-pecked milk on doorsteps, untreated water, and domestic pets with diarrhoea. It is rare for Campylobacter to be passed from person to person, only if personal hygiene is very poor.

How does the laboratory confirm the diagnosis?

The bacteria are cultured on selective media from faeces samples and results are usually available in 2 – 3 days.

How is it treated?

Symptomatic treatment and rehydration. Antibiotics are required only in severe cases.

10th January 2008

Appendix 13.5: *Clostridium difficile*

iid2
The Second Infectious Intestinal Disease Study

Micro_IID2_Clostridium difficile_05

FACT SHEET

Clostridium difficile

Common clinical features

Clostridium difficile is the most commonly identified cause of clinically significant antibiotic-associated diarrhoea. Many antibiotics cause loose stools but *C.difficile* associated diarrhoea (CDAD) may be mild or severe and there is often fever and abdominal pain. In severe cases colitis may develop. There may be relapses after treatment. The incubation period is variable within one day of starting or several weeks after finishing a course of antibiotics.

Where is it found?

C.difficile is a spore forming bacterium that is found in the faeces of humans and other animals, in soil and water, and on environmental surfaces in homes and hospitals. Carriage rates are low (less than 3%) in healthy adults with no diarrhoea. Rates are high (greater than 50%) in children up to the age of 2 years and moderate rates (greater than 10%) are found in the elderly, with higher rates in those in hospital and in residential care.

How is it acquired by affected individuals?

Spores may be ingested from the environment. Colonisation rates are higher in the elderly, particularly in hospitals and residential homes where antibiotic use is common. The environment is more heavily contaminated around individuals who have diarrhoea. Antibiotics kill some of the normal "healthy" gut bacteria and allow *C.difficile* to multiply, producing toxins that cause ulceration and diarrhoea.

How does the laboratory confirm the diagnosis?

A faeces sample is tested for the presence of *C.difficile* toxins using an immunoassay test. Results will usually be available in two days. Toxins can be detected in the faeces of healthy, asymptomatic children up to the age of 2 years, and a positive test result is not clinically significant in this age group. Studies have shown that toxins are rarely detected in asymptomatic older children or adults living in the community. However, toxins may be detected in the faeces of individuals who have received antibiotics recently, but who do not have diarrhoea.

How is it treated?

C.difficile associated disease can be severe (colitis) and even life threatening. If a patient has significant diarrhoea while on antibiotics or has a positive *C.difficile* toxin test, the causative antibiotics should be discontinued. If the patient requires continuing treatment for their initial infection a Consultant Microbiologist should be consulted. Fluid and electrolyte losses should be replaced and the use of anti-motility agents should be avoided. If symptoms
are moderate to severe or measures above are ineffective, oral metronidazole 400 mg three times daily should be given for ten days.

12th January 2008

Appendix 13.6: *Clostridium perfringens*

Micro_IID2_Clostridium perfringens_07

FACT SHEET

Clostridium perfringens

Common clinical features

An intoxication which causes a sudden onset of colicky pain followed by diarrhoea. Nausea is common but vomiting and fever are usually absent. Generally a mild disease of short duration.

Incubation period

8 to 22 hours (usually 12 to 18 hours)

Where is it found?

Gastrointestinal tract of animals, soil and dust.

How is it acquired by affected individuals?

From contaminated cooked meat and poultry dishes subjected to inadequate temperature control after cooking, during cooling, and storage. It is only acquired from food and not passed from person to person.

How does the laboratory confirm the diagnosis?

Low numbers of this organism are present in normal faeces samples but high counts are present when it is causing illness. An immunoassay test can be used to detect the toxin in faeces and the organism can be grown from suspected food. Results will usually be available in 2 days. The tests will only be carried out if food poisoning with *Clostridium perfringens* is strongly suspected.

How is it treated?

Symptomatic treatment only.

Appendix 13.7: *Cryptosporidium*

iid2
The Second Infectious Intestinal Disease Study

Micro_IID2_Cryptosporidium_05

FACT SHEET

Cryptosporidium

Common clinical features

Watery or mucoid diarrhoea, accompanied by cramping abdominal pain. Symptoms commonly last for several days, up to 4 weeks. Asymptomatic infection is common. Prolonged and severe infection occurs in individuals with severe immunodeficiency.

Incubation period

Average 7 - 10 days, range 1 – 28 days.

Where is it found?

Gastrointestinal tract of man and animals, particularly farm and other domesticated animals. Drinking and recreational water contaminated with faeces or sewage.

How is it acquired by affected individuals?

Contact with infected animals or animal faeces. Outbreaks have been associated with drinking water supplies and rarely contaminated food. Seasonal outbreaks are associated with farm visits (open farms). Infection has been reported following contamination of swimming and paddling pools. Person to person spread does occur particularly in households and nurseries. The cysts are not killed by the levels of chlorine used to disinfect drinking water supplies.

How does the laboratory confirm the diagnosis?

The cysts are detected by microscopy or using an immunoassay test on the faeces. Results are usually available within 2 days of receipt in the laboratory.

How is it treated?

Rehydration and symptomatic treatment. There is no specific treatment although several anti-cryptosporidial agents are under investigation for treatment of immunodeficient patients.

Appendix 13.8: *Cyclospora cayetanesis*

Micro_IID2_Cyclospora cayetanensis_03

FACT SHEET

Cyclospora cayetanensis

Common clinical features

Watery diarrhoea, loss of weight, loss of appetite, bloating, nausea, vomiting, muscle aches and persistent fatigue. Illness may last from a week to a month or longer if untreated.

Incubation period

1 – 11 days, on average one week.

Where is it found?

The gastrointestinal tract of humans, no known animal reservoir. Once excreted the oocysts sporulate in the environment before becoming infectious and this process occurs over several days to weeks.

How is it acquired by affected individuals?

From drinking or swimming in contaminated water and eating contaminated food, particularly fresh produce such as salad vegetables and fruit. Direct person to person spread (faecal oral) is unlikely as the oocysts are not infectious when first excreted in faeces. Although infection may be acquired worldwide, it is more common in developing countries and travellers are at increased risk.

How does the laboratory confirm the diagnosis?

Oocysts are detected in faeces samples examined by microscopy. Results are usually available within 2 days of receipt in the laboratory.

How is it treated?

One of the few gastrointestinal infections for which there is a specific antibiotic treatment, Trimethoprim/Sulfamethoxazole.

Appendix 13.9: Enteroaggregative *E. coli* (EaggEC)

Micro_IID2_Enteroaggregative Escherichia coli (EAggEC)_03

FACT SHEET

Enteroaggregative Escherichia coli (EAggEC)

Common clinical features

Variable. EAggEC can cause either an acute or chronic (greater than 14 days) diarrhoeal illness. The most commonly reported symptoms are watery diarrhoea with or without blood and mucus, abdominal pain, nausea, vomiting and low grade fever.

Incubation period

Generally 8 – 18 hours

Where is it found?

The gastrointestinal tract of humans, cattle, sheep, pigs and dogs.

How is it acquired by affected individuals?

EAggEC is described as a cause of large outbreaks of diarrhoeal disease across the world probably through ingestion of contaminated food and water. EAggEC is a common bacterial cause of diarrhoea among travellers to developing countries and among children and HIV-infected persons living in both developing and developed regions of the world. Direct person to person spread (faecal oral) is unlikely unless hygiene is very poor.

How does the laboratory confirm the diagnosis?

There is no test in routine use in clinical diagnostic laboratories. In the **IId2** Study a research molecular test is being used to identify EAggEC at the reference laboratory and the result will be available within seven days.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Antibiotic treatment is only recommended for persistent diarrhoea. Advice on antibiotic treatment should be sought from your local microbiology laboratory.

12th January 2008

Appendix 13.10: Enterotoxigenic *E. coli* (ETEC)

Micro_IID2_Enterotoxigenic E.coli_ ETEC_03

FACT SHEET

Enterotoxigenic Escherichia coli (ETEC)

Common clinical features

Diarrhoea which may be mild to severe, typically profuse and watery without blood or mucus. Abdominal pains, vomiting and low grade fever may be present. Usually the symptoms last for less than 5 days.

Incubation period

12 – 72 hours.

Where is it found?

The gastrointestinal tract of humans, no known animal reservoir.

How is it acquired by affected individuals?

From ingestion of contaminated food and, less often, contaminated water. Direct person to person spread (faecal oral) is unlikely unless hygiene is very poor. ETEC is the major cause of travellers diarrhoea particularly among travellers to developing countries. ETEC is also the major cause of severe diarrhoea and dehydration in young children in developing countries.

How does the laboratory confirm the diagnosis?

There is no test in routine use in clinical diagnostic laboratories. In the **iid2** study a research molecular test is being used to identify ETEC at the reference laboratory and the result will be available within seven days.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Antibiotic treatment is only recommended for severe and continuing diarrhoea. Advice on antibiotic treatment should be sought from your local microbiology laboratory.

12th January 2008

Appendix 13.11: Vero cytotoxin-producing *E. coli* (VTEC) O157

FACT SHEET

Vero cytotoxin-producing Escherichia coli (VTEC) O157

Common clinical features

Diarrhoea which may be mild to severe and can contain a large amount of blood (haemorrhagic colitis). In severe cases haemolytic uraemic syndrome (HUS) may occur leading to renal failure, particularly in the very young and very old.

Incubation period

Generally 1 – 6 days

Where is it found?

The gastrointestinal tract of cattle, sheep, pigs and some wild animals e.g. rabbits.

How is it acquired by affected individuals?

From contaminated food generally animal products – meat, particularly undercooked beef, milk, cheese and occasionally contaminated vegetables. Direct contact with infected animals on farms or animal sanctuaries, or contaminated land. Person to person spread can occur by direct contact (faecal oral), particularly in households, nurseries and infant schools.

How does the laboratory confirm the diagnosis?

E.coli are cultured from faeces on selective media and the O157 strain has special biochemical characteristics. Presumptive results are usually available within 2 days. Other VTEC (non-O157) are a much less common cause of illness. Suspected *E.coli* strains are confirmed at the Reference Laboratory and tested for toxin production. Suspected foods are tested when outbreaks occur.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Some reports suggest that antibiotics may be harmful rather than beneficial (killing the bacteria and releasing more toxins into the bloodstream). Hospital treatment is required for severe cases. HUS is one of the most common causes of acute renal failure in children.

Appendix 13.12: Vero cytotoxin-producing *E. coli* (VTEC) non-O157

Micro_IID2_Vero cytotoxin-producing Eschericia coli (VTEC) non-0157_07

FACT SHEET

Vero cytotoxin-producing Escherichia coli (VTEC) [non- O157]

Common clinical features

Variable, from asymptomatic to diarrhoea, which may be mild to severe and can contain a large amount of blood (haemorrhagic colitis). In severe cases (which are rare) haemolytic uraemic syndrome (HUS) may occur leading to renal failure, particularly in the very young and very old. Outbreaks and individual cases of severe diarrhoea caused by VTEC (producing VT1 and/or VT2 toxins) that belong to serogroups other than O157 are very rarely identified in the UK, but reported more frequently from mainland Europe and the rest of the world. It is not clear whether all non-O157 VTEC are capable of causing human illness.

Incubation period

Generally 1 – 6 days.

Where is it found?

The gastrointestinal tract of humans, cattle, sheep, pigs and some wild animals. Some of the animal strains are known to be non-pathogenic in humans and the source of most human infections is not identified.

How is it acquired by affected individuals?

Presumed to be similar sources or vehicles to *E.coli* O157. Potentially, therefore:

- From contaminated food, generally animal products – meat, particularly undercooked beef, gravy, milk, cheese and occasionally contaminated vegetables.
- Direct contact with infected animals on farms or animal sanctuaries, or contaminated land.
- Person to person spread by direct contact (faecal oral), particularly in households, nurseries and infant schools.

How does the laboratory confirm the diagnosis?

In the UK, *E.coli* producing VT1 and VT2 toxins that cause disease are most commonly the O157 serogroup. Less is known about the other serotypes and there is no test available to identify them in routine diagnostic laboratories. A molecular test is used in the IID2 Study at the reference laboratory to directly identify the toxin genes in the faeces specimen. Where possible this test is followed by culture of the suspected *E.coli* strains from the faeces for confirmatory tests, typing and testing for other properties associated with the capacity to cause illness. Suspected foods and other potential sources are tested when outbreaks occur.

How is it treated?

Rehydration and symptomatic treatment of diarrhoea. Some reports suggest that antibiotics may be harmful rather than beneficial (killing the bacteria and releasing more toxins into the bloodstream). Hospital treatment is required for severe cases. HUS, although rare, is one of the most common causes of acute renal failure in children. Treatment for bloody diarrhoea and HUS is related to clinical need and the same approach is required irrespective of whether an O157 or non-O157 strain of *E. coli* is the causative infective agent.

17th October 2008

Appendix 13.13: *Giardia*

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Micro_IID2_Giardia_04

FACT SHEET

Giardia

Common clinical features

Variety of intestinal symptoms including chronic diarrhoea, abdominal cramps, flatulence, leading to weight loss and fatigue. Duration can extend to months or years if undiagnosed. Often asymptomatic.

Incubation period

5 – 25 days

Where is it found?

Gastrointestinal tracts of people and animals.

How is it acquired by affected individuals?

Either by person to person spread or from faecally contaminated food or water. Food borne transmission is rare. Spread within families and nurseries is well documented. Cysts are resistant to chlorine levels in drinking water, so deficiencies in filtration or sewage contamination can result in outbreaks.

How does the laboratory confirm the diagnosis?

Faeces samples are examined by microscopy for cysts or tested with an immunoassay test. Results are usually available within 2 days of receipt in the laboratory.

How is it treated?

One of the few gastrointestinal infections for which there is a specific antibiotic treatment, Metronidazole.

Appendix 13.14: *Listeria*

Micro_IID2_Listeria_04

FACT SHEET

Listeria

Common clinical features

Infection may cause a mild acute illness with fever and may be associated with diarrhoea. Asymptomatic systemic infection can occur. In pregnant women the infection can be transmitted to the foetus and cause septicaemia and meningitis and spontaneous abortion. Septicaemia and meningitis also occur in adults, usually in older people or the immunocompromised.

Incubation period

Variable 3 – 70 days

Where is it found?

Environment, cattle, sheep, soil, silage. The bacterium has been isolated from a range of raw foods including vegetables and uncooked meats as well as processed foods. A wide range of food products have been implicated in outbreaks including soft cheeses and meat based patés. It is commonly carried in the human gut.

How is it acquired by affected individuals?

The majority of cases are believed to be food borne, from foods where the counts are very high because of contamination or poor storage. Some cases are from direct contact with animals. The organism can be transmitted from mother to foetus in utero or at delivery. Infants may acquire infection from person to person spread shortly after delivery.

How does the laboratory confirm the diagnosis?

Culture of blood and cerebrospinal fluid for cases of systemic infection. Culture of faecal specimens in cases with diarrhoea as the main symptom. Results are usually available within 2 days. This test would only be carried out if infection with Listeria was strongly suspected.

How is it treated?

No specific treatment for diarrhoeal illness. Antibiotics are required for treatment of systemic illness.

Appendix 13.15: Clinical significance of *Listeria monocytogenes*

CLINICAL SIGNIFICANCE OF LISTERIA MONOCYTOGENES IN HUMAN FAECES

Distribution

Listeria monocytogenes is very widely distributed in nature in soil, water, sewage, plant material and numerous species of birds and mammals. Approximately 5% of healthy humans carry *Listeria monocytogenes* in the gut.

Food

Listeriosis is a serious but rare food-borne disease. Many foods can contain *Listeria monocytogenes*, albeit usually at low levels which are considered to be of very low risk for health.

Febrile Gastroenteritis and significance of *Listeria monocytogenes*

Outbreaks of gastroenteritis caused by *Listeria monocytogenes* have been described with cases having fever, malaise, headache, vomiting and diarrhoea. As noted above, 5% of humans carry in the gut and it is not known how frequently *Listeria monocytogenes* causes sporadic cases of gastroenteritis. Hence, finding *Listeria monocytogenes* in a faecal sample may be incidental and not related to the actual cause of the diarrhoea. Diagnosis of Listeriosis in these cases is achieved by culturing the patient's blood.

Invasive Disease, Septicaemia and Meningitis

Septicaemia and meningitis can be caused by *Listeria monocytogenes*, particularly in elderly patients, and those who are severely immunocompromised or on immunosuppressive drugs. Septicaemia in patients over 60 years of age is the most common presentation of the disease.

Pregnancy Associated Disease

Listeriosis can occur when the bacterium infects the unborn infant and is most often diagnosed during the third trimester of pregnancy. The mother may be asymptomatic or have a mild 'flu-like illness and a diagnosis can be made by culturing *Listeria monocytogenes* from maternal blood. Trans-placental spread can occur and the foetus can develop severe infection. Pregnant women (as well as the immunocompromised) are advised to avoid mould ripened soft cheese (such as camembert and brie) and pâté, as well as to re-heat cook chill food until piping hot. Routine screening of healthy pregnant women for *Listeria monocytogenes* is not recommended.

Antibiotic Treatment

If *Listeria monocytogenes* is isolated from a high risk patient, e.g. elderly (>60y), pregnant woman or immunocompromised person, and there is evidence of systemic symptoms, e.g. pyrexia then antibiotic treatment may be considered. Advice on antibiotic treatment should be sought from your local microbiology laboratory.

12th December 2007

Appendix 13.16: Norovirus

Micro_IID2_Norovirus_04

FACT SHEET

Norovirus

Common clinical features

Vomiting, diarrhoea, fever, nausea, headache, malaise for 24 – 48 hours. All age groups affected.

Incubation period

Usually 24 – 48 hours

Where is it found?

Gastrointestinal tract of man

How is it acquired by affected individuals?

Very easily transmitted from person to person by the faecal oral route. Easily acquired by persons in the vicinity of vomiting individuals, when aerosolised particles are ingested. Infection may also be acquired from the contaminated environment. Food may be contaminated by affected individuals, including those who are asymptomatic or incubating or convalescing from illness (for 48 hours after symptoms cease). Shellfish (bivalve molluscs) filter the virus particles from sewage in sea water and can be the source of infection if eaten raw. Large outbreaks occur in hospitals, nursing homes, schools and other semi-closed communities such as cruise ships.

How does the laboratory confirm the diagnosis?

An immunoassay test to detect virus antigens in faeces may be available locally and molecular tests are available in specialist laboratories. Results are usually available within 1 day of the laboratory receiving the specimen. When a large outbreak has been confirmed later cases with similar symptoms will not be tested.

How is it treated?

Symptomatic treatment only required, no specific treatment.

Appendix 13.17: Rotavirus

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Micro_IID2_Rotavirus_03

FACT SHEET

Rotavirus

Common clinical features

Diarrhoea and vomiting with a duration of up to 5 days. Can be severe watery diarrhoea leading to dehydration in young children. Major cause of hospital admission for diarrhoea in young children. Infection in adults can be mild but outbreaks can occur in elderly hospital patients and nursing home residents.

Incubation period

Usually 2 days.

Where is it found?

Gastrointestinal tract of man. Rarely, infections are caused by animal strains.

How is it acquired by affected individuals?

Transmitted directly from person to person by faecal oral route and sometimes from environmental contamination. More common in cooler months of year.

How does the laboratory confirm the diagnosis?

Rotavirus antigens are detected in faeces using an immunoassay test. The result is usually available within 1 day of receipt of the sample.

How is it treated?

Symptomatic treatment and rehydration.

Appendix 13.18: *Salmonella* spp.

iid2
The Second Infectious Intestinal Disease Study

Micro_IID2_Salmonella_04

FACT SHEET

Salmonella

Common clinical features

Diarrhoea, vomiting and abdominal pain. Malaise and fever almost always present. Dehydration may occur, particularly in infants and the elderly. Septicaemia with abscess formation in virtually any organ is an uncommon complication. Diarrhoea and fever often persist for several days. Blood may be present in the stool in 20% of cases.

Incubation period

12 hours to 3 days.

Where is it found?

Gastrointestinal tract of wild and domestic animals, birds (especially poultry) reptiles, amphibians (for example terrapins) and occasionally humans become long term carriers.

How is it acquired by affected individuals?

Predominantly from food (most commonly red and white meats, raw and undercooked eggs, milk and dairy products) following contamination of cooked food by raw food or failing to achieve adequate cooking temperatures. Contact with infected animals or animal faeces. Person to person spread from the case by close contact, usually when the case has diarrhoea. These so-called “secondary” cases are common in outbreaks.

How does the laboratory confirm the diagnosis?

The bacteria are cultured on selective media from faeces samples. Foods may be tested for the bacteria in outbreaks. A result will usually be available within 2 to 3 days but it may take several days to confirm the particular type of Salmonella.

How is it treated?

Symptomatic treatment and rehydration. Generally, antibiotics are not required for adults who are otherwise healthy and have mild to moderate disease. Antibiotics may be required for more severe cases.

Appendix 13.19: Sapovirus

Micro_IID2_Sapovirus_02

FACT SHEET

Sapovirus

Common clinical features

Mild self limiting diarrhoea that lasts 2-3 days occasionally associated with fever and vomiting.

Incubation period

1-3 days.

Where is it found?

Human gastrointestinal tract, sewage and contaminated water.

How is it acquired by affected individuals?

Sapovirus is predominantly an infection in children under 5 years of age and occurs as sporadic cases or outbreaks of diarrhoea and vomiting in child day care centres and schools. Transmission is by person to person by the faecal oral route or through contact with contaminated surfaces in nurseries.

How does the laboratory confirm the diagnosis?

There is no test available in routine hospital laboratories but specialist virology laboratories can use a molecular test to detect the virus.

How is it treated?

Symptomatic treatment and rehydration.

12th January 2008

Appendix 13.20: *Shigella* spp.

Micro_IID2_Shigella_04

FACT SHEET

Shigella

Common clinical features

Typically causes bloody diarrhoea, but the most common species found in the UK (*Shigella sonnei*) causes a mild illness. Species found outside the UK, particularly in the tropics, can cause severe dysentery with blood mucus and pus in the stool sample. Gastrointestinal complications may occur and occasionally haemolytic uraemic syndrome.

Incubation period

1 - 7 days.

Where is it found?

Human gastrointestinal tract, sewage and contaminated water.

How is it acquired by affected individuals?

Usually transmitted by the faecal oral route from cases with diarrhoea, in households and institutions, mainly those containing young children. Occasionally spread by sewage contamination of food or water.

How does the laboratory confirm the diagnosis?

Culture of the bacteria from a faecal sample on selective media. Results are usually available in 2 days but confirmation of the particular type of Shigella may take several days.

How is it treated?

Rehydration and antibiotics.

Appendix 13.21: *Staphylococcus aureus*

Micro_IID2_Staphylococcus_aureus_04

FACT SHEET

Staphylococcus aureus

Common clinical features

Typically, an abrupt onset of nausea, vomiting and prostration often accompanied by diarrhoea. Illness lasts for 1-2 days.

Incubation period

30 minutes to 8 hours, usually 2 – 4 hours.

Where is it found?

Human skin – carried by 25–30% of individuals. Rarely, infected cow udders lead to contaminated milk.

How is it acquired by affected individuals?

Food handlers contaminate food that is left at room temperature for several hours, so that the bacteria multiply and produce the toxin in the food. Food handlers with infected skin lesions such as boils are a particular risk.

How does the laboratory confirm the diagnosis?

Toxin of the bacteria may be detected in food. High counts of *Staphylococcus aureus* may be found in faeces of affected individuals but occasionally high counts are present in faeces of individuals with no symptoms. The test results will usually be available in 2 days, but tests will only be carried out if *Staphylococcus aureus* is strongly suspected as the cause of illness.

How is it treated?

Rehydration and symptomatic treatment.

Appendix 13.22: *Vibrio*

Micro_IID2_Vibrio_03

FACT SHEET

Vibrio

Common clinical features

Vibrio species are uncommon causes of infectious intestinal disease in the UK. One species, *Vibrio cholerae* is the cause of cholera, a severe diarrhoeal disease. *Vibrio parahaemolyticus* is the most common species causing food poisoning in the UK. This causes watery diarrhoea and abdominal cramps in the majority of cases, occasionally with nausea, vomiting fever and headache. Occasionally a dysentery like illness is seen with blood and mucus in the stools and a high fever. More commonly it is a disease of moderate severity lasting 1-7 days.

Incubation period

Usually 12-24 hours.

Where is it found?

In fish or shellfish.

How is it acquired by affected individuals?

By eating raw or inadequately cooked seafood.

How does the laboratory confirm the diagnosis?

The bacteria can be cultured from faeces on selective media. Results are usually available within 2 or 3 days. The tests will be carried out only if the history and symptoms strongly suggest infection with Vibrio.

How is it treated?

Symptomatic treatment and rehydration with antibiotics for the more severe cases.

Appendix 13.23: *Yersinia*

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Micro_IID2_Yersinia_03

FACT SHEET

Yersinia

Common clinical features

Watery diarrhoea, abdominal pain and fever. Abdominal pain is often severe and may mimic appendicitis particularly in children. An immune reaction may occur after infection with *Yersina* leading to arthritis particularly in adolescents and adults. Septicaemia occasionally occurs in the immuno compromised.

Incubation period

3-7 days.

Where is it found?

Gastrointestinal tracts of many species of wild and domestic animals and birds.

How is it acquired by affected individuals?

From eating contaminated food and drinking contaminated water. It is particularly associated with pork. Direct contact with infected animals and person to person spread are also possible routes of transmission.

How does the laboratory confirm the diagnosis?

The bacteria are cultured from faeces samples on selective media. Results will usually be available after 2 to 3 days. Tests will be set up only if symptoms strongly suggest infection with Yersinia.

How is it treated?

Symptomatic treatment and rehydration. Antibiotics may be required for more severe disease.

Appendix 13.24: Reports with multiple pathogens

Micro_IID2_reports with multiple pathogens_03

FACT SHEET

iid2 MICROBIOLOGY REPORTS

Why might the laboratory reports be more complex than the reports from local diagnostic laboratories?

Around 500 different species of micro-organism (bacteria, viruses, fungi, protozoa) have been detected in the human intestinal tract. Most of these have no known harmful effects and, on the contrary, help to keep the gut lining healthy. A small minority of species are known to be present in cases of infectious intestinal disease (IID). Usually, these micro-organisms are present in very large numbers in the gut when they are associated with illness.

In this study we are trying to detect all the major micro-organisms known to cause IID, and toxins made by some of the harmful micro-organisms. This range of tests is more extensive than that carried out in hospital laboratories that routinely investigate gastroenteritis. So we expect to find a wide range of "suspect" micro-organisms. We are also carrying out some very sensitive research tests which will detect small numbers of suspect micro-organisms when present among the many millions of harmless ones.

In routine investigation of cases or outbreaks of IID only one micro-organism is identified as the "cause" of the illness in most cases. Occasionally we find more than one suspected cause is present in the stool specimen. In this study, because of the wide range of tests and the use of super-sensitive research tests we expect to find a lot of cases with more than one potentially causative micro-organism.

Interpretation of laboratory tests

So how can we interpret the investigations of a case when we find more than one potentially harmful micro-organism present in the specimen? There are a number of different interpretations.

1. The person with IID ate food or drank water contaminated with, or was otherwise exposed to, a wide range of micro-organisms and more than one is producing harmful effects in the body causing the symptoms.
2. One (or more) of the micro-organisms is causing the disease and the others, although detected, are not causing harm on this occasion:
   - because they are similar to but missing some key properties of the disease-causing species.
   - because they are in very low numbers and greater numbers are needed to give a harmful effect.
   - because they caused illness some weeks or months previously, and the person is now immune to their effects, but they are still present in small numbers of the intestinal tract.

Most cases of IID will only require supportive therapy such as fluids. Few cases of IID require specific antimicrobial therapy. If micro-organisms are detected that are of particular clinical or significance requiring specific therapy these will be reported by telephone to the practice concerned. There will also be urgent reporting of organisms that are of a serious public health concern. So, important results will be highlighted by the laboratory. However there will be many cases where it will not be possible or necessary to differentiate the disease producing micro-organisms from those present but not producing the symptoms in the patient.

Appendix 14: Newsletters

Appendix 14.1: Participant Newsletter

Insider

IID2 Newsletter April 2009

Thank you for all your help!

We are now almost half way through the IID 2 Study (the Second Study of Infectious Intestinal Disease in the community) and things are going really well!

There are now 88 general practices across England, Wales, Scotland and Northern Ireland who are involved and over 7,500 people who are taking part in the study!

We would like to thank you all for your help and support in making this the biggest ever study into the gut health of the nation.

The information we have collected so far has been very interesting and we are all getting excited to see the final results. These results may be used to shape government policy on food safety to try and reduce tummy bugs.

If you have said that you would like a summary of the results you will receive this when the results are ready after May 2010. If you didn't tick this box on the consent form but have decided you would like a summary then just tell the research nurse at your GP surgery and we'll be happy to send you one.

Further information about the study can be found at www.iid2.org.uk and if you have any other questions then just ask to speak to your research nurse.

Remember to send in your questionnaires!

Remember, if you do have any episodes of diarrhoea and/ or vomiting then please tell us ASAP and send in the questionnaire and stool sample. These are both really important for us to find out about how much gut infection happens in the community and what bugs are causing it. For those of you using e mails to keep in touch, if you are having any problems please let your research nurse know.

Even if you can't get a stool sample please still send the questionnaire/ e mail as this provides us with very useful information!

Helping us to reduce tummy bugs across the nation!

Do I need to send a sample if...

I have just been vomiting and not had diarrhoea?

Yes: Even if you have just been sick there may still be bugs in the stool that we can detect in the lab.

I forgot to send a sample straight away and feel better now?

Yes: With the specialised techniques our labs use we can detect bugs up to 10 days after you have been ill so it is still very useful for us to have a sample.

NHS · MANCHESTER 1824 The University of Manchester · MRC General Practice Research Framework · FOOD STANDARDS AGENCY · Gut Feelings – The UK's largest ever national research study of intestinal health

It's what's on the inside that counts!

Appendix 14.2: General Practice Newsletter

Insider

New Website

Welcome to the third IID2 newsletter. This month's newsletter focuses on the website, study updates from both the cohort and GP Presentation study and an article from our study administrator Hansa Shah, based on her own experiences of working on the IID2 study.

We are pleased to announce that the new 'Gut Feelings' website is now up and running and can be found at www.gutfeelings.org.uk (if you type in the old IID2 web page link you will be automatically re-directed to the new site). The site contains links to all of the new study material.

'Gut Feelings' website - front page

Cohort study update

We currently have over 6,700 participants recruited into the cohort study which is an incredible achievement! Thank you to all of the nurses and administrative staff for your incredibly hard work enabling us to achieve this.

We are also starting to see some younger participants joining in those practices that have started the re-recruitment phase, which is very encouraging. We have a few more months to go on the study and are keen to recruit as many participants as possible, as soon as possible. Every person and every follow up week counts!

We know that younger people are notoriously hard to recruit to any research study, so don't be disappointed if the recruitment rate is lower than before, every patient recruited to the study in this age group is crucial.

For those participants that become ill with diarrhoea and/or vomiting it is really important for us to obtain a sample and questionnaire so that we can identify what has caused the illness. Please remember to run the web reports on a weekly basis and follow up all participants who have reported symptoms to ensure they return a questionnaire and sample.

Administrative challenges on the Gut Feelings study

The IID2, Gut Feelings Study has been a very challenging and enjoyable study to work on.

It has been a pleasure to work with some of the nurses that I know from previous studies. This has helped me to build very good working relationships with all the nurses I am in contact with during my day to day tasks.

A lot of my time is involved around answering queries and training the nurses over the phone, on how to change and transfer information onto the study register. I get a real sense of achievement when the nurses get really happy and excited, "I've done it, I've done it!', as they manage to complete the task using an Excel spreadsheet, which many of them have not used before. To find a solution to a problem on Excel and then explain it over the phone can be quite difficult but together we always get there in the end!

It makes me really happy when I receive appreciative comments as it further highlights the fact that I can help the nurses and that we are all one big happy team working together on this study.

Other duties also include checking and logging consent forms and validation study forms received from the practices. If there are any discrepancies I have to pass them back to the nurses to correct. I must say that these discrepancies are usually sorted out very quickly and efficiently by the nurses which is great.

Another part of my job involves obtaining approvals and sending amendments to the local PCT's for the study to commence in the practices. This can be quite a challenging job as the staff may have changed or their contact details may not be correct as previously published. This can sometimes be like trying to find a needle in a haystack!

My job keeps me very busy and is also interesting and challenging, and keeps me out of mischief!

Thank you to all the nurses and the whole team on this study for making it very enjoyable and somewhere we can all work to the best of our abilities and beyond to help others.

Hansa Shah

IID2 Study Administrator

GP Presentation practice visits and study update

Over the last four months the IID2 study team have been on the road visiting the GP Presentation practices to feedback on the progress of the study to the doctors and nurses and introduce the new study material. The study team have really enjoyed visiting the practices, meeting the staff and viewing the setup at each practice. The new materials have been well received both by the practice staff and patients.

Since the beginning of April we have been sending fortnightly feedback graphs to all the GP Presentation practices so that you can monitor your own progress and the progress of the study in general. Please ensure the doctors and nurses are kept informed of study progress and continue to offer them friendly encouragement!

Please encourage all doctors and nurses to ask all patients with diarrhoea and/or vomiting to speak to the IID2 study nurse about the possibility of participating in the study. Please stress to your doctors and nurses the importance of giving patients the opportunity to participate.

Finally, thank you for your commitment to this study and to all the GPs and nurses that have referred patients. We really value your practice's participation and your continued enthusiasm for the study. If you would like to discuss any aspect of the study, please do not hesitate to contact a member of the IID2 study team.

GP PRESENTATION STUDY TARGET RECRUITMENT: 4-5 PARTICIPANTS PER PRACTICE PER WEEK

Contacts at GPRF

Julie Dodds (IID2 Study Manager) tel: 020 7670 4869 email: jdo@gprf.mrc.ac.uk

Hansa Shah (IID2 Administrator) tel: 020 7670 4832 email: h.shah@gprf.mrc.ac.uk

Louise Letley (Senior Nurse Manager) tel: 020 7670 4860 email: lhletley@gprf.mrc.ac.uk

MRC General Practice Research Framework, Stephenson House, 158-160 North Gower Street, London, NW1 2ND

Fax: 020 7670 4897

Appendix 15: Web-based data system: Data Security and Access

Appendix 15.1: Access Levels

Only the system administrator was permitted to set up new individual user accounts. Different levels of access to the website were assigned to each authorised user and restricted to information necessary for the performance of their own particular role within the study team. Levels of access to the web based data system were assigned as follows;

App 15.1.1: GP Practice Research nurse.

Individual general practices had ownership of all records for participants from within their own practice. The nurses only had access to data from their own practice and were unable to view any other records. The authorised user within the practice was the research nurse and s/he was able to add new participants to the system and update information e.g. weekly follow-up responses, episode details. It was also possible to view laboratory results on their own practice participants.

Once a record had been generated edit facilities were not available at practice level however the system incorporated a record amendment notification field. This field which was within the individual participant record enabled the nurses to notify any errors or changes to participant information and this was automatically flagged at the GPRF co-ordinating centre.

App 15.1.2: GPRF Co-ordinating Centre

The co-ordinating centre had access to practice information from all participating practices in order to permit real-time monitoring of the study. The study manager was assigned edit facilities should any changes be required to participant record be required.

N.B. the co-ordinating centre did not have access to edit any of the microbiology data.

App 15.1.3: Diagnostic Microbiology - Manchester HPA Microbiology laboratory.

Assigned users at the diagnostic laboratory had the ability to view (but not edit) participant information and research microbiology results and were able to record receipt of samples and add results, both manually and by batch upload. They were also able to view results uploaded at the research laboratory.

The system also permitted tracking of specimens being transferred between the laboratories, with fields being available to record the date and time of transfer and the courier log number. Within the laboratory one super-user was assigned additional functionality to permit editing of results.

App 15.1.4: Research Microbiology - HPA Centre for Infections

Assigned users at the laboratory had the ability to view (but not edit) participant information and Manchester laboratory results. They were able to record receipt of samples thereby ensuring full tracking of specimens between laboratories. They were able to add results of research and reference tests to the system via both manual and batch upload. Within the laboratory one super-user was assigned additional functionality to permit editing of results.

App 15.1.5: London School of Hygiene and Tropical Medicine

Authorised users at the LSHTM were not given access to any patient identifiable information but were able to view and download all data from pseudonomysed records. They were not able to amend or edit any records.

App 15.1.6: The University of Manchester IID2 Study Group-

Authorised users had access to anonymised data only in order to monitor recruitment and follow-up and generate reports, but were not be able to amend the data in any fields.

Appendix 15.2: Data security measures

Access to the server was assigned through a secure shell (SSH) via unique user names and passwords. All information was encrypted prior to transfer using secure socket layer certificates (SSLs) providing 128 bit encryption. The range of Internet Protocol (IP) addresses were restricted to national IP ranges.

Levels of access for individual authorised users; Practice Staff, MRC GPRF co-ordinating centre, Microbiology laboratories, LSHTM and University of Manchester was provided by the assignment of a bit flag – a number unique to that access level. Each page and operation in the system was assigned a number which consisted of a sum of bit flags, representing the groups who are able to use the page/perform the operation. When a user tried to access a page/perform an operation the page's security number was first checked against the user's bit flag using bitwise operations. Anyone attempting to access a page from which they were excluded was returned to their home page and their session cleared.

Participant weekly follow-up - Automated emails were sent on a weekly basis to all cohort participants. Emails sent out to participants did not contain any sensitive information. Contained within the body of the email was a specific response link to notify the presence or absence of diarrhoea and/or vomiting in the previous week. The reply was encrypted using SSL, and additional security measures were in place to minimize the probability of a brute force attack. This involved the generation of a random hexadecimal number for each participant in each follow-up (with 16^32 permutations) which was passed back in the response. Any tampering (attempting to provide a response without the correct hash) was flagged in the database and any response for that participant blocked.

Appendix 15.3: Hardware

App 15.3.1: Server

The data were stored on a study specific server housed behind a dedicated Cisco firewall. A Redundant Array of Independent Disks (RAID 5 array) was employed for the server to provide additional fault tolerance and hence security of the data.

App 15.3.2: Network

The system was hosted by a managed hosting company (Rackspace™) which provided 24x7x365 staffed security and the monitoring of both internal devices and external threats. Due to its high integrity only Cisco certified equipment was used throughout the network. This Cisco certified network, built on hardened routers was audited every quarter to ensure its security.

Rackspace™ constantly monitored the server to ensure network connectivity. These monitoring tests assessed both the performance of the server and the individual ports every few minutes. This level of support ensured that failure of any signal tests would be highlighted within minutes and an authorised engineer to provide a rapid response.

Appendix 15.4: Infrastructure

The data centre employed multiple levels of security (in SAS 70 certified buildings) to ensure that only data centre operations engineers are physically allowed near to the routers, switches and servers e. g. no public access; live video surveillance; on-site security personnel 24/7; biometric security and pass cards e.g. access to the data centre where the server is held, requires a specific security card linked to a palm print. Since this is an automated service requiring two identical matches any discrepancy would not permit access. In addition the company use background checks and certifications to ensure the integrity of all data centre personnel.

Appendix 15.5: System administration

Uploading new information e. g. software patches from the developers of the system, was managed using the secure shell (SSH) thereby providing a higher level of security to the standard file transfer protocol (FTP).

Appendix 15.6: Data Back-up

There was managed back-up of the data with daily incremental and full weekly back-up with 2 weeks retention.

Appendix 16: Quality control/Audit procedures

Appendix 16.1 Study nurse – Quality control visit form

MRC General Practice Research Framework

IID2

Quality Control Form

Clinic Number_____ **Nurse**_____

Regional Nurse_____

Date of Visit _ _/_ _/_ _

Follow up visit required
In line with GPRF SOP for QC

YES ☐ NO ☐

Please return to Louise Letley, Senior Nurse Manager, Stephenson House, 158-160 North Gower Street, London NW1 2ND

	GENERAL (Cohort Study)	YES	NO
	Do you consider that the nurse understands:		
	. The aims of the IID2 Cohort study?		
	. The importance of and types of weekly follow-up for the Cohort Study?		
	. The inclusion and exclusion criteria?		
	. The cohort study case definition		
	Is the nurse able to identify the following cohort study documents: • Information sheets (adult and child) • Flow charts (adult and child) • Consent and Assent forms • Baseline questionnaires (adult and child) • Symptom questionnaires (adult and child) • Post cards and explain when and how these are to be used?		
	Does the nurse know the correct procedures for recruiting patients into the Cohort study?		
	Is the nurse maintaining the Cohort study log/register?		
	Is the nurse sending a copy of the study register to the GPRF each week?		
	Is the nurse adhering to the estimated timings for the study?		
	Does the nurse know who to contact to order general study supplies?		
	Is the MRC research notice displayed in the waiting room? (if not, please ask nurse to inform practice manager)		
	Does the practice leaflet contain information about MRC research? (if not, please ask nurse to inform practice manager)		

	Informed consent (Cohort and GP Presentation Studies)		
		YES	**NO**
	Does the nurse give every patient: • A clear correct explanation of each study including info about • Faeces samples • Baseline questionnaire • Symptoms questionnaires (Cohort study only) • Weekly follow up by email or post card (Cohort study only) • An opportunity to ask questions?		
	Does the nurse ask the patient to complete, initial & sign appropriate consent/assent forms for each study?		
	Does the nurse check that the consent forms have been completed correctly?		
	Does the nurse do the following once the consent form is complete • Send the original consent form to the study manager at the GPRF? • Give a copy to the patient? • File a copy in the patient's research record?		

	First patient interview (Cohort study)		
		YES	**NO**
	Does the nurse explain correctly to the participant the follow-up procedures for • email and postcard follow-up?		
	Does the nurse know the correct procedures for • Attaching pt ID labels to postcards? • Entering week dates on post cards? • Completing week numbers on postcards?		
	Does the nurse explain correctly to the participant • how and when to complete the symptom questionnaire?		
	Does the nurse explain the importance of obtaining faeces samples?		
	Does the nurse complete the correct details on the specimen pot and specimen request form?		
	Does the nurse explain correctly the procedures for returning • specimens and • symptom questionnaires?		
	Does the nurse give the patient her contact details at the surgery?		
	Does the nurse explain the importance of informing him/her if the patient changes home address or email address?		
	Does the nurse ensure s/he has up to date contact details for the patient?		
	Does the nurse enter the baseline data on the web based system?		

	Cohort study follow-up (email)		
		YES	**NO**
	Does the nurse check weekly emails not returned on the web based system?		
	Does the nurse contact the participants who have **not** replied to the weekly email?		
	If the participant does not return emails for 6 weeks does the nurse enter **withdrawn** on the database?		
	Does the nurse check the list of emails bounced back on the web based system on a weekly basis? *(If the answer is" yes" to this question)* Does the nurse then do the following:		

	• Check each bounced back email address with each participant? • Record the new email address in the database? • Resend the email to the new email address?		
	Cohort study follow-up (postcard)		
		YES	**NO**
	Each week does the nurse enter the data from returned postcards in the web based data collection system?		
	If the participant does not return postcards does the nurse enter withdrawn on the database after 6 weeks?		
	Each week does the nurse check postcard non responders on the web based system?		
	Does the nurse call participants who have not returned their postcards (**by Thursday of each week**) to remind them to send their postcard for the previous week to the practice?		
	Cohort study follow-up symptom questionnaires		
	Does the nurse enter data from the returned symptom questionnaires in the web based data collection system each week?		
	Does the nurse post **a symptom questionnaire and specimen pot** to participants who report subsequent episodes of IID symptoms 3 weeks after the previous episode?		
	Each week does the nurse check the web based data collection system to identify participants with symptoms who have **not returned** their symptom questionnaire?		
	Does the nurse contact the participants who have **not returned** their symptom questionnaire within 7 days?		

	GENERAL (GP presentation study) ***For discussion in relevant practices if interview not attended***		
		YES	**NO**
	Do you consider that the nurse understands:		
	The aims of the GP presentation study?		
	The inclusion and exclusion criteria?		
	The study case definition		
	Is the nurse able to identify the following study documents; • Information sheets (adult and child). • Flow charts (adult and child). • Baseline questionnaires. • GP referral notepad. and explain when and why these are to be used?		
	Does the nurse check out of hours faxes, emails and letters on a daily basis to see if patients with IID2 have presented?		
	Does the nurse know the correct procedures for recruiting patients into the GP presentation study?		
	Is the nurse maintaining the GP presentation study log/register?		
	Does the nurse know who to contact to order general study supplies for the GP presentation study?		

	First patient interview (GP Presentation study) *where applicable*		
		YES	**NO**
	Is the nurse reminding GP's and practice nurses to refer patients for the GP presentation study?		
	Are patients being referred through the note pad system? If **no**, how are patients being referred? *(Please write here)*		
	Does the nurse explain the procedure for returning specimens if the patient does not bring a specimen to the interview?		

	Enumeration and Validation study *(as applicable)* ***For discussion***		
		YES	**NO**
	Does the nurse understand the procedures for the Enumeration Study?		
	Does the nurse understand the procedures for the Validation study?		

	Web Based data collection		
		YES	**NO**
	Can the nurse log into the web-based data collection system?		
	Can the nurse create new participants on the web-based system?		
	Can the nurse find existing participants on the web-based system?		
	Can the nurse generate the following reports on the web based data collection system? • Emails bounced back • Phone calls to non responders of email follow up • Phone calls to non responders of postcard follow up • Symptoms questionnaires not received at the practice • Samples over due at the lab (*Cohort and GP presentation studies)* • Replacement sample posts and questionnaires required • Numbers withdrawn from the study		

Recruitment

Number of participants recruited to the Cohort Study:_____

Number of participants recruited to the GP Presentation Study:_____

Regional Nurse comments *(to be completed before the nurse signs form)*

Signature of Regional Nurse .....

Study Nurse comments

Study nurse signature .....

Appendix 16.2: Telephonist QC checklist

TeleSurv_IID2_Quality checklist for telephonists_05.xls

Call details												
Telephonist interviewing												
Date & Time of call												
Call ID (if available)												

Quality checklist for completed calls												
Opening statement read exactly as on page												
Request for consent/assent clear												
Asks same questions, in same order												
Avoids adding own words & so changing the question meaning												
Follows script but doesn't appear too mechanical												
Asks questions slowly, clearly & at a reasonable volume												
Randomisation done or explains why not.												
Access file labelled as expected & saved properly.												
Audio file saved and labelled correctly w Call ID added to tape.												
Comments												

Appendix 16.3: Internal audit form – Telephone Survey

ProjMan_QC Site Visit_UEA_02

IID2 Study Quality Control Site Visit

Site:

Date of visit:

Research Staff present:

Auditor(s):

Item	Yes	No	No Evidence	Document title/Filename
Staff				
Is there a documented organisational structure showing line management responsibility				
Is there a list of personnel associated with the project?				
Are there up to date CVs (and job descriptions) available for all staff involved in the project?				
Are there signed confidentiality agreements for all staff?				
Are there Induction and Training portfolios for all staff?				
Training manual – Is there an up to date validated version of the training manual?				
Is there a Safety manual available?				
Is there a Work alone procedure?				
Worksheets/worklists for telephonists				
Work Area:				
Telephone booths Clean and tidy, Suitable for purpose				
Instructions available in the telephone booths?				

Item	Yes	No	No Evidence	Document title/Filename
Copy Call software – Is there an up to date license for this software				
Are there documented procedures for any statistical analyses performed at UEA				
Are there approved and documented procedures for data collection				
Is there an approved questionnaire?				
Does the database follow the same flow as the paper questionnaire?				
Risk assessments for all procedures?				
Database and data quality:				
Database – description of structure and security. • where is the data stored, what security is in place for access to the server where data is stored? • data security encryption?				
Standard Operating Procedure - Data quality control procedure				

Item	Yes	No	No Evidence	Document title/Filename
Standard Operating Procedure - Data archive procedure				
Standard Operating Procedure - Downloading data for transfer to LSHTM				
Is it possible to conduct a full audit trail from the retained record?				
Standard Operating Procedure- Requests for further information • Evidence that the SOP is being followed				
Forms for telephonists to request written information • Does this log the filename of the call?				
Standard Operating Procedure- What is the procedure for telephonists to record any problems encountered during telephone calls? • Abusive or threatening calls • Child alone • Domestic violence procedures				
Telephonist QC:				
Standard Operating Procedure for QC of telephonists • Evidence that the SOP is being followed				

Item	Yes	No	No Evidence	Document title/Filename
Monitoring calls *Select a number of records at random for each telephonist*				
Did the telephonist introduce the study in a friendly and professional manner?				
Did the telephonist check to ensure that the respondent consented to take part?				
If this is a child or teenager, did the parent consent for them to take part the study?				
Did the telephonist inform participant that the call would be recorded for monitoring purposes?				
Did the telephonist follow the script?				
Requests for additional information:				
Did the participant request further information about the study?				
Did the telephonist refer the potential participant to the iid2 website?				
If the participant asks for written information, did the telephonist explain that they needed to pause the recording of the call? Did the telephonist pause the recording so that no record of PII was made?				

Item	Yes	No	No Evidence	Document title/Filename
Double Data Entry				
Standard Operating Procedure for DDE • Evidence that the SOP is being followed				
How are discrepancies highlighted? • Evidence that discrepancies are highlighted				
Standard Operating Procedure for correction of discrepancies • Evidence that the SOP is being followed				
Select a number of records at random where discrepancies have been highlighted				
Were discrepancies highlighted appropriately?				
Were discrepancies recorded correctly?				

Is a further visit required? Yes ☐ No ☐

Auditor Comments (*to be completed before the auditor signs the form*)

Signature of auditor(s)

…… **Date:**……

…….... **Date:**……

Site Researcher Comments (*to be completed before the auditor signs the form*)

Signature of site researcher(s)

…….... **Date:**……

…….... **Date:**……

Appendix 16.4: Internal audit form – Diagnostic Microbiology

IID2 Study Quality Control Site Visit

Site: Manchester Regional Laboratory

Date of visit:

Research Staff present:

Auditor(s):

Item	Yes	No	No Evidence	Document title/Filename
Staff				
Is there a documented organisational structure showing line management responsibility?				
Is there a list of personnel associated with the project?				
Are there up to date CVs (and job descriptions) available for all staff involved in the project?				
Are there Induction and Training portfolios for all staff?				
Health and Safety				
Is there a documented safety manual? Are staff made aware of it? Is it the latest version? Is this documented in staff training portfolios?				
Are there COSHH and risk assessments in place for all the procedures used in the project? Are they in date? Are they readily available? Are staff aware of these and been signed off against them?				

Item	Yes	No	No Evidence	Document title/Filename
Are there procedures for breakages and spillages?				
Are work areas suitable for purpose?				
Handling of samples and materials				
Are there SOPs in place for sample receipt, labelling and tracking, retention and disposal?				
Is there evidence of who enters samples on to Telepath?				
Documentation of procedures and methods				
Are there SOP's/protocols in place for the tests undertaken?				
Is there evidence of regular review and document control?				
Are the SOPs authorised versions and have these been reviewed?				
Quality Assurance				
Is there participation in all relevant EQA schemes? Is performance good and monitored?				

Item	Yes	No	No Evidence	Document title/Filename
Is there appropriate IQA? Is there replicate testing (IQC)? Are internal controls used on all tests? Is there QC of media used?				
Work methods/audit				
Are work books used to record experimental details and results e.g. machine readouts, batch details, printed data or photographic records obtained of all work performed?				
Are all records archived and recoverable?				
Is it possible to construct a full audit trail from the retained records?				
Vertical Audit				
Request Form				
Is the request form easily located? Has the request form been correctly completed? Are there any transcription errors to LIMS?				
Specimen receipt				
Is there a specimen reception policy?				

Item	Yes	No	No Evidence	Document title/Filename
Is there a rejection policy for				
a) inadequate identification?				
b) broken/leaking specimen?				
c) inadequate specimen?				
Are reception staff aware of study policies?				
Are reception staff aware of safety policies?				
Specimen				
Has any material been stored and is it easily located?				
Is storage adequate and appropriate?				
Is all material adequately labelled and uniquely identifiable?				
Is all material logged?				

Item	Yes	No	No Evidence	Document title/Filename
Tests				
Are there procedures for all tests on this specimen?				
Were all appropriate tests carried out?				
Can an audit trail be constructed for all tests on this sample?				
Report				
Is a copy report able to be generated?				
Are there any transcription errors?				
Is there a procedure for interpretive comments?				
Is there a telephone procedure and was this followed?				
Is there an amended report procedure and was this followed?				
Was the specimen reported within the appropriate turn around time?				

Item	Yes	No	No Evidence	Document title/Filename
Staff				
Are there staff competency/training records for those processing this sample?				
Equipment				
Does equipment used (list) have				
- Routine maintenance?				
- Calibration checks?				
Reagents				
Check media used (if applicable), are the use by dates and media batch numbers recorded for traceability? Document what media is used (if a vast amount of media has been used for this sample, only pick a few and document below).				
Check kits/reagents used. Are the use by dates and batch numbers recorded for traceability either in work books or on works sheets? Document which kits/reagents are used.				

Item	Yes	No	No Evidence	Document title/Filename
Check the storage facilities for the current media, kits and/or reagents. Are these all stored at the correct temperature? Are fridges and freezers monitored?				
Is the storage area clean and tidy?				
Check the worksheets/work books /work instructions for the sample/tests. Are these controlled documents?				
Is there an inventory for the contents held in the fridge/freezer/room storage? Who maintains this?				
Who is responsible for monitoring stock? Is there a first in, first out stock rotation system in place?				

Is a further visit required? Yes ☐ No ☐

Auditor Comments (*to be completed before the auditor signs the form*)

Signature of auditor(s)

…… **Date:**……

…… **Date:**……

Site Researcher Comments (*to be completed before the researcher signs the form*)

Signature of site researcher(s)

…… **Date:**……

…… **Date:**……

Appendix 16.5: Internal audit improvement actions

iid2 The Second Infectious Intestinal Disease Study

IID2 Study Quality Control Site Visit
Improvement Actions and Recommendations

Site:
Date of Audit Visit:
Research Staff present:
Auditor(s):

Finding No.	Description of Finding	Suggested improvement action	Agreed timescale	Date Completed	Improvement action reviewed by

Appendix 16.6: External audit – Research Management and Governance

NHS
Halton and St Helens

Audit Report

Audit of Research Study 12/09

Audit Team: Kirsty Pine, Research and Development Manager
Paul O'Connor, Research and Development Officer

Issued to Professor Sarah O'Brien – Chief Investigator
Kathryn Jackson – Study Project Manager

Research and Development
Suite 1 Unit 1H
Midwood House
Midwood Street
Widnes, WA8 6BH
0151 495 5480

NHS
Halton and St Helens

Project Title: The second study of infectious intestinal disease in the community determining disease burden and calibrating national surveillance systems in the UK.

1. Trust R&D Office Research Project Approval:

(i) Does the project have a research sponsor? (All studies started after May 2004 should have a recognised sponsor, usually the Chief Investigator's employer or project funder.) YES – University of Manchester
(ii) Does the project have R&D Office Project approval? YES – Halton and St Helens, Warrington and Knowsley.
(iii) If Trust approval was subject to modifications being made to the research design and protocol, were these amendments made prior to the study commencing? *N/A*
(iv) Do you have indemnity provided by the Trust and/or commercial funder? *YES – University of Manchester*

2. Scientific Requirements:
(i) Is this project a clinical trial undertaken to ascertain the efficacy or safety of a medicine? *NO*
(ii) Does this project involve an investigative medical device or device not usually used for treatment? NO
(iii) Has the project been peer reviewed? *YES – Project has been scientifically peer reviewed which has been accepted by the main funder, the Food Standards Agency.*
(iv) Are there copies of all correspondence relating to an external funder's scientific review? *YES*
(v) If applicable, have all recommendations made during the scientific review been addressed? *YES*

3. Ethical Requirements:
(i) Is there a record of full approval from the relevant Research Ethics Committee (REC)? *YES – North West Research Ethics Committee*
(ii) If the study is Multi-centred is there a record of local Site Specific Assessment (SSA) approval? *SSA Exempt*
(iii) If the research protocol has been amended in any way since full ethics approval was obtained has the research ethics committee approved any substantial amendments? *YES*
(iv) Have procedures been put in place to ensure confidentiality of patient identifiable data? *YES – The details of the participant are kept at the G.P Practice. The data is then sent to the co-ordinating centre anonymised. This information is kept on a secure password protected, encrypted web based tool. The researcher has limited access to the data respective of where they are based. Hard data is kept in locked filing cabinets in a locked office. The study data will be kept in G.P Practices for 25 years.*
(v) Is there a system for the recording of all research participants' written informed consent and/or where appropriate written carer assent? *YES – The participant has to initial the specific sections of the research they agree to take part in, the*

consent form includes signature and dates. The participant is given a study I.D number.

(vi) If the research involves Trust patients in research on interventions/therapies, is there a copy of patients' written informed consent and/or written carer assent, included in patients' medical notes? *N/A*

(vii) And details of the research project? *N/A*

(vii) Is there a system for the recording of all research participants (clients, staff or healthy volunteers)? *YES – Quality control audits are completed on the research nurses involved in the study. These audits are recorded and kept with document files.*

4. Health and Safety Requirements:

(i) Is there a system for the recording of all adverse events (clinical and non-clinical including any not specified in the protocol) that may have resulted from participation in the research? *YES – No adverse events occurred within the study. If they did occur the event would be logged at the coordinating centre*.

(ii) Will all serious adverse events been reported to the appropriate:

Research Ethics Committee	*YES*
Research Sponsor	*YES*
Host Trust	*YES*

(iii) Do all members of the research team who have access to patients, their organs, tissues, data or access to NHS staff, information and facilities hold an in date Trust employment contract/NHS honorary contract? *YES – NHS Staff members and honorary contracts for Non NHS Staff members.*

5. Information Requirements:

(i) Are there any arrangements in place to disseminate the research findings, to the research participants and other users/carers? *YES – Presentations of the final report will be given to the Food Standards Agency May 2010. R&D Departments and REC will be given a summary report of the findings.*

(ii) Are there plans to publish research findings in professional and where appropriate in peer reviewed journals? *YES*

6. Finance and Intellectual Property Rights (IPR) requirements:

(i) Has the Trust Finance Department approved all agreements/contracts made with external funders? *N/A*

(ii) Have the Trust Finance Department and the Trust R&D Office given approval for all Treatment Costs and Service Support Costs incurred during the course of the research? *N/A*

(iii) As Chief / Principal Investigator, are you taking responsibility for the project being conducted according to strict financial probity, and compliance with the law and rules laid down by H. M. Treasury and the Trust, for the use of public funds? *YES*

(iv) Are there agreements covering intellectual property rights (IPR) with any third party researchers/organisations/companies?
If yes have these been approved by the Trust Finance Department, and by R&D Office? (This may include sharing of data/materials etc with any parties outside the Trust.) *N/A*

Conclusions, recommendations and actions required.

The standard of the research management was excellent. The Chief Investigator and research team have endeavoured to conduct this project to a high standard and safeguard participant data throughout the research, which is ongoing. From the study files reviewed no issues were highlighted with regards to protocol compliance. Documentation to demonstrate adherence, in accordance with the above criteria was evidenced.

To further emphasise the standard of research management for this study, there is evidence in the documentation of the project being extensively and regularly reviewed at Executive Committees. These meetings are well documented and the actions agreed are effectively monitored.

The following points requiring consideration were highlighted during the course of the audit:

No actions required.

Appendix 16.7: External audit- UK Accreditation Service

United Kingdom Accreditation Service

Commercial in confidence

[redacted]

ASSESSMENT REPORT

Name & Address of Research Contractor	University of Manchester Department of Health Science and Epidemiology Division of Medicine & Neurosciences Clinical Sciences Building Hope Hospital Salford Manchester M6 8HD	**Date of Assessment**	26th March 2008
		Date of Assessment Plan	18 March 2008
		Funding Body	FSA
Assessment Location	As above	**Contact**	Prof S. O'Brien
Assessment Criteria	Joint Code of Practise for Research (JCoPR)	**UKAS Assessor**	Rachel Oakley
Research Contractor Representatives	**Project Representatives** Prof Sarah O'Brien Kathryn Jackson	**Project Number**	B18021
		Project Reference	IID2 Study
Report Issued by	Rachel Oakley	**Recommendations**	2
Report Issued Date	28/3/08	**Report Acknowledged Method**	Email

1. Executive Summary
The project is being conducted to a very high standard. It is evident that the requirements of the Joint Code of Practise have been carefully considered and the systems in place have been very well thought through and are being effectively implemented.

The project has been meticulously planned and the project team at Manchester has all aspects under effective control. The staff are knowledgeable and enthusiastic and cooperated fully through this audit. The level of detail of the documentation is excellent and the records relating to the project are well-organised and maintained to a very high level.

Only two recommendations were made for potential improvements and this low number is indicative of the standard to which the project is being managed. The audit provides assurance that the project is progressing well and shows a high level of compliance with the requirements of the Joint of Practise For Research.

2. Scope
The purpose of this visit was to conduct an assessment of the laboratory's project (Project number B18021) in order to assess compliance with the Joint Code of Practise for Research. The audit took place at the University of Manchester's Department of Health Science and Epidemiology at the Hope Hospital where the project is being coordinated.

The audit included a discussion regarding the current status of the project and future work followed by assessment of project documentation, collaborators' records including CVs and collaborator agreements, personnel records, review meeting records, training procedures, ethical approvals, audit procedures and records, data collection processes.

The project started in 2006 and to date the pilot study has been completed. The main study is due to start from the beginning of April and the anticipated completion date for the project including reporting of results to the FSA is March 2010.

3. Overview of Research Contractor
The project is being managed and coordinated by the staff working at the University of Manchester. The Project Coordinator (Sarah O'Brien) has been working at the University since August 2004 and has experience of managing other research projects including other FSA funded projects. Kathryn Jackson (Project Manager) and Emma Dixon (Administrative Assistant) have been employed specifically to work on this project.

4. Observations & Assessment Findings

4.1 Responsibilities
The responsibilities of all personnel working on this project are clearly defined. In addition there is been close communication between all participants throughout the project, which is ensuring that requirements are clearly understood by all parties.

The level of experience and expertise of personnel working on this project is extensive. The project is being managed by staff at the University of Manchester, however there are a large number of collaborators also working on this project as follows:

HPA Centre for Infections (CfI) – responsible for microbiological analysis of stool samples using molecular methods – CPA accredited
HPA North West Regional Laboratory – responsible for microbiological analysis of stool samples using traditional methods – CPA accredited

London School of Hygiene and Tropical Medicine - statistical input including analysis of patient data to ensure representative data is produced.

MRC General Practice Framework (GPRF) – Studies in Primary Care e.g. Cohort studies/GP Presentation, Enumeration Study – coordination of the research nurse training.

University of East Anglia (UEA) – design and conduct of the telephone survey work

Provision of scientific Advice
University of Nottingham
CDSC Northern Ireland
Cardiff University (formerly University of Wales College of Medicine)
University of Glasgow
NHS Direct/HPA Collaborative Group

Collaborator agreements are held for each participant and this provides details of the terms and conditions for this involvement on this project, including a requirement to comply with the JCoPR.

4.1.1 Project Personnel
The University of Manchester personnel are well-qualified and have appropriate experience.

4.1.2 Subcontractors
One subcontractor has been used to develop the web-based data collection system. The subcontractor was assessed and appointed using the University's procurement procedure. Records show that a thorough evaluation was done of a number of potential suppliers before the chosen provider was selected.

4.2 Competence

4.2.1 CVs of Project Personnel
CVs for University of Manchester staff and for all personnel working for the collaborators are held and indicate appropriate experience and support the selection of the relevant participants. These records are well-maintained in an ordered manner.

Roles are also defined through job descriptions and these were checked for University of Manchester staff. The records are well-documented and clearly define responsibilities for individuals relevant to their position in the project team.

4.2.2 Training Records
University of Manchester staff have had to complete an induction programme including health and safety training and records of these are maintained, although it was noted that Kathryn's record had not been signed off by the relevant training manager and the records need to be completed.

Whilst most training is the responsibility of individual collaborators to ensure staff are up-to-date and competent, the training involving practice nurses has involved the University of Manchester staff and other project members. The training agenda appears comprehensive and the training material supplied is clearly documented and easy to follow. As a result of the pilot study some changes have been made to procedures and further training has been conducted with nursing staff to ensure they are up-to-date. This will continue into the main study as other practices become involved with the project. There is a very good system in place using QC audits, which enables the effectiveness of these training sessions to be monitored in order to ensure that nurses are following procedures correctly particularly as this is a critical part of the project. This will continue to be done during the main study, although the audits will be delegated to research nurses located in the regions. Training of the research nurses to do these audits is already planned and it is expected that records of this training and assessment of competence will be documented.

4.3 Project Planning

4.3.1 Risk Assessment
There has been on-going assessment of risks since the start of the project, which are documented

using the risk register (currently at version 16). The system is ensuring that risks are reviewed and addressed, where possible, as and when they are identified. The register is under constant review and this aspect appears under effective control.

4.3.2 Project Plan
The key document, which details the requirements for each stage of the project, is the project proposal, which provides clear details regarding the delivery of the project. In the main milestones have been achieved and where delays have occurred these have been communicated to the FSA. Whilst the project proposal is the key point of reference, further planning and development is done through regular review meetings, which involve all project personnel. The decision to generate sub-groups is very good because it is enabling regular reviews on a quarterly, monthly and weekly basis to be conducted by relevant project personnel. There is a good and effective system in use for monitoring actions identified at these meetings to ensure that they are progressed effectively and within agreed timescales.

4.3.3 Approved Procedures for Sampling Materials
This is not applicable to the work being done at the University of Manchester location, but would be relevant e.g. to the laboratories, research nurses. Whilst this could not be assessed directly, protocols were seen detailing sampling requirements and these appeared to be adequate.

4.3.4 Ethical Approval
Due to the nature of this project it has been necessary to obtain the relevant ethical approvals from the Multi Centre Research Ethics Committee and from the NHS R&D organisations. These initial approvals were obtained to enable the pilot study to proceed. Since then some amendments have been made to the study and these changes have been re-submitted for further approval by the relevant committees and these have been completed successfully.

Some approvals are still awaited from the local Research Management and Governance committees to permit the involvement of individual practices in the study, but there are a sufficient number of practices where approval has been obtained to enable the main study to commence.

4.4 Quality Control
Whilst individual collaborators are responsible for the quality of the data being generated, some additional QC checks have been instigated to verify the data being collected. This is done in a variety of ways, e.g. through QC audits which are working well. Telephone survey data is subject to double-checking, by comparing conversations recorded on tape against the records/notes made by telephonist when making the call. University staff will be responsible for reviewing this data and following up any significant discrepancies.

4.4.1 Auditing & Assessment Procedures
An audit programme is in place, which ensures that at least one aspect of the IID2 study is audited quarterly. An audit has already been done of the telephone survey work being coordinated by the University of East Anglia and the record of this audit is well-documented. A few relatively minor non-conformities were raised, which had reportedly been addressed, but it would be useful for the record to indicate this and in particular to show that someone (i.e. the auditor) has followed this up.

Further audits are scheduled and will ensure that each area of the project is audited within the set timescales. It will be important to ensure that these audits cover the requirements of the Joint Code of Practise for Research to verify collaborators' compliance with those requirements. Auditors appear to have been allocated an audit area that they are not directly involved in enuring a degree of independence, which should enable a thorough and objective assessment.

The QC audits done on nurses participating in the Cohort and GP Presentation studies were done as scheduled during the pilot study. The process also enabled nurses to provide feedback and this has been effectively collated enabling further correction/improvement actions to be taken e.g. further training, amendment of the forms used in the data collection.

The breach of contract that was identified was handled very well and records indicated that all relevant parties were notified at the time. Corrective/preventive actions taken were appropriate. The recent audit at UEA involved a check of this aspect, however no such incidents had occurred since the breach so this could not be audited fully. The project team could consider another follow-up audit at a later time to verify that correct procedures are being used, if they felt this to be a particular issue.

4.4.2 Internal Project Reviews
The project is being extensively and regularly reviewed, which is critical for a project of this size and the project team has recognised this. The Executive Committee meetings are held quarterly and are attended by all project personnel where possible and provide a good overall review of the project. A number of sub-groups have been set up who meet more regularly and enable the day-to-day issues to be reviewed and actions agreed which ensures continued focus and timely follow-up of any issues where needed. The team is making effective use of the expertise of the collaborators on this project and the meetings are proving to be an effective management tool. Records from the meetings are well-documented and actions agreed are being effectively monitored.

4.4.3 Publication Policy & Authorisation Procedures
The project personnel are aware of the need to notify and agree with the Funding Body any publications of material associated with this project. A publications policy is documented, although this is still currently in draft and now needs to undergo a final review before being issued. It is expected that all project personnel including collaborators will follow this procedure.

4.5 Health & Safety
There are no specific requirements relating to the work being done at the University of Manchester. It is expected that individual collaborators will have their own health and safety systems in place, which comply with the JCoPR.

4.6 Handling of Samples & Materials
There are no specific requirements relating to the work being done at the University of Manchester. It is expected that individual collaborators will have their own systems in place to deal with this aspect, which comply with the JCoPR.

4.7 Facilities & Equipment
There are no specific requirements relating to the work being done at the University of Manchester. It is expected that individual collaborators will have their own systems in place to deal with this aspect, which comply with the JCoPR.

4.8 Documentation of Procedures & Methods
Documentation relating to this project is of a very high standard. Standard Operating Procedures have been produced specific to the project and are expected to be followed by all project personnel. These are readily accessible via the intranet, which each collaborator is able to access using a username and password. Most documents are prepared under the responsibility of the project manager. These are being effectively reviewed and input is provided by the other collaborators.

SOPs specific to collaborators are their responsibility to maintain, however copies of all protocols are held centrally by the University of Manchester team. The documentation is comprehensive and very well-maintained although due to the size and variety of documents held it would be useful to hold a masterlist which details all the documents held and their current revision status to make using the system and locating documents easier.

4.8.1 Validated Standard Operating Procedures
A web-based data collection system is being used to collect data generated from this project. It is key to ensure that the system is operating effectively and much work has been done to trial this throughout the pilot study. Further validation is planned at the start of the main study to give assurance that the system is operating effectively and the proposed plan has been well thought out and should ensure all aspects of the system are appropriately verified.

United Kingdom Accreditation Service – Assessment Report – Continuation Sheet
Research Contractor: Manchester

4.8.2 Document Control Procedures
The system for preparing, reviewing and issuing documents is excellent and ensures that these aspects are done effectively. There were a few occasions when the document control procedure did not appear to have been followed in its entirety, e.g. issued documents not always marked as final when required, although the overall impact of this is small. It would be useful to remind project staff of the procedure and ensure it is followed. Document changes are communicated effectively and documents are easily accessed by project personnel via the intranet.

4.9 Research/Work Records

4.9.1 Experimental Records, Sampling records, Project related records
Records held by the University of Manchester department are comprehensive and very well-maintained.

4.9.2 Data Management & Archiving Procedures
Most records relating to the project are stored on the web-based data collection system. This can be accessed by different members of the project team, but access is restricted depending on level of participation and this arrangement appears to ensure appropriate security and to ensure patient confidentiality where necessary.

There are procedures in place, which describe the arrangements for data security, firewall, back-up systems, archiving etc and these are satisfactory and demonstrate adequately that appropriate measures are in place.

5. References
Joint Code of Practice for Research

6. Appendices
Improvement Action Report & Recommendations prepared by Rachel Oakley

Commercial in confidence	**IMPROVEMENT ACTION REPORT & RECOMMENDATIONS**	**REF NO: RMO/MAN**	[redacted]

Name of Research Contractor	University of Manchester	**Project Reference**	**B18021**
Assessment Location	Department of Health Science and Epidemiology Division of Medicine & Neurosciences Clinical Sciences Building Hope Hospital Salford Manchester M6 8HD	**Research Contractor Representatives**	Prof Sarah O'Brien Kathryn Jackson

Finding No.	**UKAS Assessor**	Rachel Oakley	**Date of issue: 26/3/08**	**Please read in context with the Assessment Report**
	Description of Finding (including reference to the Joint Code of Practise for Research)		**Suggested Improvement Action** (discussed with the Research Contractor)	
1	**JCoPR, Section 8** There are a significant number of documents in use for this project and it would be useful to implement a system, which enables these documents to be quickly and easily identified e.g. through use of a masterlist, which includes their current revision status. This would be particularly beneficial due to the number of documents and would assist collaborators in their use and application.		Generate an up-to-date list of documents to include current revision status for use by all members of the project team.	
2	**JCoPR, Section 8** Audit records do not indicate timescales for completing corrective actions in order to demonstrate that appropriate timescales have been agreed with the person designated to take the action. In addition whilst corrective actions raised during internal audits are verified when complete, no record of this is currently held to show when and who completed this check. This is important to show that appropriate follow-up has been taken and actions identified as agreed.		Audit record was amended during the audit to enable timescale/follow-up etc to be recorded. The updated record needs to be formally issued.	

END

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