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A pilot study of infectious intestinal disease in England

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SUMMARY

Pilot studies to test methods to determine the incidence, agents, risk factors and socioeconomic costs of infectious intestinal disease (IID) in England were carried out as recommended by the Committee on the Microbiological Safety of Food (the Richmond Committee) by eight general practices. There were case control and enumeration studies of patients presenting to general practice with IID, a population-based prospective cohort study, and a survey of socioeconomic costs of cases of IID. Information on risk factors was obtained by questionnaire (self-administered compared with interview) and a stool sample was requested on all cases and controls. Response rates in the GP case control study were 75% for case questionnaires and 74% for stools; for controls the figures were 70% and 68% respectively. The acceptance rate into the cohort study was 49%; this was significantly higher where phone contact was made. The rate was similar if recruitment was by individual or household. Follow-up of the cohort by negative reporting was complete for up to 6 months. Direct postage by subject was required to obtain fresh stool specimens. Estimates were obtained of presentation rates of IID and the distribution of risk factors which were used to plan the main study. The pilot study demonstrated that it is possible to undertake a national study based in general practice to determine the incidence of IID in the population and presenting to GPs and its agents, risk factors and costs.

INTRODUCTION

National surveillance of infectious intestinal disease (IID) in England and Wales, based on laboratory reports, reports of outbreaks, and statutory

notifications, has shown marked increases over the last decade [1]. Recent reports on the costs of illness associated with human salmonellosis infection have indicated that the overall costs of IID are likely to be high [2].

The Committee on the Microbiological Safety of Food (the Richmond Committee) recommended that epidemiological studies be undertaken to investigate the incidence and causes of IID that can be microbiologically confirmed, both of general practice (GP) consultations and in the community, and how these incidence figures relate to the estimates from the national surveillance [1].

This paper describes the design and results of the pilot phase of a national study in England which will address these recommendations. The aim of the pilot study was to explore the feasibility of a proposed design, to compare alternative methods, and to provide estimates necessary to the designing of the main national study. The pilot investigation and the development of the protocol for the national study were taken forward under the aegis of the Steering Group on the Microbiological Safety of Food, which is a joint committee of officials from the UK Health and Agriculture Departments and outside experts set up in response to the recommendations in the Richmond Committee Report.

METHODS

Design

The pilot study was undertaken in eight general practices between October 1991 and May 1992; all were members of the Medical Research Council's General Practice Research Framework (MRC GPRF). In each practice a doctor and a nurse were trained in the study procedures. There were four components to the study: a GP case control study (in two practices) to investigate the incidence and causes of IID presenting to GPs, a population cohort study (in four practices) to determine the incidence of IID in the population, a GP enumeration study (in two practices) to assess what proportion of cases of IID have a stool sample taken in routine GP consultations and the results of the stool examination, and a socioeconomic costs study run at the same time (in four practices). In each component, practices were located in the same area of England with a balance when possible of urban and rural settings so as to test feasibility of recruitment and stool transport in different settings. We did not perform more than one substudy (except socioeconomic costs) in any one practice so as to test the feasibility separately and to assess nurse time.

The first two studies used the following case definition of IID: 'people reporting loose stools or significant vomiting preceded by a symptom free period of at least three weeks in the absence of a known non-infectious cause (e.g. ulcerative colitis)'. Loose stools had to be present for fewer than 14 days and vomiting for less than 48 h. Significant vomiting had to either incapacitate the case or to be forceful and accompanied by systemic symptoms.

GP case control study

General Practitioners identified all patients presenting to the surgery, or seen on a home visit (including deputizing service visits), with diarrhoea or vomiting who fulfilled the case definition, and each case was asked to provide a stool sample.

Cases were systematically allocated by date of birth to complete a questionnaire either self-administered (on even days e.g. 10.6.58) or by nurse interview (odd days e.g. 11.6.58). The questionnaire asked about sociodemographic details and factors of long-term relevance to risk of IID and recent activity (see below). Non-responders were followed up by letter or telephone. The next three age and sex matched controls adjacent to the case were selected from the practice's age-sex register. They were invited sequentially by letter followed where possible by a phone call, until one had accepted. Each control was asked to provide a stool sample and to complete the questionnaire by the same method as the case. To estimate the completeness of ascertainment, consultations were reviewed over a 2-week period during the early and late stages of the pilot study, by a random sample of the GP notes in one practice, and by review of the diagnostic codes given to each consultation held on the practice's computer in the other.

Population cohort study

Simple random samples were drawn from the age-sex registers of four GP practices. These samples were based on individuals (in two practices) or on households (in the other two). The nurse first checked the lists with the patients' practice notes to see if they were still registered. Subjects/households were initially invited by letter only but because of the poor response new samples were drawn. In this second round each initial letter was followed up by a telephone call whenever possible. Searches were made of the practice records, telephone directories, and directory enquiries to obtain the telephone number. All non-responders and refusers were sent a brief questionnaire to determine the household composition and the social class of the individual/head of household.

Individuals and households were randomly allocated to 3 or 6 month follow-up. Subjects were briefed by the nurse on the follow-up procedure and a questionnaire on factors of potential long-term relevance for risk of IID (see below) was completed. Follow-up was by 'negative reporting' whereby subjects were asked to send a postcard to the practice each week stating whether the subject or household member had developed diarrhoea or vomiting. If their card was not received each week the nurse telephoned or wrote to the participant. If symptoms occurred participants were instructed to collect a stool sample and contact the nurse. If subjects fulfilled the case definition a second questionnaire on recent activity was completed as part of a nested case control study. An age and sex matched control was selected from the cohort to complete the questionnaire and provide a stool sample.

Enumeration study

The general practitioners ascertained all cases presenting in surgery or at home with diarrhoea or vomiting not due to an obvious non-infectious cause. The definition used was less specific than in the two studies above in order to document how many less severe or chronic cases presented. Each case was given a short self-administered questionnaire to document symptoms to determine how many subjects fulfilled the stricter case definition. The study nurse searched the practice records for details of whether a stool sample was collected and the result of the stool examination.

Socioeconomic costs study

All cases identified in the GP case control and enumeration practices were sent a socioeconomic costs questionnaire 4 weeks after presentation. The 4-week period was adopted because some individuals may have prolonged illness and there was a need to identify as many of the costs as possible associated with the illness. The questionnaire was accompanied by an explanatory letter and instructions on its completion. It explored the length and severity of illness, the use of primary care and hospital-based services, sickness-related work absence, and the costs of illness to the individual. Details of costs incurred by others involved either in the care of the case or affected by their illness were also sought.

The response rate was taken to be the proportion of those completing the baseline questionnaire in the relevant practices who also filled in the socioeconomic costs questionnaire.

Microbiology

All specimens were first taken to the practice and from there sent to the nearest Regional Public Health Laboratory. The times taken between patient presentation, voiding and receipt in the laboratory, and the weight of the sample were recorded. The stools were divided into three aliquots in the laboratory: one for routine investigation, one for electron microscopy, and one to be sent to the Food Hygiene Laboratory and the Laboratory of Enteric Pathogens. All stool specimens were to be investigated for the following pathogens: *Aeromonas* sp. and related organisms; *Bacillus* species; *Campylobacter* sp.; *Clostridium difficile* and toxin; *Clostridium perfringens* and toxin; diarrhoeagenic *E. coli*; *Salmonella* sp.; *Staphylococcus aureus*; *Shigella* sp.; *Vibrio parahaemolyticus*; *Yersinia* sp.; adenovirus, rotavirus, small round structured virus (SRSV); ova, cysts and parasites (including *Giardia intestinalis*, *Entamoeba histolytica*, *Cryptosporidium*).

Questionnaires

These included details on factors considered to have 'long-term' relevance (such as household accommodation, household facilities, food storage and food preparation practices), and recent exposures in the 10 days before the onset of symptoms (such as food and water consumption, pets, travel and medication). There were separate versions for adults and children.

Data handling

Data collection and coding was coordinated by the MRC Epidemiology Unit at Northwick Park Hospital. Data entry and analysis was performed using EPI-INFO [3] and EGRET [4]. Incidence rates were calculated by dividing the number of cases by the person years of observation. In the GP case control and enumeration studies the person years observed in each practice were calculated by multiplying the list size by the study duration. In the enumeration study the incidence rate was adjusted for comparability by applying to all subjects the proportion of those who completed the questionnaire that fulfilled the case definition.

A summary incidence rate of IID in the community was calculated by dividing the total number of cases by the sum of the person years of risk experienced in the cohort study. A summary incidence rate of IID presenting to general practice was calculated by dividing the sum of cases presenting in both the case control and enumeration studies by the total person years at risk. Confidence intervals (CI) were calculated. Relative risks were estimated by odds ratios in univariate and multiple variable analysis, separately for adults and children. There were too few cases in the cohort study to permit analysis of risks.

RESULTS

GP case control study

Seventy-five percent of all cases ($n = 120$) presenting completed the questionnaire, 74% provided a stool sample (Table 1); 84% did one of these and 65% did both. Most cases (88%) presented in surgery, with the remainder seen in home visits. No cases were ascertained via the deputizing service in the one practice which used this system.

The ascertainment of controls is shown in Table 1. The response rates of questionnaire completion and stool sampling amongst those accepting were lower than for cases at 70 and 68% respectively. For half of the cases the first control to be invited accepted, in other cases the control was not contactable or they refused.

Controls could not be recruited for 11 cases and for a further 8 cases controls were never invited due to temporary practice difficulties. Full information on matched case control pairs (i.e. questionnaires and stools obtained from both) was achieved in 54 pairs out of 120 cases ascertained (45%).

There was little difference in the quality of responses to key questions between the nurse interview and self-administered questionnaires (SAQ). More people allocated to the interview declined to attend and complete the SAQ in lieu than vice versa. There was no evidence of underascertainment except during one period of 2 weeks when one practice was undergoing disruptive building work.

Population cohort study

The first recruitment round, based on letter only, had a low acceptance rate of 31%. In the second round where telephone contact was routinely attempted the rate was higher at 49%. This was due to the high uptake amongst those contacted by telephone: few people without a telephone attended (Table 2). Acceptance was not significantly different when subjects were asked to participate as individuals or households.

In the individual cohorts the age sex distribution of participants was compared with the cohort sample drawn from the GP list. Females had a higher response than males; males aged 15–24 and infants were under-represented (Fig. 1). The short questionnaire used to investigate the social class of non-participants had a poor response rate (28%). There was no evidence of social class bias in the practice with the highest response (46%): 17/22 (77%) of non-participants who provided social class details were non-manual compared to 78/120 (65%) of responders (chi

Table 1. *Compliance in the GP case control study*

Cases	Number	Percent of cases presenting	
Presenting	120	100	
Accepted	110	92	
Questionnaire completed	90	75	
Stool provided	89	74	
Controls	**Number**	**Percent of controls accepting**	**Percent of cases presenting**
Invited	161	—	—
No contact or moved away	57	—	—
Refused	13	—	—
Accepted	91	100	76
Questionnaire completed	64	70	53
Stool provided	62	68	52

Table 2. *Recruitment and follow-up in population cohort study: second round*

	Sample type					
	Individual		Household		Total	
Recruitment	*n*	%	*n*	%	*n*	%
Cohort list	300		120		420	
Eligible (% of list)	274	91	115	96	389	93
Letter sent and phoned (% of eligible)	191	70	90	78	281	72
Attended (% of above)	137	72	49	54	186	66
Letter only sent (% of eligible)	83	30	25	22	108	28
Attended (% of above)	4	5	2	10	6	5
Overall attendance (% of eligible)	141	(51%)	51	(44%)	192	(49%)

	Individual		Household	
Follow-up	6 month*	3 month	6 month	3 month
Participants	69	72	26	25
Person/household weeks	1097	840	676	312
Weeks contact made† (% of above)	1064 (97%)	814 (97%)	672 (99%)	309 (99%)
Withdrawal	2	1	0	0

* One practice only followed for 3 months.

† Predominantly by card return, some by phone, includes weeks where the practice knew the subject was away.

squared 0·77 $P = 0{\cdot}38$). Once subjects agreed to participate follow-up was successful in both the individual and household cohorts (Table 2). For most weeks a card was returned as required and there were very few withdrawals. Compliance did not differ amongst those followed for 6 months compared to those allocated to the 3 month follow up, in either the first or second round cohorts.

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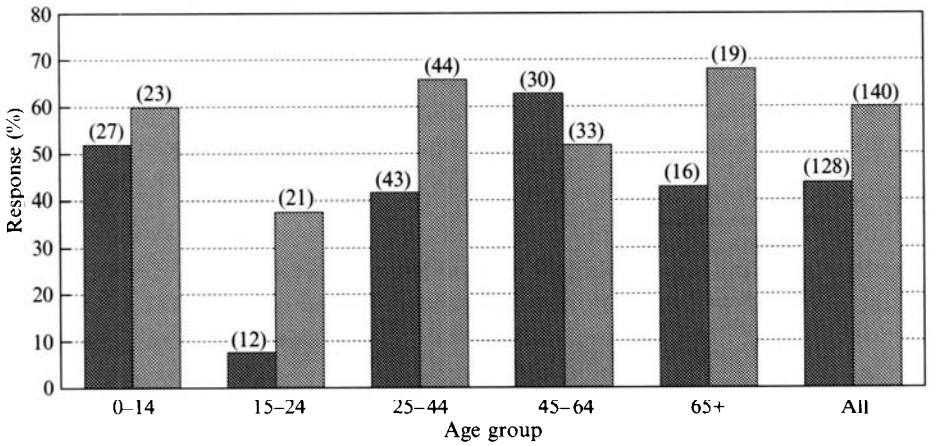

Fig. 1. Uptake rates by age and sex in the individual cohort study. ■, Males; ▨, females. Total invited in parentheses.

Table 3. *Rates of IID per 100 person years in the cohort, case control and enumeration studies*

Practice	Type of study	Number of cases	Person years at risk	Incidence of IID per 100 person years	95% Confidence intervals
Rural	Cohort, household	1	22·5	4·44	(0·11, 24·76)
Urban	Cohort, household	0	10·5	0	—
Rural*	Cohort, individual	3	30·9	9·70	(2·00, 28·37)
Urban*	Cohort, individual	5	27·4	18·20	(5·92, 42·5)
Total (in cohort)		9	91·3	9·86	(4·51, 21·56)
Rural	Case control	48	7064	0·68	(0·51, 0·90)
Urban	Case control	72	3377	2·13	(1·69, 2·69)
Urban	Enumeration	79†	942	8·40	(6·71, 10·43)
Urban	Enumeration	83†	1828	4·50	(3·65, 5·61)
Total (presenting to general practice)		282	13211	2·13	(1·90, 2·40)

* Includes data on follow-up from first-round cohorts.
† Fulfilling case definition used in GP case control and cohort studies.

Enumeration study

The short symptom questionnaire was returned by 152/221 (69%) of cases. Of these 112 (74%) fulfilled the case definition used in the GP case control study, and the remainder of cases mostly had acute symptoms of insufficient frequency or severity. We assumed that overall 162 (74% of 221) cases presenting fulfilled the case definition (Table 3). It proved straightforward to trace the microbiology results by note search of the medical records: 11 patients (7%) had stools analysed and 3 had isolates.

Microbiology (GP case control study only)

Full data on the timing of stool samples was available for 75 cases and 42 controls in the GP case control study. The median time from presentation to

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Table 4. *Organisms isolated in the GP case control study*

	Number (% of subjects)	
	Cases (n = 89)	Controls (n = 62)
Aeromonas	0	0
*Bacillus cereus**	1	0
*Bacillus subtilis**	3	1
Campylobacter	3	0
Cl. difficile	2	1
Cl. perfringens†	11 (12)	12 (19)
Diarrhoeagenic *E. coli*	13 (15)	7 (11)
Salm. enteritidis	5	0
Salm. typhimurium	1	0
Staphylococcus aureus	3	4
Shigella	0	0
Vibrio parahaemolyticus	0	0
Yersinia	1	0
Adenovirus	1	0
Astrovirus	4	0
Coronavirus	0	1
Rotavirus	0	0
SRSV	0	0
Cryptosporidium	1	0
Giardia	1	1
Entamoeba	0	0
Total isolates‡	47	27

* $> 10^4$ colony forming units/g of faeces.
† $> 10^5$ colony forming units/g of faeces.
‡ Some patients had more than one isolate.

voiding (cases only) was 1 day, 31% took 3 or more days; the median time from voiding to receipt in the laboratory (cases and controls) was 2 days, 37% took 3 or more days (especially at weekends); and the overall median time from presentation to receipt in the laboratory (cases only) was 4 days, 66% took 3 or more days.

The results of microbiological analysis of stool samples are presented in Table 4. The number of specific and potential pathogens detected is shown. Small numbers of common pathogens were detected in cases only, some organisms were found in both cases and controls. In many cases no pathogen was identified.

A further feasibility study was undertaken in two of the original practices to increase the amount of stool sample and to reduce the time for the sample to reach the laboratory. Clearer instructions were given about the amount of stool required, and samples were posted by the subject by first-class post directly to a single Public Health Laboratory. Microbiological analysis was not performed on these samples. Of 30 samples only 6 (20%) took 3 days or more from presentation to receipt in the laboratory. The volume of stool was sufficient for the full range of microbiological tests in 90% (27) of samples.

Age distribution and incidence rates

There was a similar age distribution of cases in both sexes in the GP case control

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component: of 52 male cases 19 (37%) were under 16 and 4 (8%) were over 65: the corresponding figures for the 68 female cases were 20 (29%) under 16 and 9 (13%) over 65. Table 3 presents the estimated rates of IID. The incidence rate in the cohort study was 9·9 per 100 person years (individual practices ranged from 0 to 18·2). The rate of presentation to general practice was 2·1 per 100 person years (individual practices ranged from 0·7 to 8·4).

Risk factors for IID

The pilot study examined a range of factors considered to be of likely relevance to the risk of IID in matched univariate and multiple variable analysis. Risk factors were examined separately for children and adults, and results were generally consistent. Due to the small number of cases in the pilot study, the relative risk estimates and confidence intervals are not presented here.

Socioeconomic costs study

The response rate was 43% overall; this was higher in the GP case control practices (51%) than in the enumeration practices (38%). Problems were identified with three questions. This related to duplication with the baseline questionnaire or to misunderstanding of the question. There were no differences in the age, sex and social class of responders compared to the baseline sample in the GP case control and enumeration studies.

DISCUSSION

The pilot study aimed to establish the feasibility of studies to determine the incidence, aetiology, and socioeconomic costs of IID at population and general practice levels as recommended by the Richmond Committee, and to identify the most appropriate methods [1]. The Steering Group on the Microbiological Safety of Food considered that it was feasible to proceed with a national study in England based on the results of the pilot. We discuss here the salient findings and where appropriate implications for the design of the national study.

The GP case control study was designed to address one of the Richmond Committee's recommendations and thereby to provide an estimate of the case presentation rates, to test the feasibility of obtaining information on cases, and, by a case control design, to investigate potential risk factors for IID. Two-thirds of cases presenting provided both a questionnaire and a stool sample. Cases where such data are not available can still be taken into account in the determination of presentation rates. The estimation of these rates was dependent on the diligence of the practice staff. Regular ascertainment checks are therefore needed to document completeness and these will be incorporated into the national study. Stool samples were provided by 74% of cases: this is similar to the 69% figure found in a case control study of salmonella PT4, although previous studies in single general practices had higher rates (81% and 100%) [5–7]. Self-administered questionnaires were at least as reliable as nurse interview (and will be used in the national study). To ensure controls are obtained for as many cases as possible more than three controls need to be invited. In the national study this number will be increased to five.

Stool samples were delivered in good time only if posted first-class by the

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subjects. Clear instructions about the amount required were effective. The number of stool specimens analysed microbiologically was small and therefore no firm conclusions can be made from this pilot study. Moreover delays in transport and the small amounts of some specimens which precluded full testing make interpretation of the results difficult. The data on diarrhoeagenic *E. coli* isolates were based on gene probe analysis and do not suffer as much from these problems, but the recovery of potential pathogens such as *Clostridium perfringens* was lower than expected from studies of normal gut flora [8]. The same range of organisms will be tested for in the national study. One first-line laboratory will be used for all practices. Samples will be sent on to specialist laboratories. A stool sample and isolates will be archived for future study.

It was difficult to derive comparable data from the GP case control and enumeration studies because the definition of a 'case' differed. In the national study the same definition will be used throughout and the microbiology results in both will be compared to the national surveillance. The presentation of cases to local accident and emergency departments will be documented in a sample of practices in the enumeration study.

The population cohort study aimed to address the second Richmond Committee recommendation. General Practice register was used as the sampling frame rather than an alternative sampling strategy as this was easily available and the study could be combined with the GP case control or enumeration studies in any national study. Moreover general practice was ideally suited to the detailed prospective follow-up required to maximize ascertainment of new cases of IID and to ensure fresh stool samples were sent.

In the population cohort study recruitment of individuals was more effective than households, as it was simpler to obtain the random samples from the age-sex registers, to estimate age-sex specific acceptance rates, and to determine the person time exposures (particularly as not all members of a household are registered with one practice). The response rate was similar for individuals and households, and although compliance with follow-up as judged by card return was slightly lower for individuals there was no difference in the number of weeks where no contact could be made.

The overall response rate was 49%, which compares with the 36% achieved by a recent study in Holland which sampled from the population register [9]. This does raise the possibility of selection bias in recruitment. Acceptance rates were shown to vary with age and sex as in the Dutch study [9] but it was not possible to show a social class bias. In the national study the incidence rates will be adjusted for low compliance groups, and more rigorous efforts made to determine the social class of non-participants.

The 'negative reporting' method worked well. It is a more reliable way of detecting incident cases than a 'positive reporting' system in which information is only obtained when symptoms occur, particularly when observed rates are low. Six-month follow-up did not reduce compliance. In the Dutch study, where the follow-up was by weekly questionnaire for 4 months, compliance declined slightly after 10 weeks [9]. Compliance was also high in a US study where households in a discrete community were targeted, and followed weekly by telephone for a year to document acute IID and respiratory disease [10].

The estimate of population incidence rate was lower than that found in studies in the US and Canada [10, 11] but was similar to that found in the Dutch study (their case definition required symptoms to last over 24 h) [9]. The presentation rate to GPs was similar to that found in GP studies in the UK in the early 1980s [5, 6] and in the recent Dutch study [9], but were lower than the most recent general practice morbidity statistics [12].

There was variation in the estimated rates of IID in the community and presenting to GPs. This could be due to chance effects as numbers were small; differences in ascertainment, patient behaviour, practice organization or list inflation (in the GP case control study), or it may reflect real variation in incidence. This highlights the importance of designing a national study that is of sufficient size to provide reliable estimates both in total and for specific subgroups (e.g. adults and children) and in which the general practices are as far as possible representative. The incidence and risk factor estimates have been used to determine the size of the national study. Seventy-two practices will recruit two sequential cohorts of 6000 patients each to be followed for 6 months (giving 6000 person years of follow up), and 36 practices will participate in each of the GP case control and enumeration studies for a year. The practices will be representative in terms of geographical spread, size, and the Jarman deprivation score (as a marker of the socioeconomic characteristics of the practice population) [13]. The cohort samples will be used to obtain estimates of list inflation and the denominators for the GP presentation rates will be adjusted accordingly.

A study into the socioeconomic costs of IID was shown to be feasible. The overall response rate was lower than anticipated. To enhance this in the national study the time before questionnaire administration will be reduced from 4 to 3 weeks, there will be no duplication of questions, and non-responders will be followed-up.

In conclusion, the pilot phase has shown that it is possible to design a national study to determine the incidence of IID in the population and presenting to GPs, its aetiology, risk factors and socioeconomic costs. It identified the best methods for selection and follow-up in the cohort study, for completion of the questionnaire in the GP case control study and for stool sampling. The study of IID in England started in July 1993 and fieldwork is expected to be completed in 1995.

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