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Challenges in identifying the methodology to estimate the prevalence of infectious intestinal disease in Malta

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SUMMARY

Routine surveillance systems capture only a fraction of infectious intestinal disease (IID) that is actually occurring in the community. Different methodologies utilized among various international studies in the field were reviewed in order to devise an appropriate survey to obtain current estimates of prevalence of IID in Malta. An age-stratified retrospective cross-sectional telephone study was selected for the study due to its feasibility in terms of limited resources necessary (funds, time and human). The disadvantages of this type of study include the inherent biases such as selection bias (sampling, ascertainment and participation bias) and information bias (recall and observer bias). A pilot study was carried out using a random age-stratified sample of 100 persons over a 3-month period. A total of 5·0% (95% CI $\pm$4·27) of the population was estimated to have suffered from IID during that period. This estimate was used in order to assist in sample size calculations for a large-scale community study. It also served to test the survey instrument and methodology and to identify operational problems.

INTRODUCTION

Infectious intestinal disease (IID) is one of the most common communicable diseases throughout the world [1]. In industrialized countries, although mortality is low, morbidity is still high [2]. In Malta the Disease Surveillance Unit, within the Public Health Department, is responsible for the surveillance of IID. This Unit receives notifications from general practitioners (GPs) and hospital physicians of cases seen with suspected IID and from laboratories in cases of positive stool culture results. The majority of notifications received include cases which required hospitalization or those with positive stool culture results. Notifications from GPs are rare although they have a statutory obligation to notify.

To be included in the current surveillance system, an individual must first present to the health-care provider who, in turn, is required to notify the Disease Surveillance Unit. Of those cases presenting to a health-care provider, only a small proportion eventually result in laboratory testing; moreover only the severe cases are hospitalized [3]. Thus, the existing surveillance system captures only a fraction of IID disease that is actually occurring in the community.

In order to assess the magnitude of the problem of under-reporting and to establish prevention

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initiatives, estimates of the prevalence and/or incidence of IID and the duration and severity of symptoms are required.

A number of studies have been performed in other countries to estimate the incidence or prevalence of IID. The methodologies used differ. Some researchers used a prospective cohort study [4–9] whilst others used a retrospective cross-sectional study [10–15]. A prospective population cohort study was performed in England over the period 1993–1995 which estimated the incidence of IID and identified a number of pathogens at community and at GP referral level [4–6]. A similar study was carried out in The Netherlands during the period 1998–1999 which provided an estimate of the incidence and disease burden of IID at population level [7] and at GP level [8]. This study also investigated a broad range of pathogens causing gastroenteritis [9]. The methodology used in these studies is not applicable in a country like Malta where no GP lists exist, with patients able to refer to any doctor they choose, hence the doctor is unable to follow up-patients prospectively.

Over recent years, several retrospective studies have been carried out, one of which was a retrospective telephone study of self-reported symptoms of gastroenteritis that was performed during the period 2000–2001 in Ireland [10, 11]. Additionally, the FoodNet population survey was carried out in the United States, and this too was based on retrospective self-reported symptoms [12].

The magnitude of enteric illness was estimated by a retrospective cross-sectional telephone survey in Canada [13] and also in Australia through OzFoodNet [14]. Another retrospective population-based study was carried out during 1999–2000 in Norway using a self-administered postal questionnaire [15]. Although these retrospective studies provided estimates on the prevalence of gastroenteritis in the community, they did not attempt to analyse the aetiological agents causing IID for each case and hence could not provide detailed information on the type of infectious organisms causing IID in those countries.

In Sweden a retrospective interview study was performed during 1998–1999 to determine incidence, causes and costs of foodborne illness. This was based on enhanced surveillance, encouraging persons who had symptoms to contact the study team [16]. A summary of these studies is given in Tables 1 and 2.

Since the incidence of IID is likely to change over time and differ between countries, and as no information or indicator is available for the prevalence of community IID in Malta, an age-stratified retrospective cross-sectional prevalence pilot study was performed during 2003. This study aimed to test the survey instrument, preview the survey methodology including operational problems and inform sample size calculations for a large-scale population study to be performed in 2004.

Table 1. *Prospective cohort international studies*

Country	Date of study	Incidence rate	Ref.
United Kingdom	1993–1995	194 per 1000	[4–6]
The Netherlands	1998–1999	283 per 1000	[7–9]

MATERIALS AND METHODS

Study design

The study was a retrospective cross-sectional telephone study.

Selection of participants

The study population consisted of all residents (of all ages) of the Maltese Islands, a population of ~400 000 persons. An age-stratified representative random sample of 100 persons was drawn from the general population database.

Inclusion criteria

Individuals who reported at least three episodes of diarrhoea (defined as loose stools) within 24 h or vomited at least three times in 24 h, *or* suffered diarrhoea or vomiting with two or more additional symptoms in 24 h over the previous 28 days were included as cases. Additional symptoms sought included abdominal cramps, abdominal pain, fever, nausea, blood in stool, mucus in stool, and diarrhoea or vomiting. The retrospective period of 28 days was selected to be comparable with United States, Irish, Canadian and Australian study results.

Exclusion criteria

Individuals were excluded as cases if they reported any pre-existing illness or non-infectious conditions diagnosed by a medical doctor in which vomiting/diarrhoea was a symptom or were concurrently taking any medications which could cause diarrhoea/vomiting as side-effects.

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Table 2. *Retrospective cross-sectional international studies*

Country	Date of study	Monthly prevalence of IID	Ref.
United Kingdom	1994	8%	[24, 25]
United States	1996–1997	11%	[23]
Sweden	1998–1999	3·8%	[16]
Norway	1999–2000	14·4%	[15]
Ireland	2000–2001	4·5%	[10, 11]
Canada	2001–2002	10%	[13]
Australia, Queensland	2001	13·6% for adult population; 13·9% for child population	[14]
Malta (pilot study)	2003	5%	

Questionnaire design and development for major study

The questionnaire was developed by modifying questions from existing standard, validated tools used in several international studies. These were obtained from published sources for the English IID study [17] and by direct communication with the investigators of the study at the relevant authority, namely the Unites States FoodNet study (A. Banerjee, personal communication), Australian OzFoodNet study (M. Kirk, personal communication), Canadian Study (S. Majowicz, personal communication), Swedish Institute (Y. Andersson, personal communication), the All Ireland study (E. Scallan, personal communication) and The Netherlands study (Y. van Duyhoven, personal communication).

Questionnaire topic areas

The questionnaire topic areas covered demographic data, symptomatology and burden of illness. Demographic data included age, sex, locality and socio-economic status. The symptomatology was assessed including the frequency and duration of symptoms. Other questions were included to aid in the ascertainment of cases of IID by identifying possible causes other than IID. Other cases involved, and travel abroad were also assessed. Burden of illness included limitations in normal activities, leisure and loss of school/work by the cases and the carers. Health-seeking behaviour was assessed as to advice, visits to health-care providers and hospital admissions. Information was also requested regarding stool culture requests, treatments taken and other non-medical costings.

Field work

Telephone interviews were used to collect information with verbal consent being obtained at the time of the telephone call before administering the questionnaire. Two doctors who work in the field of communicable disease surveillance conducted the interviews at the Disease Surveillance Unit. They were given appropriate training in order to reduce inter-observer bias. The interviews were conducted over a 3-month period from August to October 2003.

Laboratory investigation

All identified cases were asked to submit stools for analysis in order to identify the causative agent. Samples were analysed for *Salmonella*, *Campylobacter*, *Shigella*, *E. coli*, *Rotavirus*, *Norovirus* and *Sapovirus*. Stool samples were submitted directly to the Pathology Department of St Luke's Hospital, the main state hospital and laboratory in Malta, and by air charter to Istituto Superiore di Sanita (ISS) in Italy where viral testing was carried out.

The fresh stool samples were suspended in saline. This suspension was inoculated on commercial and differential culture media and in Salinide and Campylobacter broth. After incubation for 3 days at 37 °C, the samples were plated on Salmonella/Shigella agar for detection of *Salmonella* and *Shigella* spp. on days 1, 2 and 3. For detection of *Campylobacter* spp. the samples were incubated for 3 days at 42 °C in a microaerophilic environment with the use of Campylobacter medium. For detection of *E. coli* O157, the samples were incubated for 3 days at 37 °C on Sorbitol MacConkey agar. All work was carried out at the Microbiology Department of St Luke's Hospital.

Samples were tested for *Rotavirus* by the use of ELISA at the Virology Department of St Luke's Hospital and for *Norovirus* and *Sapovirus* by use of reverse transcription–polymerase reaction (RT–PCR) at ISS [18]. Intestinal parasites were analysed by

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means of microscopic examination of fixated samples at the Pathology Department of St Luke's Hospital, Malta.

Data entry and analysis

The data obtained from the questionnaire were entered and analysed in SPSS version 12 for Windows (SPSS Inc., Chicago, IL, USA). Following quality checks in the data, the monthly prevalence rate was calculated from the number of cases, as per the case definition.

RESULTS

Response rate

Only one of the 100 persons selected refused to participate in the study. This gave a very high response rate of 99%. Another randomly selected person within the same age group replaced the person who refused to participate.

Estimated prevalence of IID

During the study period from August to October 2003, five cases were identified. Hence, 5·0% (CI = $\pm$4·27 based on 95% confidence level) of people were estimated to have suffered from infectious intestinal illness in a 4-week period. This percentage is an estimate of the percentage of persons in the population who, at that time of the year, were able to report having had such symptoms in the previous 4 weeks. Hence it is clear that IID is a relatively frequent and important cause of morbidity on the island.

Burden of illness

The five persons, who reported symptoms and were included as cases since they met the defined criteria, described their illness as having a mean duration of 2·8 days. One of the cases visited a GP for advice. None required hospital admission. The other cases did not seek professional advice regarding their illness.

Sample size calculation for the large-scale population study

The prevalence calculated from the pilot study had a wide confidence interval ($\pm$4·27) since the sample size was relatively small. In the subsequent large-scale study, greater numbers will be utilized to estimate the true population prevalence with a higher level of accuracy. The estimate of 5% obtained was used to calculate sample size for the larger population study. The confidence interval used to calculate the sample size for the larger study was taken at $\pm$0·83%. To work out the sample required for the actual study, the sample size formula used was:

$$\mathrm{ss} = z^2(p) * (1-p)/c^2,$$

where ss = sample size, $z = z$ value (1·96 for 95% confidence level), p = percentage making a choice, expressed as decimal (0·5 used for sample size needed), c = confidence interval, expressed as decimal (0·0083 = $\pm$0·83%) [19].

Hence,

$$\mathrm{ss} = 1{\cdot}96^2 \times 0{\cdot}05 \times (1-0{\cdot}05)/(0{\cdot}0083)^2 = 2652.$$

The sample size required for a population prevalence study, which allows the frequency of IID to be estimated to within a confidence interval of $\pm$0·83% based on 95% confidence level, was 2652. This study commenced in 2004.

Results of stool analysis

All of the cases identified had a stool sample tested. No sample was found to be positive for any of the pathogens tested.

DISCUSSION

This was the first epidemiological pilot study of IID in Malta at the community level. IID is a common but preventable illness, which is characterized by diarrhoea and vomiting, and is often managed at home without referral to hospital and frequently without referral to a health-care service. Hence this study was the first step to estimate the burden of this condition nationwide.

In designing the study, the options for different methodologies were carefully studied and consideration was given to performing either a cohort or a cross-sectional study. Various factors were assessed including the feasibility, costs, limited human resources, time limitations and also the inherent biases, which exist with each type of study.

There are a number of advantages in choosing the cross-sectional methodology. Because the participants are studied over a short period of time, the

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study is considerably less expensive than a cohort study. This type of study can be performed quickly, enabling a large sample size to be used, consequently reducing type II error. Since the study is conducted over a short period of time, attrition of participants is not a concern. Here too, the researcher is not faced with the difficulty and cost of maintaining contact with the subjects over a long period of time. Another advantage is that selection of participants does not rely on individuals who present for medical treatment, hence one can capture those cases who do not refer to a doctor.

However, there are a number of disadvantages to this approach. In this type of study, the researcher often finds it difficult to separate fully the chronology of cause and effect because only a short period of time is studied. This type of study suffers from a number of biases including selection bias and information bias.

Ascertainment bias can also occur but can be minimized by strict adherence to definition for selection of cases.

The cross-sectional method is particularly susceptible to recall bias due to the retrospective nature of the study design. One form of recall bias called 'telescoping' is especially important in this type of study. This describes the tendency for people to displace events in time. Someone may recall an event as occurring in the past 4 weeks when it actually occurred more than a month before. This would give an overestimate of the frequency of IID. Estimates obtained prospectively were 2–3 times lower than those obtained retrospectively [4]. Attempts were made to reduce this bias by asking the actual date of onset, which gives more accurate results. A review of literature on recall accuracy suggests that the extent of inaccurate recall is related to the characteristics of the event and of the respondents, although a distinction must be drawn between recall, which is biased, and that which is simply inaccurate [20, 21]. Interviewing techniques and the outlining of the study protocol, including the design of the questionnaire, and the motivation of respondents play a central role in decreasing this form of bias [22].

A cross-sectional study was chosen as the method to estimate the prevalence of IID in Malta. Since cross-sectional studies provide an estimate of the probability that an individual will be ill at a point in time, only prevalence can be calculated from this type of study. However, this type of study was chosen since it provided an assessment of the public health impact of IID, which is the main aim of the survey, and it is simple, low cost, quick and the inherent bias can be minimized with careful planning of the study design.

The study showed that IID is a potentially important public health problem causing a relatively large burden of illness in the community. In the 4 weeks during the study period, 5·0% (CI $\pm$4·27) of the people suffered from IID.

A similar large-scale study performed in Ireland during 2000–2001 [10, 11] estimated that 4·5% (CI $\pm$0·8) of the population reported suffering from acute gastroenteritis in the 4 weeks prior to the interview giving a frequency of 0·60 episodes of acute gastroenteritis each year. Another retrospective study in the United States during 1996–1997 reported 11·0% (CI $\pm$0·8) of the people suffering from diarrhoeal illness in the 4 weeks before the interview [23]. The retrospective study in Sweden during 1998–1999 gave a frequency of 3·8% [16]. Retrospective studies in the United Kingdom in 1994 found higher rates, with between 7·0% and 8·0% of people reporting acute gastrointestinal illness in the previous month [24, 25]. However, the retrospective studies in the United States and United Kingdom were carried out some 6–10 years before the study in Malta. Reported statistics indicate that there has been a decline in enteric illness over this period [3]. Another factor, which may have influenced the rate obtained from the pilot prevalence study in Malta, is that the study was performed over 3 months of the year. IID is known to have seasonal distribution, hence the rate obtained cannot be extrapolated for the whole year. The large-scale population study will, therefore, incorporate the whole year to account for seasonal variation.

The Canadian-based population study showed a monthly prevalence of 10% and an adjusted incidence rate of 1·3 episodes per person per year [13]. In the Australian study in Queensland in 2001, 13·6% (CI $\pm$2·4) of the adult cases ($\geqslant$18 years) and 13·9% (CI $\pm$8·1) of children (7 months to 4 years) reported diarrhoea in the preceding month [14]. In the study performed in Norway during 1999–2000 the prevalence of acute gastroenteritis was 14·4% (CI $\pm$2·6) of which 17% consulted a physician [15].

During 1998–1999 the cohort study in The Netherlands estimated that 28·3% (CI $\pm$6·3) of the population suffered from gastroenteritis and 1·4% consulted their GP [7]. In the UK cohort study carried out during 1993–1995, it was estimated that 19·4% (CI $\pm$2·7) of the population of England suffered from IID in a year and 3·3% of the population presented to their GP with IID [5, 6].

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Due to the small size of the samples analysed and the delay between onset to collection, it is not surprising that no enteric pathogens were detected in the stools. The absence of these pathogens can be related to the age of subjects, the time the sample was taken, the range of pathogens tested for, prior antibiotic usage, and to the period of the study.

This pilot study provided an approximate estimate of the prevalence of IID occurring in the community in Malta. This enabled the calculation of the sample size required to perform the larger national study, which would give the best estimate of the true population prevalence as practically possible. Therefore, in the larger study, a larger sample size will allow for increased precision of the estimate of the prevalence of illness. Greater accuracy will then follow for improved cost analysis.

The pilot study also served to test the survey instrument and methodology and to identify operational problems. A number of questions in the questionnaire were modified as a result of this pilot.

CONCLUSION

Since there was no information about the frequency of IID in the community in Malta, the study team carried out a study to estimate the frequency, epidemiology and burden of infectious intestinal illness in Malta. This paper explored the types of studies that could be performed in the local context in order to obtain the information required. Based on the studies performed abroad; the local health-care system and resources available, an age-stratified cross-sectional study was chosen. The pilot study forms the basis of a larger study that commenced in 2004.

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DECLARATION OF INTEREST

None.

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