

# Chapter 10

## Summary

This was the largest microbiological epidemiological and economic study of IID yet undertaken. Seventy general practices were involved, covering a population of nearly a half a million (1% of the national population). The sample was broadly representative of the population of England in terms of age and sex distribution, residence in a particular geographical area (the North, Midlands and South West and the South East) and an urban or rural location. The general practices were also geographically representative but tended to be larger than average, reflecting the characteristics of practices in the MRC's General Practice Research Framework. In contrast, previous studies of IID in general practice have been small, involving one or a few general practices.

The study was necessarily complex to address the study objectives:

- To estimate the number and aetiology of cases of IID in the population, presenting to GPs, and having stool specimens sent routinely for laboratory examination.
- To compare these numbers and the aetiologies with those recorded by the national laboratory reporting surveillance system.
- To estimate the prevalence of asymptomatic infection with agents associated with IID.
- To document differences between cases of IID (in the population and presenting to GPs) and similar but well people (controls).
- To estimate the socio-economic burden of IID and its distribution.

### 10.1 THE INCIDENCE AND MICROBIOLOGICAL CAUSE OF IID IN THE COMMUNITY AND PRESENTING TO GPs

#### 10.1.1 Community rates

Two large population based cohorts were recruited and followed prospectively for six months to obtain a complete year of follow-up. Although uptake was only 40%, this was consistent with other studies and was perhaps expected, given the nature of the study. The final cohort was reasonably representative of the national population in terms of age and sex except amongst males aged 15–24 years, and where there were slight differences in social status and social class.

There was a very high level of compliance with follow-up which used a weekly negative reporting system. This gives more valid results than a prospective positive reporting system (i.e., only IID events are reported) or a retrospective recall.

Microbiological sampling was satisfactory with high compliance, minimal delays in postage and transport, and standardised and comprehensive testing of faecal specimens in one main laboratory, Leeds PHL. Specialist laboratories were used for more specific tests. The majority of specimens had all the planned tests performed on them, and in two thirds there was sufficient stool remaining to be archived for possible future testing. All isolates were also archived.

One in five of the study population had an episode of IID in the course of the year. The rate was highest in children under 5 years of age and was also high in women of reproductive age. The results are similar to a recent Dutch population based survey. Previous studies in the US found higher rates which may reflect the selective nature of the populations studied (e.g., with more families and young children).

If we discount *Aeromonas* which were found in almost as many controls as in cases, target microbial pathogens or their toxins were identified in only a third of cases, most frequently SRSV and *Campylobacter*.

### 10.1.2 General practice rates

Robust estimates of GP presentation rates were achieved, firstly by adjusting the denominators for practice list inflation, derived from the cohort study above. The average level was 10%. Previous studies report a range from 5–30%. Secondly, the numerator was adjusted for the estimated underascertainment of cases by GPs.

Compliance by the subjects with microbiological sampling was reasonable (74% from cases and 80% from controls) given the difficulties of collecting stool specimens from individuals suffering from presumed IID. For example, a primary care based study in Wales had a 67% compliance rate with stool sampling.

A higher proportion (55%) of cases had an organism identified than in the population cohort study (37%). Frequently identified target organisms included *Campylobacter* in 12%; rotavirus in 8%; SRSV in 7% and *Salmonella* in 5%. There were only three isolates of *E.coli* O157. This pattern is similar to that found in national surveillance.

Overall, one in 30 people presented to the GP (or one in six of those with IID identified in the community). The rate of presentation to A & E was low, suggesting patients largely used primary care for consultations. These rates are similar to other UK-based primary care studies and to a recent Dutch study. The rate was again higher in children under 5 years of age and greater in adult females than in males.

Severity of illness, use of primary health care services and accessibility to services may explain some of this difference. Symptoms were more severe, more frequent and of longer duration in both adults and children presenting to GPs compared with cases in the population cohort component. There were similar distinctions between bacterial and viral infections in general, although some rotavirus infections in children were more severe than many of the bacterial infections.

Symptoms were evaluated when there were sufficient cases associated with individual target organisms. Of those evaluated, *Campylobacter* and *Salmonella* were associated with severe illness. Raised temperature and bloody motions being most frequently reported with these pathogens both in adults and children presenting to a GP. Vomiting was most frequently reported in association with SRSV infection in adults and with SRSV and rotavirus group A in children. The most frequent infection in the population cohort component, SRSV, generally caused a

short-lived illness with a median duration of only two days, even in those adults presenting to a GP. Rates of target organism or toxin detection were higher than in previous studies. The relative proportions of *Salmonella* types identified were similar to those identified routinely through national reference laboratory surveillance, thus showing the value of the current surveillance system in monitoring trends in sub-types of this organism. The most commonly identified serotype was *S. enteritidis*, and in particular PT4. The second most common was *S. typhimurium*, in particular DT 104. We found relative proportions of the different types of enterovirulent *E. coli* that was markedly different from those identified routinely; the importance of EAaggEC as a cause of IID was particularly noteworthy. The very small number of sporadic cases of *E. coli* O157, which may cause serious disease, reflected the national reported figures. This was also the case with *Vibrio*, *Giardia intestinalis* and *Cryptosporidium parvum*. *Clostridium perfringens* was shown to be a common cause of sporadic IID. The importance of SRSV as a common cause of sporadic, community-acquired IID which was relatively mild in duration and severity was demonstrated. Other viruses, notably rotavirus followed by adenoviruses, astroviruses and, to a lesser extent, caliciviruses, were important causes of IID presenting to GPs.

Results on age and seasonality of IID in England are consistent with previous studies. The study did not clarify the role of *Aeromonas*, *Yersinia* and some of the enterovirulent *E. coli* in sporadic IID in the community in England since these were found in similar proportions in cases and controls.

A high proportion of cases had no target organism or toxin identified. This was not explained by the time lapse between voiding and testing of stool specimens, or completeness of testing, although there were some delays, and 30% of samples were insufficient for complete analysis. The most likely explanations are the limited sensitivity of the tests used, compounded by the inevitable time-lag between the onset of symptoms and the production of a stool specimen, the occurrence of IID due to as yet unrecognised organisms and toxins, and the inclusion of patients with non-infectious causes (despite the application of a clear case definition).

It is likely that the routine use of modern molecular tests such as polymerase chain reaction (PCR) amplification for pathogens and toxins would have improved the study's sensitivity. The improvement might not have been great for bacterial pathogens such as VTEC, where the gene probe used detected no more cases of *E. coli* O157 than the culture method chosen. On the other hand, the PCR technique might have increased the identification rate for viral pathogens more significantly, as it is well recognised that electron microscopy is a subjective and relatively insensitive technique. The quality control exercise undertaken during the study confirmed this assessment and, although viruses were pre-eminent as a cause of IID, it is likely that the true number of cases of viral infection (excluding rotavirus group A which were identified by EIA) was even greater than that reported in this study.

Other important issues remain unanswered. For example, the data on infection with multiple organisms were complex and require further analysis. This study provides a very valuable source of information and materials for further studies, which should include the development of methods for detection and isolation of organisms, and typing and virulence properties.

## 10.2 COMPARISON OF COMMUNITY AND GP RATES OF IID WITH NATIONAL LABORATORY SURVEILLANCE DATA

Routine stool sampling practice was observed in 36 general practices. The laboratories used by these practices were representative in terms of whether they belonged to the PHLS or not, and their size. Overall, the normal practice of GPs was to request stool samples from about a quarter of the patients who presented to them with IID. This reflects a tendency to request stool specimens on clinical grounds, rather than for surveillance purposes. Our study will provide valuable evidence to assist in the formulation of advice to GPs on which patients should have specimens taken in order to achieve epidemiological and public health objectives.

Two methods were used to estimate the factor by which national surveillance data should be multiplied to describe the incidence of IID in the population and the number of cases presenting to GPs, the so-called reporting pyramid. In the first — a direct method — the names of those cases for whom positive stools were obtained in the enumeration component were searched for in the national database and the degree of under-reporting calculated.

In the second — an indirect method — we compared the rates of IID which we estimated to occur in the whole population of England with the rates appearing in national surveillance figures and the degree of under-reporting was calculated.

By our own direct method we estimated that for every 136 cases of IID in the community 22 presented to a GP, 6.2 had a stool sent routinely for microbiological examination, 1.4 had a positive result, and one was reported to PHLS CDSC.

By our indirect method we estimated the ratio to be 88 cases in the community for every one reported to CDSC.

Our first estimate of the proportion of actual cases in the community appearing in CDSC's surveillance statistics based on the direct method may be pessimistic. This is because this estimate included only those cases reported to CDSC after presenting to their GPs. Cases may also arise in outbreaks, and these may be reported to CDSC by routes other than the GP. For example, outbreak cases identified by EHOs may be asked to send stool samples directly to laboratories. The direct method would identify these cases in the community, but not in the enumeration component, leading to an under estimate of the system's sensitivity. Another reason could be that our study did not include certain institutions (e.g., prisons, hospitals or long-stay institutions) from which stool samples would go direct to laboratory without any GP involvement. Two effects may act in the opposite direction leading to a spurious overestimate of the sensitivity of the national surveillance system. Firstly, it is possible that repeat specimens, specimens of materials other than stools, and specimens taken for research purposes could artificially inflate the CDSC reports, despite the efforts made to remove them from CDSC's data. Secondly, study nurses may have failed to record positive laboratory results.

The proportion of different target organisms causing IID identified in the population and presenting to GPs varied, and these proportions were different again from those were routinely identified in laboratories and reported to the national surveillance scheme.

This reporting pyramid was estimated to be steepest for SRSV where for every case reported to CDSC there were about 1,500 in the community. This is entirely

understandable, for four reasons: firstly, people experiencing mild symptoms in the community are much less likely to consult their GP; secondly, the GP, being motivated by clinical considerations, is much less likely to request a stool specimen for cases with mild short-lived illness; thirdly, unless a case is part of a known outbreak, the laboratory is unlikely to perform EM for SRSV; and, fourthly, even when a stool specimen is sent to the laboratory, the routinely available tests for SRSVs (EM) are less sensitive than the culture test used for detection of the common bacterial pathogens. In contrast, there were three cases of *Salmonella* infection in the community for each case reported to CDSC. This may be because a higher proportion of cases of salmonellosis than viral gastroenteritis consulted their GP because their illness was more severe, or because laboratory tests are more sensitive for salmonellas than SRSV, or because laboratory reporting to CDSC is more complete, or a combination of all three. Thus it would appear that severe cases of IID, that are mainly due to bacterial infection, tend to be less under reported than milder forms of IID mainly due to viral infection. It is worth noting that a consequence of this is that national laboratory surveillance is at its most efficient in identifying what matters most: the more severe end of the spectrum of IID, and, as it is bacterial, IID more likely to have resulted from the consumption of contaminated food.

Organism specific results from the direct and indirect estimating methods of completeness of reporting to CDSC were compared. The viruses appear to be poorly reported by both estimates compared with the bacteria. If it were true that outbreaks were the reason for the discrepancy between the direct and indirect estimates we would have expected it to be less for *Salmonella*, *Campylobacter* and rotavirus infections where outbreaks are relatively uncommon (5%, 0.04%, 0.4% percent of reports from outbreaks, respectively 1995 data) and rather worse for SRSV (47% of reports from outbreaks in 1995). This was indeed the case. Both estimates showed a similar reporting ratio for *Campylobacter* and *Salmonella*. The estimate from the indirect method was well within the confidence intervals for the direct method. With SRSV the discrepancy was even greater than we had anticipated. This is probably because the actual proportion of cases recorded as part of an outbreak is unpredictable, as EHOs usually obtain stool specimens from only very few cases in an outbreak. This is understandable, given that it is seldom possible to contact all cases, and that once the organism responsible for an outbreak is identified, it is reasonable to assume that other cases are due to the same organism if they are clinically similar. There may also be an artefactual trend in the reporting of outbreaks, since the number reported is increasing, particularly those due to viruses, which have increased 4-fold from 1992–96. The two-fold discrepancy between our two estimates of the under-reporting of rotavirus remains unexplained, as the few outbreaks associated with this virus are almost always localised outbreaks in young children, which should have been identified by both our direct and indirect estimates. The indirect estimate does, however, lie within the confidence intervals of the direct estimate, and the difference could thus be due to chance.

In summary, IID is very common in the community and presenting to GPs but only a proportion is reported to national surveillance, this figure varying by organism. This suggests that a primary care based sentinel IID surveillance scheme with microbiological testing is required to assist in the monitoring of trends.

### 10.3 RISK FACTORS FOR IID

Most existing information on IID risk factors is derived from outbreaks or sporadic cases reported to routine surveillance. Such cases may not reflect the generality of IID in the community or in primary care.

The data on risk factors in this study were based on a case control design in the GP study and a nested case-control design within the population cohort component. Cases and controls completed risk-factor questionnaires and provided stools. Matching of controls was quite high though not complete despite up to five attempts to obtain an appropriate control. Most cases and controls completed questionnaires and provided stools. Controls had a higher compliance than cases, probably as they had self-selected to participate in the study. As expected, compliance was even higher in the nested case-control study of the cohort. This design is less prone to selection bias than the GP study but the numbers of cases was smaller, limiting the power to detect significant differences. Risk factors of all IID were estimated from subjects in the GP case-control study, and risks by target organism from subjects in both the GP case-control study and the population cohort component study.

Despite the size of this study, it was not designed to demonstrate risk factors for specific organisms, or sub-groups of organisms, and the number of cases was too small to allow it to do so for many of the target organisms studied. Studies targeted specifically at certain organisms or toxins are required to obtain meaningful information on risk factors for these. However, the present study is unique in defining the relative numerical importance of the different organisms and toxins sought.

Social factors were associated with a higher risk of all IID, SRSV and rotavirus. The influence of social factors on viral IID was mediated by living in purpose-built flats or rented accommodation. Contact with another ill person outside the home was associated with higher risk for all organisms for which it was investigated (rotavirus, SRSV, *Salmonella* and *Campylobacter*). Contact with an ill child in the household carried a risk for rotavirus and SRSV. These findings highlight the importance of person to person spread of viral IID in the community.

Travel abroad was associated with higher risk of all IID for adults and children, IID with no target organism in adults, and *C.jejuni* and enteroaggregative *E.coli*. The effect was restricted to trips outside northern Europe, except for babies. Swimming was associated with lower risk of all IID in adults and in children.

As anticipated, breastfeeding was highly protective against all IID in infants. How the bottle was disinfected was also associated with risk of all IID.

The study showed no association between domestic practices and hygiene and an increased risk of IID. This may be because our case definition included all infectious intestinal disease, not merely that acquired from food.

None of the 50 hygiene practices and 10 hygiene beliefs showed a consistent association with risk. This lack of association could be an artefact, since hygiene practices and knowledge are notoriously difficult to measure, and we asked about normal practice, not practice in the days before illness. If real, the lack of effect could mean that the current levels of contamination of foods entering the domestic kitchen are so low that individual susceptibility is a more important determinant of sporadic illness than kitchen hygiene. Another explanation could be that most transmission occurs outside home.

Another unexpected finding was that reported consumption of very few foods was found to be associated with increased risk. For example, reported consumption of chicken and eggs was not associated with IID due to *Salmonella enteritidis* PT4. This could be an artefact: the study was not designed to provide precise data on food eaten. The questionnaire sought information on foods eaten in the ten days before the onset of symptoms, which is longer than the usual incubation period for

most food poisoning pathogens. This reduces the power of the study to identify food vehicles. Responses may have been biased (although cases would be more likely to bias their answers so as to implicate foods they consider to be risks, such as chicken and eggs).

Alternatively, it might give a truer picture of the overall risk of those foods. Contaminated chicken may, for example, cause many outbreaks, but few of the sporadic cases which account for 95% of the total and in that sense present a small risk overall.

A plausible explanation of our not finding an association between IID and most food types could include intermittent low dose contamination of many food types exists to a degree that would be insufficient to endanger most people's health. If this were the case, we could postulate that most sporadic cases result from eating one of a wide variety of lightly contaminated foods, rather than one of a narrow range of heavily contaminated foods with individual variation in susceptibility, rather than the type of food consumed, determining who develops disease.

In contrast, we found that a group of six foods was associated with a very consistent and statistically significant lower risk of disease. The effect typically reduced the risk of IID by between 30% and 70%. These foods were pulses, salad, fruit, rice, fish and pasteurised dairy products.

This could be artefactual, due to confounding factors: people who report eating these foods may have a lower risk of IID for reasons we did not measure, or measured imprecisely. Although this is unlikely because we collected and analysed comprehensive information about a large range of social, educational, and behavioural practices .

Alternatively, it could be due to selection bias: people who agreed to be a control in the study may have been more likely than cases to eat those foods. This is also unlikely, as a preliminary analysis of the data from the nested case-control study suggests that the effect is also present in this study. The community controls had a much lower refusal rate, lessening the likelihood of selection bias. It is unlikely that reporting bias caused this effect, as there is no widespread belief that the foods protect against diarrhoea. Reverse causation is a possible source of artefact, if people change their eating habits after their illness and fail to remember or deliberately misreport their consumption before they fell ill. If none of these biases exist, then these foods may actually reduce the risk of IID. Causal mechanisms for such an effect could include food consumption changing the intestinal flora (by exposure to other micro-organisms, fibre) or boosting general or specific immunity. Specific immunity could be boosted by repeated exposure to low dose of microorganisms in food. General immunity could be boosted by ingestion of micronutrients, particularly antioxidants, in food. Fruit and fresh vegetables are rich in antioxidants.

Interpretation of risk factors from the GP case-control study should be cautious for a number of reasons. Cases were atypical in that they presented to GPs so risk factors for contracting IID may be different from the average case. The fact that they were atypical in one respect, their presentation to GPs, introduces the possibility of confounding, and selection bias. In other words, the risks identified may be risks associated with presentation to GPs rather than with IID itself, and risks of IID even if correctly identified may be different in cases who present to GPs when compared with all cases occurring in the community. In addition, as many associations were sought, some may be statistically associated with IID merely by chance.

In summary, we found many differences between cases and controls; however we

were generally unable to demonstrate an association between specific food vehicles, or domestic hygiene practices and IID, even for organisms which are predominantly transmitted in food. Factors favouring person-to-person transmission were important in the acquisition to IID due to viruses. We found the consumption of certain foods to be associated with a lower risk of IID.

#### 10.4 COSTS OF IID

The cost questionnaire had a lower overall response rate, perhaps because it was a detailed questionnaire which coincided with the reminder for the main risk-factor questionnaire that had been sent three weeks before. However, the response rate from those who had responded to the risk factor questionnaire was high. Responders were representative, in terms of age and social class, of all cases in the study.

The overall national cost of predominantly community acquired IID was estimated at £745 million at 1994/95 prices. Of this total, 37% fell to the NHS, 8% to individuals and 56% were employment costs.

The costs of community cases who did not see a GP were low. This is because such cases generally had milder and shorter lived symptoms than those who saw a GP. The overall costs identified in our study appear to be lower than those estimated elsewhere. There are a number of possible reasons for this. Firstly, our study, unlike previous studies, was of a representative sample of all cases, including the mild cases not normally seen by the health services. Secondly, our study measured the costs of these milder cases to be less than many previous estimations. Thirdly, our study did not measure costs to the public health services from investigating IID apart from the costs of the laboratory tests. Fourthly, as our study did not include deaths, we have placed no value on the raised risk of mortality caused by illness. And fifthly, our study did not measure any of the costs due to outbreaks, which may involve more tests and more expensive tests and which will absorb more public health investigative resources.

NHS costs are mostly GP costs. They represent the opportunity costs of use of hard-pressed GP time but not directly representing financial outlay. Whilst average costs per case are useful for aggregating up to national figures, hospitals attempting to cost the impact of IID may be more interested in the cost of average cases presenting for treatment. The costs to in-patients are quite high and this study may have underestimated the hospitalisation rate for IID from general practice.

The largest item of cost is loss of time in paid employment. However, time off normal activities at home and leisure are not costed here.

The range of cost per case varied almost as much amongst cases with any particular organism as amongst cases infected by different organisms. The SRSV cases are the exception to this with short duration, fewer symptoms persisting at three weeks and lower costs.

People do appear to be willing to pay for safer food but this is an attitude study and it is not clear that this willingness would be translated into demand for safer goods at higher prices. The responsibility for food hygiene is placed firmly with National Government. Irradiated produce is viewed with suspicion by many although some might be convinced of its safety.

#### **Suggestions for the future:**

1. We suggest that consideration is given to raising public and professional

- awareness of the importance of viral gastroenteritis.
2. We suggest that consideration should be given to formulating advice to GPs on which cases they should obtain stool specimens from for microbiological testing to aid surveillance.
  3. We suggest consideration be given to setting up primary care sentinel surveillance schemes to monitor the aetiology of IID presenting to GPs and in the community in the longer term. The latter could entail repeated population based cohorts.
  4. We suggest national laboratory reporting should continue to develop, with particular emphasis on obtaining more complete reporting by laboratories. The system would also benefit from the addition of denominator data, i.e., the reporting of negative as well as positive tests, and linkage to primary care sentinel surveillance of clinical IID, and to the statutory notification of food poisoning.
  5. We suggest that consideration be given to a review of which organisms should be routinely sought in diagnostic microbiology laboratories for clinical and surveillance purposes, and that particular consideration be given to enteroaggregative and other enterovirulent *E.coli*, and viruses. Any review should address the issue of laboratory funding for tests whose main use lies in surveillance rather than in clinical management.
  6. We suggest urgent consideration of a scheme to require the statutory notification of laboratory identification of certain organisms.
  7. We suggest research to clarify the pathogenic role of some of the target organisms in the study, notably *Aeromonas* and *Yersinia*.
  8. We suggest that resources earmarked for the prevention of IID be targeted particularly at areas with social disadvantage and crowding as this is where most IID occurs, and therefore effective prevention in these areas promises the greatest health gain.
  9. We suggest that tour operators should ensure that travellers receive advice before travelling to high-risk areas. In addition, tour operators should be made aware of their obligation to monitor their providers closely to ensure that they maintain the best hygiene standards.
  10. We suggest that the national and international surveillance of travel associated IID should be developed so that problem areas can promptly be identified and investigated.
  11. We suggest that eating of pulses, salads, fruit and fish already recommended for the prevention of heart disease or cancers may also have a protective effect against IID.
  12. We suggest that efforts continue to be made to educate foodhandlers in the commercial and domestic setting of the necessity of scrupulous food hygiene, especially in the preparation of poultry, and foods such as salads which do not require heat treatment.
  13. We suggest that breast-feeding should continue to be promoted, and when it is not possible scrupulous care should be taken in the disinfection of bottles.

