

THE INFECTIOUS INTESTINAL DISEASE
(IID) STUDY
SEMINAR AND WORKSHOP
LONDON – 28 FEBRUARY 2000

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SESSION I: FINDINGS OF THE INFECTIOUS INTESTINAL DISEASE (IID) STUDY

Chairperson: Professor Douglas Georgala

PROFESSOR DOUGLAS GEORGALA:

This is the largest study of its kind to date and was a collaborative effort between the Medical Research Council (MRC), the Public Health Laboratory Service, the London School of Hygiene and Tropical Medicine and the Centre for Applied Microbiology and Research. General practices began to be recruited in 1993 and the collection of data was completed in 1996. A total of 70 practices covering a population of nearly 500,000 were involved. Nearly 10,000 individuals were studied for six months in order to find out about the incidence of IID in the community.

PLAN AND METHODS OF DATA COLLECTION:

DR DINESH SETHI

The case definition for infectious intestinal disease in our study was loose stools or significant vomiting (which is defined as going more than once in 24 hours or if incapacitating or with fever and cramps). Its duration was for less than two weeks and it had to be preceded by a three-week symptom free period. Other cases of diarrhoea or vomiting were excluded, such as inflammatory bowel disease or obstruction. The definition of the controls were that they were age and sex matched and of course they had no loose stools or significant vomiting for three weeks prior to this.

All cases and controls in the GP case control component sent items to Leeds Public Health Laboratory whereas in the enumeration component routine testing was carried out at the local laboratory. There was a priority staging for different microbiology tests from stage 1 to stage 8 depending upon the size of the stool specimen. To achieve stage 8 there had to be a 10-gram sample and 90% of specimens reached stage 8 in the analysis.

On the compliance and representativeness of the study the practice study population was 1% of England, and was reasonably representative. Cohort compliance in terms of the proportion that was recruited was 40%, and it was slightly lower amongst

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males and those aged between 15-24 years. The median adjustment to correct for predicted practice list inflation was 90%. 95% of the cohort component returned baselines questionnaires and the median 70% of cases returned questionnaires and 25% submitted stool samples in the general practice case control component. Controls were found for 75% of cases. There was higher compliance in the nested case control component and low compliance in males; those aged between 15-24 and in urban practices from the south east. In the socio-economic costs questionnaire 63% had also returned a risk factor questionnaire and they had similar characteristics so we think they were reasonably representative.

**RATES OF IID IN THE COMMUNITY, PRESENTING TO
GENERAL PRACTICE AND REPORT TO NATIONAL SURVEILLANCE
DR JOHN COWDEN**

We looked at over 4,000 person years of data, found 781 cases of IID, 20% of those when asked to look real time or prospectively at their illness said they had suffered IID, although when asked to recall the previous year 80% said they had had IID. Now the 20% translates into 9.4m cases per year in England. This 20% we believe is the more reliable figure and it is compatible with Hoogenboom-Verdegaal's study in the Netherlands, which was also prospective and came up with a figure of 18%. Our 80%, which we think is biased by recall, is similar to Roger Feldman's study in England which came up with a figure of 93% and Stephen Palmer's in Wales which came up with a figure of 89%.

I think there are at least two important messages. The first is that although small round structured virus is the least common in national statistics it is by far the most common cause of diarrhoea or infectious intestinal disease in the population. The second is that while campylobacter is the commonest reported cause of IID it is even more important at the GP level.

Our study was not of food poisoning or of foodborne disease, it was on infectious intestinal disease and rotavirus is almost exclusively spread from person to person and predominantly in the under fives. But nevertheless a loss to national surveillance is even greater for the viral pathogens where every rotavirus case reported to CDSC is the result of 35 in the population.

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**MICROBIOLOGICAL FINDINGS IN CASES AND CONTROLS:
DR DAVID TOMPKINS**

Back in 1992 we eventually decided on the microbiological tests that would give the maximum information from the single, small stool samples from each case and control which we would receive at Leeds Public Health Laboratory. We used well-established tests to pick up a wide range of potentially pathogenic bacteria, viruses, protozoa, helminths and clostridial toxins, and sent an aliquot to the PHLS Laboratory of Enteric Pathogens for DNA testing for enterovirulent *E.coli*.

We received hundreds of specimens – 2893 from cases and 2264 from controls in the GP case-control study and 761 from cases and 555 from controls in the population cohort study (which includes people who went to the GP). SRSV (Norwalk-like virus) were the most common target organism in cases in the community, with *Campylobacter* and Rotavirus more common than SRSV in cases presenting to GPs. Rotavirus was the most common organism in under 5's in the GP study. In other words, we found the organisms which caused more severe disease (*Campylobacter*, *Salmonella*, Rotavirus) were more frequently present in those cases who went to see their GP.

Some target organisms e.g. *Aeromonas*, *Yersinia*, some *E.coli* were found as frequently, or more frequently, in controls than in cases, suggesting that some of these organisms were not causing disease.

The overall positivity rate was 37% in the population cohort study and 55% in the GP case-control study. So with all the different tests used we still got quite high negativity rates. Why was this? I think I should emphasise that figures we obtained for positives were comparable with a number of other studies that have been carried out. Our figure of 12% of GP cases having *Campylobacter* is higher than that in other UK studies. A number of different factors could have contributed to the cases with negative findings. Some cases, within the case definition, may not have actually had IID.

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**RISK FACTORS FOR IID:
DR LAURA RODRIGUES**

This was a case control study and we had cases occurring in the community. These are people who would not normally have stool specimens taken, so they are much closer to the total universe of cases of diarrhoea than the usual cases that studied. A lot of what we know about causation of diarrhoea is based on outbreaks and people who have severe enough disease to have stool specimens taken in the course of routine investigation. So this is a critical bit of information about our findings and I think it would help us interpret that.

For adults, of the social factors we found lower social class increased risk and that became a higher risk after travelling was controlled for. So richer people have more diarrhoea because they travel internationally, when you take that away then poverty is more of a risk factor. Surprisingly people who are in part time employment have much lower risk.

In terms of decreased risk, shopping for food in a supermarket once a week was associated with lower risk, owning a food processor and that was also associated with eating more home prepared food and vegetables but even when we controlled food aspects the lower risk stayed.

Having a cat, dog or rabbit were all associated with a lower risk and we're trying to investigate this a little further. When you consider people without diarrhoea, but with organisms in their stools, pets are a risk. So this is early days but maybe having a pet increases your risk of having the organism without the disease and may, to some degree, be protective.

In terms of food we were not able to identify a major burden of disease associated with food consumption.

Question:

I was a GP in one of the practices taking part. Dr Cowden quoted a figure that only 69% of positive results from labs reporting ordinary GP samples were reported as a statutory notification. One reason for this may be some uncertainty as to whose responsibility it is to make the notification. We used to do it in general practice, then we were told that we needn't do it because the lab was doing it and then sometime

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later we realised, without our having been told, that the lab was no longer doing it and we'd better start again.

Answer:

I think we must make a distinction here between the Statutory Notification of Food Poisoning which is the responsibility of the medical practitioner who suspects the diagnosis and that will fall primarily to the general practitioner and the voluntary reporting of positive isolates. I think that is, unquestionably, the responsibility not of the GP but of the laboratory.

Question:

Have you been able to work out anything about combinations of factors that are in the diet, rather than any specific factor? Have you had a chance to look at that?

Answer:

No, we didn't look at whether the diet was right. What we looked at was to see if the effect that we find with pulses and salad and fruit was to do with eating less chicken. So we looked separately at whether this was just a marker for consumption of less of the suspected risk factors and we didn't find that.

Question:

When you were conducting your questionnaire, did you attempt to find out anything about the food handling knowledge of the people who were ill or the controls; whether they were a professional food handler, whether they'd received training?

Answer:

We did have a large section of the questionnaire on hygiene practices, things like separate chopping boards, how they stored fruit in the fridge and care with separating cooked and raw foods. We explored that exhaustively and there was no statistically significant effect at all. But there was no question about professional food handlers and we didn't explore cooks or restaurants, which seems to appear much more frequently as a risk factor.

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Question:

I wonder if you took the very best samples, what the yield is then? Because otherwise it is rather remarkable that in the majority of faecal samples from people with infectious diarrhoea, we don't know what the causative organisms are.

Answer:

The median delay in sending the samples was not very great but if we looked at the overall spread I think it is something like up to 43 days between one specimen being taken and arriving in a laboratory. So you wouldn't expect to get very much from a specimen that had been 43 days in the post for whatever reason. We did look at the effect of delay on campylobacter and salmonella isolations. From memory I would say that it didn't actually make much difference up to about seven days and then there was certainly a drop off in positivity rates after about a week's delay. I think that the vast majority of the specimens that we got were within the seven days.

Question:

What about those with raging diarrhoea, what proportion of those do you get a good organism from?

Answer:

We haven't done an analysis, obviously we've yet to talk about the archiving, but it would be possible to go back and look at symptoms and see who had the most severe symptoms and look at the isolation rates in those individuals and we haven't done that analysis yet.

Question:

I think there's two ways of looking at the positivity/negativity and I would say that in the GP component positivity was pretty high and in fact it was 55%, which is much higher than many other studies. Perhaps on that point, I could put a question and that would be how does that compare with positivity rate in normal diagnostic tests in a laboratory and I would estimate that it was a lot higher.

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Answer:

Yes it is higher. Obviously the range of organisms that you would be looking for in normal diagnostic practice would be much more limited than the ones we were looking for. In most diagnostic laboratories you would only be looking for salmonella, shigella, campylobacter and *E. coli*O157 in all diarrhoeal specimens, perhaps hospitalised patients for *Clostridium difficile* and rotavirus in the under-fives and that's about it really, unless you've got indications that someone's travelled or might have food poisoning. I think overall laboratories would expect to get something like a 20-25% positivity rate, but it's a different set of organisms that they are looking for and a different set of specimens.

**THE SOCIO-ECONOMIC COSTS OF IID:
DR JENNY ROBERTS**

Our aims for the socio-economic impact were really to find the cost to the healthcare sector, hospitals and primary care and cost to the cases and their families. We did this by sending a questionnaire at three weeks.

We asked the people at three weeks, how the illness had affected their daily living. We chose the number of days of activity that were impaired because of the illness as our measure of the impact.

We were surprised at the duration and severity of some of the illnesses and we found that the cost of illness associated with bacteria was higher than those associated with virus. Those who saw a GP were ill, on average, for nine days, those who did not, for four days.

Here are the costs for organisms. Salmonella is top of the pops, coming out at about £600 per case, then *Campylobacter*, then all enterovirulent *E. coli*. I must reinforce that this is not *E. coli* O157. Had we had more cases of O157 that cost would have been considerably higher, it works out at approximately £10,000 per case.

Direct costs to cases were similar with salmonella still leading. Lost employment is where we find most of the costs arising.

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For the share of the costs in the GP cohort, the NHS costs were about 25% of the total burden. In the community survey it was higher and that I think is explained by the fact that we had more of the hospitalised cases in that group.

**LONG TERM FOLLOW UP:
DR PAUL RODERICK**

We aimed to follow up all cases and controls in the components of the study to pick out clinical sequelae and the consequence to the NHS and to individuals.

We knew that IID was associated with various clinical sequelae. We looked at reports of Guillain-Barre associated with campylobacter and haemolytic uraemic syndrome with verocytotoxic *E. coli*. We discussed with some gastroenterologists, whether IID could be a trigger for Inflammatory Bowel Disease, and we didn't know at the time that it could be a trigger for or be associated with Irritable Bowel Syndrome. We also didn't really know the chronicity of the symptoms. We say acute IID, but how long did it last?

We searched GP's notes at three months looking at all consultations after the very acute phase, up to three months. Also any referral submissions to hospitals where we tried to chase up with the hospital for the diagnoses made, for example reactive arthritis. All these data were re-coded.

What happened at three weeks? Diarrhoea was the most common persisting symptom with about a quarter of cases still complaining of diarrhoea. Compared to their controls, the risk was six fold increased in all ages, and this persistence occurred in all ages. So diarrhoea persists and in both components of the study not only diarrhoea, but vomiting also persisted to a lesser degree, as did abdominal pain and loss of appetite.

What happened at three months? There was a slight excess of musculoskeletal problems, though it wasn't significant, about 1.2 fold increase.

We then tried to chase up the hospital referrals. There were 17 Irritable Bowel Syndrome cases at the GP level but most of those were not referred to hospital so the diagnoses there are relying on the GP notes. There were four cases of query Inflammatory Bowel Disease and a couple of them were referred to hospital. But we

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have no confirmation that they had Inflammatory Bowel Disease. We found no excess of any other condition. We had no clinical diagnoses of any reactive arthritis or any neurological problem.

But I think what we can say is that after what appears to be an acute episode of IID, symptoms do persist certainly for three weeks and longer. This leads to excessive GP presentation, some excess hospital referral and from the point of view of your last speaker, obviously an associated impact in terms of cost to the NHS and patients.

**ARCHIVING OF DATA AND ISOLATES:
MIKE HUDSON**

A sample of some 4-5 grams was sufficient to take samples to Stage 4 and perhaps Stage 5, which would cover most of the important enteric pathogens or target organisms, as they are called in the report. Right down at the bottom of the priority list is archiving a portion of that stool specimen for a rainy day, for those unforeseen investigations that might turn up later in the day and for that purpose we needed a stool sample in excess of 9 or 10 grams.

I want to emphasise that only 0.2g of stool was archived in a 1ml tube for logistic purposes, otherwise it would have needed two freezers, which does rather minimise what can be done with this particular archive of specimens.

About three years ago we decided to have a look at how well common pathogens would survive in these stool specimens. We can see with the *Salmonella* there's a relatively small loss of viability, perhaps a little surprising. But all of these specimens are preserved with glycerol and in an optimised system. In contrast, *Campylobacter* survived much less well, so very quickly we saw a fall in numbers of two three and four orders of magnitude, according to the specimen. *E. coli* O157 decline is intermediate between these two organisms.

So what are we going to do with these specimens and isolates? The obvious advantage to study now is that we can apply, with some confidence, DNA technologies like the polymerase chain reaction (PCR) to search for new target organisms, to look for new genotypes and, as mentioned this morning, genotypes of *Cryptosporidium*.

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For the isolates, here we are not constrained by the size of the specimen. We have an endless supply of these organisms because we can subculture them and set down new stocks. We can use these isolates for comparison with new typing methods, for determination of pathogenic subsets, particularly for organisms such as the *Aeromonas*, some of the enterovirulent *E. coli* and the *Yersinia* that we failed to differentiate between cases and controls. We can also look at other properties of these isolates such as antibiotic resistance.

More immediately we need to work out the best strategies for isolating the nucleic acid, the DNA and the RNA, to give the best recovery of genetic material for identification of novel enteropathogens from these specimens and some of these studies are ongoing at present. We need to continue to monitor viability if culture is going to be an option for further study.

Question:

A comment and question. A comment first for Dr Hudson. I notice you listed antibiotic resistance or antimicrobial resistance testing as one of the future studies. I would just say that based on some of our experience in our national antimicrobial resistance monitoring system that could be something that's quite valuable especially now as agricultural and veterinary use of antibiotics changes.

The question I have is for Dr Roberts, one finding you showed was the difference in the duration of illness between those who sought care and those who did not. I think clearly some of that or all of it is difference in level of severity of illness. Are you able to look at a subset of patients who were treated and look at who received antimicrobials and who didn't and whether that changed the duration of their illness?

Answer:

Basically, the way we collected the information was such that we asked them if they'd had any prescriptions for their illness. We didn't get specific enough details of what had been prescribed to enable us to do that study. We could, however, go back to GP notes as part of our longer-term database searches to find out such things. There didn't seem to be an awful lot of evidence of any prescribing to do with the illness.

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Question:

Can you tell us how the cost per case for the various organisms compares with previous studies either in the UK or elsewhere?

Answer:

Well, it is very difficult. If we're doing an epidemiological study of cost of illness we have certain things that you can get much more accurately in terms per case than if we had an outbreak costing. But an outbreak costing would enable us to estimate, for example, the cost to industry or public health laboratory investigations, etc. So in that way it might be more comprehensive. In terms of the studies in the US, we do estimate things slightly differently although it would be possible now that I have those who saw the GP and those who don't to co-ordinate much more closely with Tanya Roberts' work and be able to make better comparisons.

Question:

I wonder if you could tell me a bit more about the data archive that you mentioned, which is registered with the University of Essex. When will it be available, who will it be available to. Are there restrictions on access and do we have to register to get into it?

Answer:

I was responsible, as a statistician, for doing the archiving. It should be available about a month after the main report's published. In terms of access, you have to register with the archive and say what you want to use the data for. Then the Food Standards Agency will have a look at that. Basically there won't be any restriction but it will just be looked at by the Food Standards Agency.

Question:

You talked very much about economic costs, there are obviously social costs and you mentioned quality of life issues. Did you attempt in any way to quantify pain, suffering if there was a mortality, the cost of mortality and grief associated with it?

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Answer:

I went for activity of daily living, how they were feeling, what they could do, rather than more subjective things like pain. The six month's questionnaire and part of the IID questionnaire does include the SF36 so that we should be able to find out how people are feeling. Transferring that into some kind of quality of life index that includes a value to pain and suffering, we haven't been able to do.

SESSION II:

IID AND THE INTERNATIONAL PERSPECTIVE

GASTROENTERITIS IN THE UNITED STATES:

DR THOMAS VAN GILDER, CDC ATLANTA

I want to discuss briefly this afternoon, FoodNet which is the foodborne diseases active surveillance network, I want to give you a description of it and its major projects and findings so far. Particularly how it is ascertained with diarrhoeal illness and foodborne diarrhoeal illness in the US. I also want to present the updated estimates for overall gastrointestinal illness and food related morbidity and mortality in the US and then describe briefly the role of PulseNet which is the national molecular sub-typing network for foodborne diseases.

The geographical distribution of FoodNet covers a population of about 28m, which is roughly 11 or 12% of the US population.

The active surveillance component of FoodNet looks at seven bacterial pathogens, *Campylobacter*, *E. coli* O157, *Listeria*, *Salmonella*, *Shigella*, *Vibrio* and *Yersinia*. We also have two parasitic organisms under surveillance, cryptosporidium and cyclospora and three syndromes, haemolytic uraemic syndrome, Guillain-Barré Syndrome and congenital toxoplasmosis.

When FoodNet began we started with a list of 230 clinical laboratories that we thought captured all of the diarrhoeal specimens in the FoodNet catchment area. In 1997 we repeated the survey this time in a larger area. We had seven sites at that time. We had 310 clinical laboratories and at that time they reported that all stool specimens sent to them were routinely cultured for salmonella and shigella.

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In 1996 we undertook a physicians' survey which was an attempt to understand physician practices in the FoodNet catchment areas in the US. This survey asked physicians about the last patient they saw with diarrhoea, whether they get a culture and then asked about various characteristics of the patient to see if that changed the likelihood of the physician obtaining a stool culture. Generally we found that about 44% of physicians ordered a stool culture on the previous patient they saw with diarrhoea. That went up to 77% when the patient reported bloody diarrhoea and was more or less than 44% depending upon whether the patient had had a travel history or had clear contact with another person with diarrhoea or was involved in a known outbreak.

A sizeable percentage of people report engaging in what we would term risky food eating behaviour, preferring pink hamburger and runny eggs. But we did find that 90% reported washing their hands after handling raw meat or poultry. We were at least encouraged that the message was out there.

One of the main purposes of FoodNet was to address the general burden of diarrhoeal illness but specifically of foodborne diarrhoeal illness in the country. We wanted to generate both pathogen-specific and overall estimates of foodborne illness and gastrointestinal illness.

In the population at hand we observed 37,000 illnesses due to salmonella. This was actually based on the old system, the passive reporting system for salmonella which comes in through the laboratories and that number has been declining slightly but

37,000 is where we were a couple of years ago. This number is well up in the estimates that FoodNet would generate for a population-based burden of salmonella based on stimulated passive laboratory reporting.

Using the hospitalisation rates and applying them to the pathogen-specific numbers we get the numbers of 8,000 and 290 for total hospitalisations and number of deaths. We came up with a doubling factor of two for salmonella, for hospitalisations and fatality rate leading to an annual estimate of 16,000 hospitalisations and 580 deaths due to salmonella infection. Then based on our estimate of 95% foodborne transmission for salmonella we get a burden of foodborne related salmonella infections to be about 1.3m, roughly 15-16,000 hospitalisations and 550 deaths.

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We did that procedure for each of the known foodborne pathogens and as you can imagine the variable quality of data and variable intensity of surveillance makes those estimates variably reliable.

If we move then into an effort to identify the unknown agents and the characteristics of the diseases that are caused by agents, as yet unknown. We start with again the overall burden, which we estimate to be 211m illnesses per year and 937,000 hospitalisations and 6,400 deaths and subtract from that known pathogens, we end up with figures for the number of illnesses caused by unknown agents.

This leads to an overall burden of foodborne illness being again 62m in the unknown agents and 14m among known agents. Which gives us our total of 76m illnesses due to foodborne transmission of known and unknown pathogens.

Overall conclusions were that there were more illnesses than previously estimated but fewer deaths. A large proportion of foodborne illnesses are due to unknown agents.

So future work that remains is to follow trends and explain the variations that we see, specifically within FoodNet because we have a captive population, but even overall. We also would like to refine our surveillance data for known pathogens and do a better job of capturing some of the sequelae that follow some of these infections.

I want to just take a couple of minutes to mention PulseNet, the national molecular sub-typing scheme that has been set up at CDC. It is an effort to improve the infrastructure of laboratory surveillance in the US and also add the element of modern technology to it. We started with *E. coli* O157, we have some standards for salmonella, shigella and listeria and those are going to grow on an annual basis. It allows the standardised testing of isolates and the use of molecular finger printing. Currently we are using pulsed field gel electrophoresis, but that will almost certainly change. We are looking at ribotyping for *Listeria* and we'll certainly be able to take advantage of the DNA sequencing technologies that are just round the corner.

Question:

You have vast distances between the various states that you're looking at, do you have considerable differences between the data for the various organisms?

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Answer:

We do see quite a lot of regional variation for a number of the organisms, in particular *Campylobacter* and *E. coli* O157 and then *Yersinia* as well and that's been an area that we've really tried to explore recently. One of the strengths of FoodNet, I think is our collaboration with the regulatory agencies, particularly with USDA which allow us to compare their sampling of slaughterhouses and retail sampling with some of our human illness. For example for *Yersinia*, some of the dietary patterns of the south eastern United States are substantially different than other parts of the country. Particularly the patterns that are risk factors for *Yersinia* infection are higher in the south east than elsewhere. They are reflected in a higher incidence of *Yersinia* infections in the south east.

**GASTROENTERITIS IN THE NETHERLANDS:
Yvonne van Duynhoven, RIVM**

I have used the abbreviations (NIVEL) for the GP based study and SENSOR for the cohort study in the Netherlands.

I would like to start with the general practice based study. Before this most recent study two previous studies were performed in the past. The first one was performed in the period 1987-1991. This was mainly a type of a pilot study to study whether it was feasible to estimate gastroenteritis through general practices. There were two urban areas involved in this study and the incidence that was found was 150 per 10,000 person years. It basically looked at three bacteria: *Campylobacter*, *Salmonella* and *Shigella* and these were found in 14%, 5% and 2% respectively. After this study was done, we repeated it on a national level. This was done in 1992-93 and we used the general practice network from the NIVEL (the Netherlands Institute of Primary Healthcare). It is the same network that was used in the study I am going to talk about this afternoon. The incidence that was found in this national study was 90 per 10,000 person years, so it was somewhat lower, but the detection of pathogens was quite similar to the first study.

Since these last studies, it became more and more clear that a lot of other pathogens are involved in causing gastroenteritis and therefore we wanted to repeat this study. Also because there were some measures, mainly in the veterinary sector in the poultry to reduce the number of salmonella infections in poultry and they wanted to

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know whether that had any effect on salmonellosis observed in human cases. Finally we wanted to identify risk factors for some pathogen-specific gastroenteritis.

For the study we used the general practice network of the Netherlands Institute of Primary Healthcare. This institute incorporates a network of about 40-45 general practices in which 60-65 practitioners are active. The practice population of this network is representative for the Netherlands with regard to age, sex, geographical distribution and degree of urbanisation. The coverage is about 1% of the Dutch population.

The crude incidence that we found in our study was 58 per 10,000 person years, but of course we knew that there should be some under-ascertainment in this enumeration by the general practitioners. We used some information from our population based cohort study to estimate the percentage of list-inflation and then we arrived at the final estimate of 80 per 10,000 person years.

In the Netherlands we saw some regional differences and the northern part of the Netherlands showed lower incidence than the western and the eastern part of the Netherlands.

Almost half of the cases had to stay in bed because of their illness, for a median duration of two days. Also there was some absence from day-care, school and work because of illness and it varied between 41% for those who attended day-care, to 60% for those who are working and the median duration was two or three days.

56% of the cases used some kind of medication, and these were mainly anti-diarrhoea drugs. Antibiotics were very seldomly used.

Similar to the IID study, *Campylobacter* was the leading cause of gastroenteritis in general practices in the Netherlands. Other important pathogens were rotavirus, Norwalk-like virus and salmonella but we also saw a great amount of giardia. However, giardia was also relatively often observed in controls.

Overall in about 40% of the cases the pathogen could be found and in about 10% of the controls (we exclude a lot of parasites that we observed but it is still under debate whether they are pathogenic or not).

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The aims that were planned for this study were to estimate the incidence, the pathogens and the burden of the disease in the community, to estimate the ratio of patients in the population consulting their general practitioner and to study characteristics that are related to consultation of a GP.

The study population of this SENSOR study is an age-stratified sample from all the registers of the NIVEL practices that were willing to participate. The sample size that we needed was based on the two most important study questions, the age-specific incidence estimates and the estimate of the incidence ratio for the population and the GP. The basic goal was to achieve at least 2,310 person years of follow-up and that would make it possible to estimate the age-specific incidence with a precision of 10% and a ratio with a precision of 20%.

The data collection was performed between December 1998 and December 1999 and it was a cohort study with a nested case control study, like the IID cohort component.

If we look at the response rate, overall we were surprised it was 42% and we expected 35% similar to the previous Dutch study. The 50% presented, published for the pilot IID study was considered the real maximum and for the invitations we used the worst case scenario, so we expected a response rate of 35%. In the first cohort it was 44% and therefore we adjusted the number of invited individuals for the second cohort and then it was slightly lower, 40%, mainly because of the summer holidays.

We have a total follow-up period in the Netherlands of 2,293 person years and the crude incidence that comes out of this is 436 per 1,000 person years.

What we want to do for the future is to make these preliminary results into definite results and get them published as soon as possible. Furthermore we want to identify risk factors for some specific pathogens, especially the viruses and some of the parasites are of interest. We want to also study the role of torovirus in the cases and in the controls. It is still under debate whether it plays a role, there are some publications recently that state that it might be important. We don't know but we are able to look into it because we have also stored the remainder of samples in a faeces bank. We want to do a cost of illness study with this data and we want to study all the follow-up samples that we have of cases and of the controls.

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SESSION III:

THE FUTURE DIRECTION FOR IID SURVEILANCE AND RESEARCH

WORKSHOP I: MICROBIOLOGICAL ASPECTS OF IID

RAPPORTEUR: DR MIKE HUDSON

- **It was recognised that several putative pathogens were not sought in the study as 'Target Organisms', including:**
 - ◆ Enterotoxigenic *Bacteroides fragilis*
 - ◆ *Listeria monocytogenes*
 - ◆ some enterococci
 - ◆ some of the protozoal parasites (e.g. microsporidia)
 - ◆ several viruses
 - ◆ anaerobic spirochetes

All of these need to be better defined as pathogenic or non-pathogenic organisms.

A measure of dysbiosis, i.e. the change from a balanced to an unbalanced flora, could be useful inasmuch as it might help define those patients that were ill for a particular reason.

For stored specimens with a negative result, it is not clear whether they are negative because the micro-organisms that were looked for were not there at all or that the numbers present were below the level of sensitivity for the methods used. A measure of the lack of sensitivity might be calculated by carrying out more research and by reviewing the literature.

Q2: Where are the priorities for future work on isolates and faecal specimens? Should this be a traditional microbiological approach or a molecular approach?

Priorities for the isolates:

- The isolates are essentially a long lasting resource inasmuch as we can regenerate the archive by subculture.

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- The pressing need is to apply modern genotyping methods i.e. the type of methods that were not established in 1993 when the methods used for the IID study were agreed
- The initial focus should be on *Campylobacter*
- Further work needs to be carried out on enterovirulent *E.coli*, e.g. Enteroaggregative *E.coli*, which is a very heterogeneous group, to identify other virulence factors and study their epidemiology in more detail

Priorities for the faecal specimens:

- The faecal specimens should be left untouched until appropriate methods for extracting the bacterial, viral and protozoal nucleic acids present are established/optimised
- There is also a need to formulate the best questions for use of the archive, such that best use is made of this very small and precious resource

Q3: Do we look only for microorganisms that we know are associated with IID or should we look for other organisms as well (e.g. Listeria)

It could be worth looking for the following:

- Mycobacteria
- Toxoplasma
- Lactobacilli intake as probiotic supplements and what effect they do or don't have on gastroenteric symptoms.
- Genotyping of *Cryptosporidium* present in specimens positive for that protozoon.

The following discussion points were raised:

Comment:

Just a very general comment on how sensitive the methods were in this study and I think we sort of got our gold standard usage. I was thinking certainly on the stored samples where you have got a negative result, whether they are negative because

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the pathogens that we have been looking for weren't there, or were below the level of sensitivity. That was an issue which we didn't discuss at all and I wonder whether we ought to address it at some point.

Panel Member:

You mean that we ought to do studies with the methods that we used in comparison with other methods to determine the sensitivity of the methods that we used.

Reply:

We used electron microscopy for viruses as a catch-all method, although at the time we started the study I don't think the PCR methods had been developed to the extent that they are now. In fact, as is actually quoted in the report, some specimens from the IID study were tested by Dr David Brown (CPHL, PHLS) using a PCR method and we found that the electron microscopy method used was 70% sensitive in comparison with the PCR. We accept that the PCR only picks up 90% of the strains that were circulating in the UK at that time. We used a wet prep and we also used the formol ether method for concentration of giardia, so we could ask what is the comparison of that with the method that has been used for the study in the Netherlands? I am sure there must be published evidence on that, or using ELISA techniques, so that we could see what the sensitivities are. So to a certain extent by trawling the literature a bit more carefully than we have done so far, or by doing a bit more work, we could actually work out some of the lack of sensitivity.

Comment:

We've talked a lot about organisms that we might have to consider that we haven't found because there's this quite large proportion in which no pathogenic organism was found. What is the general view on those organisms which are thought to be pathogenic but in this study were found to be more common in the controls than in the cases. By the same logic should we forget about them and if we shouldn't, why not?

Reply:

I'm not going to answer for the *E. coli*, because I think Henry Smith (CPHL, PHLS) could perhaps answer that. I think as regards things like *Yersinia* and *Aeromonas*,

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well we know that if we looked at the symptom profiles of *Aeromonas* and *Yersinia* in the study, that some of the cases did have severe symptoms with those organisms. I think that we accept that there are subsets of pathogenic types within the whole group. With some organisms e.g. *Aeromonas*, we've done the analysis with all isolates lumped together, we haven't even separated the analysis into different species. Then with the *E coli* we've actually gone for enterovirulent types, so in a lot more detail. So I think we really need to go into those organisms like *Aeromonas* and *Yersinia* in a lot more detail. We haven't mentioned virulence factors as a high priority on this list, because the feeling of the microbiology group was that the virulence factors are not so clearly defined yet that we can actually apply them. So we've got to wait until someone gets good virulence factors to apply to the archived material.

As regards *E. coli*, I wouldn't like to comment on that.

Comment:

I'll just make a comment about the *E. coli*. I think the isolates give us excellent opportunity to look at these further, for example the Enteroaggregative *E. coli* which came out as really quite a surprising observation and were in a higher percentage than salmonella in the case control study. Those are a very heterogeneous group and we need to look at those further to identify other virulence factors, look at their epidemiology in more detail as well, so I think there is a lot of scope there.

I think the other question that needs to be asked, and will come out in a more detailed analysis is that some of this information needs to be looked at very carefully in relation to the age data. You get quite significant associations with different groups and particularly very young children that are so different from the older age groups. That is an analysis question which will have to be resolved. But we do need to look at both the *E coli* and some of the other organisms but I think that although the question really is prioritising what will be done on the isolates which is a resource that can be kept going for quite some time.

Comment:

Could I just make a suggestion of future studies, the exploitation of outbreaks of unknown aetiology? If you think about the yield that you'd get from those rather than

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from sporadic cases, I think O157 was identified because of an outbreak, SRSVs have been established from outbreaks. I think we should think about targeting outbreaks of unknown aetiology for our high powered microbiology, perhaps rather than, if it is a choice, going for the sporadic cases.

WORKSHOP II:

IID SURVEILLANCE AND TOOLS FOR SURVEILLANCE

RAPPORTEUR: PROFESSOR BILL REILLY

Q2: While the IID study provided useful baseline data, the way forward is more likely to be with ongoing sentinel studies

Sentinel schemes would be intended to monitor trends at national and regional level and would not necessarily detect local outbreaks. Sentinel studies don't have a role in local management but it is vital they retain local interest. They would supplement existing national routine surveillance data.

Integration maximises effectiveness.

One of the best ways to supplement national surveillance data is to integrate the information with animal and food data. As well the importance of integration in surveillance, the second take home message was that surveillance is for Action. It should be '**SMART**': **S**pecific, **M**easurable, **A**ction-Orientated, **R**ealistic, and **T**imely.

Q2: Discuss new opportunities for gathering surveillance data, especially for milder infections (e.g. NHS Direct)

- Need to be sure why we want to collect new information, particularly on the milder infections, and
- Need to be sure that new data collected will supplement existing laboratory data and outbreak data

NHS Direct had been identified as perhaps one way forward and there was some feeling that this would be a way of getting a handle on some of the softer data that would be underpinned by laboratory data. This type of system might be of value in gathering flu data, for example, if people are being directed away from GPs. The following suggestions were made:

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- Make better use of GP IT systems
- Make better use of web based technologies - perhaps there is a role for a local, regional and national web based surveillance system.
- Need to consider new approaches as to how we look at IID – perhaps looking at food purchasing practices as against food consumption might be an opportunity for generating new hypotheses.

Again integration is important with the sentinel systems, we have to be sure that people are using the same definitions and the same methodologies so that we have consistency.

Q3: How can we improve the data we gather through routine surveillance, especially with respect to travel associated illness

It was concluded that this was needed to exclude confounding factors with UK-acquired data so there could be targeted intervention not only in the country where the imported infection had been acquired but also to allow primary prevention measures to be used appropriately within the UK. This information could be gathered through, for example, the travel industry (through customer-satisfaction reports) or through insurance claims.

- Integrate routine surveillance data, data from humans, from animals and from food

Integration also featured in improving routine surveillance such as integration of antibiotic resistance data that are available from animals and from food. Here the message of common methodologies and definitions and comparing like with like are crucial.

Q4: How can we “tease out” food poisoning from the background of all IID

- **It is difficult to separate out food poisoning from IID**

The question “what is food poisoning?” was raised, and the suggestion was made that the notification of food poisoning needs to be fundamentally reviewed. There was some, but not universal, support for a concept of measuring IID and not measuring food poisoning at all. It was suggested that one way of separating out

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food poisoning would be to improve the design of surveillance systems to identify outbreaks because these are an extremely important source of knowledge. And through the integration of routine surveillance data from humans, animals and foods, we would also be able to quantify the sources of foodborne disease.

The following discussion points were raised:

Comment:

Food poisoning has got a definition, which is any disease of an infectious or toxic nature caused by or thought to be caused by the consumption of food or water. I think the problem comes down to the fact that whatever we as the bean counters regionally and nationally think food poisoning is, the GPs who do the notifying have no idea what it is or what we think it is. So the notification of food poisoning has to be fundamentally reviewed.

Reply:

I think question 4 may be difficult but it is very important. The ACMSF's first task that it set itself in about 1990 was to define what food poisoning was and it took it two years and eventually it did it. I think it is very confusing to say there are 9m cases of IID a year, but we don't know how many of them are due to food. Unless we can give some idea, people are going to say there are 9m cases of food poisoning a year, and that is going to be very confusing. I'd like to know how many of these diseases are due to the consumption of food or how many of them meet our definition of what food poisoning is. At least that would be a start.

Comment:

The ACMSF, under its Scottish Chairman, Heather Dick, recommended the same definition for England and Wales as for Scotland. It failed because, until at least 1995, the Scots were stripping campylobacter infections out of their food poisoning statistics. The ACMSF may have defined food poisoning to its own satisfaction and to the satisfaction of epidemiologists nationally, but I have yet to meet a GP who knows there is a definition and I would challenge anybody to produce a GP who could recite that definition. That is not what they are notifying.

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Reply:

That's not the fault of the ACMSF, with great respect there are a lot of people who don't know that the ACMSF exists, including virtually everyone outside this room. That's a failure of communication not a failure of the definition and if you're going to do a study the first thing that you want to do is get everybody that participates to understand the definition.

Comment:

We're talking about surveillance rather than the study. I am not suggesting that it is the ACMSF's fault, but I am suggesting that any epidemiologist who puts any great confidence in the trends illustrated by the food poisoning graph is deluding himself.

Reply:

I think if my memory serves me correctly, the discussion in the ACMSF was about redefining foodborne disease and in fact the phrase 'food poisoning' was dropped to enable the broadest focus. Foodborne disease was a working definition to focus people's minds on what food could do in terms of health and I think in that sense it has been useful and it allowed us to include campylobacter. The fact that Scotland stripped it out was I'm afraid outside of the ACMSF's responsibility.

Comment:

The ACMSF may like it to be foodborne disease rather than the term 'food poisoning' but that is the term used in statute and it's a Statutory Notification of Food poisoning. A cardinal characteristic of the food surveillance system is that it must be flexible and the surveillance system based on primary legislation is not flexible and whether the ACMSF wants it to be foodborne disease it is still, in statute, food poisoning.

Comment:

We have tremendous continuous changes in food consumption patterns. Food is being traded more widely and more rapidly than ever before, we've got bigger production units where if something goes wrong you could have a mass of people at

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risk. I think everybody involved in this should try and keep food as a focus even though it is extremely difficult, from a surveillance point of view, to pinpoint it.

Comment:

If I acquired SRSV from direct contact with someone here today and then went home to my wife and prepared a meal for her, how would anyone be able to differentiate if my wife acquired SRSV from me directly or by food? In those circumstances, for certain organisms, I think it would be very difficult to actually say whether something was caused by foodborne disease or direct contact.

Reply:

That is an example where you may not want to differentiate but in an episode of projectile vomiting in a food factory where, for example sandwiches are being made, it could immediately expose hundreds of people to the food acting as a vehicle. So all I am pleading is that we keep the food role either as a vehicle, as a multiplying component, for example in salmonellas on a warm day, we try and keep that as high in our visibility as possible.

Reply:

Now I would suggest, that back to question four it should be stated that one of the ways that one could separate out food poisoning was to improve the design of surveillance systems to identify outbreaks because outbreaks is an extremely important source of knowledge. We should think about using modern technology, both typing methods and electronic ways of detecting outbreaks in order to enhance our knowledge and then these outbreaks should be investigated and there are a number of methods of doing that.

Then of course another thing is that we integrate routine surveillance data and in an intelligent way use data from food and from animals then we would also be able to quantify the sources. The day's experience clearly shows that with an integrated surveillance system we are able to quantify the sources of salmonella. So far we haven't been able to do that for campylobacter because the epidemiology is different. But at least for salmonella and probably also VTEC these methods are available. So it is difficult, but it is possible and it should be stated.

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**WORKSHOP III: RISK FACTORS FOR IID
RAPPORTEUR: PROFESSOR STEPHEN PALMER**

Q1: What further studies are required to investigate the apparent differences between risk factors for sporadic cases and outbreaks?

Concern was raised about the over-interpretation of associations from case control studies and the danger of misleading the public by giving wrong messages, or exposing ourselves to misinterpretation. The essential point about case control studies is that when they're "fishing expeditions" they tend to be difficult to interpret and can at best only generate hypotheses. Analytical studies, however, where a hypothesis is specified clearly, precisely and specifically ahead of time, can test those hypotheses. When designing a case control study it is important to involve experts from the food and environmental side in defining these hypotheses.

Priorities for further studies:

- The role of cross-contamination in sporadic cases
- Focus on susceptibility as opposed to the exposure
- "Protective" effect of fruit needs to be explored

Q2: Discuss the significance of foods found to be associated with a lower risk of disease – is there a protective role for certain foods?

Concern was raised about using the word 'protective' and about using the idea of causation when the associations, although statistically significant, are but one of a number of factors that need to be taken into account. Biological plausibility also needs to be specified ahead of time. So we say remember the criteria for causation but keep an open mind, don't close our minds to the interesting data. Allow it to stimulate our thought, to challenge our preconceptions, but bear in mind that statistical significance is but one of a number of factors and take that into account.

Q3: Are case control studies the best way of addressing further work on risk factors relating to individual target organisms?

Once the hypothesis is specified clearly, case control studies are very useful. If you want to know what steps need to be taken, for example, to change people's

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behaviour making them eat fruit to decrease their risk of food poisoning, intervention studies need to be considered at the appropriate time.

Q4: How do the findings impact on risk communication and what messages do we need to get over to the public?

A lot of caution was expressed in how the findings are translated into messages to the public. We also need to bear in mind that this study was set to test the surveillance system and it has succeeded in doing that and that's the main finding of the study. The risk factor study was an add-on study and it is not powered to test specific hypothesis, even salmonella in eggs can't be tested with any robustness in the sample size that was identified. Therefore you cannot draw messages from it, you can only draw hypotheses which need to be tested in the future. We must not over-interpret the findings. The study wasn't set up to draw public health messages about the aetiology of foodborne disease. Some of the findings were very unexpected, for example, there was an apparently protective effect in eating runny eggs. Similarly, bathing in fresh water is known to be associated with gastroenteritis, but in this study it was, apparently, protective and we must be very cautious about how this is presented to the public. A surprising find of the study was that we failed to implicate any of those vehicles which we know to be important from outbreaks, that is not to say that the result of outbreak investigation is wrong, but that this study failed to implicate those foodstuffs in sporadic cases. However, the study did show that 9m people a year are victims of IID, that a large proportion of them are viral infections and that many of those will be involved in the commercial handling of food, in which hundreds of thousands of people are engaged. The concept that something like SRSV is very common and can be transmitted by food besides person-to-person contact is a very strong message.

The following discussion points were raised:

Comment:

I support what Dr Palmer has just said insofar as we have to be cautious. I would like to be reassured that there are going to be some messages that go along with this report that actually take on board the issues that we've discussed. We've got these significant results, but we have contrary public health messages and I feel the public health professionals should be ready with messages to put across.

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Comment:

I think we should separate very clearly generating hypotheses. I think there's a risk that if we don't separate those things clearly we lose out on interesting hypotheses that were generated from the research. I think they are very good hypotheses, I think they are very interesting data, but I agree that this is not testing previous hypotheses and there are not conclusions to go out for public health recommendations.

Question:

If we were to say, well actually this part of the study was an attempt initially to tease out what was foodborne and in that it failed, but it generated some interesting hypotheses, would that explain it?

Answer:

I think that understates its ambition. It wasn't merely to try and tease out what was foodborne and what wasn't it was to try and tease out how people got their IID, the whole gamut of things. I wouldn't say it failed but I would say it was only partially successful.

Answer:

I think it clearly indicates the situation is more complex than we thought and I think that's a great success. If we go on overestimating how much we know we're further from being able to intervene successfully. So I think recognising that we know less than we think, marking out the limits of what we don't know, I think is a success.

Comment:

If in fact this very large study appears to reject a number of very clear outbreak-based observations, for example, if food is contaminated with salmonella, it's kept warm and it's eaten by quite a few people, then you get an association with the food. In other words we must be very careful not to undermine the established intervention on which a large part of safety processes are already based. I think there's a heavy responsibility on how we carry on this debate, identifying where it is at a research

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level, but be very cautious about kicking out what large parts of the industry have built up.

Reply:

I think what we know about outbreaks is very clear and is right and I think our messages are very right but I think we might have more confidence to cross over and extend to milder disease. I think there is a lot of IID that is originated from food, I just don't think for example that under-cooking is as important as cross-contamination. I agree with you that it would be very bad if people came up with the idea that hygiene practices are not important and that the microbiological safety of food is not important, I think it is very important that that message stays out there. I think that we've recognised that what we knew doesn't explain all the cases and there's more that we need to know to be able to prevent all cases.

Comment:

It is true that we failed to implicate a large number of traditionally suspect foods but what we are not saying and I agree with Professor Georgala, we don't want to be seen to be saying, is that we have exonerated them. Failing to implicate them and exonerating them are two different things and that's where we have to be careful. I don't think any of the investigators are sitting here saying foodborne disease is not important because we didn't show it to be important. We certainly failed to implicate many of the traditional food vehicles but we are not exonerating them.

**WORKSHOP IV: THE CLINICAL PERSPECTIVE -
HOW THE FINDINGS MIGHT INFLUENCE GP PRACTICE
RAPPORTEUR: DEBBIE ANDERSON**

Q1: Discuss current GP practice criteria for sending stool samples for routine laboratory testing

Current Practice is:

- Variable
- Dependent on whether the GP feels it will affect patient management
- May be affected by the severity of symptoms
- Has resource implications

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The clearest message that came across was that the current practice for sending stool specimens for routine laboratory testing was very variable, and to the extent that it probably varied from partner to partner within any one given practice. The issues involved surrounded whether or not the GP felt that it would actually affect patient management. If it wasn't going to make any difference to their management then the GP may not be so inclined to send off a specimen. The decision would be likely to be affected by the severity and duration of the symptoms. GPs made the point that there would be a huge resource implication if they were to send off all samples they suspected to be IID. That said, there remained the need to identify the causes of outbreaks.

- **It was clearly recognised that there is a difference between what the GP does because it will affect patient management and what the GP does in the interests of surveillance**

It was agreed that the purposes of taking specimens for clinical reasons are if it alters patient management. The distinction between clinical management and surveillance (or research) needs to be drawn. For surveillance it would be useful to have a system whereby GPs took specimens from patients on the basis of its statistical representativeness, irrespective of the clinical management. So they would take a sample of, for example, 1 in 10 of the people presenting to them with a particular case definition. If we are to take such a scheme forward, like research, it should be funded. GPs should be clear which specimens are being sent to the laboratory for clinical reasons and which ones they are taking for surveillance purposes. This dual role could be carried out by sentinel practices perhaps rather than across the board. It was also suggested that the current system of spotter practices could be extended so that we have a broader base of them rather than trying to get every practice to partake in the surveillance aspects.

- **GP guidelines for sampling stools should improve the yield of organisms**

What is clear from the IID data is that GPs do actually discriminate quite well and select those specimens to send that are likely to yield organisms. We have a great data resource that could be used for the basis of actually defining those parameters of infectious intestinal disease that make it more likely that pathogens will be found and this should be promoted as a priority.

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Q2: Is there a need to develop clinical criteria (based on patient profiles) for use when deciding to send stool samples for laboratory testing

The overriding response was that there is a need to develop clearer guidelines and these should encompass the following criteria so that GPs are actually all doing the same thing:

- Guidelines of when it is *not necessary* to send samples for laboratory testing
- Clear standardised guidance on what advice GPs should give to patients
- Better case definitions of IID
- Clear risk assessment guidelines which are based on current evidence

Q3: Consider the need to follow-up the long-term consequences of IID

There was support for funding further work on the link with IID and irritable bowel syndrome and other long-term consequences of IID such as Guillain-Barré syndrome.

The following discussion points were raised:

Question:

Did you have any discussion on who might be the most appropriate bodies/individuals/groups for looking at that sort of guideline and drawing it up and getting something that was generally acceptable?

The Prodigy Project, which is an IT-based guideline system for GPs, is in the process of drawing up guidelines for gastroenteritis. The problem I think is that there are a number of systems that are being set up for GPs and one of the problems is that not all GPs have access to, or I gather from speaking to GPs locally in Leeds, are really IT-conversant enough that they want to use these type of guidelines. But they are in the process of drawing these guidelines up and there will be datasheets present that people can download from the guidance site to actually give out to patients.

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Comment:

I think there'd be a great advantage in arriving at some guidelines for when stools can profitably be sampled in order to improve the yield of organisms. What is clear from the IID data is that GPs do actually discriminate somehow and select those specimens to send that are likely to yield organisms. But what we do have here is a great data resource that could be used for the basis of actually defining those parameters of infectious intestinal disease that make it more likely that pathogens will be found and I think this should be promoted as a priority.

Question:

Have you got any preliminary observations from the study of the indicator factors that might actually help?

Answer:

We do have those data but they were not analysed; this was not part of the objectives . But the data are there so we do have data for symptoms and organisms and whether it is possible to define symptoms, correlations that indicate what likely pathogens are in the stool, how likely it is to be positive, and then of course whether that changes treatment.

Comment:

I am sorry to intervene again but on this guideline thing, it seems to be me that there's a clean difference between everyday clinical practice and research. There is no point in everyday clinical practice, I suggest, in doing tests if this is not going to influence management. It's just going to waste the money. If you're doing it for research it has to be funded and the reason you're doing it has to be clearly drawn up.

Comment:

I would prefer to draw the distinction between clinical management and surveillance. For the surveillance, it would be nice if we could have system whereby GPs took specimens from patients on the basis of its statistical representativeness, irrespective

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of the clinical management. They would take a sample of say 1 in 10 of the people presenting to them with a particular case definition. But I also agree that if we do that, like research, it should be funded and the GPs should be clear which specimens are going off for clinical reasons, which I wouldn't dare to advise them on, they're much better at that than I am, but also which ones they are taking for surveillance purposes. I think that would be a nice solution in sentinel practices perhaps, not across the board.

Meeting closing comment:

I'd just like to reflect that we've had an overview of the study and I think that's demonstrated the sheer complexity of the study both in terms of what has been analysed and what remains to be analysed. Clearly there is work that is ongoing, the long term follow-up, the question of what to do with the samples and the isolates and more analyses of a rich mine of data.