The Second Study of Infectious Intestinal Disease in the Community

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On behalf of the IID2 Study Executive Committee
IID2 Study: Main research questions

- Principal research question: –
  - Has the incidence of IID in the community changed since the mid 1990s?

- Secondary research questions: –
  - What is the aetiology of IID in the community?
  - How much IID is acquired abroad?
  - How do molecular methods compare with traditional methods for IID diagnosis?
  - By how much do national surveillance data underestimate the community burden of IID?
  - Has the picture in England changed?
  - What is/are the “best” research method(s) for determining IID incidence in the community?
Prospective Studies

Study 1

Study 2

Prospective Cohort
88 General Practices (UK)

Study 3

GP Presentation Study
(collecting samples from every case)

37 General Practices (UK)

Study 4

GP Enumeration Study
(observing current clinical practice, not necessarily collecting samples in every case).

40 General Practices (UK)

Study 5

Validation Study

Study 6

Microbiology Study (Laboratory-based)

State of the art tests

Routine tests at local laboratory

Pos

Neg

Study 7

Calibration Study (National reporting study)

Official Statistics

Yes

No

Retrospective Study

Telephone Survey
Case definition

- People with
  - loose stools or clinically significant vomiting
  - lasting less than two weeks, in the absence of a known non-infectious cause
  - preceded by a symptom-free period of three weeks.

- Note: Vomiting was considered clinically significant if it occurred more than once in a 24-hour period and if it incapacitated the case or was accompanied by other symptoms such as cramps or fever.
Exclusion criteria

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

<table>
<thead>
<tr>
<th>Duration of recall period</th>
<th>Incidence in IID1</th>
<th>Widest acceptable confidence interval</th>
<th>Number needed to survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days</td>
<td>6%</td>
<td>4%</td>
<td>500</td>
</tr>
<tr>
<td>7 days</td>
<td>1.5%</td>
<td>1%</td>
<td>2,500</td>
</tr>
</tbody>
</table>

Allowing for differentials in response rate it is suggested that the number needed to survey is increased by 20% i.e. to 600 for recall over one month and 3,000 for recall over one week.
To estimate a single UK-wide pyramid, detecting a 20% change in incidence of severe disease (baseline incidence = 6%) with 80% power and 95% precision

<table>
<thead>
<tr>
<th>Country</th>
<th>Person-years of follow-up required</th>
<th>Practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>7,000</td>
<td>70</td>
</tr>
<tr>
<td>Wales</td>
<td>400</td>
<td>4</td>
</tr>
<tr>
<td>Scotland</td>
<td>700</td>
<td>7</td>
</tr>
<tr>
<td>N. Ireland</td>
<td>300</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8,400</strong></td>
<td><strong>84</strong></td>
</tr>
</tbody>
</table>
Microbiological methods

- **Primary diagnostics** (Manchester)
  - **Culture:** *Campylobacter jejuni/coli*, *Escherichia coli* O157, *Listeria monocytogenes*, *Salmonella* species, *Shigella* species and *Yersinia* species
  - **Immunooassay:** *Clostridium perfringens* enterotoxin, *Clostridium difficile* enterotoxin, *Cryptosporidium* and *Giardia*, and in children < 5 yrs Rotavirus and Adenovirus 40, 41
  - **Light microscopy:** *Cyclospora*
Microbiological methods

- **Reference work** (Centre for Infections, London)
  - Generate DNA and cDNA from the samples.
  - Archive samples and nucleic acid.
  - Perform molecular testing for selected microbial targets (*Campylobacter jejuni/coli*, *Clostridium perfringens*, *Clostridium difficile*, *Listeria monocytogenes*, *Salmonella* species, rotavirus, norovirus, sapovirus, adenovirus, astrovirus, *Cryptosporidium*, *Giardia* and *E. coli* (Enteroaggregative, VT1 & VT2)).
Definition of positive laboratory results

- For all organisms (except norovirus and rotavirus) tested by quantitative PCR
  - A CT value <40 considered positive
- For norovirus and rotavirus
  - A CT value <30 considered positive
Analysis

- Age-sex standardised incidence rates
  - Community cohort
  - GP Presentation Study
  - Telephone Survey (7-day and 28-day recall)
  - NHSD/NHS24
- Organism-specific incidence rates
- Rate ratios comparing incidence in prospective studies with rates in national surveillance data
- 95% confidence intervals
Rates of IID in the community – telephone survey

<table>
<thead>
<tr>
<th>Recall period</th>
<th>Cases</th>
<th>PY</th>
<th>Crude rate (95% CI)</th>
<th>Adjusted rate (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 days</td>
<td>300</td>
<td>212.2</td>
<td>1413.9 (1262.6 - 1583.3)</td>
<td>1529.6 (1135.1 - 2112.6)</td>
<td>2.9 (1.8 - 4.6)</td>
</tr>
<tr>
<td>28 days</td>
<td>107</td>
<td>158.4</td>
<td>675.5 (558.9 - 816.5)</td>
<td>533.2 (377.0 - 777.5)</td>
<td></td>
</tr>
</tbody>
</table>

N = 14,726 (7-day recall = 12,381; 28-day recall = 2,345)
Participation rate ≈ 48%
Rates of IID by UK nation – telephone survey

<table>
<thead>
<tr>
<th>Country</th>
<th>7-day recall</th>
<th>28-day recall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>England</td>
<td>1,463.4</td>
<td>(994.3 - 2,246.5)</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1,269.9</td>
<td>(932.4 - 1,774.9)</td>
</tr>
<tr>
<td>Scotland</td>
<td>2,052.9</td>
<td>(1,444.2 - 3,020.1)</td>
</tr>
<tr>
<td>Wales</td>
<td>2,066.4</td>
<td>(1,578.5 - 2,758.8)</td>
</tr>
</tbody>
</table>
Rates of IID in the community – cohort study

86% of the maximum achievable follow-up time
Participation rate ≈ 10%

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>PY</th>
<th>Rate</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude rate</td>
<td>1,201</td>
<td>4658.6</td>
<td>257.8</td>
<td>(243.6 - 272.8)</td>
</tr>
<tr>
<td>Age-sex standardised rate</td>
<td></td>
<td></td>
<td>274.3</td>
<td>(253.8 - 295.8)</td>
</tr>
</tbody>
</table>

IID affects ≈ 1 in 4 members of the population annually
Comparing the telephone survey and cohort study

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Onset 1-2 weeks before interview</th>
<th>Onset 3-4 weeks before interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone Survey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-day recall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day recall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort Study</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cases per 1000 person-years
Rates of IID presenting to primary care

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>PY(^a)</th>
<th>Rate(^b)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite cases</td>
<td>5,546</td>
<td>312,232</td>
<td>17.7</td>
<td>(14.4 - 21.8)</td>
</tr>
<tr>
<td>Definite and probable cases</td>
<td>5,968</td>
<td>312,232</td>
<td>19.1</td>
<td>(15.7 - 23.2)</td>
</tr>
</tbody>
</table>

Participation rate = 57%
History of foreign travel

- Cohort study = 8%
- GP Presentation Study = 12%
Incidence of consultations for IID in calls to NHSD/NHS24

<table>
<thead>
<tr>
<th>Age group</th>
<th>England Rate</th>
<th>(95% CI)</th>
<th>Wales Rate</th>
<th>(95% CI)</th>
<th>Scotland Rate</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>6.1</td>
<td>(6.1 - 6.2)</td>
<td>3.6</td>
<td>(3.5 - 3.6)</td>
<td>14.3</td>
<td>(14.3 - 14.4)</td>
</tr>
</tbody>
</table>
Percentage of calls to NHS Direct by outcome of call, England and Wales

<table>
<thead>
<tr>
<th>Call outcome</th>
<th>England</th>
<th>Wales</th>
</tr>
</thead>
<tbody>
<tr>
<td>999</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>A&amp;E</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>GP</td>
<td>39.6</td>
<td>37.9</td>
</tr>
<tr>
<td>Home Care</td>
<td>54.1</td>
<td>56.5</td>
</tr>
<tr>
<td>Other</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>All outcomes</strong></td>
<td><strong>100.0</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Triangulating rates around presentation to primary care

Cases per 1000 person-years

- 7-day recall
- 28-day recall
- Cohort study
- GP Presentation study
- Enumeration study
- Weekly returns service 2008

IID2 Telephone survey
IID2 Study
RCGP
Incidence of IID presenting to general practice by age group: Estimates from the Cohort and GP Presentation studies
Incidence of IID-related consultations to NHS Direct: Estimates from the Cohort study and NHS Direct
Reporting pattern for overall IID, UK

Community

Presenting to
general practice

Reported to
national
surveillance

Ratios to
national
surveillance

274
(253-295)

17.7
(14.4-21.8)

9.5
(7.7-11.7)

147
(136-158)

1.9
Comparing IID1 and IID2 in England

- IID2:
  - Community: 277 (255-303)
  - Presenting to general practice: 16.9 (13.8-20.8)
  - Reported to national surveillance: 1.9

- IID1:
  - Community: 194 (181-208)
  - Presenting to general practice: 150 (138-163)
  - Reported to national surveillance: 1.5

Ratios to national surveillance:
- IID2: 9.1 (7.4-11.2)
- IID1: 33.1 (29.4-37.5)
Incidences rates of IID presenting to general practice: Estimates from RCGP Weekly Returns Service, IID1 and IID2

<table>
<thead>
<tr>
<th></th>
<th>Weekly returns service 1996</th>
<th>Weekly returns service 2008</th>
<th>GP Presentation study</th>
<th>GP Presentation study</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCGP</td>
<td></td>
<td></td>
<td>IID1 Study (England, 1993-4)</td>
<td>IID2 Study (England, 2008-9)</td>
</tr>
</tbody>
</table>
Absence from work or school

 IID1 Study
 IID2 Study

Percentage of community cohort cases

Absence from work / school
Consulted GP

IID1 Study
IID2 Study
Reporting patterns for *Campylobacter* spp.
Reporting patterns for *Salmonella* spp.

- **IID1**
  - 2.2 (1.1-4.3)
  - 1.6 (1.2-2.1)
  - 0.6

- **IID2**
  - 0.7 (0.2-3.0)
  - 0.2 (0.1-0.5)
  - 0.13

- Ratios to national surveillance
  - 3.8
  - 2.7
  - 1.6
  - 1.4
  - 0.6

- Presenting to general practice
  - 5.6 (1.4-22.4)
  - 1.4 (0.6-3.4)

- Reported to national surveillance
  - 1.6 (1.2-2.1)
  - 1.4
  - 0.6
Reporting patterns for norovirus

IID2

Community

Presenting to general practice

Reported to national surveillance

Ratios to national surveillance

0.16

12.8 (8.7-18.8)

315 (255-389)

1025

IID1

Ratios to national surveillance

41.0 (34.0-48.0)

123

4.9 (4.3-5.5)

0.04
Reporting patterns for rotavirus

<table>
<thead>
<tr>
<th>IID2</th>
<th>12.8 (8.5-19.5)</th>
<th>1.3 (0.8-2.0)</th>
<th>0.29</th>
</tr>
</thead>
<tbody>
<tr>
<td>IID1</td>
<td>7.1 (4.8-10.4)</td>
<td>2.3 (1.8-3.9)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Ratios to national surveillance

Community Presenting to general practice Reported to national surveillance
Norovirus 2,905,278

Rotavirus 783,737

Campylobacter 571,949

Salmonella 38,606

GP consultations 128,022

Laboratory reports 7,735

49,404

6,430
Study Limitations

- Power and person-years of follow-up
- Participation rates and compliance
- Case definition for IID
- Questionnaire submission and stool sample submission
- Definition of positive stool samples
- Inaccurate recall and digit preference
- Sampling within households
- Inability to perform data linkage
Study Strengths

- Cohort and GP Presentation studies
  - Information on aetiology without which cannot calibrate national surveillance data
- Telephone survey
  - Cheaper than a cohort study
  - Incidence rates for each UK nation
- Prospective and retrospective methods side by side
How do the numbers stack up?

- ≈ 17 million cases of IID per year in the UK (around 1 in 4 of the population)
  - Norovirus ≈ 3 million cases
  - Campylobacter ≈ 500,000 cases
- 1 million cases present to General Practice
  - Norovirus ≈ 130,000
  - Campylobacter ≈ 80,000
- Estimated school/working days lost
  - 18.8 million
  - 11.4 million in people of working age
And what about in England?

- Rate of overall IID in the community ↑ by 50%.
- Rate of IID presenting to primary care halved.
- Ratio of cases reported to national surveillance to cases in the community changed.
  - 1:85 in IID1 to 1:150 in IID2
    - Salmonella, 1:4 to 1:6
    - Campylobacter, 1:10 to 1:10
    - Norovirus, 1:1000 to 1:300
What next?

- Food-related IID
  - Norovirus
- Trend monitoring
  - IID3?
    - Longitudinal prevalence?
- Campylobacter control
- Community-acquired *C. difficile*?
The Team

- Medical Research Council General Practice Research Framework
- UK Primary Care Research Networks
- Universities of Manchester, Cardiff, East Anglia, Glasgow & Nottingham
- London School of Hygiene and Tropical Medicine
- Health Protection Agency, Health Protection Scotland, Public Health Wales, Public Health Agency of Northern Ireland
- NHSD/NHS24
Acknowledgments

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- Department of Health (Northern Ireland)
- Scottish Government
- Welsh Office for Research and Development
- North West MREC
- 37 R&D Organisations
Questions?