



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

Retrospective Study

Study 1

Telephone Survey

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**

Study 7

**Calibration Study
(National reporting
study)**

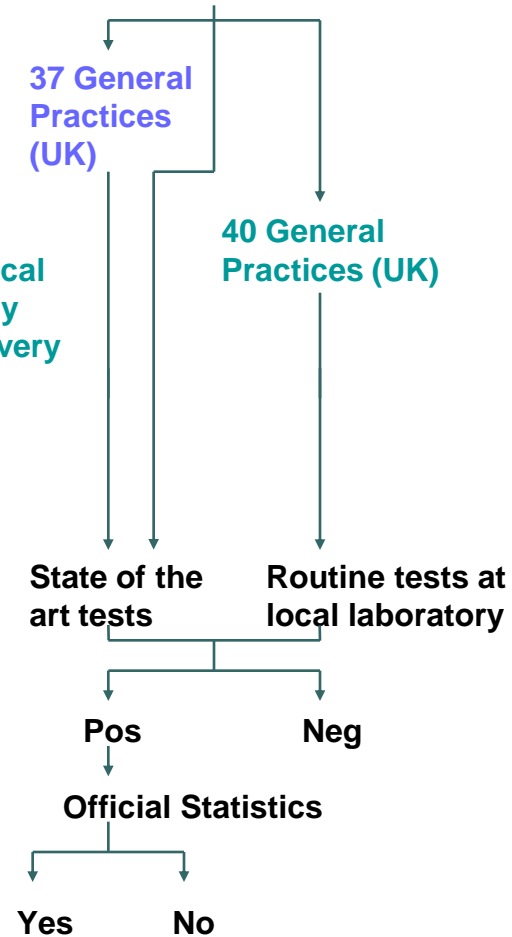
Pos

Neg

Official Statistics

Yes

No



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)

Duration of recall period	Incidence in IID1	Widest acceptable confidence interval	Number needed to survey
28 days	6%	4%	500
7 days	1.5%	1%	2,500

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.

Sample size (cohort study)

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

Country	Person-years of follow-up required	Practices
England	7,000	70
Wales	400	4
Scotland	700	7
N. Ireland	300	3
Total	8,400	84

Microbiological methods

- **Primary diagnostics** (Manchester)
 - **Culture:** *Campylobacter jejuni/coli*, *Escherichia coli* O157, *Listeria monocytogenes*, *Salmonella* species, *Shigella* species and *Yersinia* species
 - **Immunoassay:** *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* (Enterohaemorrhagic, 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

Recall period	Cases	PY	Crude rate		Adjusted rate		RR	(95% CI)
			Rate	(95% CI)	Rate	(95% CI)		
7 days	300	212.2	1413.9	(1262.6 - 1583.3)	1529.6	(1135.1 - 2112.6)	2.9	(1.8 - 4.6)
28 days	107	158.4	675.5	(558.9 - 816.5)	533.2	(377.0 - 777.5)		

N = 14,726 (7-day recall = 12,381; 28-day recall = 2,345)

Participation rate \approx 48%

Rates of IID by UK nation – telephone survey

	7-day recall			28-day recall	
Country	Rate	(95% CI)		Rate	(95% CI)
England	1,463.4	(994.3 - 2,246.5)		449.4	(279.8 - 766.7)
Northern Ireland	1,269.9	(932.4 - 1,774.9)		801.8	(512.9 - 1,324.9)
Scotland	2,052.9	(1,444.2 - 3,020.1)		1,195.5	(756.4 - 2,007.0)
Wales	2,066.4	(1,578.5 - 2,758.8)		661.6	(397.6 - 1,183.5)

Rates of IID in the community – cohort study

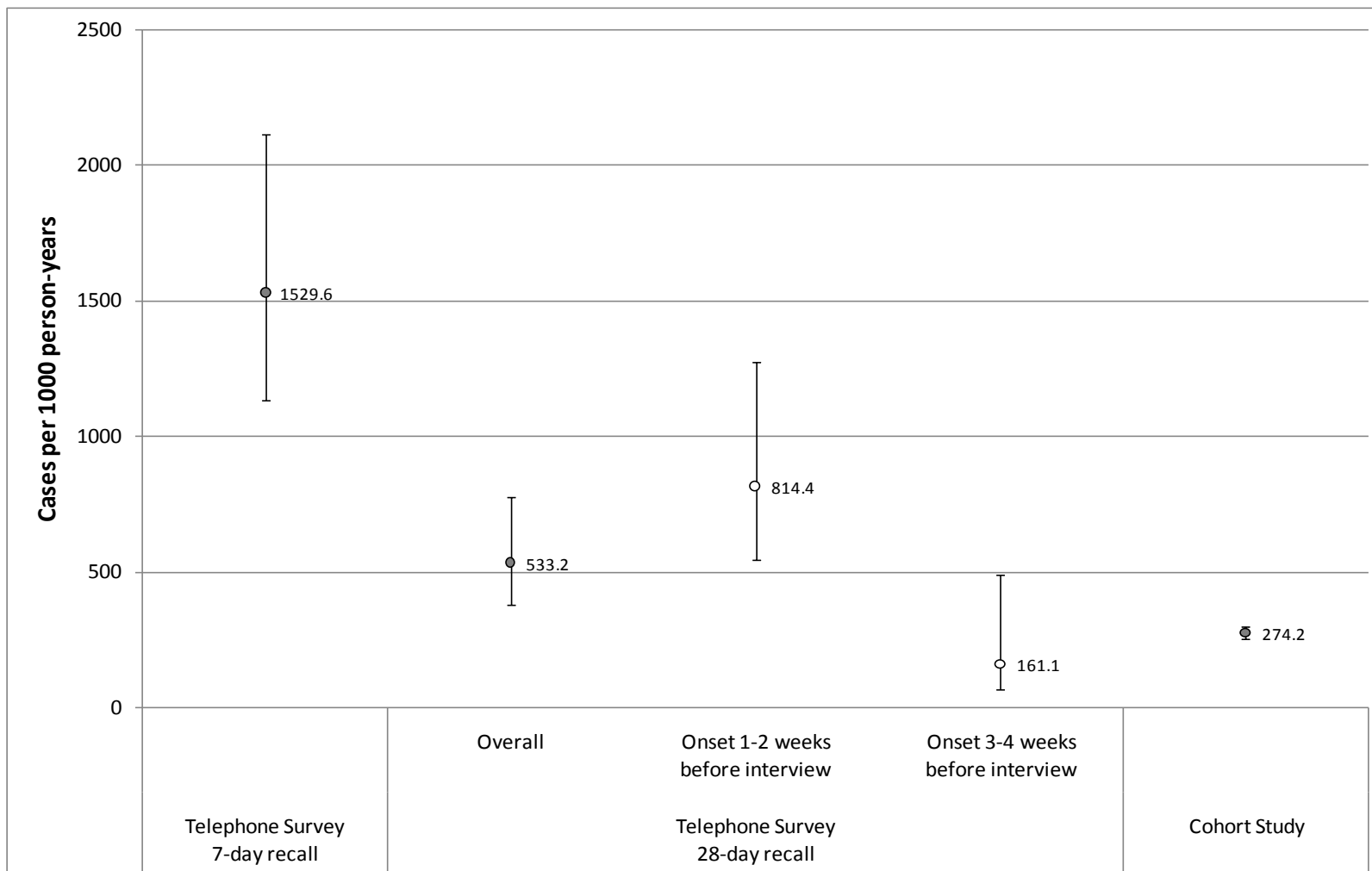
	Cases	PY	Rate	(95% CI)
Crude rate	1,201	4658.6	257.8	(243.6 - 272.8)
Age-sex standardised rate			274.3	(253.8 - 295.8)

86% of the maximum achievable follow-up time

Participation rate \approx 10%

IID affects \approx 1 in 4 members of the population annually

Comparing the telephone survey and cohort study



Rates of IID presenting to primary care

	Cases	PY ^a	Rate ^b	(95% CI)
Definite cases	5,546	312,232	17.7	(14.4 - 21.8)
Definite and probable cases	5,968	312,232	19.1	(15.7 - 23.2)

Participation rate = 57%

History of foreign travel

- Cohort study = 8%
- GP Presentation Study = 12%

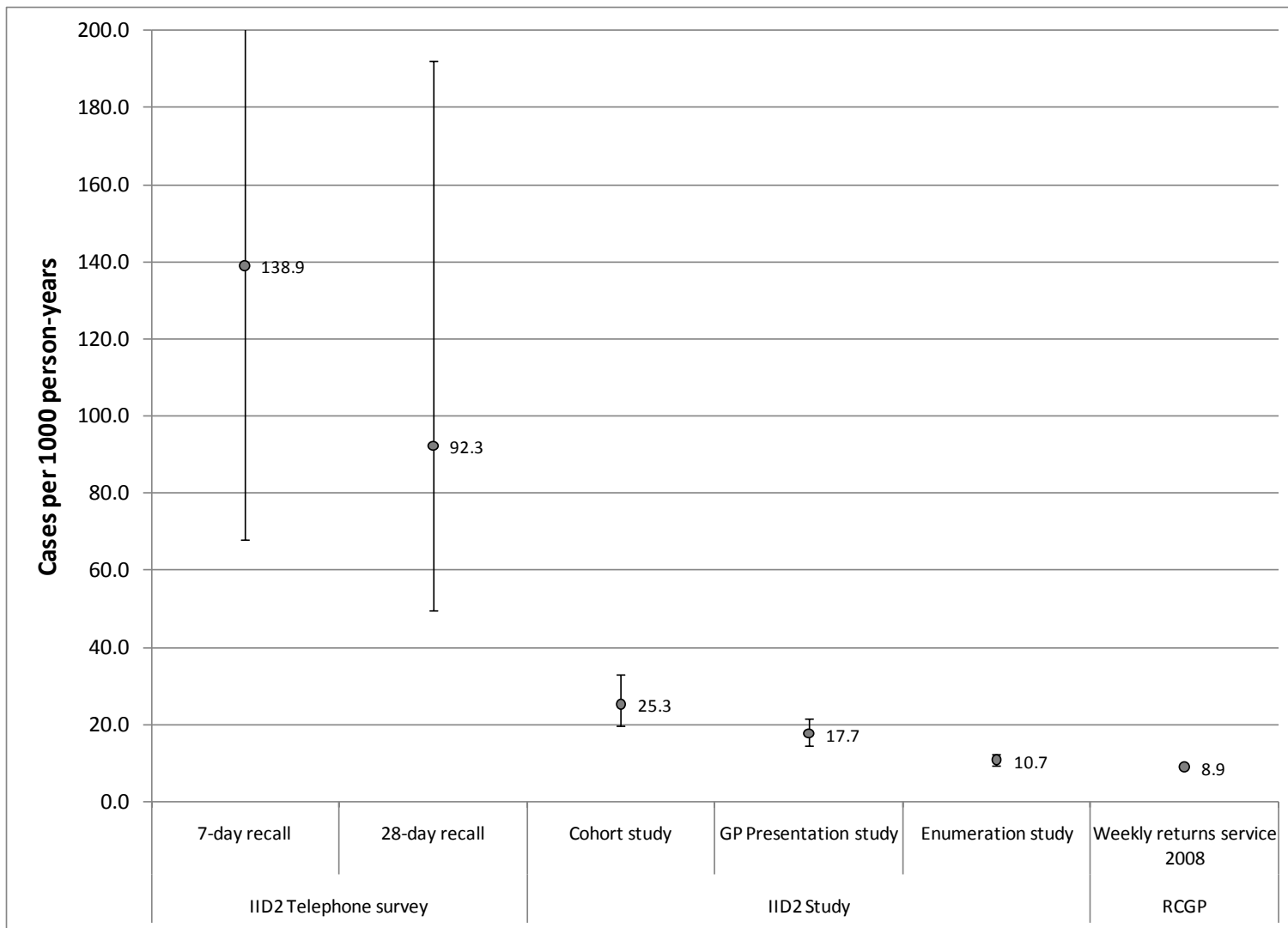
Incidence of consultations for IID in calls to NHSD/NHS24

	England			Wales			Scotland	
Age group	Rate	(95% CI)		Rate	(95% CI)		Rate	(95% CI)
<i>All ages</i>	6.1	(6.1 - 6.2)		3.6	(3.5 - 3.6)		14.3	(14.3 - 14.4)

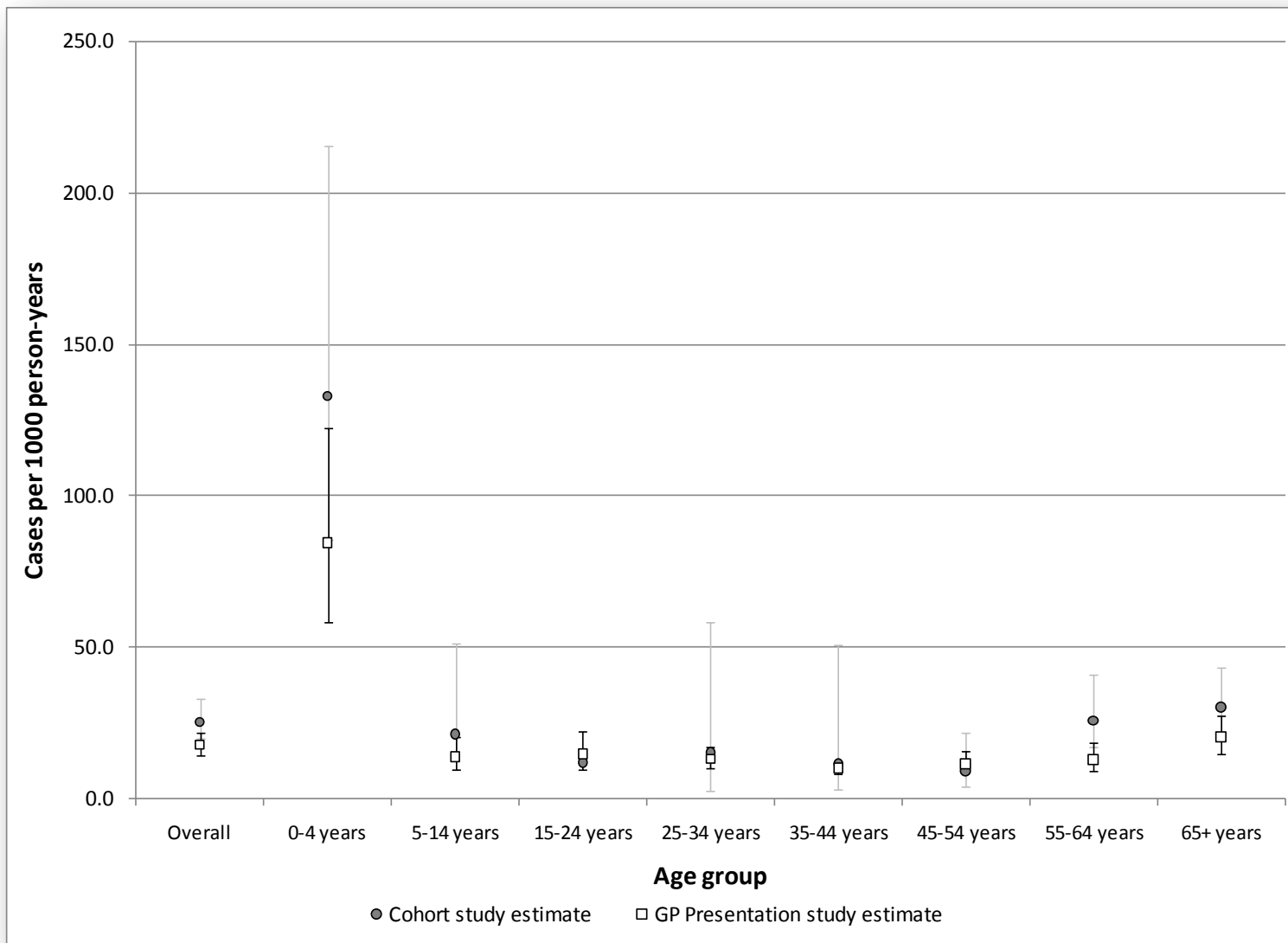
Percentage of calls to NHS Direct by outcome of call, England and Wales

Call outcome	England	Wales
999	0.7	0.6
A&E	2.8	2.3
GP	39.6	37.9
Home Care	54.1	56.5
Other	2.8	2.7
<i>All outcomes</i>	<i>100.0</i>	<i>100.0</i>

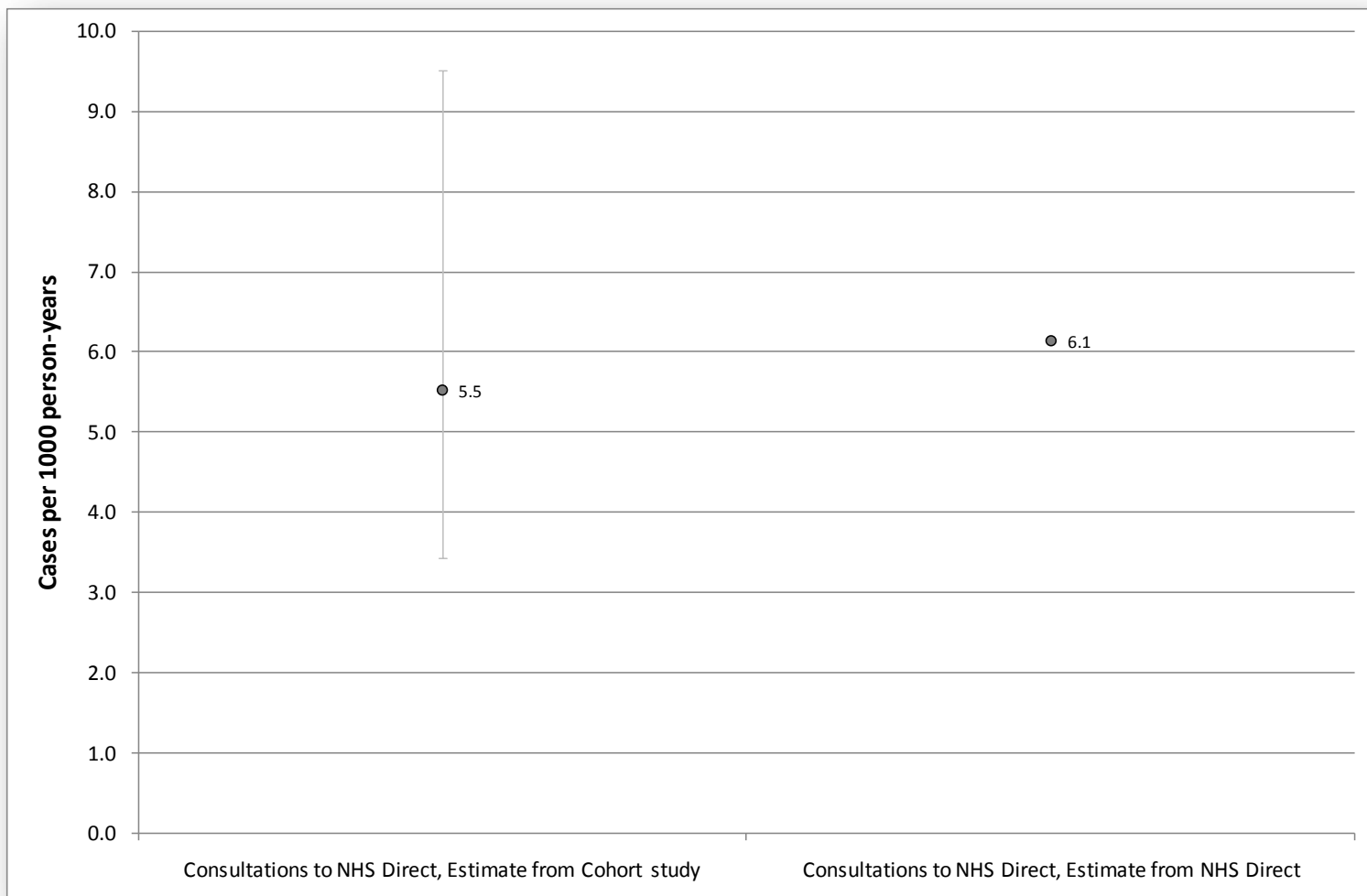
Triangulating rates around presentation to primary care



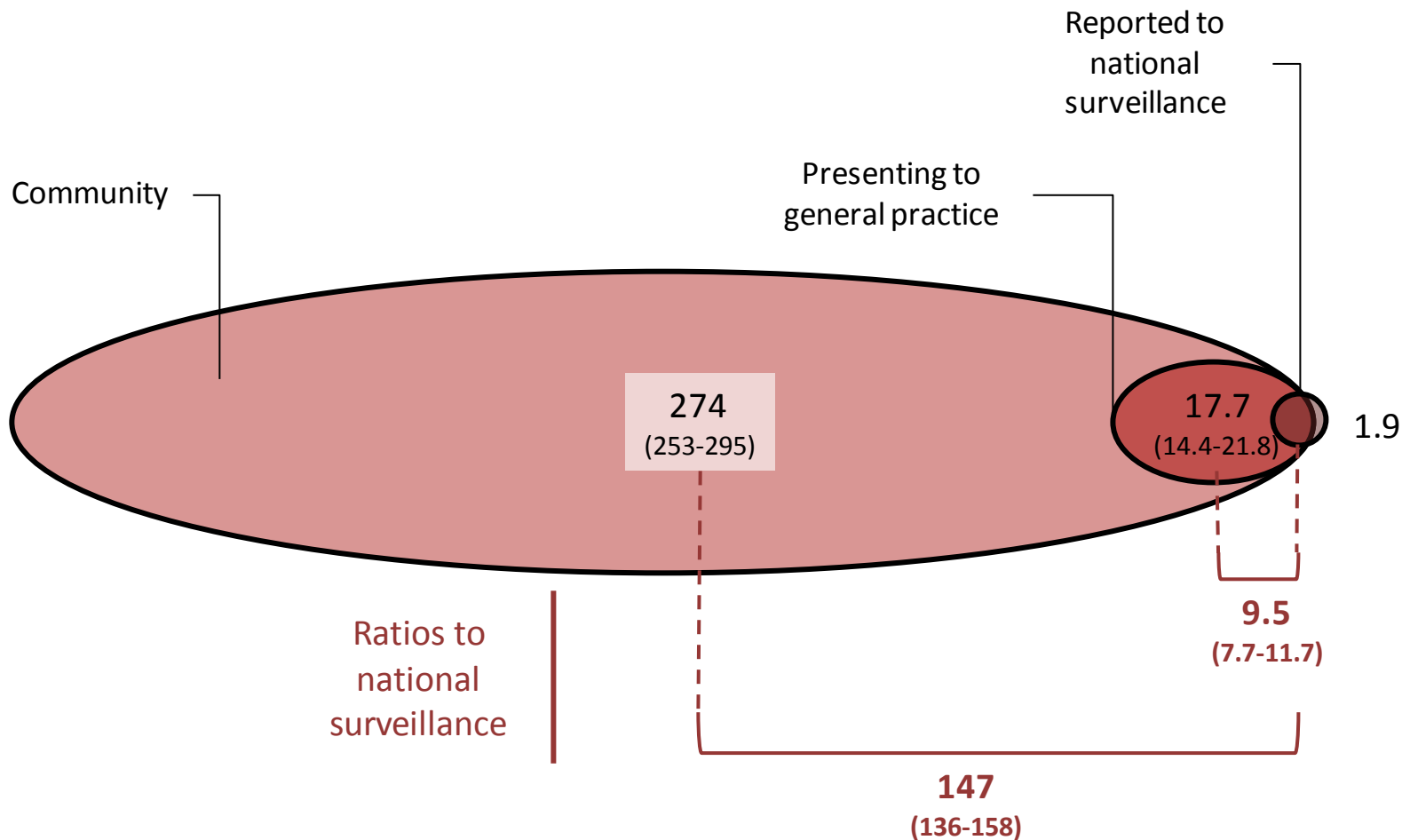
Incidence of IID presenting to general practice by age group: Estimates from the Cohort and GP Presentation studies



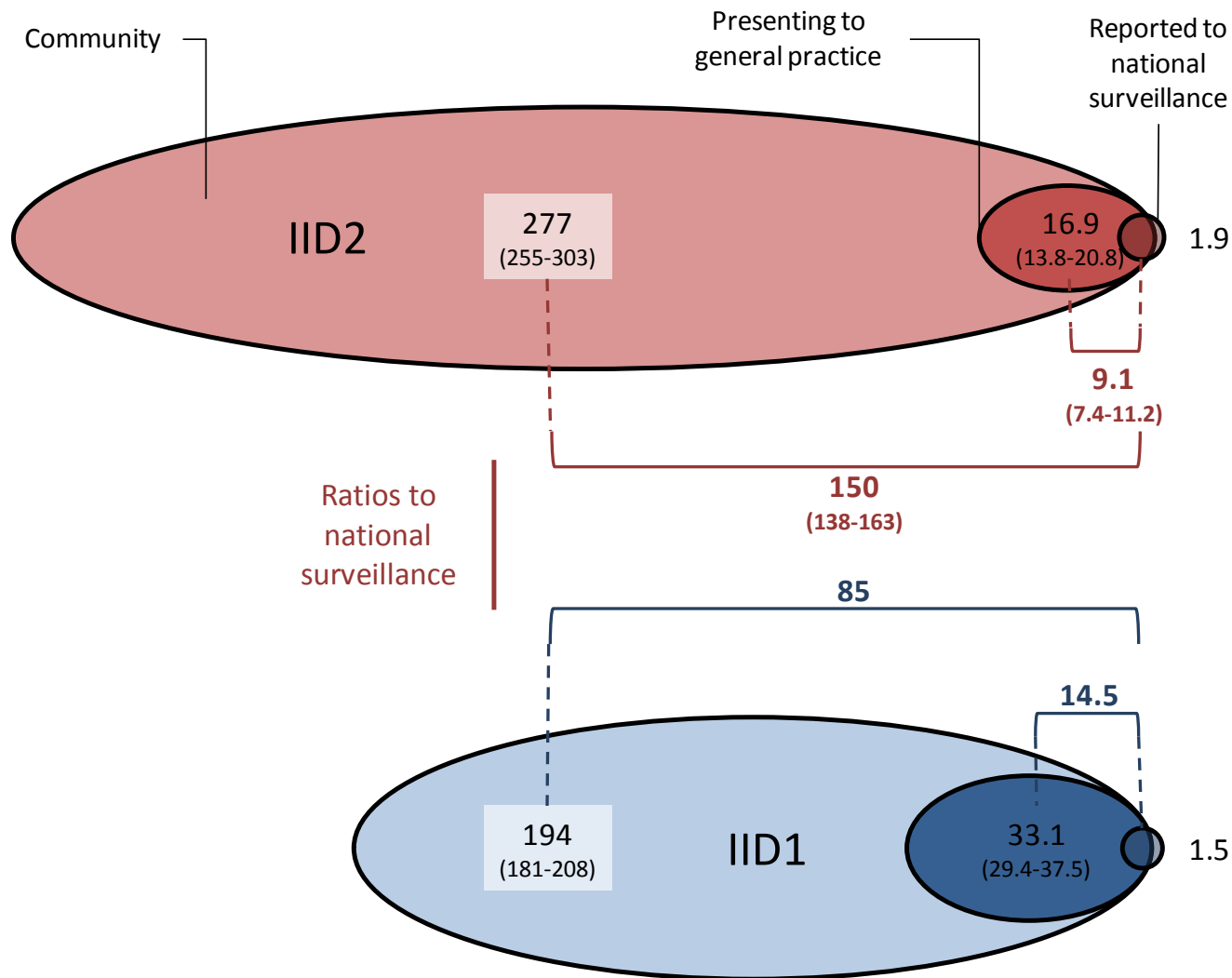
Incidence of IID-related consultations to NHS Direct: Estimates from the Cohort study and NHS Direct



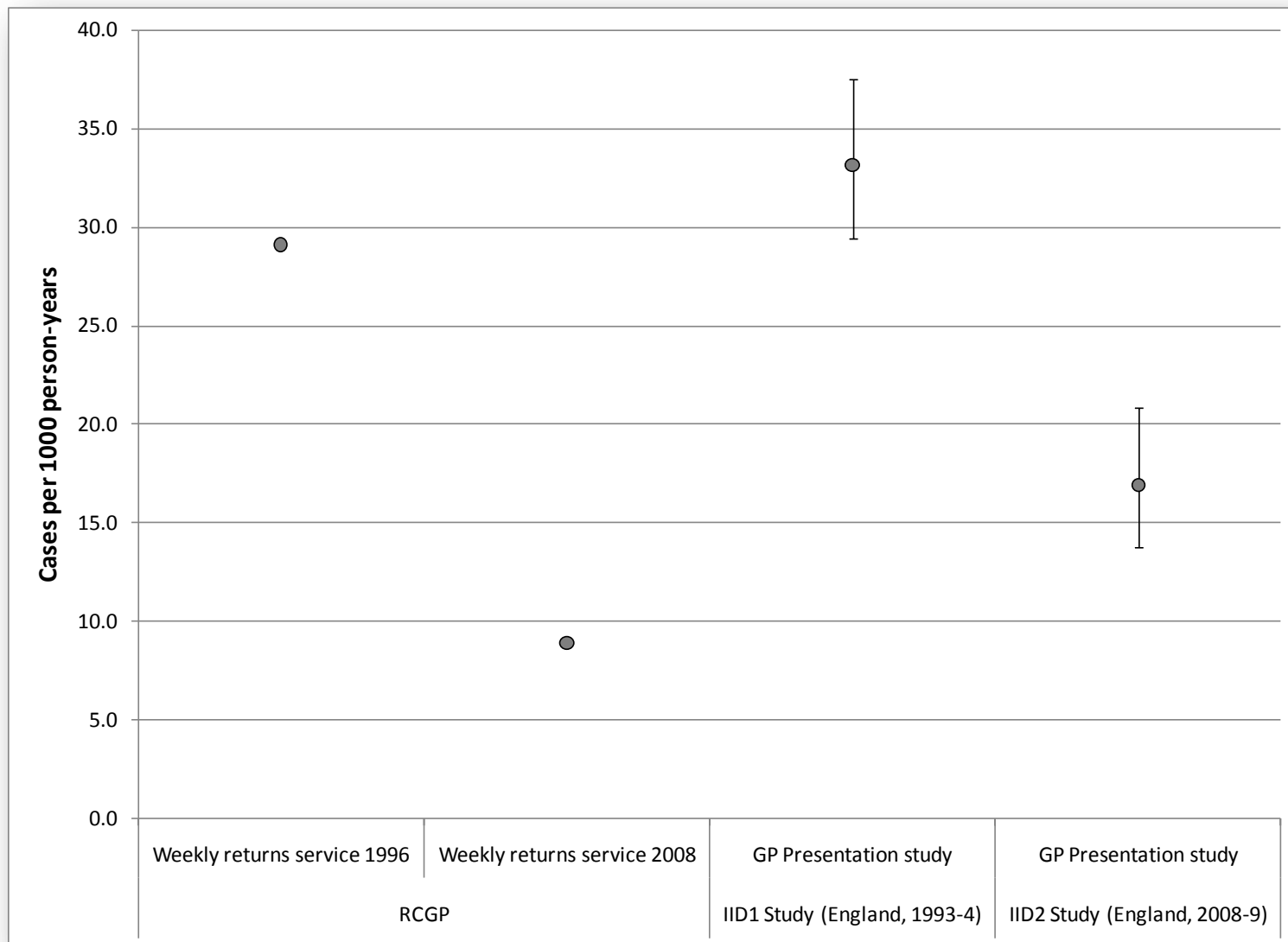
Reporting pattern for overall IID, UK



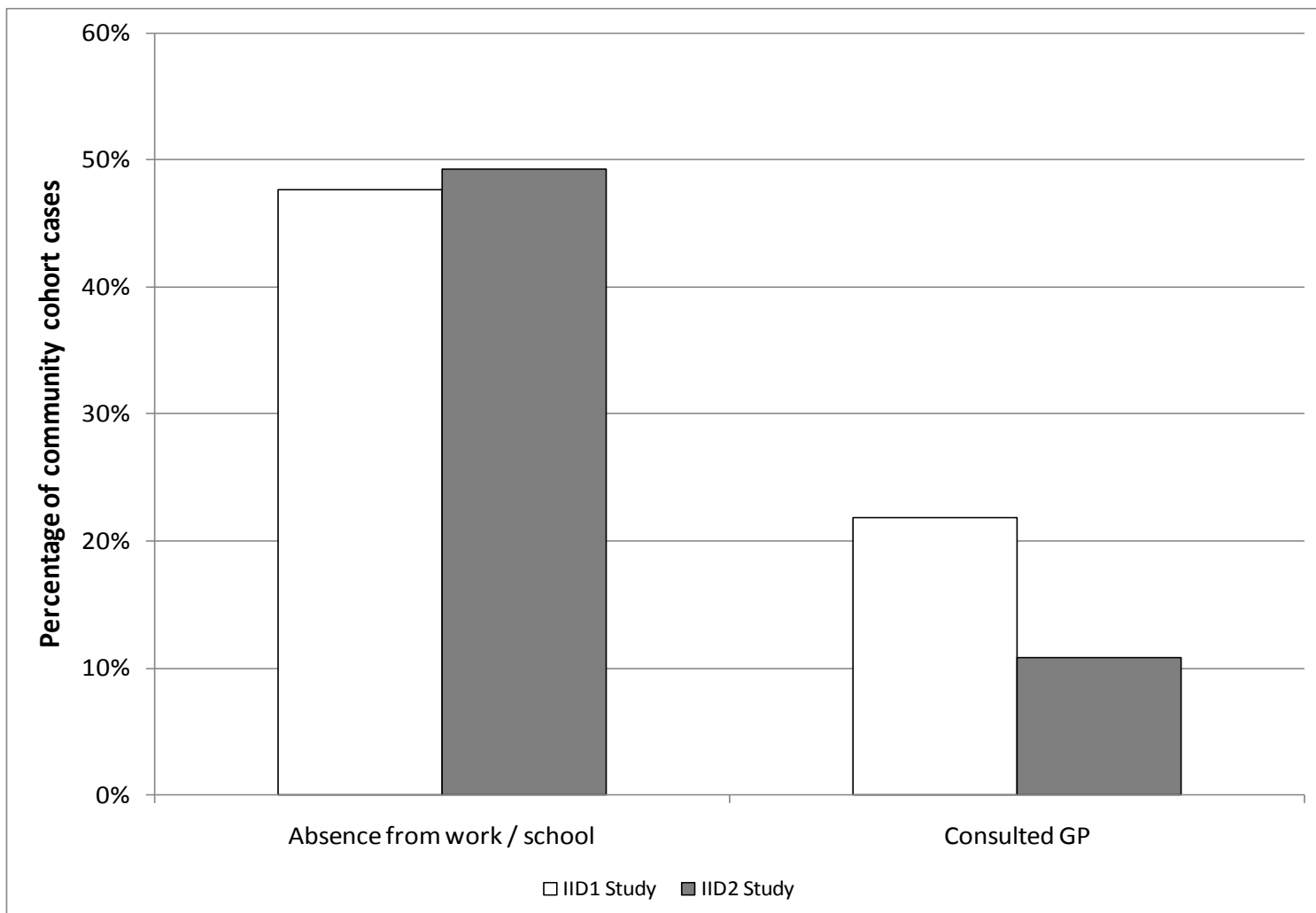
Comparing IID1 and IID2 in England



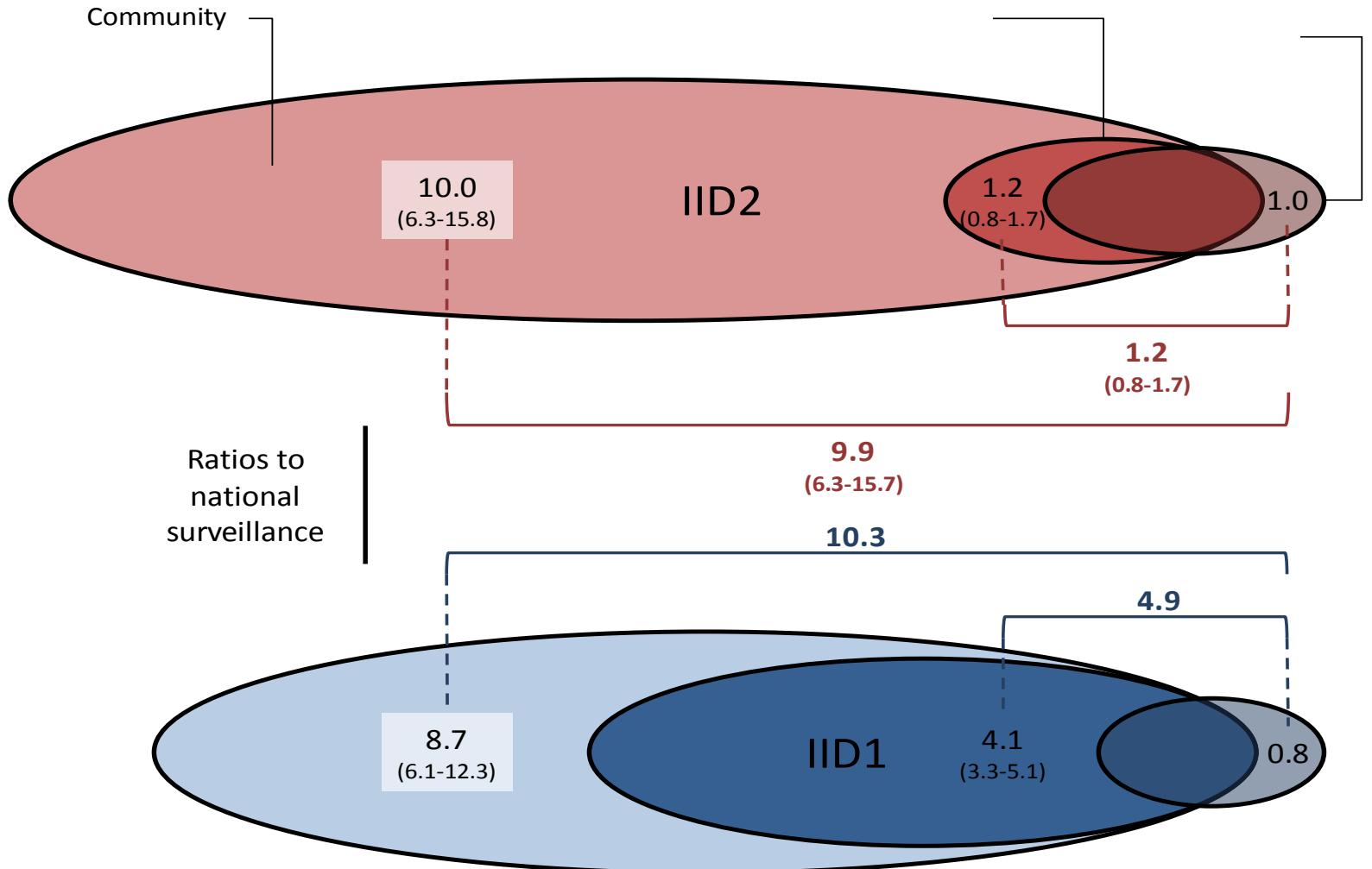
Incidence rates of IID presenting to general practice: Estimates from RCGP Weekly Returns Service, IID1 and IID2



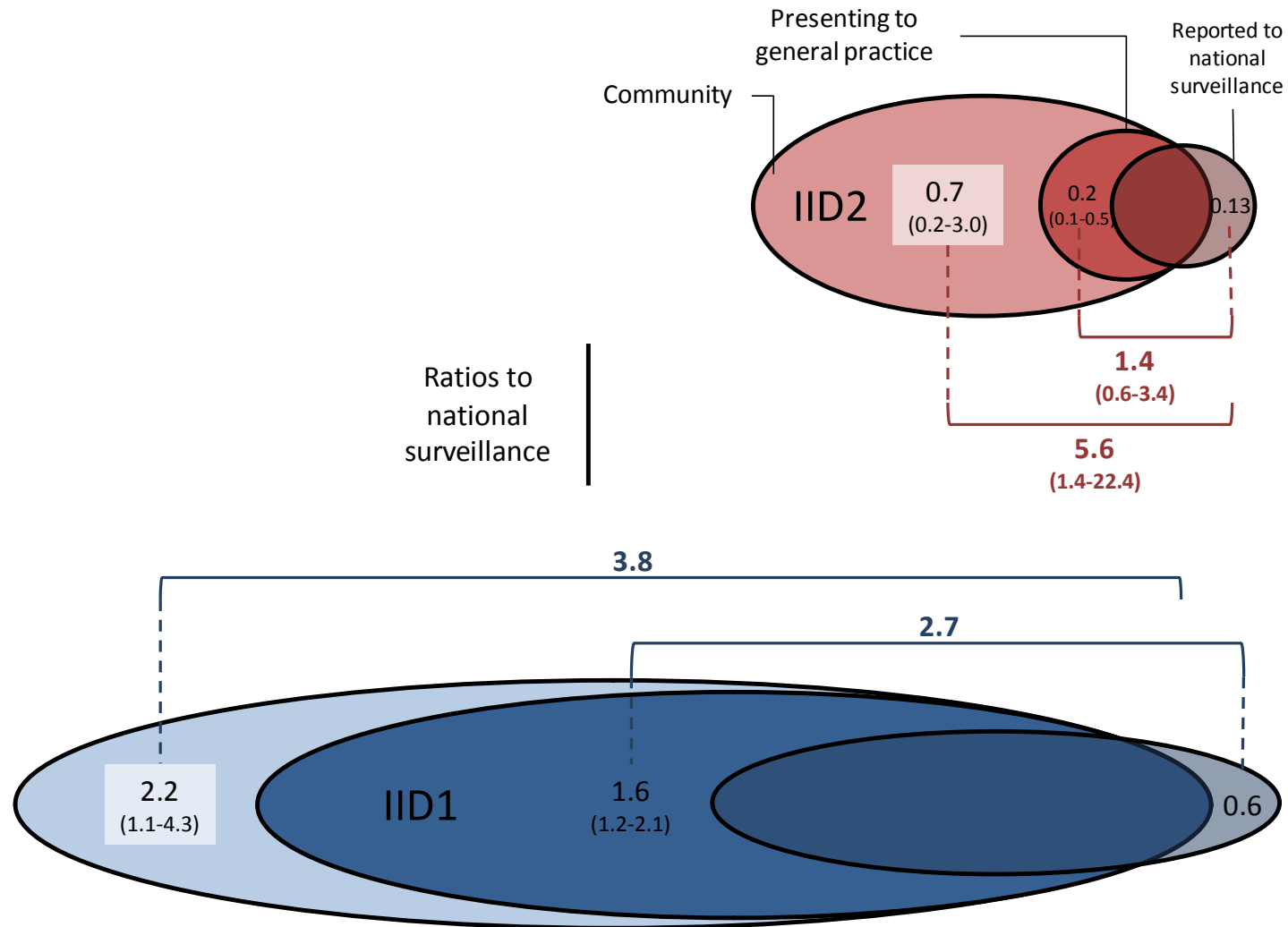
Absence from work or school



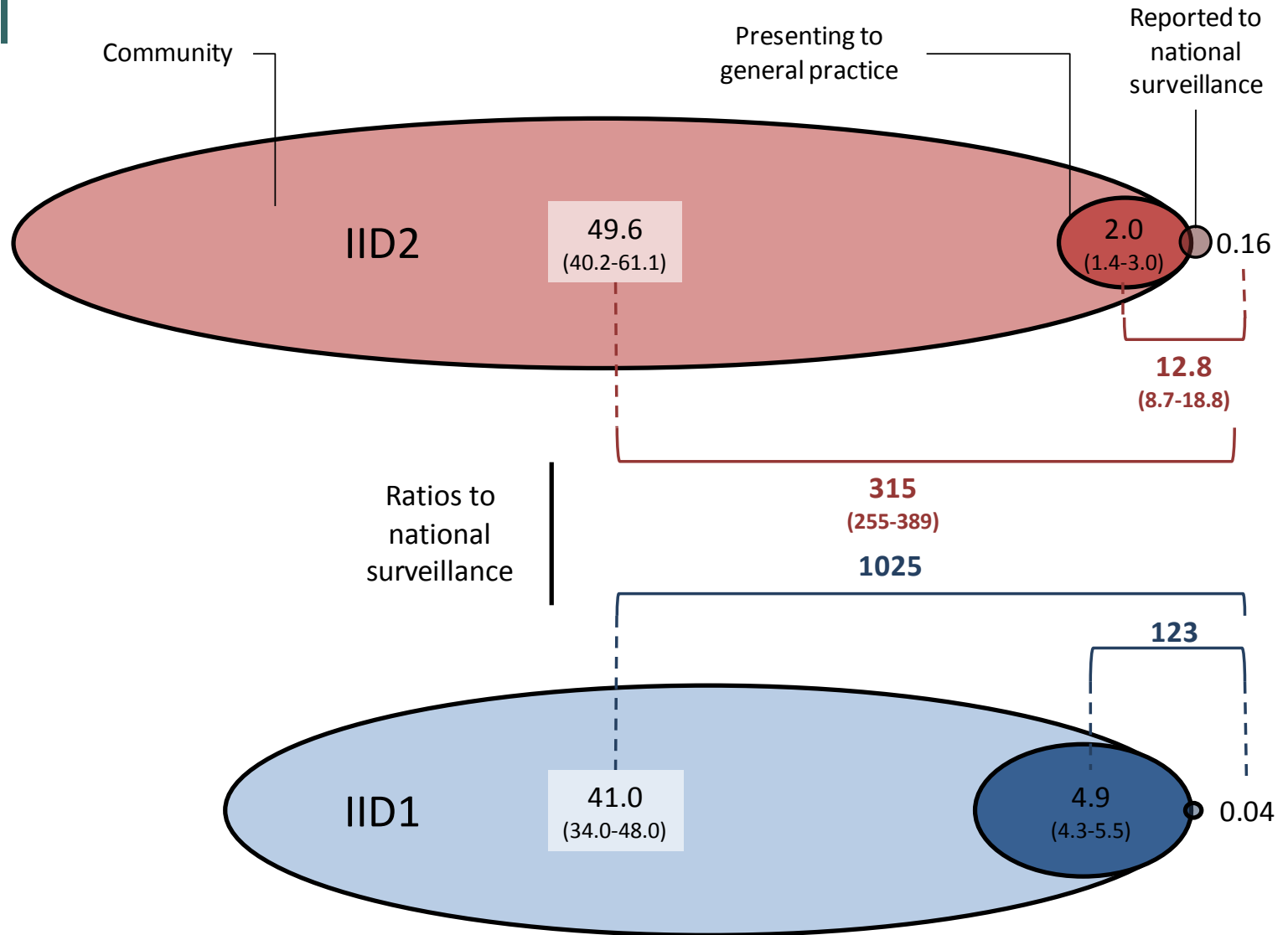
Reporting patterns for *Campylobacter* spp.



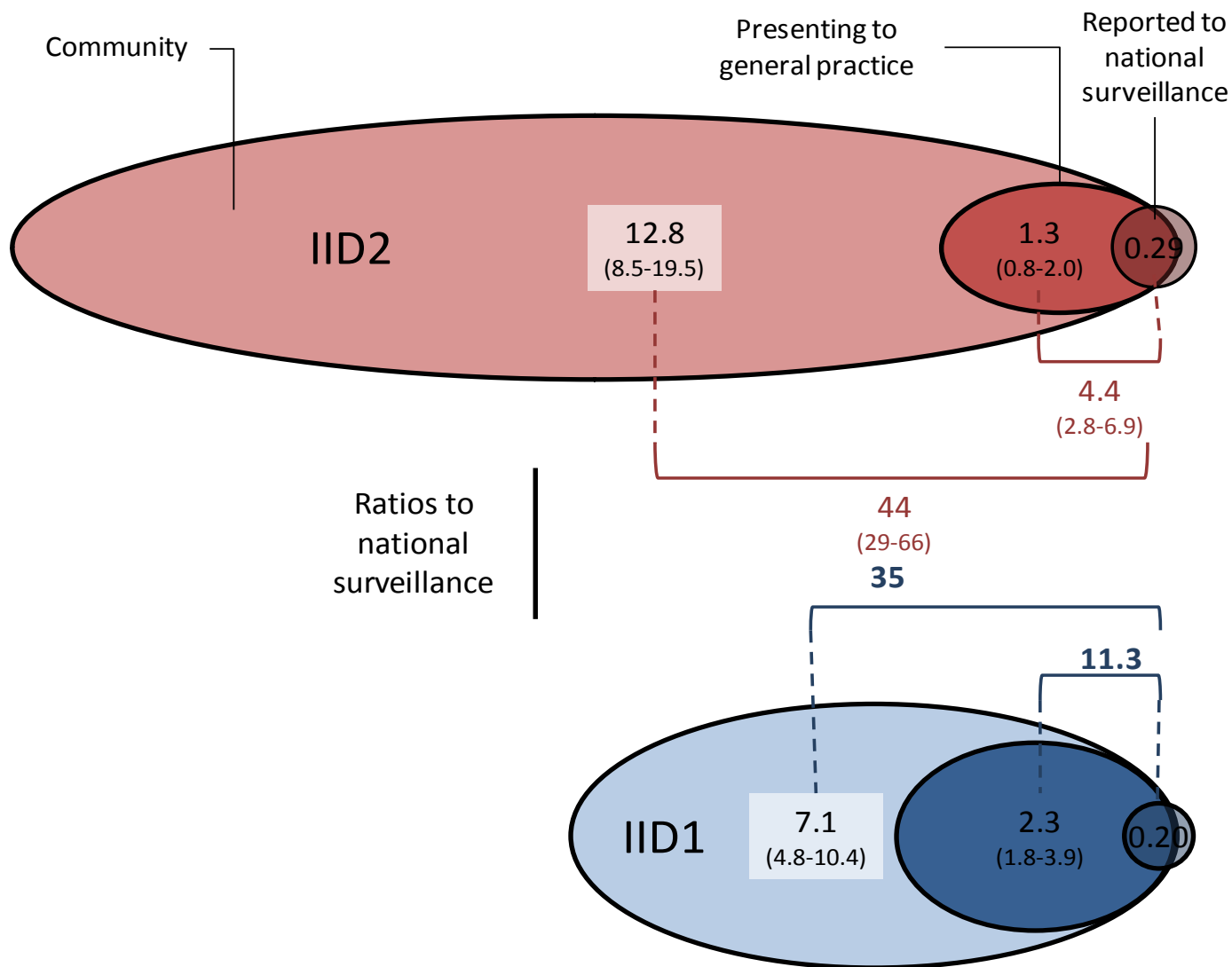
Reporting patterns for *Salmonella* spp.



Reporting patterns for norovirus



Reporting patterns for rotavirus



7,735

Laboratory reports

14,452

49,404

6,530

128,022

GP consultations

83,850

78,973

11,291

Norovirus
2,905,278

Rotavirus
783,737

Campylobacter
571,949

Salmonella
38,606

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?