Card, Timothy and Enck, Paul and Barbara, Giovanni and Boeckxstaens, Guy E.E and Santos, Javier and Azpiroz, Fernando and Mearin, Fermin and Aziz, Qasim and Marshall, John and Spiller, Robin C. (2018) Post infectious IBS: defining its clinical features and prognosis using an internet-based survey. United European Gastroenterology Journal . ISSN 2050-6414 (In Press)

Post Infectious IBS: Defining its clinical features and prognosis using an internet-based survey

Tim Card[1,2], Paul Enck[3], Giovanni Barbara[4], Guy E.E. Boeckxstaens[5], Javier Santos[6], Fernando Azpiroz[6], Fermin Mearin[7,] Qasim Aziz[8], John Marshall[9], Robin Spiller[1]

[1] Nottingham Digestive Diseases Centre, University of Nottingham and National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham.

[2] Division of Epidemiology and Public Health, University of Nottingham

[3] University Hospital Tuebingen, Dept. of Internal Medicine VI: Psychosomatic Medicine and Psychotherapy, Tuebingen, Germany

[4] Department of Medical and Surgical Sciences, University of Bologna, Italy

[5] Translational Research Center for Gastrointestinal Disorders, University Hospital Leuven, Leuven, Belgium

[6] Digestive System Research Unit, University Hospital Vall d'Hebron, Bellaterra, Spain

[7] Institute of Functional and Motor Disorders. Centro Médico Teknon. Barcelona. Spain.

[8] Wingate Institute of Neurogastroenterology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

9 Department of Medicine , McMaster University, Ontario, Canada

Key words: irritable, infection, prospective, survey, internet

Disclaimer

This is a summary of independent research supported by the National Institute for Health Research Biomedical Research Unit. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Abbreviations used in this paper:

PI-IBS= postinfectious Irritable Bowel Sydrome

IBS= Irritable Bowel Sydrome

PHQ12-SSS= patient health questionnaire 12 somatic symptom

HADS= Hospital Anxiety and Depression Scale

UK= United Kingdom, USA= United States of America

Correspondence**:** Professor Robin Spiller, Nottingham Digestive Diseases Centre, University of Nottingham and National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham. Nottingham NG7 2UH, UK. Tel: +44 (0) 115 8231090. Fax: +44 (0) 1158231409. E-mail: Robin.Spiller@nottingham.ac.uk.

Declaration of conflicts of interest and funding

Supported by a grant from the United European Gastroenterology Association (UEG) GASTRO 2009

Conflicts of interest

PE: research funding from Shire-Movetis and SymbioPharm. Advisory Boards from Allergan Pharma, Almirall, Boehringer-Ingelheim, Heel Pharma, and AstraZeneca, and speaker fees from Almirall, Bayer Healthcare, Falk Pharma, Heel Pharma and SymbioPharm,

RS: research funding from Lesaffre and Ironwood. Advisory Boards for Almirall, Yuhan Corporation, Ibsen and Danone and speakers fees from Menarini.

JKM Advisory Boards and/or Consulting for AbbVie, Boehringer-Ingelheim, Celgene, Celltrion, Ferring, Hospira, Janssen, Merck, Pfizer, Pharmascience, Procter & Gamble,

Shire, Takeda. Speaker for AbbVie, Allergan, Ferring, Janssen, Procter & Gamble, Shire, Takeda.

Author Contributions: PE & RS co-chaired UEG Working Party, PE established and managed websites www.pi-ibs.eu and www.postinfectiuous-ibs.eu from which survey was coordinated, RS,PE,FA,GB,GB,JM,JS,FM,QA developed protocol, TC analysed data, TC and RS produced first draft, all reviewed and approved final manuscript

The technical support of Hendrik Buschkamp of Buschkamp-dv, Grevenbroich, Germany for hosting the websites and providing the data readouts is gratefully acknowledged.

Key Summary

Established knowledge on this subject

- Bacterial gastroenteritis quadruples the risk of developing IBS but the proportion of all IBS that is postinfectious is unclear
- Risk factors include severity of initial illness, female gender and adverse psychological factors
- What determines prognosis is uncertain

What are the significant and/or new findings of this study?

- 13% of 7,811 IBS patients met criteria for postinfectious IBS
- PI-IBS was associated with childhood hygiene, somatisation and living in Northern Europe / America
- Prognosis in PI-IBS was not different from non-PI-IBS
- High somatisation, female gender and living in North America and Northern Europe were associated with lower recovery rates

Abstract:

Background: Gastrointestinal infection is an important risk factor for developing IBS. Our aim was to characterise postinfectious IBS (PI-IBS) compared to other IBS patients.

Methods: An internet survey of IBS patients using Rome III diagnostic questionnaire, Hospital Anxiety & Depression Scale (HADS) and Patient Health Questionnaire-12 somatic symptom score (PHQ12-SS) documenting the mode of onset.

Results: 7811 participants, 63.2% female of whom 1004 (13.3%) met criteria for PI-IBS. 70% of PI-IBS described sudden onset, 35% onset while travelling, 49.6% vomiting, 49.9 fever and 20.3% bloody diarrhoea. Compared to other IBS, PI-IBS was significantly associated with living in Northern Europe and North America, having a hysterectomy, not having an appendectomy, higher PHQ12-SS score and having more than one toilet in the family home. PI-IBS patients had more frequent stools. At 1 year recovery rate in PI-IBS and non-PI-IBS group was 19.7% and 22.2%, p=0.15. Recovery rates were lower for females (20.7%) versus males (38.8%), those with somatisation (23.0%) versus those without (33.2%) and living in North America or Northern Europe (21.1%) versus living elsewhere (33.9%) p=<0.001.

Conclusion: PI-IBS accounts for around 13% of all IBS in this internet sample, with some distinctive features but a similar prognosis to the remainder.

Introduction

IBS developing *de novo* after an acute infection in an individual with normal bowel function with gives an ideal opportunity to study the underlying mechanisms causing IBS. Earlier studies suggested that patients with postinfectious IBS (PI-IBS) would have a better prognosis and a lower frequency of psychological disorders compared to other IBS patients [1]. However prospective studies found neuroticism, hypochondriasis[2] ,depression [3] and somatisation[4] all increase the risk. Recent meta-analysis has summarised the extensive literature finding that the incidence of new IBS 12 months after infection was 10.1 (95% CI 7.2-14.1)% . The incidence appears higher after parasitic or protozoan infections at 49% compared to 13.8% after bacterial gastroenteritis. Most studies agree that females and those with anxiety, depression or somatisation are at increased risk [5]. Underlying possible mechanisms include ongoing increased permeability [6], abnormal serotonin metabolism[3], ongoing chronic immune activation together with altered microbiota [7]

We hypothesised based on previous studies (for review see [8]) that PI-IBS would be most likely in those with severe gut inflammation. Many infections such as Campylobacter are less severe in childhood and lead to adaptive immunity[9;10]. We hypothesised that a rural upbringing and reduced hygiene in the family home during childhood would reduce the risk of PI-IBS. We also wanted to test the previous findings that psychological vulnerability was associated with PI- IBS and how this might impact on recovery rates.

Methods

This was an internet survey which allowed recruitment throughout the world and was funded by the United European Gastroentrology Federation, Gastro2009. We created two identical web sites (http://www.pi-ibs.eu; http://www.postinfectious-ibs.eu) which provided bowel symptom questionnaires in 8 languages, namely English, Dutch, German, Belgian, Spanish (two versions: for Spain, for Mexico), Italian, Polish and Romanian. Ethics approval was sought for and received from the University of Nottingham Medical School Ethics Committee, Division of Therapeutics and Molecular Medicine, Nottingham, UK) (P/9/2008, as of Sept 26, 2008) conforming to the ethical guidelines of the 1975 Declaration of Helsinki. Where legally required, national ethics board permissions were requested and received. Recruitment took place from December 5th 2008 with the main recruitment taking place within the first 3 years though more continued to accrue until the website was closed in January 2015.

Inclusions and exclusions:

Consecutive patients attending clinic were all invited to complete the survey online. Access to one of the web sites (www.pi-ibs.eu) was using a unique password for each patient provided by the investigators who all were specialists in functional GI disease; individuals without a password who found the website themselves without being directed there, entered the web at (www.postinfectious-ibs.eu). This allowed us to differentiate between patients with an investigator confirmed diagnosis of IBS using Rome III criteria and the rest who responded yes to the question "Have you been diagnosed with IBS by a doctor?" The introductory information asked those with a history of major GI surgery, inflammatory bowel disease, colon cancer and taking drugs known to alter bowel function especially opiates and anticholinergics not to take part. Completing the questionnaire was accepted as giving informed consent.

Questionnaire details:

Participants were asked to answer questions of demographics including age, gender, country (of birth and also of current residence), schooling, current occupation, previous surgery and psychiatric treatment. We enquired about childhood living conditions including whether they shared a bed with their siblings or whether they had more than 1 toilet or running hot water in the home. GI symptoms at the present time were documented with the Rome III IBS modular questionnaire (http://www.romecriteria.org/pdfs/AdultFunctGIQ.pdf), together with bowel frequency, days per week of urgency, bloating and their commonest stool form using the Bristol Stool Form Scale [11]

Details of diagnosis of postinfectious IBS:

Participants were asked to describe whether their IBS symptoms began gradually or suddenly and if suddenly whether this was an infectious illness. Evidence to support a diagnosis of postinfective IBS included sudden onset of IBS after an infective episode diagnosed either by a positive stool culture showing a named organism or acute onset of new bowel symptoms associated with 2 or more of the following; fever, vomiting, diarrhoea, rectal bleeding or onset during foreign travel. Subjects were then asked to record their bowel habit before the acute episode using the Rome IBS module to determine whether they had IBS before the presumed infectious illness.

Psychological assessments:

Participants completed the Hospital Anxiety and Depression Scale (HADS)[12] and the Patient Health Questionnaire-12 Somatic Symptom Scale (PHQ12-SSS) [13]. Values of HAD anxiety or depression >7 and PHQ12-SS > 6 were considered abnormal. They were asked to provide a contact email address to which a second questionnaire would be sent out 1 year later. Provision of the email was taken as permission to do so. Data is reported showing the total population and then those with postinfectious IBS (PI-IBS) compared with those with non-postinfectious IBS (Non-PI-IBS).

Analysis

Duplicate entries were removed and country of origin recoded as either Northern Europe (defined as North of Alps or Pyrenees) and North America OR the rest of the world.
We present summary statistics as proportions for categorical variables which we have compared using chi squared tests, and as means and standard deviations or medians and interquartile ranges for normally and non-normally distributed continuous variables which were tested using t-tests or Wilcoxon's rank sum respectively. We went on to carry out multivariable analyses using logistic regression to examine potential confounding of the relationships between PI-IBS and prognosis.

Results

There were a total of 7836 lines of data in the dataset, and after exclusion of 75 duplicate email addresses and 209 lines with duplicate IP address, age and gender this provided a total of 7,552 subjects. The majority of cases came from the investigators countries with the largest numbers from Italy(46%) , Netherlands (14%), Germany (8%) and Spain (6%) but there was at least one return from 107 countries. 63% met strict Rome III criteria but 37% did not despite having had a diagnosis of IBS by their doctor.

Similarity of subjects with and without a password

The 2622 (34.72%) of subjects who had a password to access the questionnaire did not differ from those without a password in the proportion meeting Rome III criteria which was 1648 of 2622 (62.9%) and 3097 of 4930 (62.8%) respectively. There were minor differences between these two groups, those without a password were more likely to be female (66.6% versus 56.1%, $p<0.001$) and were slightly older (mean 40.8 years versus 39.9 years $p=0.0058$). They were also less likely to score abnormally high on the

HADS anxiety scale (84.7% versus 87.6%, p=0.003) though more likely to score abnormally high on the PHQ12-SS scale (61.4% versus 57.1%, p=0.002).

Diagnosis of PI-IBS

A total of 1,080 subjects met our definition of PI-IBS and after excluding 76 with prior IBS the proportion of IBS that was PI-IBS was 1,004/7,552 (13.3%).Those with PI-IBS were slightly more likely to meet the Rome III criteria than those without (68.5% vs 62.0% respectively P<0.001), they had however a similar gender distribution (63% female for both PI-IBS and non-PI-IBS) and age (median age 38 IQR 29-49 for PI-IBS and median 38 IQR 30-49 for non-PI-IBS). Table 1 shows the frequency of features used to diagnose PI-IBS. The commonest feature was sudden onset which was seen in 72% followed by fever, vomiting and onset during travel. Only 24% had a positive stool culture. Most of those meeting our criteria, met 2 (62%), with 27% meeting 3 criteria and 11% 4 or more. When asked "Do you remember how your doctor treated your infection?" only 713 recorded a response. 293 replied that they received no specific treatment, 275 received antibiotics , 35 probiotics and 45 Loperamide with 65 reporting other drugs. Those taking antibiotics were slightly more anxious than those taking no treatment with HADS scores of 10.9±2.7 and 10.6±2.7 respectively, p=0.036. Antibiotic usage was significantly increased in of those with bloody diarrhoea 12.2% of whom took antibiotics while just 3.2% with no blood in their stools took antibiotics, Fisher's exact test, $p < 0.001$.

Differences between PI-IBS and non-PI-IBS

Current GI symptoms

PI-IBS patients tended to have more stools per day, median (IQR) being 2(1-3) compared to 1.5(1-3) (p=0.0002, Mann Whitney U test). Comparing both the hardest and softest forms recorded as typical between the groups, distributions were similar for PI-IBS and non-PI-IBS (both p>0.05). Subjects reported the frequency of loose and hard

stools on a 5-point scale ranging from never or rarely to always. PI-IBS reported significantly more frequent the passage of loose stools (Figure 1, p=0.03) but not hard ones (p=0.716).

Psychometrics

The total HADS scores and anxiety or depression sub scores were similar between patients with and without PI-IBS (See Table 2). A high proportion of patients were being treated for anxiety both PI-IBS (77.4%) and non-PI-IBS (74.5%), (difference not significant p=0.051). Treatment for depression was also common but in this case those with PI-IBS were slightly less likely to be treated 79.3% versus 82.0% (p=0.04). Respecting somatisation, a significantly greater proportion of PI-IBS scored above the upper limit of normal for the PHQ12-SS scale (6), 64.3% versus 59.0% (p=0.002).

Childhood environment, surgical history and PI-IBS

Childhood living conditions as assessed by having running hot water in the home, having to share a bed as a child or having contact with animals were not associated significantly with PI-IBS (Table 2), and having more than one toilet was commoner in PI-IBS being reported in 50.1% versus 45.9% in non-PI-IBS (p=0.004). PI-IBS patients were more often from an urban childhood environment (67.1% vs 63%, p=0.011). As can be seen in Table 2 59% of PI-IBS came from Northern Europe or North America, significantly more than the 37% of non-PI-IBS. PI-IBS was also significantly associated with a history of hysterectomy among women and was negatively associated with a history of appendicectomy.

Follow up data

Of the initial 7552 subjects 3,256 provided an email address indicating they were prepared to do a repeat symptom survey at 1 year. We obtained follow up data after 1 year on 1,056 (32.43%) of these of whom 200 (18.9%) met our definition of PI-IBS. Of the 846 who met Rome III criteria initially 618 still met the criteria at one year so that

the rate of spontaneous remission was 27% in the year. The proportion who improved (as judged by ceasing to meet these criteria) varied across the age groups from 23% in those aged 21-30 to 37.5% in those aged over 70, these differences were however not significant (p=0.18). Significant effects on recovery rates were seen for gender, somatisation and country of origin (Figure 2). Significantly more males (38.8%) ceased to meet Rome III than females (20.7%) (p<0.001). Those with somatisation, indicated by an abnormally high PHQ12-SS score, were significantly less likely to recover than those without somatisation, remission rates being 23.0% versus 33.2 % respectively, p<0.001 The remission rate in PI-IBS at 22.8%, was not significantly different from that in the non-PI-IBS group at 27.9% (p=0.19).

Remission of symptoms was significantly less in those from North America / Europe 21.1% compared to those from elsewhere 33.9% (Table 3). A multivariable logistic regression adjusting the effect of PI-IBS upon improvement for the effects of the other variables showed only slight confounding by them: Odds ratio for still being Rome III for PI-IBS versus non-PI-IBS was 1.31 (0.87-1.95) in univariate analysis, and 1.14 (0.75-1.75) in multivariate regression. If we altered the definition of improvement to be a reduction in abdominal pain over the previous 3 months, or reductions in the number of hard or of loose stools, we similarly found that some individuals improved while others got worse but there was no significant association with PI-IBS according to our definition. Finally, we repeated analyses defining PI-IBS either as only those with a positive stool culture at onset, or as patients who self identified as PI-IBS. Again, no significant difference in prognosis was noted (data not shown).

Longer duration of IBS symptoms reduced recovery rates. 272 had IBS onset 0-3 years before the survey of whom 38% recovered at the 1 year follow up while 819 had onset >3 years before and of these just 25% recovered, Chi2=3.3, p=0.07.

In view of the response rate of only 32.43% at follow up we compared baseline data for those with and without follow up. Amongst those providing email addresses, those providing follow up were slightly older (mean age 43.2 vs 39.9, p<0.001), more likely to satisfy Rome3 criteria (80.1% vs 72.6%, p<0.001), more likely to be from northern

Europe or the USA (52.1% vs 31.7%, $p<0.001$) but less likely to have an abnormal PHQ12-SS score (59.7% vs 64.6%, $p=0.007$, gender and HAD sub scores (or overall) were not significantly different.

Discussion

This large pragmatic study of IBS, PI-IBS and its prognosis found that about 13% of included cases satisfied criteria suggestive of PI-IBS. The commonest diagnostic feature was sudden onset followed by vomiting and fever but only 24% reported having a positive stool culture. Compared to non-PI-IBS cases, PI-IBS had greater stool frequency and looser stools which is in keeping with earlier reports that the commonest IBS subtype in PI-IBS was IBS-D [3] [14]. Whether this is related to the common axis of dysbiosis in which PI-IBS and IBS-D overlap remains to be determined [7]. Those with PI-IBS had a slightly greater tendency to somatise, a lower rate of previous appendicectomy and a higher rate of hysterectomy. They were also more likely to have lived in an urban environment and in a house with multiple toilets during childhood, and more likely to be from Northern Europe or North America. Contrary to our hypothesis PI-IBS was not associated with a significantly improved prognosis. We were however able to show that prognosis is better in those without somatisation, in males, and in those not from Northern Europe and North America.

Subjects who used a password to access the questionnaire were known to be from participating clinics diagnosed by the authors and their colleagues, (all experts in functional gastrointestinal diseases) and their diagnoses were therefore of known validity. We found no difference between those with and without password as regards to meeting our gold standard for IBS diagnosis (namely the Rome III criteria). This encourages us to believe that those who took part without a password were also likely truly to suffer from IBS, i.e. to believe that they were valid cases to study. This lack of difference also reassured us that subjects from investigators clinics were not grossly atypical (a risk when examining the practice of those with a special interest in the area). Where we have limited analysis to those using passwords, the results should be generalisable to patients with IBS seen in the secondary care. An inevitable limitation to our study is that we have recruited exclusively patients prepared to complete a quite lengthy survey, who may not be typical of all patients.

There was a risk that our survey would selectively recruit those with a postinfectious origin however we do not believe this is the case for a number of reasons. Firstly the proportion that were PI-IBS 14% is within the range of 6-17% reported by others using a number of different recruitment techniques [15]. Secondly others have modelled the proportion of IBS that is PI-IBS and using the most conservative model concluded that 9% of IBS was postinfectious[16]. Finally although the website was labelled "piibs" we don't think the general public would necessarily recognise these initials and questions about infection only appear in the middle of quite extensive set of questions about other factors.

Though only 28% of our PI-IBS cases reported a positive stool culture, the absence of this does not excludes the diagnosis of PI-IBS since it is common practice only to request stool culture in cases of acute gastroenteritis which are not settling. One prospectively survey in the UK found that stool samples were only requested in 27% of gastroenteritis cases presenting to primary care[17] so the rate of culturing for all cases must be much lower given that many do not seek health care. To examine the possibility of bias we varied our definition of PI-IBS to include only those with positive stool cultures but this did not appreciably alter our results. We therefore think it unlikely that our definition of PI-IBS has greatly biased the results, and in addition as the criteria we used mirror those we would commonly use in clinical practice, we feel our results are likely both to be valid and to be informative to clinicians.

We found PI-IBS cases to have more frequent bowel movements but to be remarkably similar to non-PI-IBS with respect to age, gender and anxiety though they were less likely to have been treated for depression. Contrary to our original hypothesis we found no evidence that remission at 1 year differed from non-PI-IBS being 22.8% and 27.9% respectively.

Childhood living conditions were generally good with for example 86% having hot running water in their homes but we did find that having more than one toilet in the home was slightly commoner in PI-IBS than non-PI-IBS partially supporting the idea that childhood affluence might increase ones risk of developing PI-IBS.

This might explain why the proportion of PI-IBS that was from Northern Europe / North America (59%) was significantly higher than the 37.4% of non-PI-IBS ($p<0.001$). An alternative explanation is that one third of PI-IBS develops during foreign travel which might occur for frequently in those from the more affluent Northern Europe/ North America. Campylobacter is the commonest cause of PI-IBS in adults in the UK at least [18]. However the majority of Campylobacter infections in tropical countries occur in childhood[19] when they are often mild with a few days of watery diarrhoea. A similar mild character was reported in adult patients infected with *Campylobacter jejuni* from southern Spain with 96% having only watery diarrhoea[20]. By contrast adults with *Camplyobacter jejuni* infection in the US experience a severe illness with mucosal ulceration[21] and one third of adult cases in the UK have bloody diarrhoea and weight loss[18] indicating severe mucosal inflammation which might be more likely to result in prolonged bowel dysfunction. Whether these differences represent differences in bacterial or host characteristics remains to be determined.

The prognosis in PI-IBS did not differ from non PI-IBS with recovery in approximately 1 in 4 in the first year. However males were almost twice as likely as females to recover in the first year, a striking as yet unexplained difference which should be further explored. However the response rate for the follow up study was low at 14% (32% of those originally indicating a willingness to consider further contact) which does introduce a risk of bias. Our analysis of the difference between responders and non-responders shows that of the factors we have found to be associated with prognosis, gender is not associated with response, and the excess of Europeans and North Americans might bias towards a worse prognosis whereas the deficit of somatisers would bias in the other direction. Few other surveys have attempted such follow up so there is limited data with which to compare our recovery rate but 27% at 1 year is within the range reported in meta-analyses of postinfectious IBS[22].

Although we found few major differences in clinical features between PI-IBS and non-PI-IBS it is still important to recognise the condition both to reassure the patient that this is not unusual and also because there is a hint that response to treatment might be

different. A recent trial of an anti-inflammatory agent mesalazine showed overall no benefit in IBS with diarrhoea but a post hoc subgroup analysis did suggest that PI-IBS did respond [23]. This needs repeating but makes sense if the underlying pathophysiology of PI-IBS includes ongoing low grade inflammation.

Legend for Figures

Figure 1

Frequency of loose stools as rated by subjects on a 5 point scale was increased in PI-IBS, Chi squared test, p=0.03

Figure 2

Remission rates of IBS symptoms were worse for females, those with abnormal PHQ12-SS and those residing in North America and Northern Europe (NA/N Europe). *** p=0.001

Table 1 Frequency of PI-IBS criteria %		
	PI-IBS	Non-PI_IBS
Sudden onset	72.4	16.8
Onset during travel	34.5	2.8
Vomiting	50.1	4.4
Fever	50.6	2.4
Bloody diarrhoea	19.4	2.4
Stool culture positive	24.0	1.8

Table 2 Univariate associations of PIIBS at baseline questionnaire			
	PI-IBS	Non-PI-IBS	P
Number	1004	6548	
Age (Median(IQR))	38 (29-49)	38 (30-49)	0.33
HADS Anxiety score (Median(IQR))	11 (9-13)	11 (9-13)	0.40
HADS Depression score (Median(IQR))	10 (8-11)	10 (8-11)	0.06
PHQ12-SS (Median(IQR))	8 (5-11)	7 (5-11)	0.003
History of cholecystectomy	6.0%	4.7%	0.075
History of Appendicectomy	14.1%	17.2%	0.016
History of Hysterectomy (in women)	8.2%	5.2%	0.002
Characteristics of childhood home			
Contact with animals	8.37%	8.15%	0.813
More than one toilet	50.8%	45.9%	0.004
Running hot water	89.5%	90.6%	0.292
Shared a bed	13.7%	12.3%	0.225
Urban	67.1%	63.0%	0.011
Geographic origin			
N Europe and USA	59.1%	37.3%	<0.001

Table 3 Univariate associations of recovery of IBS as measured by ceasing to be ROME3 positive among those with follow up data who were Rome 3 +ve at outset			
	Rome 3 -ve at FU	%	p
Total	228	27	
Male	113	38.8	<0.001
Female	115	20.7	
Age bands			
0-20	1	33.3	0.29
21-30	39	23.4	
31-40	62	26.2	
41-50	51	23.6	
51-60	45	32.4	
61-70	20	33.9	
>70	9	37.5	
Country of residence			
N Europe/America	96	21.1	<0.001
Rest of the world	132	33.9	
HADS anxiety			
Normal	27	24.55	0.54
Abnormal	201	27.31	
HADS depression			
Normal	33	33.67	0.11
Abnormal	195	26.07	
PHQ12-SS			
Normal	108	33.2	0.001
Abnormal	120	23.0	

Subtype of IBS			
PI-IBS	37	22.8	0.19
Non PI-IBS	191	27.9	

Reference List

(1) Chaudhary NA, Truelove SC. The irritable colon syndrome. *Quart J Med* 1962; 123:307-322.

(2) Gwee KA, Leong YL, Graham C, McKendrick MW, Collins SM, Walters SJ et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999; 44(3):400-406.

(3) Dunlop SP, Jenkins D, Neal KR, Spiller RC. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. *Gastroenterology* 2003; 125(6):1651-1659.

(4) Schwille-Kiuntke J, Enck P, Zendler C, Krieg M, Polster AV, Klosterhalfen S et al. Postinfectious irritable bowel syndrome: follow-up of a patient cohort of confirmed cases of bacterial infection with Salmonella or Campylobacter. *Neurogastroenterol Motil* 2011; 23(11):e479-e488.

(5) Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M et al. Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. *Gastroenterology* 2017; 152(5):1042-1054.

(6) Dunlop SP, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC et al. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol* 2006; 101(6):1288-1294.

(7) Jalanka-Tuovinen J, Salojarvi J, Salonen A, Immonen O, Garsed K, Kelly FM et al. Faecal microbiota composition and host-microbe cross-talk following gastroenteritis and in postinfectious irritable bowel syndrome. *Gut* 2014; 63(11):1737-1745.

(8) Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology* 2009; 136(6):1979-1988.

(9) Calva JJ, Ruiz-Palacios GM, Lopez-Vidal AB, Ramos A, Bojalil R. Cohort study of intestinal infection with campylobacter in Mexican children. *Lancet* 1988; 1(8584):503-506.

(10) Martin PM, Mathiot J, Ipero J, Kirimat M, Georges AJ, Georges-Courbot MC. Immune response to Campylobacter jejuni and Campylobacter coli in a cohort of children from birth to 2 years of age. *Infect Immun* 1989; 57(8):2542-2546.

(11) Heaton KW, O'Donnell LJ. An office guide to whole-gut transit time. Patients' recollection of their stool form. *J Clin Gastroenterol* 1994; 19(1):28-30.

(12) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67(6):361-370.

(13) Spiller RC, Humes DJ, Campbell E, Hastings M, Neal KR, Dukes GE et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. *Aliment Pharmacol Ther* 2010; 32(6):811-820.

(14) Wouters MM, Van WS, Nguyen A, Dooley J, Aguilera-Lizarraga J, Van BW et al. Psychological comorbidity increases the risk for postinfectious IBS partly by enhanced susceptibility to develop infectious gastroenteritis. *Gut* 2015.

(15) Longstreth GF, Hawkey CJ, Mayer EA, Jones RH, Naesdal J, Wilson IK et al. Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. *Aliment Pharmacol Ther* 2001; 15(7):959-964.

(16) Shah ED, Riddle MS, Chang C, Pimentel M. Estimating the contribution of acute gastroenteritis to the overall prevalence of irritable bowel syndrome. *J Neurogastroenterol Motil* 2012; 18(2):200-204.

(17) Wheeler JG, Sethi D, Cowden JM, Wall PG, Rodrigues LC, Tompkins DS et al. Study of infectious intestinal disease in England: rates in the community, presenting to general practice, and reported to national surveillance. The Infectious Intestinal Disease Study Executive. *Br Med J* 1999; 318(7190):1046-1050.

(18) Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *BMJ* 1997; 314(7083):779-782.

(19) Georges-Courbot MC, Cassel-Beraud AM, Gouandjika I, Monges J, Georges AJ. A cohort study of enteric campylobacter infection in children from birth to two years in Bangui (Central African Republic). *Trans R Soc Trop Med Hyg* 1990; 84(1):122-125.

(20) Gallardo F, Gascon J, Ruiz J, Corachan M, Jimenez de AM, Vila J. Campylobacter jejuni as a cause of traveler's diarrhea: clinical features and antimicrobial susceptibility. *J Travel Med* 1998; 5(1):23-26.

(21) Siegal D, Syed F, Hamid N, Cunha BA. Campylobacter jejuni pancolitis mimicking idiopathic ulcerative colitis. *Heart Lung* 2005; 34(4):288-290.

(22) Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: the incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007; 26(4):535-544.

(23) Lam C, Tan W, Leighton M, Hastings M, Lingaya M, Falcone Y et al. A mechanistic multicentre, parallel group, randomised placebo-controlled trial of mesalazine for the treatment of IBS with diarrhoea (IBS-D). *Gut* 2016; 65(1):91-99.