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**Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: a Systematic Review and Meta-analysis**

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Siddharth Singh: study design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript; statistical analysis; obtained funding

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**ABSTRACT**

**Background & Aims:** Foodborne illness affects 15% of the United States population each year and is a risk factor for irritable bowel syndrome (IBS). We evaluated risk of, risk factors for, and outcomes of IBS after infectious enteritis

**Methods:** We performed a systematic review of electronic databases from 1994 through August 31, 2015 to identify cohort studies of the prevalence of IBS 3 months or more after infectious enteritis. We used random effects meta-analysis to calculate the summary point prevalence of IBS after infectious enteritis, as well as relative risk (compared to individuals without infectious enteritis) and host- and enteritis-related risk factors.

**Results:** We identified 45 studies, comprising 21,421 individuals with enteritis, followed for 3 months–10 years for development of IBS. The pooled prevalence of IBS at 12 months after infectious enteritis was 10.1% (95% CI, 7.2–14.1) and at more than 12 months after infectious enteritis was 14.5% (95% CI, 7.7–25.5). Risk of IBS was 4.2-fold higher in patients who had infectious enteritis in the past 12 months than in individuals in those who had not (95% CI, 3.1–5.7); risk of IBS was 2.3-fold higher in individuals who had infectious enteritis longer than 12 months ago than in individuals who had not (95% CI, 1.8–3.0). Of patients with enteritis caused by protozoa or parasites, 41.9% developed IBS; of patients with enteritis caused bacterial infection, 13.8% developed IBS. Risk of IBS was significantly increased in women (odds ratio [OR], 2.2; 95% CI, 1.6–3.1) and with antibiotic exposure (OR, 1.7; 95% CI, 1.2–2.4), anxiety (OR, 2; 95% CI, 1.3–2.9), depression (OR, 1.5; 95% CI, 1.2–1.9), somatization (OR, 4.1; 95% CI, 2.7–6.0), neuroticism (OR, 3.3; 95% CI, 1.6–6.5), and clinical indicators of enteritis severity. There was a considerable level of heterogeneity among studies.

**Conclusion:** In a systematic review and meta-analysis, we found more than 10% of patients with infectious enteritis to later develop IBS; risk of IBS was 4-fold higher than in individuals who did not have infectious enteritis, although there was heterogeneity among studies analyzed. Women—particularly those with severe enteritis—are at increased risk for developing IBS, as are individuals with psychological distress and users of antibiotics during the enteritis.

**KEY WORDS:** Post-infectious irritable bowel syndrome; gastrointestinal infections; functional gastrointestinal disorders; microbes

## INTRODUCTION

Irritable bowel syndrome (IBS) affects 7-18% of the population worldwide.<sup>1</sup> Infectious enteritis (IE) is a commonly identified risk factor for development of IBS<sup>2</sup>; this subset is referred to as post-infectious IBS (PI-IBS). Since one of the original descriptions by Chaudhary and Truelove in 1960,<sup>3</sup> our understanding of PI-IBS was limited until the late 1990s, when the prevalence and risk factors for PI-IBS were investigated.<sup>4,5</sup> Bacterial (*Campylobacter jejuni*, *Salmonella enterica*, *Shigella sonnei*, *Escherichia coli* O157:H7),<sup>6</sup> viral (Norovirus)<sup>7-10</sup> and protozoal (*Giardia lamblia*)<sup>11-13</sup> enteritis have all been associated with the development of PI-IBS. A wide range from 4-36% is reported to develop PI-IBS and long-term follow up studies have shown that the IBS symptoms can persist for  $\geq 10$  years following the IE episode.<sup>14,15</sup> The PI-IBS risk associated with IE has been shown to be independent of other potential risk factors.<sup>16,17</sup> Foodborne IE affects 1 in 6 individuals in the U.S. (48 million people) annually placing a significant population at-risk for development of PI-IBS.<sup>18</sup> Additionally, travelers' diarrhea can also add significantly to the burden of PI-IBS.<sup>19</sup>

The reported PI-IBS prevalence depends upon the pathogen(s) involved, geographic location, clinically suspected or laboratory proven enteritis, time of assessment following the IE, and the criteria used to define IBS.<sup>2</sup> The IE outbreak in Walkerton, Ontario affected >2000 residents and resulted in 36% of that population developing PI-IBS at 2 years post-infection.<sup>20,21</sup> Younger age, female gender, bloody stools, abdominal cramps, weight loss, and prolonged diarrhea during IE were independent risk factors for PI-IBS.<sup>20,22</sup> However, other studies have reported a much lower prevalence of PI-IBS and have not confirmed the same risk factors to be associated with the development of PI-IBS.<sup>23</sup> Previous meta-analyses (most recent published in 2007) concluded that IE increases the risk of PI-IBS. However, it included few studies, with

limited assessment of time-dependent point prevalence and relative risk of PI-IBS (compared to non-exposed controls), and could not comprehensively study host- and enteritis-related risk factors associated with PI-IBS development.<sup>6</sup> Additionally, pathogen-specific risk and natural history of PI-IBS were not reported. With increased recognition of PI-IBS, there have been several epidemiological studies since the previous meta-analysis.

Hence, we conducted a systematic review and meta-analysis of studies evaluating the association between IE and PI-IBS, evaluating the time- and pathogen-specific point prevalence, relative risk, host- (sex, psychological distress, and smoking) and enteritis- (abdominal pain, antibiotic use, bloody stool, diarrhea duration >7 days, fever and weight loss) related risk factors and outcomes of PI-IBS.

## METHODS

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The process followed *a priori* established protocol (PROSPERO # CRD42016035317).

### *Selection Criteria*

We included cohort studies with documented IE, reporting the prevalence of PI-IBS on at least one-time point  $\geq 3$  months following the IE. The IE episode was either laboratory proven or clinically suspected with presence of at least 2 of the following 3 symptoms: pain, fever and diarrhea or self-reported by the patient as “acute onset” of symptoms convincing of IE. The diagnosis of IBS was based on established criteria (Rome I, II or III) or ICD codes. We excluded (a) case-control studies (those examining IBS cases and controls and determining past IE

exposure), (b) cross-sectional studies, case series and case reports, and (c) studies with insufficient data to estimate prevalence.

### *Data Sources and Search Strategy*

We identified studies from a well-conducted prior meta-analysis on the prevalence of PI-IBS published in 2007<sup>6</sup> (AMSTAR rating<sup>24</sup>, 10/11), that used criteria similar to the current study. In addition, we searched multiple electronic databases for cohort studies of PI-IBS, from 2006-August 31, 2015, with the help of a medical librarian. The databases included Ovid Medline, EMBASE, Web of Science, and Cochrane Database of Systematic Reviews (detailed search strategy available in **Appendix Protocol**). Briefly, search items used included “Post-infectious irritable bowel syndrome”; “PI-IBS”; “Irritable bowel syndrome” OR “IBS” OR “Functional GI disorder” AND “Gastroenteritis” OR “Viral Gastroenteritis” OR “*Giardia* Gastroenteritis” OR “Giardiasis” OR “Norovirus” OR “*Campylobacter jejuni*” OR “*Salmonella*” OR “Salmonellosis” OR “*Shigella*” OR “Shigellosis”. Two investigators (FK and AW) independently reviewed the title and abstracts of all studies to exclude studies that did not address the research question of interest, based on pre-specified criteria. Subsequently, they independently reviewed the full texts of the remaining articles to determine whether they met inclusion criteria and contained relevant information. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article in consultation with the senior investigator (MG). Reference lists from included original articles and recent reviews on PI-IBS were hand searched to identify any additional studies. Proceedings of major gastroenterology conferences from 2012-15 were reviewed for relevant abstracts. In case of missing data, corresponding authors of included studies were contacted electronically on two occasions with request for missing data.

*Data Extraction and Quality Assessment*

Data extraction was performed independently by two investigators (FK and AW) using a standardized data extraction form. The variables abstracted included: author, year, geographic location, number of subjects in IE exposed group and control group (when available), accrual characteristics (inclusion criteria, exclusion criteria, study methods, case and control cohort identification), pathogen involved, time-point (s) studied following IE and the definition used for PI-IBS assessment. Additionally, we extracted host- and enteritis-related risk factors associated with development of PI-IBS. Host-related risk factors included: age, sex, smoking status, and psychological distress at time of IE; and IE-related factors included: abdominal pain, fever, duration of diarrhea, bloody stools, weight loss, and antibiotic use.

Quality assessment of the selected studies was assessed by two authors independently (FK and AW) using the modified Newcastle-Ottawa scale<sup>25</sup> (rated on a 0-6 scale for studies without a comparator group and 0-9 for studies with a comparator group) for cohort studies; within this, studies with scores 5 or 6 (out of 6, for point prevalence studies) and 8 or 9 (out of 9, for comparative studies on risk in exposed vs. non-exposed cohorts) were considered high quality, studies with scores 4/6 or 6 or 7 out of 9, were considered medium quality, and all other studies were considered low quality. The inter rater agreement between the two reviewers (FK and AW) for the questions on the Newcastle-Ottawa scale was 80%. The discrepant items were resolved by senior investigator (MG) independently reviewing the original study for that specific variable on the scale.

*Outcomes Assessed*

**Primary outcome:** The primary outcome of interest was the point prevalence of PI-IBS. This was estimated within 12m (overall, and at 3m, 6m and 12m) and >12m (overall, and at 13-



59m,  $\geq 60$ m) after IE, by type of pathogen (bacterial, viral and protozoal/parasitic). When studies reported prevalence of PI-IBS at multiple time points, then a hierarchical assessment of prevalence at 12m, 13-59m,  $\geq 60$ m, 6m and 3m was used to estimate “overall” point prevalence. Since gastrointestinal symptoms, and consequently the diagnosis of IBS based on symptom criteria can vary over time, we chose point prevalence of PI-IBS at different time points as more accurate representation, as compared to incidence or cumulative incidence of PI-IBS after IE.

### **Secondary outcomes:**

- (a) Relative risk of PI-IBS: To estimate the relative impact of IE on risk of IBS, we compared rates of new-onset IBS after IE with non-exposed individuals, overall, and within 12m and  $>12$ m after exposure (to compare time-specific risk). This was assessed separately by type of pathogen (bacterial, viral and protozoal/parasitic);
- (b) Risk factors for PI-IBS: We performed meta-analysis of demographic (age, sex, smoking), psychosocial (anxiety, depression at time of IE, measured using Hospital Anxiety and Depression Scale [HADS], somatization, and neuroticism) and enteritis-related risk factors (duration of IE, bloody stools, abdominal pain, fever, weight loss, antibiotic exposure) comparing individuals who developed PI-IBS after IE with those who did not;
- (c) Natural history and PI-IBS phenotype: Using studies which reported prevalence and outcome of PI-IBS at multiple time-points after IE, we assessed the natural history and prognosis of PI-IBS. Additionally, we reviewed the IBS subtype [constipation predominant IBS (IBS-C), diarrhea predominant IBS (IBS-D) and mixed IBS (IBS-M)] when it was reported.

To assess robustness of association between IE and PI-IBS, and to identify potential sources of heterogeneity, we conducted *a priori* subgroup analyses based on: geographic location (North America vs. Europe vs. Asia), method of assessing IE (laboratory confirmed vs. clinically

suspected), definition of IBS (Rome I vs. II vs. III), patient population (adults vs. children), attrition rate (survey response rates:  $\geq 80\%$ , 60-79%, 40-59% and  $< 40\%$ ) and study quality (high vs. medium vs. low). Sensitivity analysis based on type of publication (full-text vs. abstract) was also performed.

### *Statistical Analysis*

We used the random-effects model described by DerSimonian and Laird to calculate summary point prevalence and 95% confidence interval (CI).<sup>26</sup> Rates of PI-IBS in patients exposed to IE were compared with non-exposed individuals to estimate summary relative risk (RR) and 95% CI. To identify risk factors associated with PI-IBS, we pooled maximally adjusted odds ratio (OR; to account for confounding variables), where reported, using random-effects model. To estimate what proportion of total variation across studies was due to heterogeneity rather than chance,  $I^2$  statistic was calculated. In this, a value of  $< 30\%$ , 30%-59%, 60%-75% and  $> 75\%$  were suggestive of low, moderate, substantial and considerable heterogeneity, respectively.<sup>27</sup> Once heterogeneity was noted, between-study sources of heterogeneity were investigated using *a priori* defined subgroup analyses by stratifying original estimates according to study characteristics (as described above). In this analysis, a p-value for differences between subgroups ( $P_{\text{interaction}}$ ) of  $< 0.10$  was considered statistically significant, i.e., significant differences in summary estimates (either point prevalence of PI-IBS or relative risk of PI-IBS) were observed in different subgroup categories. Publication bias for PI-IBS prevalence and RR was assessed qualitatively using funnel plot, and quantitatively, using Egger's test.<sup>28</sup>

All p values were two tailed. For all tests (except for heterogeneity), a probability level  $<0.05$  was considered statistically significant. All calculations and graphs were performed using Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, NJ).

## RESULTS

From the previous systematic review, 16 studies were identified reporting prevalence of PI-IBS. With our updated systematic literature review, we identified an additional 29 unique articles meeting inclusion criteria. Therefore, we included 45 studies (n=21,421 participants with IE exposure) that reported the prevalence of PI-IBS.

<sup>4, 5, 7-13, 15-17, 20, 23, 29-59</sup> The flow diagram summarizing study identification and selection is shown in **Figure 1**.

### *Characteristics and Quality of Included Studies*

**Appendix Table 1** shows the baseline characteristics of the studies, and of the participants in the individual studies. Thirty five and 15 studies provided sufficient data for estimation of prevalence of PI-IBS within 12m and  $>12$ m of IE, respectively. The number of subjects examined in the individual studies in the IE exposed group ranged from 23-5894, and 1.2-80.5% of those developed PI-IBS. Four studies were in pediatric ( $<18$ y) population. The follow-up time period for assessment of PI-IBS ranged from 3m to 10y. Thirty seven studies used Rome criteria for diagnosing PI-IBS (12 Rome III, 17 Rome II, and 8 Rome I). Ten studies were conducted in North America, 26 in Europe, 6 in Asia, 1 in New Zealand 1 study was conducted in both Europe and North America and 1 in Israel. The mean age of participants in IE exposed group ranged from 5.3-65.4 years with 0.5-67.2% females. Bacterial enteritis was the

most common IE type studied. IE was laboratory confirmed in 24 studies and clinically suspected in 21 studies. **Appendix Table 2** outlines cohort characteristics (inclusion and exclusion criteria), methodology for PI-IBS assessment (presence of IBS prior to IE, survey response rates, and data completeness) and selection of controls. Out of the 45 studies, 41 studies used online or mailed survey questionnaires or in person or telephone interviews and 4 studies were conducted using electronic databases. Of the ones using databases, two used ICD codes alone,<sup>7, 33</sup> one used ICD codes plus clinician documentation<sup>17</sup> and one used ICD codes plus IBS confirmation by a physician.<sup>16</sup> The survey response rate was variable (36-96%). Exclusion of pre enteritis IBS was specified in 35 of 45 studies and IBD in 26 of the 45 studies. Additionally, one study excluded IE episodes within 12 m before the current IE episode<sup>33</sup> and one excluded patients with another IE episode anytime in the past.<sup>16</sup>

The median quality score for prevalence studies included was 5 (range 3-6) on a 0-6 scale and 7 (range 4-9) for RR studies on a 0-9 scale (**Appendix Table 3**). There was variability in the survey response rate among the studies (<40% to  $\geq 80\%$  response); 16/45 studies had  $\geq 80\%$  response rate.

### *Prevalence of PI-IBS*

Overall, pooled prevalence of PI-IBS was 11.5% (2217/21421, 95% CI=8.2-15.8), with no significant difference in the reported PI-IBS prevalence among studies estimating prevalence at 3, 6, 12, 13-59 or  $\geq 60$  months following IE ( $P_{\text{interaction}}=0.63$ ) (**Appendix Table 4**). At 12m and beyond 12m, the point prevalence of PI-IBS was 10.1% (911/15800, 95% CI=7.2-14.1) and 14.5% (1466/12007, 95% CI=7.7-25.5), respectively. Summary estimate shows significant heterogeneity ( $I^2 \geq 90\%$ ) among studies.

Overall, the rates of PI-IBS were highest after protozoal/parasitic IE,<sup>11-13, 46</sup> followed by bacterial IE,<sup>4, 5, 17, 20 15, 31, 34, 35, 38-44, 47, 50-55, 57, 58</sup> and lowest rates were seen with viral IE<sup>7-10</sup>

(**Figure 2**). Summary estimate shows significant heterogeneity ( $I^2 \geq 95\%$ ) among studies.

However, when examining rates within and beyond 12m, viral IE was associated with high rates PI-IBS within 12m of IE (prevalence=19.4; 95% CI, 13.2-27.7), but this declined beyond 12m of exposure (prevalence=4.4; 95% CI, 0.3-39.9) (**Appendix Table 5**). Four studies evaluating pediatric age patients found a PI-IBS prevalence of 14.7% (95% CI=7.3-27.2;  $I^2=79$ ) compared to 11.1% (95% CI=7.8-15.6;  $I^2=98$ ) in 41 adult studies ( $P_{\text{interaction}}=0.48$ ). Given the significant heterogeneity, summary estimates should be used with caution.

Considerable heterogeneity is observed in the reported prevalence of PI-IBS. To understand the variability in prevalence, several *pre-specified* subgroup analyses were performed (**Table 1**). We observed significantly higher prevalence of PI-IBS (18.6%; 95% CI, 13.7-24.8) in studies with low response rates (particularly, <40% response), suggesting a responder bias; in studies in which response rates was  $\geq 80\%$ , overall prevalence of PI-IBS was 7.9% (95% CI, 4.1-14.6). We did not observe significant difference in reported prevalence of PI-IBS in patients with laboratory confirmed IE (prevalence, 12.9%; 95% CI, 8.6-19.1) as compared to clinically suspected IE or self-reported (prevalence, 9.9; 95% CI, 6.0-16.1), based on criteria to define IBS (Rome I, II or III) or geographical location of study. On sensitivity analysis, observed prevalence was lower in studies published as full-text as compared to those published in abstract form.

### *Relative risk of PI-IBS*

Thirty studies included both IE exposed and non-exposed individuals (IE exposed n=18023 and non-exposed n=649496). Controls were age- and sex-matched (18 studies) and

derived from the same geographic population and using the same search strategy as the IE cases (28 studies). Overall, patients exposed to IE had 3.8 times higher risk of developing IBS as compared to non-exposed individuals. The magnitude of increased risk was higher within 12m after IE (RR, 4.23; 95% CI, 3.15-5.69;  $I^2=61\%$ ; 23 studies), and decreased (though remained significantly higher compared to non-exposed group) beyond 12m (RR, 2.33; 95% CI, 1.82-2.99;  $I^2=76\%$ ; 12 studies) [p-value for difference in RR within and beyond 12m=0.002] (Table 2; **Appendix Table 6**). Except for studies examining relative risk at 6 months ( $I^2=20\%$ ), summary estimate shows substantial heterogeneity ( $I^2=71-79\%$ ) among studies pooling estimates at different time-points. Four studies evaluating pediatric population observed a 4.1 times increased risk of PI-IBS (95% CI= 2.05-8.15;  $I^2=0$ ) compared to the 3.8 fold increased risk in 26 adult studies (95% CI= 2.89-5.09;  $I^2=81$ ), as compared to the non-exposed individuals ( $P_{\text{interaction}}=0.87$ ).

Due to considerable difference in RR of PI-IBS within and beyond 12m, further analysis was stratified by time since exposure. Within 12m of IE, the observed RR of PI-IBS was higher in European and Asian countries as compared to studies conducted in North America (**Table 2**). There was no difference in observed RR based on criteria for IBS diagnosis, method of confirming IE, or by the type of the organism. Beyond 12m of IE, we observed a significant difference in RR of PI-IBS based on organism of exposure, with higher rates observed with protozoal/parasitic and bacterial IE as compared to viral IE, and based on study quality (high rates observed in medium and high quality studies, as compared to low quality studies).

On comparing the magnitude of increased risk of IBS by time since exposure to IE, we observed that RR of PI-IBS due to protozoal/parasitic remained stable over time, whereas the RR of IBS decreased in magnitude with bacterial (RR for within 12m of IE vs. >12m after IE: 4.2 vs.

2.2,  $p=0.01$ ); there was a non-significant decrease in magnitude of risk with viral IE with increasing time (RR for within 12m of IE vs. >12m after IE: 4.5 vs. 1.2,  $p=0.13$ ).

### *Risk factors for development of IBS after infectious enteritis*

Of the 45 included studies, 33 assessed at least one risk factor for PI-IBS development (**Figure 3**). These are divided into demographic, enteritis-related and psychological factors below.

Demographic factors: Five studies assessed age as a risk factor.<sup>17, 32, 37, 50, 54</sup> Variability in classification and lack of data precluded calculation of pooled OR. Twenty one studies appraised sex as a risk factor. Female sex was associated with a 2.2 times higher odds of developing PI-IBS (OR, 2.19; 95% CI, 1.57-3.07) based on 11 studies with extractable data.<sup>4, 8, 17, 20, 23, 31, 35, 40, 44, 45, 50</sup> Summary estimate shows substantial heterogeneity ( $I^2=72\%$ ). Three of the 9 studies without extractable data also showed a significant association for female sex.<sup>5, 13, 56</sup> Based on two studies,<sup>17, 23</sup> smoking was not associated with increased odds of PI-IBS (OR, 1.15; 95% CI, 0.90-1.46); an additional study without extractable data also observed a non-significant association.<sup>42</sup>

Psychological factors: Prevalent anxiety (OR, 1.97; 95% CI, 1.32-2.94) and depression (OR, 1.49; 95% CI, 1.17-1.90) measured using HADS, at time of IE was associated with PI-IBS development, based on 5<sup>5, 17, 31, 44, 56</sup> and 4 studies,<sup>17, 31, 44, 56</sup> respectively. Summary estimate shows considerable heterogeneity for anxiety ( $I^2=90\%$ ) and moderate for depression ( $I^2=48\%$ ). Four additional studies were not included due to lack of sufficient data for meta-analysis; however, 3 of those 4 also showed a significant association.<sup>5, 15, 37</sup> Somatization at the time of IE was assessed in four studies using the somatic symptom checklist and was associated with PI-IBS (OR, 4.05; 95% CI, 2.71-6.03).<sup>5, 31, 37, 56</sup> Neuroticism at the time of IE was also associated

with PI-IBS development (OR, 3.26; 95% CI, 1.62-6.55) based on two studies.<sup>5, 56</sup> Adverse life events in preceding year,<sup>5</sup> hypochondriasis,<sup>5</sup> extroversion,<sup>56</sup> negative illness beliefs,<sup>44</sup> prior history of stress<sup>17</sup> and sleep disturbance<sup>17</sup> were also found to be associated with PI-IBS development in isolated studies.

Enteritis-related factors: Abdominal pain during IE was assessed in 15 studies as a risk factor for PI-IBS development, 9 of which found a significant association, 4 of which<sup>10, 20, 31, 33</sup> had data for summarization (OR, 3.26; 95% CI, 1.30-8.14). Summary estimate shows considerable heterogeneity ( $I^2=86\%$ ). Based on 8 studies,<sup>4, 20, 23, 31, 39, 40, 50, 54</sup> diarrhea >7 days was associated with increased odds of PI-IBS (OR, 2.62; 95% CI, 1.48-4.61). Summary estimate shows considerable heterogeneity ( $I^2=86\%$ ). Bloody stool was associated with PI-IBS development based on 4 studies<sup>20, 23, 31, 40</sup> with an OR of 1.86 (95% CI, 1.14-3.03). Summary estimate shows substantial heterogeneity ( $I^2=65\%$ ). Fever and weight loss with IE were not observed to be risk factors for PI-IBS. Based on 7 studies,<sup>17, 23, 31, 40, 44, 45, 59</sup> antibiotic exposure at time of PI-IBS was associated with an increased odds of developing PI-IBS (OR, 1.69; 95% CI, 1.20-2.37) ( $I^2=32\%$ ).

#### *Natural history of PI-IBS*

Thirteen studies reported phenotype of new-onset IBS after IE. Three of these reported IBS-D or “non-constipation” predominant as the major IBS subtype. Of the other 10 studies, IBS-M was the most common phenotype reported (142/304, 46%, 95% CI, 31-62%) followed by IBS-D (120/304, 40%, 95% CI, 25-57%); IBS-C was the least common least common phenotype (42/304, 15%, 95% CI, 10-21%).



Overall, nine studies reported PI-IBS prevalence at multiple time points. Five of these had complete data, however, four studies had anywhere from 17-60% data missing at the longest time-point of assessment after IE. The at-risk population was the IE population at inception. Three studies observed decline in prevalence over time, whereas three observed an increase in prevalence over time since the IE episode; 2/8 reported stable prevalence over time (**Appendix Figure 1**).

### *Publication Bias*

There was no evidence of publication bias based on qualitative assessment using the funnel plot or on quantitative analysis, based on Egger's test for the primary outcome of prevalence of PI-IBS ( $p=0.15$ ) or for RR of PI-IBS ( $p=0.13$ ). However, given high heterogeneity observed in the overall analysis, these results should be interpreted with caution.

## **DISCUSSION**

In this systematic analysis of 45 studies reporting on new-onset IBS in 21,421 subjects with IE, we made several key observations. **First**, we estimated a pooled point prevalence of PI-IBS of 11% (95% CI, 8.2-15.8), i.e., about 1 in 9 (95% CI, 7-13) individuals develop new-onset IBS following an episode of IE. The most common phenotypes are mixed and diarrhea predominant IBS. The overall risk of developing IBS is 4.2 times higher in individuals exposed to IE, as compared to non-exposed individuals, within the first year of exposure, and continues to remain high beyond the first year of exposure, albeit to a lower magnitude (RR, 2.3). This increased risk was stable across adults and children, across geographic regions, and in patients

with clinically suspected or laboratory confirmed IE. **Second**, the risk of IBS is highest with protozoal enteritis, with ~40% of individuals developing IBS, followed by bacterial enteritis. Viral enteritis confers high risk of PI-IBS within the first year of exposure (RR similar to bacterial and protozoal enteritis), but this risk decreases to that of general non-exposed population beyond 1 year of exposure. In contrast, the risk of PI-IBS remains high even beyond 12m of exposure with bacterial and protozoal enteritis. **Third**, female sex, clinically severe IE (diarrhea duration >7d, bloody stools, abdominal pain), use of antibiotics to treat IE and psychological distress at the time of IE are associated with an increased risk of PI-IBS. Our findings on the chronic sequelae of gastrointestinal infections are significant from a public-health perspective. The Centers for Disease Control and Prevention (CDC) estimates that 1 in 6 U.S. adults have a reported case of foodborne illness annually and there are additional unreported cases.<sup>18</sup> In addition to the risk associated with foodborne illnesses in the community, over 60 million annual U.S. travelers to international destinations are at an increased risk.<sup>60, 61</sup> Finally, IE is common during deployment and recent studies have shown an increased incidence of IBS and other functional gastrointestinal disorders in the military personnel who are also under significant psychological stress during deployment.<sup>62</sup> Even with a conservative estimate of 15% of the U.S. population being exposed to IE annually, based on our findings, an approximate 1.6% of the U.S. population (or 5.1 million people) likely develops new-onset IBS following IE annually. Modeling studies have estimated that PI-IBS probably contributes to the majority of IBS cases.<sup>63</sup>

Our 11% pooled prevalence of PI-IBS (6-12 months post IE) is comparable to the ~10% pooled prevalence reported in the previous meta-analyses.<sup>6, 64</sup> However, the previous meta-analyses<sup>6, 64</sup> observed a higher RR of PI-IBS (5.2-7.6) than our study. This is likely due to

overestimation of RR with a small number of studies, with lower than expected prevalence of IBS in the unexposed cohorts in those studies.

The high magnitude (~40%) of PI-IBS risk observed after protozoal enteritis merits attention. Three studies published by the same group showed PI-IBS prevalence ranging from 39-80% following protozoal (*Giardia*) enteritis.<sup>11-13</sup> Two of these studies were large and had a control group.<sup>12, 13</sup> However, the incidence was studied at single time points >12 months in all 3 of these studies. Only one of these studies confirmed *Giardia* eradication in the stool sample;<sup>11</sup> hence, some of the PI-IBS could be misclassification of chronic Giardiasis. In contrast, viral enteritis was associated lowest prevalence of PI-IBS at 4% and an RR of 1.2 at >12 months (non-significant when compared to the non-exposed). The pathophysiological mechanisms for the short lasting nature of virus related PI-IBS are not completely understood. It is possible that viruses cause less mucosal invasion and hence less stimulation of the neuromuscular and immune apparatus and downstream plasticity which can then lead to PI-IBS. Additionally, it is possible that viral enteritis does not have a significant effect on the microbiota composition and function which has been hypothesized to play a role in pathophysiology of PI-IBS.<sup>65</sup>

Identification of high-risk patients and potentially modifiable risk factors for PI-IBS is of interest in preventing development of PI-IBS. We comprehensively extracted data on risk factors from all of the available studies in a time frame. Females have 2.4 times odds of developing PI-IBS, as compared to males. This likely reflects an overall increased predilection for development of IBS symptoms in females. Anxiety, depression, somatization and neuroticism at the time of IE are potentially modifiable risk factors for development of PI-IBS. Psychological distress and maladaptive coping with symptoms are commonly observed in patients with IBS.<sup>66, 67</sup> It is possible that psychological distress increases vulnerability to IBS development through

increasing pathogenic virulence<sup>68</sup> or attenuating host mucosal barrier and immune responses.<sup>69</sup> The clinical severity of IE episode is associated with PI-IBS development. This could be due to pathogen or host factors. Finally, antibiotic use is a risk factor for PI-IBS development. Plausible mechanisms include microbiota perturbations in response to pathogenic insult and impaired ability of a subset of hosts to reestablish their baseline commensal microbiome. This could also be a reflection of “clinically severe” IE subgroup that is also more likely to receive antibiotics during the IE episode.

The strengths of our meta-analysis include (a) systematic literature search of multiple databases to identify 45 cohort studies that included over 20,000 IE patients, (b) comprehensive assessment all aspects of PI-IBS (prevalence, relative risk, risk factors, prognosis/natural history), and (c) with detailed, clinically relevant, *a priori* subgroup and sensitivity analyses. Our meta-analysis builds upon initial observations in previous meta-analyses, providing more detailed insights into the risk of PI-IBS over time, by different pathogens, and provides a more comprehensive understanding of risk factors, by summarizing data from 45 studies. First, our meta-analysis provides risk estimates from a significantly larger number of studies and assesses long-term risk (>12 months after IE in 12 studies) which was not studied in the previously published meta-analysis<sup>6</sup> allowing us to conclude that increased risk of PI-IBS persists for an extended period after IE, albeit at lower rates than observed within 1 year of IE. Second, we were able to evaluate and observed differences in the risk of PI-IBS based on pathogen type (bacterial, viral, protozoal/parasitic). Third, while the previous meta-analysis assessed only anxiety and depression as risk factors for PI-IBS (based upon 4 studies), we have comprehensively assessed risk associated with several host (sex, smoking, anxiety, depression, somatization and neuroticism) and enteritis-related factors (abdominal pain, antibiotic use, bloody stool, duration

of enteritis, fever, and weight loss) based on a larger number of studies, which may help identify patients at highest risk of PI-IBS after IE, enabling risk stratification for development of early strategies to minimize risk of long-term morbid sequelae of IE. Fourth, in contrast to the previous meta-analysis, we have conducted multiple *a priori* subgroup analysis to evaluate for stability of association and identify sources of heterogeneity across a range of factors. Through these analyses, we identified significant differences in observed risk of PI-IBS based on pathogen causing IE, differences in survey response rate as well as geographical location. We also observed that the point prevalence of PI-IBS was stable at different time points, using different criteria for IBS diagnosis, and by different methods of diagnosing IE. Fifth, from the 10 studies with data available on PI-IBS phenotype, we were able to conclude that IBS-M is the most common PI-IBS phenotype (46%), followed by IBS-D (40%) and IBS-C rarest (15%). Finally, through studies that provided data on risk of PI-IBS at different time points, we were able to offer a more comprehensive insight into the natural history of PI-IBS after IE.

Our meta-analysis has several limitations. First, we observed high heterogeneity for several analyses ( $I^2 > 95\%$  for pooled point prevalence summary estimates). Additionally, certain risk-factor estimates also had substantial heterogeneity (abdominal pain, anxiety, duration of diarrhea  $> 7$  days, female sex). Heterogeneity is not uncommon in prevalence meta-analysis, partly due to large sample size of individual studies with precise estimates resulting in statistical heterogeneity. Conceptually, we minimized heterogeneity with well-defined inclusion and exclusion criteria. We also performed pre-planned subgroup analyses to assess stability of association and explore sources of heterogeneity. In our analysis, heterogeneity could be partly explained by response rates; the observed prevalence of PI-IBS, was 7.9% in studies with the survey response rates  $> 80\%$  as compared to 18.2% observed in studies with response rate  $< 40\%$ .

This is likely related to responder bias with symptomatic individuals more likely to respond to surveys. The reported rates of PI-IBS were also higher in studies published only in abstract form, as compared to studies published in full after thorough peer review; estimates derived from the latter are probably more reliable. Second, while quantifying risk factors associated with PI-IBS, we used available adjusted and unadjusted data from individual studies for pooling. Unfortunately, multivariate analysis was inconsistently reported with adjustment for different confounding variables across studies, and this somewhat limits the inference that can be drawn from these observations. We acknowledge that pooling unadjusted estimates is not able to account for confounding factors, and the implicated risk factors observed through this analysis, may not necessarily be due to the single studied factor, but rather a conglomeration of factors (e.g., clinically severe IE and antibiotic use during IE, etc.). Finally, at an individual study level, most of the included studies were periodic surveys to individuals with known exposure to IE, and hence, were able to estimate cross-sectional prevalence, as opposed to the true incidence, and incompletely assessed the natural history of IBS in this population. Similar to IBS in general,<sup>70, 71</sup> the PI-IBS diagnosis made by symptom based criteria over multiple time points following IE can fluctuate in individual subjects (complete or partial symptom resolution) or shift between different categories of FGIDs. However, the summary estimates should be interpreted with caution considering observed heterogeneity.

In conclusion, based on a meta-analysis of 45 studies, we observed that about one of every 9 individuals (95% CI, 7-13) exposed to food borne illness and other forms of infectious enteritis may develop IBS, at a rate 4 times higher than the non-exposed individuals. Protozoal and bacterial enteritis confer the greatest overall risk, although the magnitude of increased risk diminishes with time since exposure; in contrast, risk of IBS following viral enteritis is lower,

with highest burden seen within the 1<sup>st</sup> year of exposure, and risk becomes comparable to the general, non-exposed population following that. It is important to consider PI-IBS during care of patients with chronic gastrointestinal symptoms following an episode of IE, especially in patients at high-risk of developing the same: females, patients with prevalent anxiety and depression at time of IE, and patients with clinically severe IE, and those treated with antibiotics. Finally, antibiotic stewardship during IE may reduce the risk of PI-IBS development. Future research will benefit from registries for prospective follow up of patients with IE and from mechanistic studies to determine host- and pathogen-related pathophysiological mechanisms that will inform on PI-IBS and potentially IBS in general.

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Author names in **bold** designate shared co-first authorship.

**Figure Legends:**

**Figure 1:** Study selection flow-diagram

**Figure 2:** Summary point prevalence of PI-IBS with bacterial, protozoal/parasitic and viral infectious enteritis. Considerable heterogeneity ( $I^2 > 95\%$ ) was observed for all analyses.

**Figure 3:** Pooled odds ratio for host- and infectious enteritis-episode related risk factors for PI-IBS development. Moderate to considerable heterogeneity was observed for most estimates ( $I^2$  values for abdominal pain = 86%, antibiotic exposure = 32%, anxiety = 90%, bloody stool = 65%, depression = 48%, duration of initial enteritis >7 days = 86%, female sex = 72%, fever at time of enteritis = 69%, neuroticism – 0%, somatization = 0%, smoking = 8%, weight loss = 75%).

**Table 1:** Subgroup analysis of PI-IBS prevalence (regardless of the time since infection) to assess stability of association and explore sources of heterogeneity.  $P_{\text{interaction}} < 0.10$  implies statistically significant differences in the point prevalence of PI-IBS between different subgroups.

Subgroups	Events/Total exposed (No. of studies)	Prevalence of PI-IBS (%)	95% CI	$P_{\text{interaction}}$
Overall	2217/21421 (45)	11.5	8.2-15.8	-
By survey response rate				0.049
• $\geq 80\%$	429/12074 (16)	7.9	4.1-14.6	
• 60-79%	765/3490 (9)	11.7	5.7-22.5	
• 40-59%	189/1952 (9)	11.3	7.2-17.4	
• $< 40\%$	832/3905 (11)	18.6	13.7-24.8	
Rome Criterion <sup>a</sup>				0.93
• Rome I	608/3039 (9)	12.9	7.7-20.9	
• Rome II	515/8798 (18)	12.0	7.4-18.8	
• Rome III	966/6332 (12)	13.9	7.4-24.4	
Location <sup>b</sup>				0.34
• North America	613/4704 (10)	7.5	3.8-14.1	
• Europe	1497/15812 (27)	13.0	8.1-20.3	
• Asia	101/861 (7)	12.2	9.9-14.8	
Publication type				0.054
• Full text	2038/20490 (41)	10.9	7.6-15.5	
• Abstract	177/931 (4)	17.4	12.7-23.4	
Method of IE Diagnosis				0.42
• Laboratory confirmed	1169/7281 (24)	12.9	8.6-19.1	
• Clinically suspected or self-reported	1046/14140 (21)	9.9	6.0-16.1	
Study Quality				0.48
• High quality	1223/13927 (25)	13.0	8.3-19.9	
• Medium quality	838/4143 (13)	11.2	6.3-19.2	
• Low quality	154/3351 (7)	7.3	3.0-16.5	

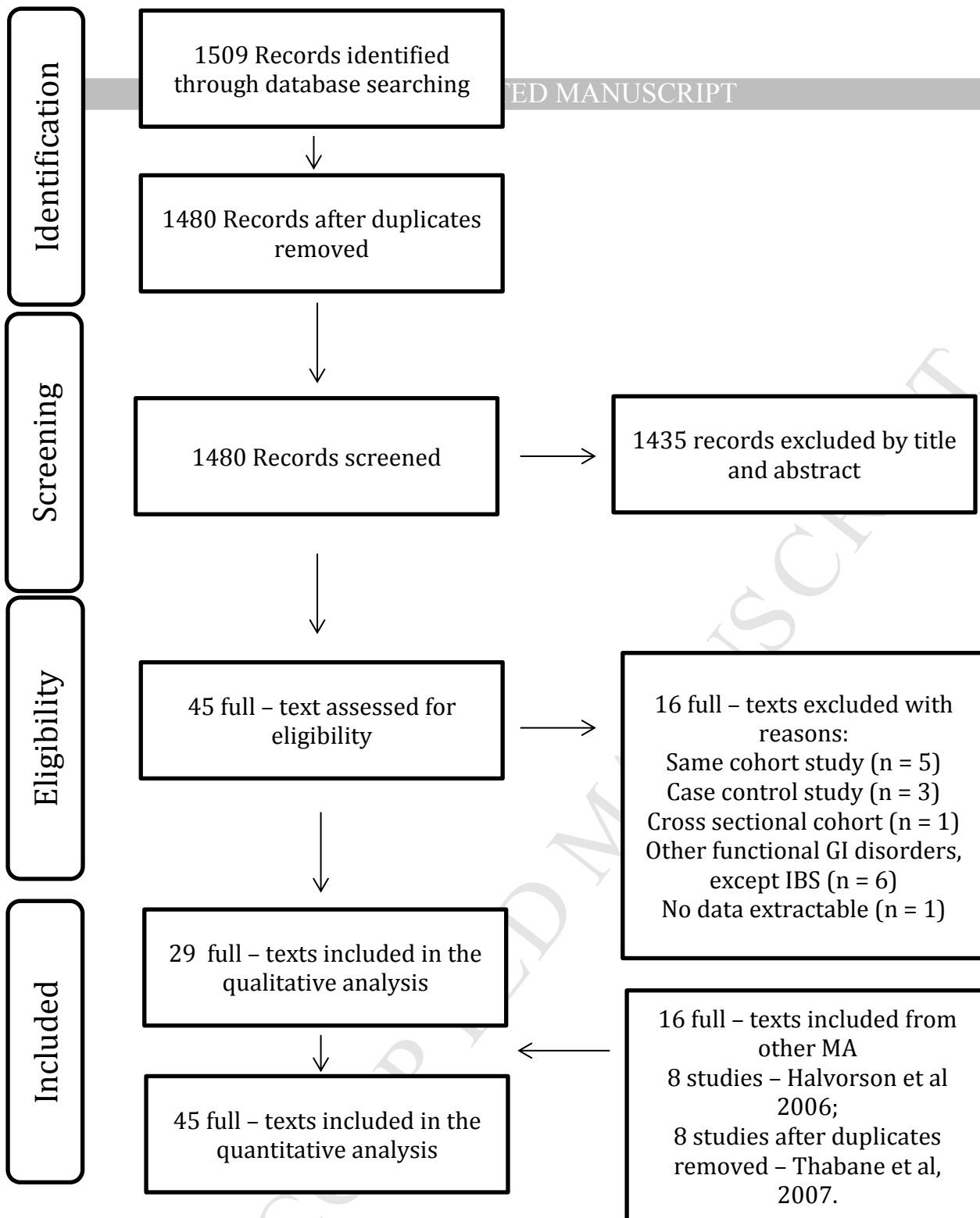
<sup>a</sup> excluded 6 studies in which criterion was not reported

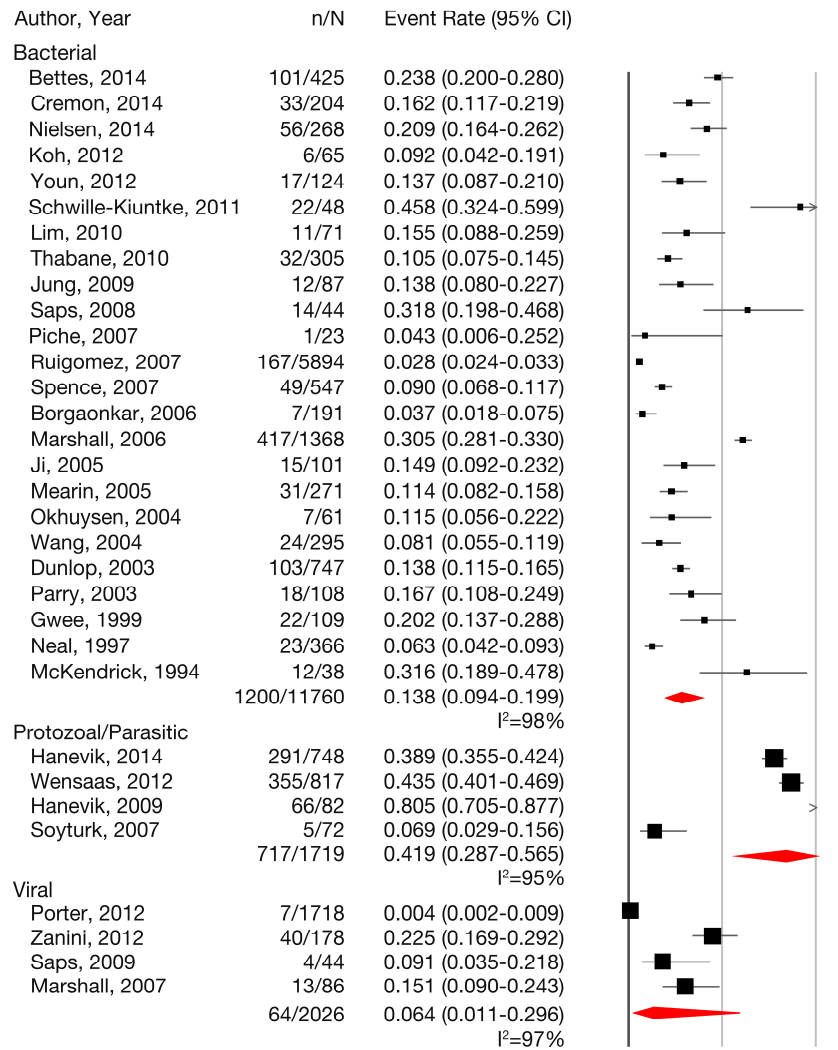
<sup>b</sup> combined 1 study from New Zealand with Europe, and excluded one study performed in both Europe and North America

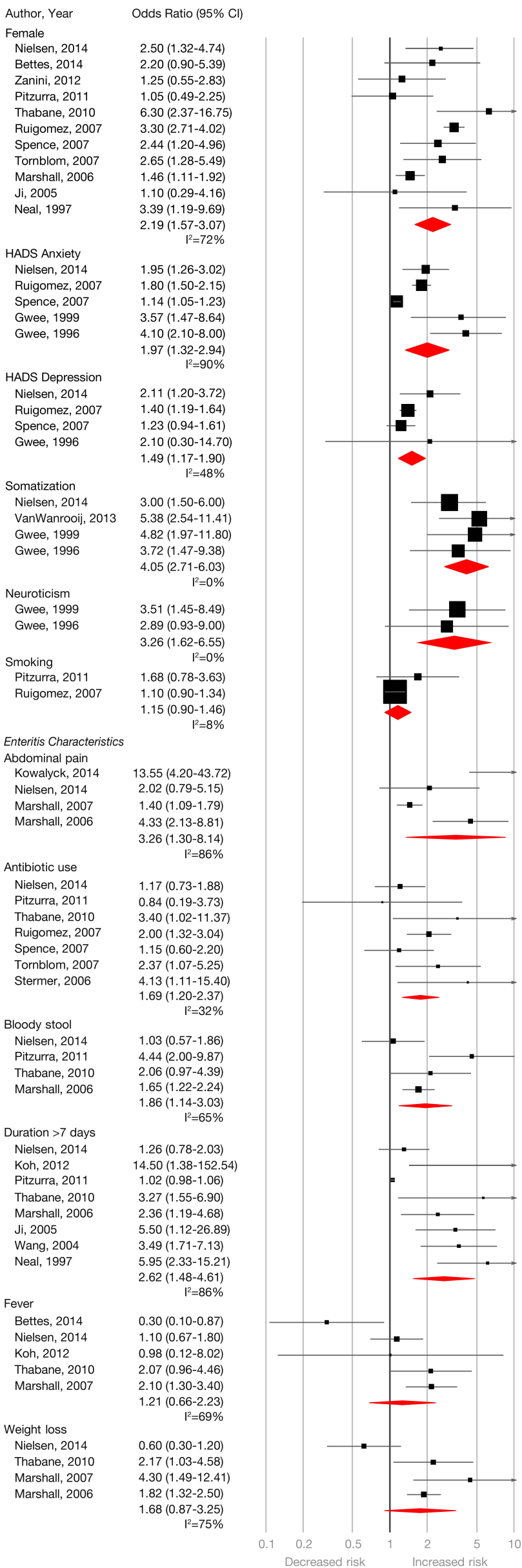
**Table 2:** Subgroup analysis for PI-IBS relative risk in exposed as compared to the participants not exposed to gastrointestinal infection.  $P_{\text{interaction}} < 0.10$  implies statistically significant differences in the relative risk of PI-IBS between different subgroups.

Subgroups (No. of studies)	Events/Total exposed	Events/Total unexposed	Relative risk	95% CI	P <sub>interaction</sub>
Within 12m of exposure					
Overall (23)	500/12831	2397/639635	4.23	3.15-5.69	
Rome Criterion <ul style="list-style-type: none"><li>Rome I (2)</li><li>Rome II (12)</li><li>Rome III (7)</li></ul>	15/134 257/8214 197/4159	3/87 268/49482 98/5553	2.10 4.17 3.13	0.62-7.12 2.93-5.92 2.18-4.47	0.37
Organism <ul style="list-style-type: none"><li>Bacterial (10)</li><li>Viral (2)</li><li>Protozoal (1)</li></ul>	254/7189 53/264 5/72	261/48340 5/147 0/27	4.22 4.48 4.22	2.84-6.25 1.01-19.95 0.24-73.83	1.00
Location <ul style="list-style-type: none"><li>North America (5)</li><li>Europe (13)</li><li>Asia (5)</li></ul>	49/697 367/11527 84/725	31/1108 2349/637701 17/826	2.02 4.69 5.50	1.24-3.30 3.20-6.86 2.96-10.21	0.01
Method of diagnosis <ul style="list-style-type: none"><li>Laboratory confirmed (8)</li><li>Clinically suspected (15)</li></ul>	141/1421 359/11528	2064/585513 333/54122	5.01 3.62	2.67-9.40 2.72-4.85	0.36
Study Quality <ul style="list-style-type: none"><li>High (9)</li><li>Medium (9)</li><li>Low (5)</li></ul>	213/9187 153/2274 134/1488	2281/643240 53/2871 63/2524	4.94 3.99 3.49	2.83-8.63 2.45-6.50 2.08-5.86	0.67
>12m after exposure					
Overall (12)	1363/11439	1060/57240	2.33	1.82-2.99	
Rome Criterion <ul style="list-style-type: none"><li>Rome I (2)</li><li>Rome II (4)</li><li>Rome III (3)</li></ul>	432/1445 216/6330 679/1769	73/725 650/47291 284/2195	2.99 2.14 2.42	2.37-3.77 1.82-2.52 1.56-3.78	0.07
Organism <ul style="list-style-type: none"><li>Bacterial (7)</li><li>Viral (3)</li><li>Protozoal (2)</li></ul>	691/8035 26/1839 646/1565	758/48291 46/6943 256/2006	2.24 1.19 3.25	1.63-3.10 0.50-2.84 2.86-3.69	0.011
Location <ul style="list-style-type: none"><li>North America (4)</li><li>Europe (4)</li><li>Asia (3)</li></ul>	417/3468 846/7663 42/264	119/7762 924/49191 15/243	2.10 2.34 2.50	0.93-4.75 1.65-3.32 1.42-4.39	0.94

Method of diagnosis					
• Laboratory confirmed (5)	690/3531	328/9114	1.92	1.20-3.08	0.31
• Clinically suspected (7)	673/7908	732/48126	2.52	2.01-3.15	
Study Quality					
• High (5)	634/7597	745/48019	2.10	1.45-3.04	<b>0.005</b>
• Medium (4)	696/1994	265/2273	3.26	2.87-3.70	
• Low (3)	33/1848	50/6948	1.23	0.58-2.62	









## Appendix Protocol

Ovid

Database(s): Embase 1988 to 2015 Week 15, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials March 2015, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 2015

Search Strategy:

#	Searches	Results
1	"Postinfectious irritable bowel syndrome*".mp.	201
2	"Post-infectious irritable bowel syndrome*".mp.	218
3	"PI-IBS".mp.	299
4	exp Irritable Bowel Syndrome/	20440
5	exp Colonic Diseases, Functional/ ((functional adj1 (colonic or GI or gastrointestinal or intestinal) adj1 (disease* or disorder* or syndrome*)) or "colon spasm*" or colonospasm* or IBS or "irritable bowel*" or "irritable colon" or "mucomembraneous colitis" or "mucomembranous colitis" or "mucous colitides" or "mucous colitis" or "spastic colitis" or "spastic colon" or "unstable colon").mp.	24986
6		34222
7	4 or 5 or 6	35992
8	exp Gastroenteritis/	176218
9	exp Giardia/	6508
10	exp giardiasis/	8140
11	exp Norovirus/	6823
12	exp norovirus infection/	486
13	exp Campylobacter jejuni/	10758
14	exp Campylobacter Infections/	7720
15	exp Salmonella/	80337
16	exp Salmonella Infections/	44946
17	exp Shigella/	20245
18	exp Dysentery, Bacillary/	9935
19	exp shigellosis/	9935
20	exp Escherichia coli/	458588
21	exp Escherichia coli Infections/	30841
22	exp infection/ ("alkalescens-dispar group" or "Bacillus coli" or "Bacillus escherichii" or "bacillus paratyphi alcaligenes" or "bacillus paratyphosus" or "bacillus schottmuelleri" or "Bacterium coli" or "bacterium E3" or campylobacter or "coli bacillus" or "coli bacterium" or colibacilloses or colibacillosis or colibacillus or "colon bacillus" or dysentery or "E coli" or eaggec or "Enterococcus coli" or "Escherichia alkalescens dispart" or "Escherichia coli" or "gastro enteritides" or "gastro enteritis" or	2702989
23		3867080

gastroenteritides or gastroenteritis or giardia or giardiasis or giardiasis or giardiosis or infection\* or infectious or lamblases or lamblasis or Norovirus\* or "Norwalk agent\*" or "Norwalk calicivirus\*" or "Norwalk gastroenteritis virus\*" or "Norwalk parvovirus\*" or "Norwalk virus\*" or "Norwalk-like Virus\*" or Salmonella or salmonellosis or salmonellosis or Shigella or shigellosis or shigellosis or "Small Round-Structured Virus\*" or "Vibrio hepaticus" or "Vibrio jejuni" or "Vibrio jejuni").mp.

24 or/8-23	4889582
25 1 or 2 or 3 or (7 and 24)	6210
26 exp evidence based medicine/	771247
27 exp meta analysis/	145619
28 exp Meta-Analysis as Topic/	32796
29 exp "systematic review"/	86935
30 exp controlled study/	4685158
31 exp Randomized Controlled Trial/	743358
32 exp triple blind procedure/	87
33 exp Double-Blind Method/	347502
34 exp Single-Blind Method/	52773
35 exp latin square design/	289
36 exp Placebos/	275762
37 exp Placebo Effect/	7657
38 exp comparative study/	2491267
39 exp Cohort Studies/	1721404
40 exp longitudinal study/	265513
41 exp retrospective study/	911666
42 exp prospective study/	729925
43 exp population research/	70237
44 exp observational study/	78682
45 exp clinical trial/	1772283
46 clinical study/	59384
((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or 12321204 "comparative study" or "comparative survey" or "comparative analysis" or cohort* or longitudinal* or retrospectiv* or prospectiv* or "population study" or "population survey" or "population analysis" or "population research" or ("follow-up" or followup) adj (stud* or survey or analysis)) or ((observation or observational) adj (study or survey or analysis)) or "clinical study" or "clinical	

trial" or "multicenter study" or "multi-center study").mp.pt.	
48 or/26-47	12416824
49 25 and 48	2676
50 from 25 keep 3491-6079	2589
limit 50 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or multicenter study or observational study or randomized controlled trial or	
51 pragmatic clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or observational study or randomized controlled trial or pragmatic clinical trial or systematic reviews) [Limit not valid in Embase,CCTR,CDSR; records were retained]	399
52 49 or 51	2688
limit 52 to (editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper	
53 article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	153
54 from 53 keep 1-105	105
55 52 not 54	2583
56 55 not (exp animals/ not exp humans/)	2423
57 from 25 keep 6080-6210	131
58 56 or 57	2478
59 limit 58 to english language [Limit not valid in CDSR; records were retained]	2276
60 limit 59 to yr="2007 -Current"	1552
61 remove duplicates from 60	1323

Web of Science

**TOPIC:** ("Postinfectious irritable bowel syndrome\*" OR "Post-infectious irritable bowel syndrome\*" OR (((functional NEAR/1 (colonic or GI or gastrointestinal or intestinal) NEAR/1 (disease\* or disorder\* or syndrome\*)) OR "colon spasm\*" OR colonospasm\* OR IBS OR "irritable bowel\*" OR "irritable colon" OR "mucomembraneous colitis" OR "mucomembranous colitis" OR "mucous colitides" OR "mucous colitis" OR "spastic colitis" OR "spastic colon" OR "unstable colon") AND ("alkalescens-dispar group" OR "Bacillus coli" OR "Bacillus escherichii" OR "bacillus paratyphi alcaligenes" OR "bacillus paratyphosus" OR "bacillus schottmuelleri" OR "Bacterium coli" OR "bacterium E3" OR campylobacter OR "coli bacillus" OR "coli bacterium" OR colibacilloses OR colibacillosis OR colibacillus OR "colon bacillus" OR dysentery OR "E coli" OR eaggec OR "Enterococcus coli" OR "Escherichia alkalescens dispar" OR "Escherichia coli" OR "gastro enteritides" OR "gastro enteritis" OR gastroenteritides OR gastroenteritis OR giardia OR giardiases OR giardiasis OR giardiosis OR infection\* OR infectious OR lamblases OR lamblasis OR Norovirus\* OR "Norwalk agent\*" OR "Norwalk calicivirus\*" OR "Norwalk gastroenteritis virus\*" OR "Norwalk parvovirus\*" OR "Norwalk virus\*" OR "Norwalk-like Virus\*" OR Salmonella OR salmonelloses OR salmonellosis OR Shigella OR shigelloses OR shigellosis OR "Small Round-Structured Virus\*" OR "Vibrio hepaticus" OR "Vibrio jejuni" OR "Vibrio jejenum")))) AND **TOPIC:** (((evidence NEAR/1 based) or (meta NEAR/1 analys\*) or (systematic\* NEAR/3 review\*) or (control\* NEAR/3 study) or (control\* NEAR/3 trial) or (randomized NEAR/3 study) or (randomized NEAR/3 trial) or (randomised NEAR/3 study) or (randomised NEAR/3 trial) or "pragmatic clinical trial" or (doubl\* NEAR/1 blind\*) or (doubl\* NEAR/1 mask\*) or (singl\* NEAR/1 blind\*) or (singl\* NEAR/1 mask\*) or (tripl\* NEAR/1 blind\*) or (tripl\* NEAR/1 mask\*) or (trebl\* NEAR/1 blind\*) or (trebl\* NEAR/1 mask\*) or "latin square" or placebo\* or nocebo\* or "comparative study" or "comparative survey" or "comparative analysis" or cohort\* or longitudinal\* or retrospectiv\* or prospectiv\* or "population study" or "population survey" or "population analysis" or "population research" or (("follow-up" or followup) NEAR/1 (stud\* or survey or analysis)) or ((observation or observational) NEAR/1 (study or survey or analysis)) or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study")) AND **LANGUAGE:** (English) AND **DOCUMENT TYPES:** (Article OR Abstract of Published Item OR Meeting Abstract OR Proceedings Paper OR Review)

Indexes=SCI-EXPANDED Timespan=2007-2015

**Appendix Table 1:** Description of studies included in the meta-analysis

Author	Year	Pathogen	Number of subjects		Geographic location	Follow-up time period	Rome Criteria
			Exposed	Controls			
Pensabene <sup>1</sup>	2015	Rotavirus, Adenovirus, Norovirus, Salmonella, Giardia	32	32	Italy	6 months	Rome III
Schwille <sup>2</sup>	2015	Blastocystis hominis, Salmonella, Shigella, Giardia, Campylobacter	135	NA	Germany	1-2 years	Rome III
Bettes <sup>3</sup>	2014	Campylobacter, E.coli, Salmonella, Shigella	425	NA	U.S.A	6 months	Rome III
Cremon <sup>4</sup>	2014	Salmonella	204	189	Italy	<1 year, 1-5 years, >5 years	Rome III
Hanevik <sup>5</sup>	2014	Giardia	748	878	Norway	6 years	Rome III
Kowalczyk <sup>6</sup>	2014	NA	2428	2354	Netherlands	12 months	Rome III
Nair <sup>7</sup>	2014	E. coli, Salmonella, Providencia, Cryptosporidium	348	469	U.S.A	6 months	Rome II
Nielsen <sup>8</sup>	2014	C. concisus, C. jejuni	C. concisus = 106 C. jejuni = 162	NA	Northern Denmark	6 months	NA
Lalani <sup>9</sup>	2013	NA	154	516	U.S.A	3,6,9 months	Rome III
Van wanrooij <sup>10</sup>	2013	Norovirus, Giardia, Campylobacter jejuni	311	717	Belgium	12 months	Rome III
Koh <sup>11</sup>	2012	Shigella, Salmonella, Vibrio cholera, E. coli	65	NA	South Korea	3 months, 6 months	Rome II
Porter <sup>12</sup>	2012	Norovirus	1718	6875	U.S.A	1-4.7 years	NA
Wensaas <sup>13</sup>	2012	Giardia	817	1128	Norway	3 years	Rome III
Youn <sup>14</sup>	2012	Shigella	124	105	South Korea	12 months, 3,5,10 years	NA
Zanini <sup>15</sup>	2012	Norovirus	178	121	Italy	12 months	Rome III
Pitzurra <sup>16</sup>	2011	NA	852	1624	Switzerland	6 months	Rome III
Schwille <sup>17</sup>	2011	Salmonella, Campylobacter	48	NA	Germany	6 months	Rome III
Lim <sup>18</sup>	2010	Shigella	71	65	NA	8 years	NA
Thabane <sup>19</sup>	2010	E. coli O157:H7, Campylobacter	305	162	Canada	8 years	Rome II

Hanevik <sup>20</sup>	2009	Giardia	82	NA	Norway	12-30 months	Rome II
Jung <sup>21</sup>	2009	Shigella	87	89	South Korea	1,3,5 years	Rome II
Saps <sup>22</sup>	2009	Rotavirus	44	44	U.S.A & Italy	>2 years	Rome II
Saps <sup>23</sup>	2008	Salmonella, Shigella, Campylobacter	44	44	Italy	6 months	Rome II
Marshall <sup>24</sup>	2007	Norovirus	89	29	Canada	3,6,12,24 months	Rome I
Piche <sup>25</sup>	2007	Clostridium difficile	23	NA	France	3 months	Rome II
Ruigomez <sup>26</sup>	2007	Shigella, Campylobacter, Salmonella	5894	46996	United Kingdom	1-12 months, 13-24 months, 24-36 months, >36 months	Rome II
Soyturk <sup>27</sup>	2007	Trichinella britovi	72	27	Turkey	4,6,12 months	Rome II
Spence <sup>28</sup>	2007	Campylobacter	547	NA	New Zealand	6 months	Rome II
Tornblom <sup>29</sup>	2007	Campylobacter, Shigella, C. difficile, E.coli, Salmonella, Rotavirus, Adenovirus, Calicivirus, Giardia	333	NA	Sweden	5 years	Rome II
Borgaonkar <sup>30</sup>	2006	Bacterial	191	NA	Canada	3 months	Rome I
Marshall <sup>31</sup>	2006	NA	1368	701	Canada	24-36 months	Rome I
Stermer <sup>32</sup>	2006	NA	118	287	Israel	6 months	Rome II
Ji <sup>33</sup>	2005	Shigella	101	102	Korea	12 months	Rome II
Mearin <sup>34</sup>	2005	Salmonella	271	335	Spain	12 months	Rome II
Okhuysen <sup>35</sup>	2004	NA	61	36	USA	6 months	Rome II
Wang <sup>36</sup>	2004	NA	295	243	China	9 months	Rome II
Cumberland <sup>37</sup>	2003	NA	815	753	England	3 months	NA
Dunlop <sup>38</sup>	2003	Campylobacter	747	NA	UK	3 months	Rome I
Il'nyckij <sup>39</sup>	2003	NA	48	61	Canada	3 months	Rome I
Parry <sup>40</sup>	2003	Bacterial	108	206	England	3,6 months	NA
Gwee <sup>41</sup>	1999	Shigella, Campylobacter, Salmonella	109	NA	UK	12 months	Rome I
Rodriguez <sup>42</sup>	1999	Bacterial	318	584308	England	12 months	NA
Neal <sup>43</sup>	1997	Bacterial	366	NA	UK	6 months	Rome I
Gwee <sup>44</sup>	1996	NA	86	NA	UK	6 months	NA

Mc Kendrick <sup>45</sup>	1994	Salmonella	38	NA	UK	12 months	Rome I
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\* Appendix Table 2 provides details on accrual characteristics for cases, controls and methods of studies included in the meta-analysis

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**Appendix Table 2:** Accrual characteristics for cases and controls methods of studies included in the meta-analysis

Study	Patients inclusion criteria	Patients exclusion criteria	Methods	Cohort selection
Post infectious functional gastrointestinal disorders in children: A multicenter Prospective study. <b>Pensabene et. al., 2015</b>	<ul style="list-style-type: none"> <li>- Age 4 to 17 yr</li> <li>- Acute diarrhea (&gt;3 liquid stools/24h for &gt;3d to &lt;2w) with positive stool culture, parasitic or viral tests</li> <li>- Recruitment &lt;1m from IE</li> <li>- Completed questionnaire for pediatric FGIDs</li> </ul>	<ul style="list-style-type: none"> <li>- Neurologic impairment, recent surgery, celiac disease, IBD, cystic fibrosis, food allergies, transplantation, immunosuppression, liver, renal, metabolic or rheumatologic disease.</li> <li>- Inability to communicate</li> <li>- No 6m F/u</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>not specified</u></li> <li>- Questionnaire completed at outpatient visit or over the phone by the same health care provider</li> <li>- Data complete on IE and control cohorts at 3 time-points (1m, 3m, 6m)</li> </ul>	<ul style="list-style-type: none"> <li>- 6 pediatric departments from 2007-2010</li> <li>- <b>Control group:</b> similar age and sex presenting for a well-child visit or emergency department for minor trauma within 4w of IE case</li> </ul>
Postinfectious irritable bowel syndrome after travelers' Diarrhea-a cohort study Schwille-Kiuntke J et al., <b>2015</b>	<ul style="list-style-type: none"> <li>- Age &gt;18 yrs</li> <li>- Travelers' diarrhea: while or up to 7 days during travel to a high risk country. 50% population had at least one pathogen confirmed on the day of assessment</li> </ul>	<ul style="list-style-type: none"> <li>- Another GI diagnosis explaining symptoms, menstrual associated symptoms excluded.</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>yes</u></li> <li>- Mailing followed by online survey (twice): 39.4% response rate to initial invitation and 72.2% among those consented. Incomplete datasets excluded.</li> </ul>	<ul style="list-style-type: none"> <li>- Travel clinic patients from 2009-10 travel</li> <li>- <b>Control group:</b> none</li> </ul>
Risks and predictors of PI-IBS among community-acquired cases of bacterial enteritis. <b>Bettes et. al., 2014 (abstract)</b>	<ul style="list-style-type: none"> <li>- Age 18-65 yrs</li> <li>- Culture proven IE patients</li> </ul>	<ul style="list-style-type: none"> <li>- Pre-existing diagnosis of IBS, IBD, microscopic colitis, abdominal surgeries</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>yes</u></li> <li>- Mailed questionnaire (twice) followed by phone calls: completed by 37% at f/up time-point</li> </ul>	<ul style="list-style-type: none"> <li>- Reported IE cases to state health department</li> <li>- <b>Control group:</b> none</li> </ul>
<i>Salmonella</i> Gastroenteritis during childhood is a risk factor for irritable bowel syndrome in adulthood. <b>Cremon et. al., 2014</b>	<ul style="list-style-type: none"> <li>- Age &gt;18 yr at the time of the questionnaire; children and adults at time of IE</li> <li>- Positive stool culture for <i>Salmonella</i></li> </ul>	<ul style="list-style-type: none"> <li>- Pre-existing diagnosis of celiac disease, IBS, IBD, dyspepsia</li> <li>- Permanent resident of Bologna</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>yes</u></li> <li>- Mailed questionnaire (up to 3 times) followed by phone calls: completed by 54% cases and 50% controls at f/up time-point</li> </ul>	<ul style="list-style-type: none"> <li>- Contaminated food in 36 Bologna schools on Oct 19, 1994</li> <li>- <b>Control group:</b> from Bologna census. Age, sex &amp; residence area matched</li> </ul>
Irritable bowel syndrome and chronic fatigue 6 years after <i>Giardia</i> infection: a	<ul style="list-style-type: none"> <li>- Lab proven <i>Giardia</i> infection</li> <li>- Resident of the outbreak area</li> </ul>	<ul style="list-style-type: none"> <li>- Excluded questionnaires with incomplete, ambiguous answers or not answered</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>not specified</u></li> <li>- Mailed questionnaire:</li> </ul>	<ul style="list-style-type: none"> <li>- Samples from only laboratory in Bergen area 10/2004-12/2005</li> <li>- <b>Control group:</b></li> </ul>

controlled prospective cohort study. <b>Hanevik et. al., 2014</b>			completed by 60% cases and 36% controls at f/up time-point	2:1. Age, sex matched.
RR of IBS following acute gastroenteritis and associated risk factors. <b>Kowalczyk et. al., 2014</b>	- Age 18-70 yr - IE patients (Coding based confirmed infection with diarrhea) with at least 1 yr f/up data in electronic database	- Pre-existing diagnosis of cancer, alcohol abuse, IBD, IBS, functional bowel disease, abdominal surgery, ≥5 prescriptions related to IBS, IBD - IE symptoms 12m before case identification	- IBS excluded at baseline: <u>yes</u> - IBS identified by ICPC code during f/u time points	- Primary care patients between 1998-2009 - <b>Control group:</b> outpatients with no IE diagnosis presenting within 1m of IE case. Age, sex matched.
Persistent abdominal symptoms in US adults after short-term stay in Mexico. <b>Nair et. al., 2014</b>	- Age >18 yr or >16 yr with consent - Traveled to Mexico (stay >5d) - Travelers' diarrhea (≥3 soft/watery stools/24h) with positive stool cultures, parasitic/protozoal	- History of unstable medical illness - Preexisting self-identified persisting GI symptoms, pregnancy, use of antibiotics in the past week of IE, lactose intolerance	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire at 6m (single F/u) - Excluded those on anti-diarrheal prophylaxis, non-responders - Data complete	- Travelers between 6/2002-1/2008 - <b>Control group:</b> no h/o of diarrhea during travel. No matching.
Psychometric scores & persistence of irritable bowel after <i>C. concisus</i> infection. <b>Nielsen et. al., 2014</b>	- Age >18 yr - <i>C. concisus</i> positive stools sample	- Co-pathogens in stool sample - Not responding telephone calls, declined or inability to participate - Resided outside area of study - Terminal illness or IBD, IBS, microscopic or other non-infective colitis	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: returned by 41% cases & 45% controls at 6m (single F/u) - Excluded new onset IBD, microscopic colitis, incomplete responses - Data complete	- Stool samples submitted for diarrhea from 1/2009-12/2010 - <b>Control group:</b> <i>C. jejuni/coli</i> . Younger, greater proportion of males & less comorbidities. No non exposed controls.
Epidemiology and self-treatment of Travellers' Diarrhea in a large, prospective cohort of department of defense beneficiaries. <b>Lalani et. al., 2013</b>	- Adult and pediatric travelers with IE: ≥3 unformed stools and ≥1 of nausea, vomiting, abdominal pain, fever and blood in stool in 24hrs. - Completed illness diary.	- Not completing any f/up surveys	- IBS excluded at baseline: <u>yes</u> . - Diary or survey: 85% responders. Missing data on 23% (3m, 6m), 38% (9m) and 41% (12m) of the cases eligible for IBS assessment	- DoD beneficiaries traveling outside US for ≤6.5 m between 1/2010-7/2013 - <b>Control group:</b> no travelers' diarrhea
PI-IBS and functional dyspepsia	- Age >18 yrs - IE: onset of self-reported acute	- No further details	- IBS excluded at baseline: <u>yes</u> - Mailed	- Drinking water contamination in 12/2010

following an outbreak of tap water contamination. <b>Van wanrooij et. al., 2013 (abstract)</b>	gastrointestinal discomfort within 2w after tap water contamination		questionnaires: completed at 1 yr by 7.5% of entire geographic population (30% of those had IE)	- <b>Control group:</b> same geographic population without IE symptoms.
Incidence and Risk Factors of IBS in Community Subjects with Culture-proven Bacterial Gastroenteritis. <b>Koh et. al., 2012</b>	- Age >15-<75 yrs. - IE: Culture proven bacterial plus $\geq 2$ of fever, vomiting and diarrhea	- Pregnancy, severe psychiatric disease, cancer, IBD, hyperthyroidism and previous abdominal surgery	- IBS excluded at baseline: <u>yes</u> - Telephone interview; complete data available at 3 and 6 m f/up	- Community cohort 1/2008-2/2010 - <b>Control group:</b> none
Postinfectious Gastrointestinal Disorders Following Norovirus Outbreaks. <b>Porter et. al., 2012</b>	- IE ICD code during the outbreaks	- <1y f/u in Defense Medical Surveillance system	- IBS excluded at baseline: <u>not specified</u> - PI-IBS determined using new onset ICD codes after IE	- Military health services database 2004-2011 - <b>Control group:</b> 4:1. Same clinical setting, branch and rank. Within & outside of IE time frame
Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. <b>Wensaas et. al., 2012.</b>	- Lab proven Giardia infection - Resident of the outbreak area	- Excluded questionnaires with incomplete, ambiguous answers or not answered.	- IBS excluded at baseline: <u>not specified</u> - Mailed questionnaire (twice, over 1 m): completed by 65% cases and 31% controls (96% complete for IBS responses)	- Samples from only laboratory in Bergen area 10/2004-12/2005 - <b>Control group:</b> 2:1. Age, sex matched.
The clinical course of PI-IBS after shigellosis: A 10-year follow-up study <b>Youn et. al. 2012 (abstract)</b>	- Employees with diarrhea, abdominal pain and fever treated for shigellosis.	- Pregnancy, IBS, IBD, medication that can affect bowel function and abdominal surgery	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: 10 yr data completed by 69% cases and 72% controls.	- Employees from hospital food outbreak in 12/2001 - <b>Control group:</b> Age, sex matched employees with no IE symptoms or exposure to contaminated food
Incidence of Post-infectious Irritable Bowel Syndrome and Functional Intestinal disorders following water-borne viral gastroenteritis outbreak. <b>Zanini et. al.,</b>	- Resident of the outbreak area - IE criteria: $\geq 2$ of: fever, vomiting, diarrhea or positive Norovirus stool culture within the epidemic period.	- Not returning questionnaire	- IBS excluded at baseline: <u>yes</u> . - Mailed and phone questionnaires responded by 96% IE cases and 72% controls at 12 month	- Water-borne outbreak summer 2009 - <b>Control group:</b> same area, no IE symptoms during outbreak, identified 6 m after IE.

<b>2012</b>				
Irritable Bowel Syndrome among a cohort of European travellers to resource – limited destinations. <b>Pitzurra et. al., 2011</b>	<ul style="list-style-type: none"> <li>- German speaking Swiss adults</li> <li>- Stayed in travel destination for 1-8 weeks</li> <li>- Travelers' diarrhea: &gt;3 unformed stools/24hrs</li> </ul>	<ul style="list-style-type: none"> <li>- Pregnant women, planning to use antibiotic prophylaxis, HIV, immunosuppressive conditions, cancer, anemia. Previous GI symptoms or diseases, IBS or chronic diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>yes</u></li> <li>- Mailed questionnaire followed by e-mails and phone calls: completed by 72%</li> </ul>	<ul style="list-style-type: none"> <li>- Travel clinic patients 7/2006-1/2008</li> <li>- <b>Control group:</b> no Travelers' diarrhea</li> </ul>
Post - infectious irritable bowel syndrome: follow-up of a patient cohort of confirmed cases of bacterial infection with <i>Salmonella</i> or <i>Campylobacter</i> . <b>Schwille et. al., 2011</b>	<ul style="list-style-type: none"> <li>- IE: Hospitalized with lab proven IE</li> </ul>	<ul style="list-style-type: none"> <li>- No questionnaire answered, lost f/u, declined to participate, pre-existing IBS/IBD</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>yes</u></li> <li>- Postal questionnaire: responded to 57% IE cases and 54% controls</li> </ul>	<ul style="list-style-type: none"> <li>- Hospitalized patients 2000-09</li> <li>- <b>Control group:</b> None</li> </ul>
The clinical course of post-infectious irritable bowel syndrome: An eight-year follow-up study. <b>Lim et. al., 2010 (abstract)</b>	<ul style="list-style-type: none"> <li>- Hospital employees with diarrhea, abdominal pain or fever during outbreak.</li> </ul>	<ul style="list-style-type: none"> <li>- Not specified</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>not specified</u></li> <li>- Standard questionnaire; completed by 53% IE cases , 62% controls at 8 yrs</li> </ul>	<ul style="list-style-type: none"> <li>- Hospital outbreak</li> <li>- <b>Control group:</b> Age and sex matched. Same hospital employees with no IE symptoms.</li> </ul>
An outbreak of acute bacterial gastroenteritis is associated with an increased incidence of irritable bowel syndrome in children. <b>Thabane et. al., 2010</b>	<ul style="list-style-type: none"> <li>- Age &lt;16 yrs at enrollment but &gt;16 yrs at f/up</li> <li>- Permanent resident of Walkerton</li> <li>- Self reported or clinically suspected IE: acute bloody diarrhea or &gt;3 loose stools/24hrs or lab proven</li> </ul>	<ul style="list-style-type: none"> <li>- Previous h/o IBS, IBD or other GI symptoms</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>yes</u></li> <li>- Standardized interview &amp; questionnaire completion: complete data available for cumulative incidence assessment.</li> </ul>	<ul style="list-style-type: none"> <li>- Walkerton outbreak: 5/2000</li> <li>- <b>Control group:</b> Resident in the same area with no IGE symptoms.</li> </ul>
Development of functional gastrointestinal disorders after <i>Giardia lamblia</i> infection. <b>Hanevik et. al., 2009</b>	<ul style="list-style-type: none"> <li>- Lab proven <i>Giardia</i> infection</li> <li>- Negative stool studies, EGD with biopsies, labs at time of assessment</li> </ul>	<ul style="list-style-type: none"> <li>- Excluded incomplete or ambiguous answers</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>not specified</u></li> <li>- Structured interviews: complete data available.</li> </ul>	<ul style="list-style-type: none"> <li>- 2004 outbreak; data collected 2006-07</li> <li>- <b>Control group:</b> Age, sex matched. 2:1.</li> </ul>
The clinical course of postinfectious irritable bowel syndrome: a five-	<ul style="list-style-type: none"> <li>- Employees with diarrhea, abdominal pain and fever treated</li> </ul>	<ul style="list-style-type: none"> <li>- Pregnancy, IBS, chronic bowel diseases, medication that can</li> </ul>	<ul style="list-style-type: none"> <li>- IBS excluded at baseline: <u>yes</u></li> <li>- Mailed questionnaire,</li> </ul>	<ul style="list-style-type: none"> <li>- Employees from hospital food outbreak in 12/2001</li> </ul>

year follow-up study. <b>Jung et. al., 2009</b>	for shigellosis.	affect bowel function and abdominal surgery	direct interview or e-mail: complete data available at 5 years post IE.	- <b>Control group:</b> Age, sex matched employees with no IE symptoms or exposure to contaminated food
Rotavirus Gastroenteritis: Precursor of Functional Gastrointestinal Disorders? <b>Saps et. al., 2009</b>	- Age 4-18 yrs - Acute diarrhea with positive stool studies	- Unable to communicate, immunosuppression therapy, IBD, IBS, celiac disease, transplant, food allergy, rheumatologic disease, stool positive for bacteria or other viruses	- IBS excluded at baseline: <u>not specified</u> - Telephone questionnaire: complete data available	- Stool studies from hospital 1/2002-12/2004 - <b>Control group:</b> Age and sex match from well child/emergency visit within 4 wk of IE case
Post-Infectious functional gastrointestinal disorders in children. <b>Saps et. al., 2008</b>	- Age 3-19 yrs - Acute diarrhea with positive bacterial stool culture	- Unable to communicate, immunosuppression therapy, IBD, IBS, celiac disease, transplant, food allergy, rheumatologic disease.	- IBS excluded at baseline: <u>not specified</u> - Telephone questionnaire: complete data available	- Stool studies from hospital 1/2001-12/2005 - <b>Control group:</b> Age and sex match from well child /emergency visit within 4 wk of IE case
Postinfectious Irritable Bowel Syndrome After a Food-Borne Outbreak of Acute Gastroenteritis Attributed to a Viral Pathogen. <b>Marshall et. al., 2007</b>	- Clinical IE: self-reported fever, abdominal pain, diarrhea or vomiting during the outbreak (conference) or within 3 days of its end.	- IBS, IBD, colorectal carcinoma, abdominal surgery, radiation enterocolitis, microscopic colitis, hereditary polyposis, intestinal ischemia or celiac disease.	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: Response rate 97% (3m), 96% (6m), 92% (12m) and 83% (24m).	- Outbreak in 2002 - <b>Control group:</b> exposed to outbreak area but no IGE symptoms.
Low risk of irritable bowel syndrome after <i>Clostridium difficile</i> infection. <b>Piche et. al., 2007</b>	- Age >18 yrs - Symptomatic and lab proven IE	- Medication that alter bowel function, IBS, IBD, microscopic colitis, celiac disease, lactose intolerance and prior CDI.	- IBS excluded at baseline: <u>yes</u> - Standardized questionnaire: Complete data available.	- Bacteriology lab 2001-02. - <b>Control group:</b> None
Risk of Irritable Bowel Syndrome after an Episode of Bacterial Gastroenteritis in General Practice: Influence of Comorbidities. <b>Ruigomez et. al., 2007</b>	- Age 20 – 74 yrs - Lab proven bacterial IE	- Cancer, alcohol abuse, prior IE, IBD or any other colitis, IBS or any use of >5 GI associated medications	- IBS excluded at baseline: <u>yes</u> - F/up based on ICD codes and corroborating symptoms in database. Complete databases.	- UK general practice research database. 1992-2001. - <b>Control group:</b> Age, sex matched, timing of IE and geographic location
Irritable Bowel Syndrome in Persons who	- Hx of consumption of contaminated	- Pregnancy, IBD, IBS, celiac disease, colon cancer,	- IBS excluded at baseline: <u>yes</u> - In person or	- Hospitalized patients - <b>Control group:</b>



acquired Trichinellosis. <b>Soyturk et. al., 2007</b>	meat. - Lab proven	abdominal surgery and another IE in last 6 months	phone interview. Complete data at 12 m.	trichinellosis negative and no clinical symptoms to suggest IE
The cognitive behavioral model of irritable bowel syndrome: a prospective investigation of patients with gastroenteritis. <b>Spence et. al. 2007</b>	- Age >16 yr with positive stool culture	- Previous GI symptoms or illnesses.	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: 52% response rate. Those with IBS at both 3 and 6 months post IE were classified as PI-IBS	- Community clinic patients - <b>Control group:</b> none.
Gastrointestinal Symptoms after Infectious Diarrhea: A Five-Year Follow-Up in a Swedish Cohort of Adults. <b>Tornblom et. al., 2007</b>	- Age > 15 yrs - Patients with lab proven (53%) or strongly suspected infectious diarrhea	- HIV	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire (twice) followed by phone interview in selected cases: 71% response rate	- Hospitalized patients 1996-97 - <b>Control group:</b> Age, sex matched. 1.1.
The Incidence of Irritable Bowel Syndrome Among Community Subjects With Previous Acute Enteric Infection. <b>Bargonkoar et. al., 2006</b>	- Age >18 yr - Positive stool with new onset of abdominal pain and/or diarrhea	- IBS, IBD, any bowel resection, hereditary polyp syndrome, use of laxatives, prokinetics (within 7 days), ongoing evaluation for unexplained gastrointestinal symptoms.	- IBS excluded at baseline: <u>yes</u> - Phone questionnaire: data available on 52% at 3 month (single F/up time point)	- Specific health regions 1999-2001 - <b>Control group:</b> none
Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. <b>Marshall et. al., 2006</b>	- Age >16 yr - Permanent resident of Walkerton - Self reported or clinically suspected IE: documented record or acute bloody diarrhea or >3 loose stools/24hrs or lab proven	- Previous h/o IBS, IBD or other GI symptoms	- IBS excluded at baseline: <u>yes</u> - Standardized interview & questionnaire completion: complete data available for cumulative incidence assessment.	- Walkerton outbreak: 5/2000 - <b>Control group:</b> Resident in the same area with no IGE symptoms.
Is Traveler's Diarrhea a Significant Risk Factor for the Development of Irritable Bowel Syndrome? A Prospective Study. <b>Stermer et. al., 2006</b>	- Age 18-65 yr - Travelling for 15-180 days - Travelers' diarrhea: >3 loose stools/24 hrs, after 48 hrs of arrival	- Previous IBS, IBD, liver transplant, declined participation	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire followed by phone call during f/u: complete data available at 6 m (single F/up time)	- Potential travelers visiting travel clinic - <b>Control group:</b> travelers with no traveler diarrhea

Post-infectious irritable bowel syndrome in patients with <i>shigella</i> infection. <b>Ji et. al., 2005</b>	- Employees with diarrhea, abdominal pain and fever treated for shigellosis.	- Pregnancy, IBS, chronic bowel diseases, medication that can affect bowel function and abdominal surgery	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: complete data available at 3,6 and 12 months	- Employees from hospital food outbreak in 12/2001 - <b>Control group:</b> Age, sex matched employees with no IE symptoms or exposure to contaminated food
Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. <b>Mearin et. al., 2005</b>	- Age: adults - IE: living in the outbreak area with: diarrhea, fever and abdominal pain within outbreak dates. Some cases had culture confirmation.	- Not specified	- IBS excluded at baseline: <u>yes</u> - Standard questionnaire: 71% IE & 46% controls responders. F/up at 3m (IE: 54%, control: 34%), 6m (IE: 50%, control: 34%), 12m (IE: 40%, control: 28%)	- 2002 outbreak - <b>Control group:</b> 2:1. Age, sex and residence area matched.
Post-diarrhea chronic intestinal symptoms and irritable bowel syndrome in North American travelers to Mexico. <b>Okhuysen et. al., 2004</b>	- Age: adults - IE: $\geq 3$ unformed stools/day and abdominal pain, excessive gas/flatulence, nausea, vomiting, fever, fecal urgency, blood and/or mucus and tenesmus	- Prophylactic antibiotics, anti-diarrheal agents during travel.	- IBS excluded at baseline: <u>not specified</u> - Standard e-mail questionnaire: complete data available at 6 months.	- North US travelers to Mexico in 2002 - <b>Control group:</b> none
Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. <b>Wang et. al., 2004</b>	- Adults - Lab proven IE or abdominal pain, diarrhea and rectal burning with leucocytes in the stools and cured with antibiotics	- Functional bowel disease	- IBS excluded at baseline: <u>yes</u> - Phone interview or mailing; complete data available at 1-2 yrs F/up (single assessment).	- Dysentery clinic 1998 - <b>Control group:</b> siblings or spouses of IE patients
The infectious intestinal disease study of England: a prospective evaluation of symptoms and health care use after an acute episode. <b>Cumberland et. al., 2003</b>	- Age (0-4 yr, 5-15 yr, > 16 yrs) - IE: loose stools or vomiting < 2w in the absence of non-infectious cause. 3 wk preceding symptom free	- Not specified	- IBS excluded at baseline: <u>Not specified</u> - Mailed questionnaire; responded by 78% IE cases and 66% controls.	- UK general practice databases - <b>Control groups:</b> sex and age match
Relative Importance of Enterochromaffin	- Age: 18-75 yr - Lab proven IE	- Celiac disease, IBD (screening labs)	- IBS excluded at baseline: <u>yes</u> - Standard	- Nottingham health authority 1999-2002



Cell Hyperplasia, Anxiety, and Depression in Postinfectious IBS. <b>Dunlop et. al., 2003</b>			questionnaires: 42% response rate; 38% eligible for analysis with complete data	- <b>Control group:</b> none (for epidemiological analysis)
Post-traveler's diarrhea irritable bowel syndrome: a prospective study. <b>Illycckj et al., 2003</b>	- Age >18y/o - Travel outside US and Canada for <3m - IE: >3 bm/8hrs, 48hrs after arrival	- Previous GI symptoms or chronic bowel diseases	- IBS excluded at baseline: <u>yes</u> - Mailed and travel questionnaire: complete data available	- Travelers between 1997-98 - <b>Control group:</b> no TD
Does bacterial gastroenteritis predispose people to functional gastrointestinal disorders? A prospective, community-based, case-control study. <b>Parry et al., 2003</b>	- Age 18-80 yr - IE: Lab proven bacterial	- Pregnancy, severe psychiatric illness, chronic illness (cancer, IBD, IBS, celiac disease)	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: Responded by 83% IE and 89% controls. Complete data available at 3 and 6 m F/up.	- Microbiology laboratory 2000-01 - <b>Control group:</b> 4:1. Age and sex matched. Within 2 yrs of IE case.
The role of psychological and biological factors in postinfective gut dysfunction. <b>Gwee et. al., 1999</b>	- Age: 18-80 yr	- IBS, IBD, abdominal surgery, medications affecting bowel function.	- IBS excluded at baseline: <u>yes</u> - Interview: 68% response rate. Complete data available at 3 m	- Hospitalized for IE - <b>Control group:</b> none (for epidemiological analysis)
Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. <b>Rodriguez et. al., 1999</b>	- Age: 25-74 yr - Lab proven 1 <sup>st</sup> IE episode	- Cancer, alcohol abuse, IBD or any other colitis, IBS.	- IBS excluded at baseline: <u>yes</u> - Database diagnosis. Confirmed by physicians of all PI-IBS patients & a random set of controls	- UK general practice research database - <b>Control group:</b> Age and sex matched.
Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. <b>Neal et. al., 1997</b>	- Lab proven IE	- Not specified	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: 72% response data. Complete data available.	- Nottingham Health Authority 1994 - <b>Control group:</b> none
Psychometric scores and persistence of irritable bowel	- Age: 18-80 yr	- IBS, IBD, abdominal surgery, medications affecting bowel	- IBS excluded at baseline: <u>yes</u> - Standard questionnaire &	- Hospitalized for IE - <b>Control group:</b> none

after infectious diarrhea. <b>Gwee et. al., 1996</b>		function.	physician interview: 75% response rate	
Irritable bowel syndrome - post <i>Salmonella</i> infection. <b>McKendrick et. al., 1994</b>	- Clinically suspected IE and Lab proven in majority	- Chronic gastrointestinal illnesses	- IBS excluded at baseline: <u>yes</u> - Mailed questionnaire: Complete data available for F/up.	- Outbreak - <b>Control group:</b> none

Appendix Table 3

Study	Selection				Comparability		Outcome			Overall Score
	1) Representatives of the exposed cohort Truly representative of the average population in the community (*)	2) Selection of the non exposed cohort Drawn from the same community (*)	3) Ascertainment of exposure Secure record (*)	4) Demonstration that outcome of interest was not present at start of study YES (*)	1) Study controls for age? YES (*)	2) Study controls for gender? YES (*)	1) Assessment of outcome Independent blind Assessment (*)	2) Was follow-up long enough for outcomes to occur? YES (*)	3) Adequacy of follow-up of cohorts Complete follow-up – all subjects accounted for (*)	
Pensabene et al, 2015	*	*	*	NA	*	*	*	*	*	8/9
Schwille-Kiuntke et al 2015	*	NA	–	*	–	–	*	*	*	4/6
Bettes et al, 2014	*	NA	*	*	–	–	*	*	–	5/6
Cremon et al, 2014	*	*	*	*	*	*	*	*	–	8/9
Hanevik et al, 2014	*	*	*	NA	*	*	*	*	–	7/9
Kowalczyk et al, 2014	*	*	–	*	*	*	*	*	*	8/9
Nair et al, 2014	*	*	*	*	–	–	*	*	*	7/9
Nielsen et al, 2014	*	NA	*	*	–	–	*	*	–	5/6
Lalani et al, 2013	*	*	–	*	–	–	*	*	*	6/9
Van wanrooij et al, 2013	*	*	–	*	–	–	*	*	–	5/9
Koh et al, 2012	*	NA	*	*	–	–	*	*	*	6/6
Porter et al, 2012	*	*	–	NA	–	–	–	*	*	4/9
Wensaas et al, 2012	*	*	*	NA	*	*	*	*	–	7/9
Youn et al, 2012	–	*	–	*	*	*	*	*	–	6/9
Zanini et al, 2012	*	*	–	*	–	–	*	*	–	5/9
Pitzurra et al, 2011	*	*	–	*	–	–	*	*	–	5/9
Schwille-Kiuntke et al, 2011	*	NA	*	*	–	–	*	*	–	5/6
Lim et al. , 2010	–	*	–	NA	*	*	*	*	–	5/9
Thabane et al, 2010	*	*	*	*	–	–	*	*	–	7/9
Hanevik et al, 2009	*	*	*	NA	*	*	*	*	*	8/9
Jung et al, 2009	–	*	*	*	*	*	*	*	*	8/9
Saps et al, 2009	*	*	*	*	*	*	*	*	*	9/9
Saps et al, 2008	*	*	*	*	*	*	*	*	*	9/9
Marshall et al, 2007	*	*	–	*	–	–	*	*	–	5/9
Piche et al, 2007	*	NA	*	*	–	–	*	*	*	6/6
Ruigomez et al, 2007	*	*	*	*	*	*	–	*	*	8/9
Soyturk et al, 2007	*	*	*	*	*	*	*	*	*	9/9
Spence et al, 2007	*	NA	*	*	–	–	*	*	–	5/6
Tornblom et al, 2007	*	*	*	*	*	*	*	*	–	8/9
Bargonkoar et al, 2006	*	NA	*	*	–	–	*	*	–	5/6
Marshall et al, 2006	*	*	–	*	*	*	*	*	*	8/9
Stermer et al, 2006	*	*	–	*	–	–	*	*	*	6/9
Ji S et al, 2005	–	*	–	*	*	*	*	*	*	7/9
Mearin et al, 2005	*	*	–	*	*	*	*	*	–	7/9
Okhuysen et al, 2004	*	NA	–	NA	–	–	*	*	*	4/6
Wang et al, 2004	*	*	*	*	*	*	*	*	*	7/9
Cumberland et al, 2003	*	*	–	NA	*	*	*	*	*	7/9
Dunlop et al, 2003	*	NA	*	*	–	–	*	*	–	5/6
Illycckyj et al, 2003	*	*	–	*	–	–	*	*	*	6/9
Parry et al, 2003	*	*	*	*	*	*	*	*	–	8/9
Gwee et al, 1999	*	NA	*	*	–	–	*	*	–	5/6
Rodriguez et al, 1999	*	*	*	*	*	*	*	*	*	9/9
Neal et al, 1997	*	NA	*	*	–	–	*	*	–	5/6
Gwee et al, 1996	*	NA	*	*	–	–	*	*	–	5/6
McKendrick et al, 1994	*	NA	*	*	–	–	*	*	*	6/6

**Appendix Table 4:** Overall prevalence of PI-IBS at 3m, 6m, 12m, 13-59m and  $\geq 60$ m after the infectious enteritis

Time since infection	Number of studies	Events/Total Exposed	Prevalence of PI-IBS (%)	95% CI	I <sup>2</sup>
3m	9	189/2096	8.9	5.1-15.0	90%
6m	19	517/9779	11.5	6.8-18.6	97%
12m	13	283/4418	11.3	6.8-18.2	95%
1-4y	11	1104/10550	13.9	6.0-29.1	99%
$\geq 5$ y	6	393/1596	17.8	8.6-33.1	97%

\* Reporting order where prevalence at multiple time points was determined: 12m, 1-4y, 6m, 3m,  $\geq 5$ y

**Appendix Table 5:** Subgroup analysis for observed differences in the prevalence of PI-IBS within 12m and >12m of infectious exposure, based on the pathogen-type

Subgroups	Events/Total exposed (No. of studies)	Prevalence of PI-IBS (%)	95% CI	I <sup>2</sup>
Within 12m of exposure*				
Overall	911/15800 (35)	10.1	7.2-14.1	96%
Organism <sup>†, ‡</sup>				
• Bacterial	656/10016 (21)	13.0	8.5-19.5	97%
• Viral	53/264 (2)	19.4	13.2-27.7	48%
• Protozoal	5/72 (1)	6.9	2.9-15.6	-
>12m after exposure				
Overall	1466/12007 (15)	14.5	7.7-25.5	99
Organism <sup>§</sup>				
• Bacterial	691/8053 (7)	12.9	4.6-31.3	99
• Viral	26/1839 (3)	4.4	0.3-39.9	97
• Protozoal	712/1647 (3)	53.0	39.9-65.7	95

\* when data at multiple time points was reported in a study, hierarchical order of 12m, 6m and 3m rates was used for estimation

† excluded 9 studies which did not report specific exposure organism or was mixed etiology

‡ p-value for difference between subgroups=0.06, suggesting that organism of exposure does not significantly influence observed prevalence of PI-IBS within 12m

§ p-value for difference between subgroups=<0.001, suggesting that the infecting organism affects prevalence of PI-IBS >12m after exposure

**Appendix Table 6:** Relative risk of IBS in those exposed to infectious enteritis as compared to the non-exposed

Time point (No. of studies)	Events/Total exposed	Events/Total unexposed	Relative risk	95% CI	I <sup>2</sup>
• 3m (4)	54/1024	5/870	5.86	2.40-14.32	0
• 6m (11)	249/7974	297/50450	2.98	2.30-3.86	20
• 12m (11)	249/4271	2099/588427	5.64	3.24-9.84	71
• 13-59m (8)	1029/10333	949/56151	2.12	1.57-2.87	79
• ≥60m (5)	365/1245	132/1214	2.20	1.28-3.78	72

p-value for difference between groups=0.012, suggesting that relative risk of IBS in patients exposed to infectious enteritis as compared to unexposed adults is lower beyond 12m, as compared to within 12m

Appendix Figure 1

