Full Title: Predictors of aetiology and outcomes of acute gastrointestinal illness in returning travellers: A retrospective cohort analysis

Running Title: Predictors of aetiology and outcomes of gastrointestinal illness in returning travellers

Authors: Robert A Lever[1,3], Louis Tapper*[2], Sophie Skarbek*[2], Peter L Chiodini[1,3,4] Margaret Armstrong[1] and Robin L Bailey[1,4]

*=these authors contributed equally to this work

Author Affiliation: 1. Hospital for Tropical Diseases, Maple House, Tottenham Court Road, London UK 2. University College London Medical School 3. University College London Division of Infection and Immunity 4. London School of Hygiene and Tropical Medicine Department of Clinical Research

Correspondence to: r.lever@ucl.ac.uk

Key Points: Gastrointestinal pathology is common in returned travellers. In this large retrospective study, we identify a number of demographic, clinical and laboratory features which are associated with the aetiology and clinical outcome of imported enteric diseases.

Key Words: returning travellers; diarrhoea; parasitic disease; gastrointestinal illness

Abstract

Background: Gastrointestinal illness is a major cause of morbidity in travellers and is a common reason for presentation to healthcare services on return. Whilst the aetiology of imported gastrointestinal disease is predominantly infectious, outcomes are variable due to a range of phenomena such as post-infectious irritable bowel syndrome, drug resistance and occult pathology (both infectious and non-infectious). Previous studies have focussed on predictors of aetiology of gastrointestinal disease in travellers; we present a retrospective study combining both aetiological and early outcome data in a large cohort of returned travellers.

Method: We identified 1450 patients who attended our post-travel walk-in clinic with gastrointestinal symptoms between 2010 and 2016. Demographic, travel, clinical and laboratory data was collected through case note review. Logistic regression analysis to examine correlates of aetiology and outcome were performed in R (CRAN Project 2017).

Results: Of 1450 patients in our cohort 153 reported bloody diarrhoea and 1081 (74.6%) reported non-bloody diarrhoea. A definitive microbiological diagnosis was made in 310 (20.8%) of which 137 (9.4%) had a parasite identified and 111 (7.7%) had a bacterial cause identified. Factors associated with a parasitological diagnosis included history of travel to South Asia (aOR=2.55; 95%CI 1.75-3.70, p<0.0001) and absence of bloody diarrhoea (aOR=0.22; 95%CI 0.066-0.53, p<0.005). Factors associated with a bacteriological diagnosis included male gender (aOR=1.69; 95%CI 1.10-2.62, p<0.05), an age <37 years on presentation (aOR=2.04; 95%CI 1.25-3.43, p<0.01), white cells on stool microscopy (aOR=3.52; 95%CI 2.09-5.86, p<0.0001) and a C-reactive protein level of >5iu/dL (aOR=4.68; 95%CI 2.91-7.72, p<0.0001). The majority (1235/1450, 82.6%) reported full symptomatic resolution by the first follow up visit; factors associated with lack of symptomatic resolution included female gender (aOR=1.45 95%CI 1.06-1.99, p<0.05), dysenteric diarrhoea (aOR=2.14 (95%CI 1.38-3.25, p<0.0005) and elevated peripheral leukocyte count (aOR=1.58 95%CI 1.02-2.40, p<0.05).

Conclusions: In a cohort of returned travellers, we were able to identify multiple factors that are correlated with both aetiology and outcome of imported gastrointestinal syndromes. We predict these data will be valuable in the development of diagnostic and therapeutic pathways for patients with imported gastrointestinal infections

Introduction:

Diarrhoea and other gastrointestinal diseases are extremely common in travellers and remain a key cause of morbidity in this group despite reports of reducing incidence of foodborne infection worldwide[1–4]. Multiple studies including large-scale GeoSentinel analyses have estimated between 20-50% of travellers experience gastrointestinal symptoms related to travel; this risk is enhanced in lower- and middle-income countries with up to 40,000 travellers to these destinations experiencing symptoms per day[5–9]. Imported gastrointestinal disease represents a spectrum of different clinical syndromes of which acute diarrhoeal illness is the most common, accounting for 60% or more of all presentations to medical care on return[1, 5, 6].

The aetiology of imported gastrointestinal pathology is predominantly infectious in nature and microbiological identification of the causative agent is successful in between 20-94% of patients with acute diarrhoeal illness[1, 5, 10]. Most cases of imported diarrhoea are bacterial in origin[1]. However, in a large GeoSentinel study, in the 39% of returning travellers with any gastrointestinal syndrome who received a microbiological diagnosis, approximately twice as many had a parasite identified (65%) as those who had a bacterial cause isolated (31%)[6]. A previous report from our centre identified a bacterial origin for symptoms in 12.5% and a parasitic cause in 11.9% of patients with acute diarrhoea [11]. Identification of factors which predict aetiology of imported gastrointestinal disturbance are therefore of interest as they may help guide empirical therapy, prognosis and follow up [1, 9, 11] Limited work has previously been done in this arena; in this work we seek to extend and strengthen these earlier observations[11].

The majority of infective gastrointestinal disease, and particularly diarrhoeal illness, is short-lived and self-limiting, with an average duration of 4-5 days [12]. However, long term complications are well-recognised of which post-infectious irritable bowel syndrome (PI-IBS), characterised by a persistence in gastrointestinal distress after convalescence, is best described and occurs in nearly 1 in 5 patients[13, 14]. Persistence of symptoms after less common imported gastrointestinal syndromes such as isolated abdominal pain or bloating are less well described. Precipitators of non-resolution of symptoms after treatment for an acute imported gastrointestinal infection can be broadly divided into five categories: resistance of pathogen to empirical treatment, failure of host response (e.g. immunocompromise), cryptic infection, primary non-infectious pathology (such as undiagnosed inflammatory bowel disease) and, functional post-infectious bowel abnormalities, of which PI-IBS is the most well described[13–19]. As functional bowel disease is a diagnosis of exclusion, the initial evaluation of patients with recalcitrant gastrointestinal symptoms usually necessitates further laboratory and imaging investigations and may include invasive assessments such as endoscopy[1].

Early identification and effective treatment of travellers with persistent gastrointestinal symptoms is clinically challenging. Despite this, only a limited number of studies have directly looked at predictive factors for non-resolution of symptoms; we seek to address this in our study.

Methods

Clinical Setting

The Hospital for Tropical Diseases (London, UK) operates a Walk-in Emergency clinic for any patient with symptoms following return from abroad. Patients self-refer and do not need a prior appointment or review by their primary healthcare practitioner before review. Each patient is assessed by a triage nurse and subsequently by a doctor, where an initial diagnosis is made, and

emergency treatment is provided. A subset of these patients will return to clinic either as a planned follow-up or re-present due to symptom persistence.

Cohort selection

All patients with gastrointestinal symptoms presenting to the Hospital for Tropical Diseases Emergency Walk-in Clinic (London, UK) have a stool sample requested for analysis for ova, cysts and parasites (OCP) at triage. We identified stool samples submitted for stool OCP to the Hospital for Tropical Diseases Parasitology Department between January 2010 and January 2016. From this we identified patient-episodes corresponding to individual attendances at the clinic. Patients were deemed ineligible for analysis if they provided samples for asymptomatic screening for parasites in the context of another, non-gastrointestinal, illness and if the sample was derived from the parallel tertiary referral outpatient clinic which operates on the same site.

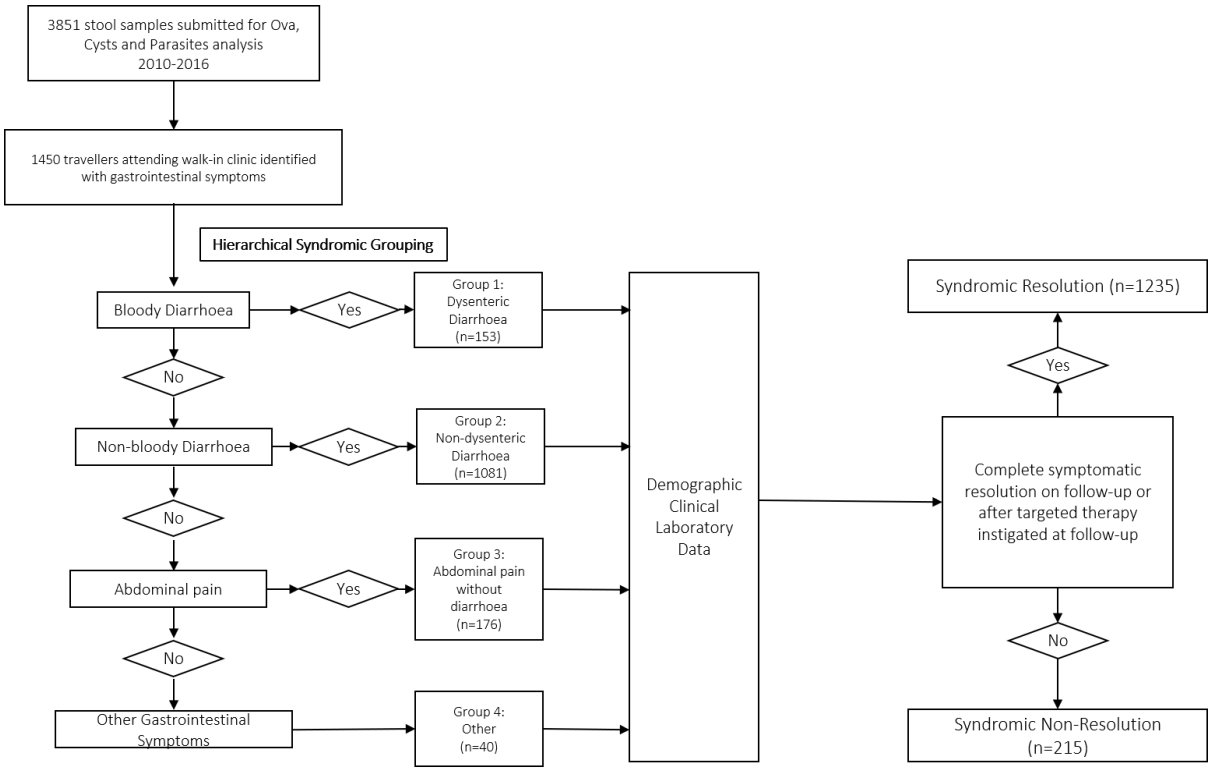

Figure 1: Cohort Identification Methodology and Hierarchical Syndromic Grouping

Data Collection

Routine data were collected via audit of historical clinical records by clinical staff and anonymised before entry onto a database. Scope of data included demographic details, clinical data from correspondence and laboratory data from electronic records. All data were collected in compliance with locally established audit standards and personal data were anonymised in compliance with GDPR legislation (European Union 2018).

Ethics and Governance

All methods and protocols employed within this study were approved by the Hospital for Tropical Diseases Audit Committee (London, UK) in accordance with legislation and regulations laid out by the NHS Human Research Authority (UK).

Data Analysis

Data were analysed in Microsoft Excel (Microsoft Corporation 2018) and R (R Development Core Team, 2008). Students' t-test was used for normally distributed continuous variables, 2 by 2 tables were analysed using Chi squared or Fisher's Exact Test. Logistic regression modelling was performed with binomial distribution parameters. Maps were produced with the MS Excel 3D Maps plugin and rworldmaps package for R (CRAN 2017).

Results

Cohort Characteristics

From 3851 stool samples submitted for stool OCP analysis, we identified 1450 consecutive patients who had attended the Emergency Walk-in clinic between January 2010 and January 2016 who had a primary gastrointestinal syndrome after return from abroad. 819 patients (56.5%) were female, and the mean age was 35.97 years (IQR 27.3-42.4 years). 445 (30.1%) of reviewed patients had visited more than one country during their trip and 430 (29.7%) had visited more than one geographical region of the world. The top geographical regions visited were South East Asia (449/1450 31.0%), South Asia (356/1450 24.6%) and East Africa (323/1450 22.3%). (Table 1.; Fig 2.)

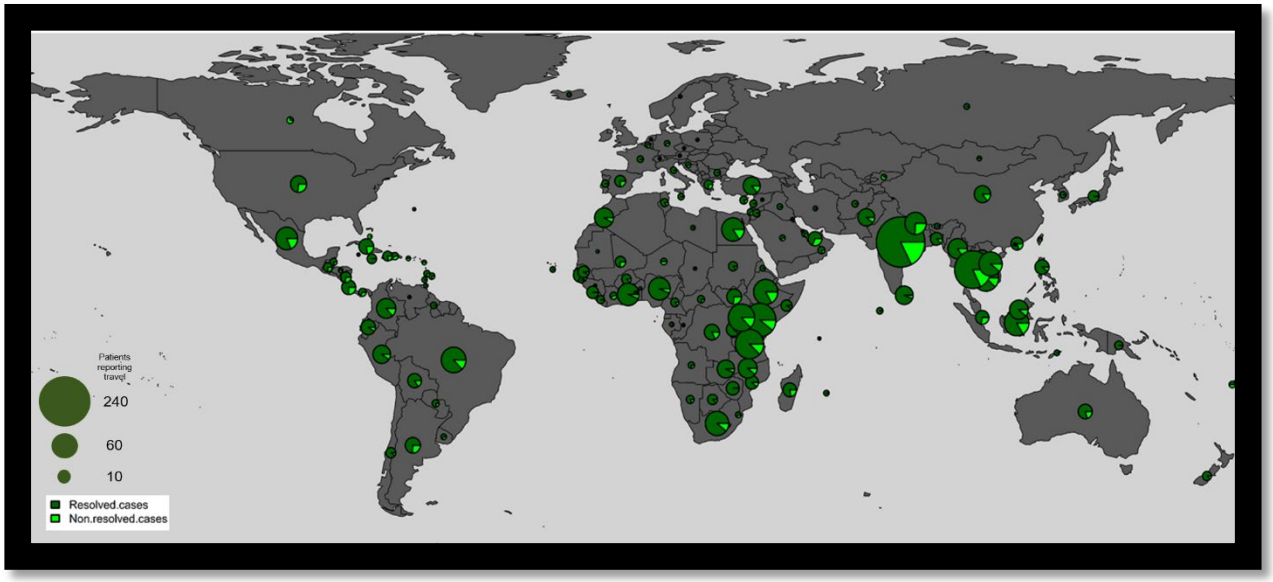

Figure 2: Patient Travel Destination Circle size indicates number of patients as referenced in left-hand scale. Light green segments indicate proportion of patients without syndromic resolution at follow-up.

	Any Parasitic Diagnosis (N=137)	p value	Any Bacterial Diagnosis (N=111)	p value	Total (N=1450)
Gender		0.802		***0.006***	
Female	76 (55.5%)		49 (44.1%)		819 (56.5%)
Male	61 (44.5%)		62 (55.9%)		631 (43.5%)
Age		0.276		***0.018***	
Mean (SD)	37.065 (12.685)		33.302 (11.987)		35.971 (12.353)
Range	16.720 - 73.200		16.930 - 73.200		15.240 - 84.540
HIV Positive	0 (0.0%)	0.901	0 (0.0%)	0.811	2 (0.1%)
Travel History					
Central Asia	6 (4.4%)	0.176	2 (1.8%)	0.574	38 (2.6%)
Europe	3 (2.2%)	0.337	2 (1.8%)	0.279	53 (3.7%)
North Africa	11 (8.0%)	0.151	14 (12.6%)	0.781	171 (11.8%)
Pacific Islands	0 (0.0%)	0.518	1 (0.9%)	0.191	4 (0.3%)
Southern Africa	5 (3.6%)	0.165	2 (1.8%)	***0.039***	93 (6.4%)
Caribbean	1 (0.7%)	0.038	4 (3.6%)	0.796	59 (4.1%)
South America	14 (10.2%)	0.484	8 (7.2%)	0.581	125 (8.6%)
Australia and New Zealand	2 (1.5%)	0.901	2 (1.8%)	0.85	23 (1.6%)
Bahamas	0 (0.0%)	0.575	0 (0.0%)	0.618	3 (0.2%)
Middle East	1 (0.7%)	0.12	1 (0.9%)	0.203	41 (2.8%)
South Asia	54 (39.4%)	***< 0.001***	14 (12.6%)	***0.013***	319 (22.0%)
Central America	8 (5.8%)	0.676	6 (5.4%)	0.573	97 (6.7%)
West Africa	13 (9.5%)	0.527	7 (6.3%)	0.094	161 (11.1%)
South East Asia	24 (17.5%)	0.433	31 (27.9%)	***0.031***	291 (20.1%)
East Africa	21 (15.3%)	0.404	26 (23.4%)	0.116	260 (17.9%)
North America and Canada	1 (0.7%)	0.264	3 (2.7%)	0.582	29 (2.0%)
Central Africa	3 (2.2%)	0.766	1 (0.9%)	0.436	27 (1.9%)
China	1 (0.7%)	0.145	2 (1.8%)	0.574	38 (2.6%)
Oceania	0 (0.0%)	0.428	1 (0.9%)	0.405	6 (0.4%)
Syndrome		***0.008***		***< 0.001***	
Non-dysenteric diarrhoea	117 (85.4%)		81 (73.0%)		1081 (74.6%)
Abdominal pain	13 (9.5%)		3 (2.7%)		176 (12.1%)
Dysenteric diarrhoea	4 (2.9%)		25 (22.5%)		153 (10.6%)
Other	3 (2.2%)		2 (1.8%)		40 (2.8%)
Stool Microscopy					
White cells	13 (9.5%)	0.751	36 (32.4%)	***< 0.001***	127 (8.8%)
Red cells	8 (5.8%)	0.342	18 (16.2%)	***< 0.001***	62 (4.3%)
Peripheral WBC Count		0.066		0.334	
Decreased	1 (0.7%)		0 (0.0%)		14 (1.0%)
Increased	23 (16.8%)		15 (13.5%)		159 (11.0%)
Normal	110 (80.3%)		88 (79.3%)		1206 (83.2%)
C-reactive Protein		0.151		***< 0.001***	
Increased	44 (32.1%)		77 (69.4%)		500 (34.5%)
Normal	90 (65.7%)		26 (23.4%)		873 (60.2%)
ALT		0.134		0.588	
Increased	25 (18.2%)		14 (12.6%)		197 (13.6%)
Normal	108 (78.8%)		89 (80.2%)		1178 (81.2%)

Table 1: Clinical Characteristics – Parasitic and Bacterial Diagnosis. Significance indicated by p value marked in bold with * where ≤0.001<p<0.05.

Syndromic Presentations of Gastrointestinal Disease

Imported gastrointestinal disease encompasses a spectrum of clinical presentations; to capture this in a clinician applicable manner we separated patients into 4 syndromic categories. Group 1: Dysenteric diarrhoea (defined as a diarrhoeal illness with the presence of blood in the stool); Group 2: Non-dysenteric diarrhoea (defined as any diarrhoeal illness without the presence of blood); Group 3: Abdominal pain/Bloating (defined as the presence of abdominal pain and/or bloating without diarrhoea); Group 4: Other (defined as all other gastrointestinal syndromes not captured in Groups 1-3; summarised in Supplementary Table 1).

The commonest syndrome in our cohort was Non-dysenteric diarrhoea (1081 patients, 74.6%) followed by Abdominal pain/Bloating (176 patients, 12.1%) and Dysenteric diarrhoea (153 patients, 10.6%) (Fig 1.).

Laboratory Investigation of Patients Presenting to the Walk-in Clinic

All our patients had microscopy performed on a stool concentrate for ova, cysts and parasites. In addition, 90.7% of patients underwent bacterial stool culture and 42.1% had molecular analysis for *Entamoeba histolytica*, *Giardia intestinalis* and *Cryptosporidium* performed via multiplex polymerase chain reaction. Peripheral blood sampling was performed in the majority of patients – 95.1% had full blood count (FBC), 94.7% had C-reactive protein and 94.8% had liver function tests performed respectively. 43.8% underwent testing for HIV infection.

Aetiology of Gastrointestinal Disease in Returning Travellers

301 patients (20.8%) received a definitive diagnosis as a result of their interaction with our travellers' clinic of which 242 (80.3%) were as a result of microbiological and parasitological analysis of stool.

The presence of a parasite was confirmed in 137 patients (9.4%) and a bacterial pathogen was identified in 111 patients (7.7%). The commonest identified gastrointestinal pathogen in our cohort was *Giardia intestinalis* which was identified in 92 patients (6.3%). The commonest causes of bacterial gut infection were *Salmonella* spp. (39 cases, 2.7%) and *Campylobacter* spp. (47 cases, 3.2%).

Patients in whom a parasite was identified were more likely to fall into syndromic Group 2 (non-dysenteric diarrhoea) (Table 1). Of note 6 of 7 *E.*histolytica infections identified by PCR presented with non-dysenteric diarrhoea. Reported travel to South Asia was associated with an increased risk for detection of a parasite during clinical workup (aOR = 2.55; 95%CI 1.75-3.70, p<0.0001) and particularly for *Giardia intestinalis* infection (aOR = 3.18; 95% CI= 2.05-4.92, p<0.00001); correspondingly, those who reported dysenteric diarrhoea were significantly less likely to have a parasite identified during testing (aOR = 0.22; 95%CI 0.066-0.53, p<0.005) (Table 2).

Patients with a proven bacterial origin to their symptoms had a younger mean age (33.3 vs 36.0 years, p=0.016) and were more likely to fall into syndromic Group 1 (dysenteric diarrhoea) (Table 1) After adjustment for confounders male gender was significantly associated with a confirmed bacterial aetiology (aOR=1.69; 95%CI 1.10-2.62, p<0.05), an age <37 years on presentation (aOR=2.04; 95%CI 1.25-3.43, p<0.01), presence of white cells on stool microscopy (aOR = 3.52; 95%CI 2.09-5.86, p<0.0001) and a C-reactive protein level of >5iu/dL (aOR=4.68; 95%CI 2.91-7.72, p<0.0001) (Table 2). These data are consistent with previously published observations from our unit[11].

	Odds Ratio for Parasitic Diagnosis	95% CI	p value
Male Gender	1.07	0.74-1.53	0.721
Age >37 years	1.42	0.98-2.04	0.058
Travel to South Asia	**2.55**	**1.75-3.70**	**<0.0001**
Syndrome - Abdominal Pain and Bloating	0.68	0.36-1.20	0.214
Syndrome - Dysenteric Diarrhoea	**0.22**	**0.066-0.53**	**<0.005**
Syndrome - Other GI syndrome	0.70	0.16-2.00	0.556

	Odds Ratio for Bacterial Diagnosis	95% CI	p value
Male Gender	**1.69**	**1.10-2.62**	**<0.05**
Age <37 Years	**2.04**	**1.25-3.43**	**<0.01**
Travel to South Asia	**0.47**	**0.24-0.83**	**<0.013**
Travel to Southern Africa	**0.11**	**0.006-0.52**	**<0.05**
Stool Microscopy - White cells	**3.52**	**2.09-5.86**	**<0.0001**
CRP >5iu/dL*	**4.68**	**2.91-7.72**	**<0.0001**

Table 2: Predictors of Aetiology of Imported Gastrointestinal Disease. *cases where CRP not performed removed from analysis.

Outcomes of Gastrointestinal Disease in Returning Travellers

Persistent abdominal symptoms are a common feature of returning travellers suffering from gastrointestinal pathology. To assess the prevalence of persistent non-resolution of symptoms within our cohort we identified the patients who had any ongoing symptoms, either at follow up after empirical treatment or the first follow up after a specific identified aetiology was identified. Those who failed to attend a pre-arranged follow up appointment were assumed to have syndromic resolution.

Of 1450 returning travellers, 215 (17.4%) had non-resolution of their symptoms at follow up; the comparative travel histories are shown in Figure 2. A higher proportion of patients with persistent symptoms compared to those with complete resolution were female (62.8% vs 55.4%) and were more likely to have travelled to the Caribbean, Pacific Islands, Bahamas and North America respectively in a univariate analysis (Table 3). Dysenteric diarrhoea as a presenting syndrome was over-represented in those with persistent symptoms at follow up (17.2% vs 9.4% of cases) however the presence of red or white blood cells on stool microscopy was not significantly different between the two groups (Table 3). No individual microbiological or parasitological diagnosis was associated with non-resolution of symptoms (Table 3). These findings may be related to new presentations of non-travel related pathology such as inflammatory bowel disease in these patients as has been previously described by our centre.[20]

In a multivariate analysis female gender was associated with an hazard ratio of 1.45 (95%CI 1.06-1.99, $p<0.05$) for persistence of symptoms in our cohort (Table 4). An initial presenting complaint of dysenteric diarrhoea, and those with a measured peripheral leucocytosis at presentation were associated with an hazard ratio of 2.14 (95%CI 1.38-3.25, $p<0.0005$) and 1.58 (95%CI 1.02-2.40, $p<0.05$) respectively for non-resolution of symptoms (Table 4). Additionally, after adjustment for other factors, travel to North America (USA and Canada) was significantly associated with ongoing symptoms at follow-up (HR 3.61, 95%CI 1.57-7.9, $p<0.005$) (Table 4).

	Resolution (N=1235)	Non-resolution (N=215)	Total (N=1450)	p value
Gender				***0.043***
Female	684 (55.4%)	135 (62.8%)	819 (56.5%)	
Male	551 (44.6%)	80 (37.2%)	631 (43.5%)	
Age				0.914
Mean (SD)	35.986 (12.241)	35.888 (13.009)	35.971 (12.353)	
Range	16.000 - 84.540	15.240 - 78.340	15.240 - 84.540	
Travel History				
Central Asia	31 (2.5%)	7 (3.3%)	38 (2.6%)	0.528
Europe	46 (3.7%)	7 (3.3%)	53 (3.7%)	0.735
North Africa	144 (11.7%)	27 (12.6%)	171 (11.8%)	0.706
Pacific Islands	2 (0.2%)	2 (0.9%)	4 (0.3%)	***0.047***
Southern Africa	84 (6.8%)	9 (4.2%)	93 (6.4%)	0.149
Caribbean	44 (3.6%)	15 (7.0%)	59 (4.1%)	***0.019***
South America	108 (8.7%)	17 (7.9%)	125 (8.6%)	0.686
Bahamas	1 (0.1%)	2 (0.9%)	3 (0.2%)	***0.011***
Middle East	32 (2.6%)	9 (4.2%)	41 (2.8%)	0.193
Australia and New Zealand	19 (1.5%)	4 (1.9%)	23 (1.6%)	0.727
South Asia	264 (21.4%)	55 (25.6%)	319 (22.0%)	0.17
Central America	79 (6.4%)	18 (8.4%)	97 (6.7%)	0.285
West Africa	144 (11.7%)	17 (7.9%)	161 (11.1%)	0.106
South East Asia	248 (20.1%)	43 (20.0%)	291 (20.1%)	0.978
East Africa	227 (18.4%)	33 (15.3%)	260 (17.9%)	0.285
North America and Canada	19 (1.5%)	10 (4.7%)	29 (2.0%)	***0.003***
China	32 (2.6%)	6 (2.8%)	38 (2.6%)	0.866
Oceania	6 (0.5%)	0 (0.0%)	6 (0.4%)	0.306
Central.Africa	22 (1.8%)	5 (2.3%)	27 (1.9%)	0.586
Syndrome				***0.002***
Non-dysenteric diarrhoea	936 (75.8%)	145 (67.4%)	1081 (74.6%)	
Abdominal pain	146 (11.8%)	30 (14.0%)	176 (12.1%)	
Dysenteric diarrhoea	116 (9.4%)	37 (17.2%)	153 (10.6%)	
Other	37 (3.0%)	3 (1.4%)	40 (2.8%)	
Stool Microscopy				
White cells	108 (8.7%)	19 (8.8%)	127 (8.8%)	0.965
Red cells	51 (4.1%)	11 (5.1%)	62 (4.3%)	0.509
Peripheral WBC Count				0.251
Decreased	12 (1.0%)	2 (0.9%)	14 (1.0%)	
Increased	127 (10.3%)	32 (14.9%)	159 (11.0%)	
Normal	1034 (83.7%)	172 (80.0%)	1206 (83.2%)	
C-reactive Protein				0.209
Increased	435 (35.2%)	65 (30.2%)	500 (34.5%)	
Normal	732 (59.3%)	141 (65.6%)	873 (60.2%)	
ALT				0.447
Increased	164 (13.3%)	33 (15.3%)	197 (13.6%)	
Normal	1004 (81.3%)	174 (80.9%)	1178 (81.2%)	
Any Definitive Diagnosis	261 (21.1%)	40 (18.6%)	301 (20.8%)	0.399
Microbiological Diagnosis	214 (17.3%)	28 (13.0%)	242 (16.7%)	0.153
Bacterial	100 (8.1%)	11 (5.1%)	111 (7.7%)	0.118
Parasitic	119 (9.6%)	18 (8.4%)	137 (9.4%)	0.559
Diagnosis				
Giardia intestinalis	78 (6.3%)	14 (6.5%)	92 (6.3%)	0.913
Entamoeba histolytica	6 (0.5%)	1 (0.5%)	7 (0.5%)	0.968
Blastocystis hominis	27 (2.2%)	2 (0.9%)	29 (2.0%)	0.225
Cryptosporidium parvum	13 (1.1%)	2 (0.9%)	15 (1.0%)	0.87
Cyclospora cayatanensis	6 (0.5%)	0 (0.0%)	6 (0.4%)	0.306
Campylobacter spp.	43 (3.5%)	4 (1.9%)	47 (3.2%)	0.215
Shigella spp.	22 (1.8%)	3 (1.4%)	25 (1.7%)	0.688
Salmonella spp.	35 (2.8%)	4 (1.9%)	39 (2.7%)	0.415
Plesiomonas shigelloides	5 (0.4%)	0 (0.0%)	5 (0.3%)	0.35

Table 3: Clinical Characteristics – Outcome at first follow-up

	Odds Ratio for Persistence of Symptoms	95% CI	Pr(>|z|)
Female gender	**1.45**	**1.06-1.99**	**<0.05**
Age - 28-37 years	0.76	0.52-1.10	0.150
Age - >37 years	0.84	0.58-1.22	0.369
Travel to North America	**3.61**	**1.57-7.9**	**<0.005**
Syndrome - Abdominal Pain and Bloating	1.41	0.89-2.18	0.133
Syndrome - Dysenteric Diarrhoea	**2.14**	**1.38-3.25**	**<0.0005**
Syndrome - Other GI syndrome	0.58	0.14-1.67	0.380
Leucocytosis*	**1.58**	**1.02-2.40**	**<0.05**

Table 4: Predictors of Outcome of Imported Gastrointestinal Syndromes. *Cases where peripheral white cell count not performed removed from analysis

Discussion

To our knowledge this is the largest contemporary study which focusses both on the aetiology and the outcomes of returning travellers with gastrointestinal symptoms. The results of this work therefore provide valuable data to inform both empirical treatment of imported gastrointestinal disease and facilitate the early identification of those patients who may have recalcitrant symptoms possibly due to non-infective causes and require follow-up.

Consistent with previous reports, our study demonstrates that despite extensive investigation, only a minority of patients with imported gastrointestinal disturbance receive a microbiological diagnosis but that the majority resolve completely with conservative, empirical, or targeted management.

In agreement with a smaller earlier report from our unit, travel to South Asia was associated with a positive parasitological diagnosis, of which infection with *Giardia intestinalis* was by far the most common. Similarly, the identification of a causative bacterial agent was associated with dysenteric symptoms, white cells on stool microscopy and an elevated C-reactive protein level, in accordance with the existing literature. Interestingly younger age and male gender were significantly associated with a positive bacterial culture; this may have implications for guidelines surrounding empirical antibiotic therapy in returning travellers.

Persistent abdominal symptoms are recognised complications of travel related gastrointestinal disease and management of these presentations may be challenging. In our study a variety of demographic, travel, syndromic and laboratory factors were found to influence the persistence of symptoms at follow-up. Dysenteric diarrhoea, peripheral leucocytosis at presentation and female sex all predicted lack of resolution in our cohort. The strength of this study is that it may allow earlier identification of those who would benefit most from further investigations, such as abdominal imaging, endoscopy and specialist blood tests at the point of presentation to healthcare providers upon return from abroad.

The retrospective nature of this study represents its key limitation. Unfortunately, this means that the pathways for investigation and follow-up were not consistent across all the cases included and led to our making several assumptions regarding resolution. The decision to deem those not attending follow-up appointments as having had resolved disease (either with or without planned future appointments) means that we may have biased the cohort of non-resolving patients. However, we believe this risk is somewhat mitigated by several points specific to our setting; the clinic is not only free at the point of use to all patients but also does not require a prior appointment, hence the barriers (perceived or otherwise) to access are minimal. In addition, a standard part of the care pathway for all patients at the unit was a telephone follow-up, often up to a week after the

initial assessment, to inform patients of investigation results and ensure no further formal clinical follow-up was required. Standardisation of investigation and collection of therapeutic data would form the core of a future prospective study.

In conclusion, we have demonstrated a number of predictive factors related to both the aetiology and prognosis of gastrointestinal disease in returning travellers. We hope this will aid clinicians with initial assessment of such patients and allow practical early triage of patients for enhanced follow up.

Declarations

Ethical Approval and Consent

All data presented was collected according to UK Health Research Authority regulations for collection and publication of routine single-site audit data (https://www.hra.nhs.uk/) and locally approved by the Hospital for Tropical Diseases Audit Committee (http://www.thehtd.org) which is a part of University College Hospitals NHS Foundation Trust London UK. Informed consent requirements were waived by the responsible ethical committee (Hospital for Tropical Diseases, London, UK).

Consent to Publish

Consent to publish has been given

Availability of data

Primary code for analysis will be made available on http://www.github.com (@rlever). Further data sharing will be considered in accordance with NHS HRA regulations and accepted practice.

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Conflicts of interest

The authors declare no conflicts of interest

Author Contributions

R.A.L., L.T., S.S. and M.A. collected the data. R.A.L and R.L.B. analysed the data, R.A.L., P.L.C. and R.L.B. wrote the main manuscript text. All authors reviewed the manuscript.

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