Travel-Associated Health Risks for Patients With Inflammatory Bowel Disease

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BACKGROUND & AIMS: There are few data on risk of travel for patients with inflammatory bowel disease (IBD). We assessed rates of illness while traveling among patients with IBD. **METHODS:** We performed a retrospective, case-controlled study of illnesses among 222 patients with IBD and 224 healthy individuals (controls) during 1099 total trips. Data were retrieved by structured questionnaires, personal interviews, and chart review. **RESULTS:** Participants had 142 episodes of illness during the trips; 92% were enteric disease. An episode of illness occurred during 79/523 (15.1%) trips made by patients with IBD compared with 63/576 (10.9%) trips made by controls (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.01–2.0; $P = .04$). However, this difference was mostly attributable to the increased incidence of illness among IBD patients traveling in industrialized countries. In contrast, the rate of illness among travelers to developing countries was similar among patients with IBD and controls (34/200, 17% vs 52/243, 21% of trips, respectively; $P = .24$). Moreover, numerically more controls that traveled to the tropics developed illness than travelers with IBD (43/135 vs 23/97, respectively; $P = .18$). In multivariate analysis, factors that increased risk for travel illness included frequent flares of IBD (OR, 1.9; 95% CI, 1.1–3.4; $P = .02$) and prior IBD-related hospitalizations (OR, 3.5; 95% CI, 1.3–9.3; $P = .01$); remission within 3 months before traveling reduced the risk for illness (OR, 0.3; 95% CI, 0.16–0.5; $P < .001$). Use of immunomodulatory drugs was not independently associated with risk of illness during travel. **CONCLUSIONS: Patients with IBD have a higher rate of illness compared with controls during trips to industrialized countries, but not to developing or tropical regions. These findings indicate that most travel-associated illnesses stem from sporadic IBD flares rather than increased susceptibility to enteric infections.**

Keywords: Crohn's Disease; Ulcerative Colitis; Enteric Infection; Diarrhea.

Inflammatory bowel disease (IBD) is a chronic, often debilitating intestinal disorder which adversely affects the quality of life of afflicted patients.[1,2] The etiology of IBD has not been fully elucidated, but several lines of evidence point to a possible role of intestinal bacteria in the instigation of IBD via immune system activation.[3] In addition, IBD patients are often treated by immune-suppressing drugs, thereby increasing their susceptibility to infections.

These considerations give rise to many safety issues pertaining to traveling of IBD patients abroad. This is particularly relevant in an era when international traveling is increasingly common, with more than 1 billion people traveling outside their residence country annually.[4] Despite this upsurge in international traveling and the rise of travel-medicine clinics world-wide, there are no data pertaining to the risks of traveling among IBD patients. In the absence of data, many physicians advise IBD patients against traveling, especially to developing regions of the world. This recommendation is likely driven by fears of a higher risk for contracting infections and/or experiencing disease flares in destinations with poor hygiene. Moreover, insurance companies are often reluctant to insure IBD travelers, a refusal that is hard to rebut in the absence of data. Taken together, these restrictions on traveling, whether self-imposed or dictated by others, severely impede the overall quality of life of IBD patients. However, it remains undefined whether this significant toll is based on a genuine increase in health risk during traveling in IBD patients.

Therefore, the aim of the present study was to evaluate the incidence and characteristics of travel-associated risks among IBD patients compared with healthy control subjects.

Methods

Study Population

IBD patients attending the outpatient clinics of the Gastroenterology Department of Sheba Medical Center were recruited. The control population was composed of volunteers without known IBD, who were enrolled from among the hospital personnel, family members of personnel, and individuals attending the gastroenterology department as escorts to relatives undergoing endoscopies.

All participants gave an informed consent and the study was approved by the Sheba Medical Center ethics review committee.

Procedures

A structured questionnaire was developed and pretested on a sample of senior gastroenterologists and IBD patients ensuring validity and comprehensibility. The questionnaire inquired about respondents' demographics, medical history, and all history of traveling abroad in the last 5 years prior to the study. Details on traveling included the destination countries, the duration of travel, season of traveling, and details about any

Abbreviations used in this paper: BMI, basal metabolic index; CI, confidence interval; HDI, human developmental index; IBD, inflammatory bowel disease; IM, immunomodulators; OR, odds ratio.

1542-3565/$36.00
doi:10.1016/j.cgh.2011.10.025

Table 1. The Background Demographics and General Travel Characteristics of the 2 Study Groups

	IBD patients (n = 222)	Healthy control subjects (n = 224)	*P* value
Age, mean ± SD, *y*	37 ± 13	37 ± 14	.8
Females, n (%)	95 (43)	110 (49)	.18
BMI, mean ± SD	20 ± 4.6	21 ± 4.9	.8
Smokers, n (%)	42 (19)	25 (11)	.02
Comorbidities, n (%)	62 (28)	48 (21)	.1
Total number of trips	523	576	
Number of trips per person, mean ± SD	2.4 ± 1.3	2.7 ± 14	.7
Mean length of trip in days, mean ± SD (range)	22 ± 48 (1–730)	22 ± 46 (1–730)	.9
Rate of trips to developing countries, n (%)	200/523 (38)	243/576 (42)	.3
Rate of trips to tropical countries, n (%)	97/523 (18)	135/576 (23)	.04
Prophylactic antibiotics for trips to developing countries, n (%)	26/200 (13)	22/243 (9)	.2

illness experienced by the respondent during or within 3 months after the trip. Pretravel counseling in specialized travel clinic, immunizations, and prophylactic medicines taken (eg, antimalarial) were also inquired upon, as well as any regular medications taken during each trip. An identical questionnaire, but exclusive of the IBD-specific items, was administered to the healthy controls. One of the investigators (SBH) further interviewed respondents with missing or unclear data in their questionnaire. In addition, the charts of all IBD patients participating in the study were retrieved and clinical data, such as disease duration and medication history, were extracted from their charts.

Definitions

Travel destination countries were classified according to the United Nations' Human Developmental Index (HDI) of the year 2009.[5] Destination countries that are not 1 of the 38 countries with an HDI >0.902 were considered developing countries. In addition, a subanalysis was performed to specifically assess the risk of traveling to developing countries in tropic regions of the world. These encompassed Central and South American countries (excluding Argentina and Chile), Southeast Asia (excluding Japan, South Korea, and Singapore), and sub-Saharan African countries (excluding South Africa). Illness was designated as any illness episode, whether gastrointestinal or other. Severe illness was defined as any health condition requiring hospitalization or cutting short the trip in order to return for medical care at home. All other disease episodes were classified as mild.

Study Outcomes and Analysis

The main outcome tested in the present study was the rate of illness during traveling to developing countries among IBD patients versus controls. In addition, we compared the rate of illness while traveling to tropical parts of the world, and also subanalyzed the occurrence of travel-associated diseases according to the immune status of the traveler (immune suppressed or not). Because each trip constitutes a distinct at-risk event, and an individual patient may undertake several trips during the study period, the rate of illness was analyzed per trip rather than per patient. In order to control for the possible confounding effect of different trip durations, an additional analysis was performed for illness-per-day-traveling.

Statistical Analysis

Continuous variables were analyzed by 2-tailed Student *t* test or Mann–Whitney *U* test, as appropriate, and categorical variables were analyzed by Fisher exact test. All variables differing between the 2 groups with a significance level of ≥ 0.1 were then entered into multivariate analysis using a multiple backward logistic regression model to identify factors independently affecting dichotomous clinical outcomes. For calculation of the odds ratios, continuous variables were entered to the model as categorical variables according to their respective quartile rank in the corresponding parameter. All statistics were performed using MedCalc software (Version 12.4; Mariakerke, Belgium). $P < .05$ was considered significant.

Assuming a 40% rate of traveler diarrhea during trips to endemic areas, a sample size of 342 trips to developing countries (171 in each group) was computed to be required in order to detect a 15% difference in the rate of illness with a power of 80% and with an α level of 5%. Using a subject-to-item ratio of 1:10 and taking into account 16 variables, at least 160 IBD subjects were needed to reduce the risk of overfitting the logistic regression model.[6]

Results

Study Population and Primary Outcome

A request to participate in the study was directly made by 1 of the investigators to 245 control subjects and 237 IBD patients. Of the control subjects, 21 contacted individuals were excluded (19 had not been abroad in last 5 years, 1 refused, 1 missing data). Fifteen IBD patients were excluded (14 not traveling abroad, 1 missing data). Thus, the final analysis included 224 controls with 576 trips and 222 IBD patients with 523 trips.

The background demographic and general travel characteristics of the 2 study groups are shown in Table 1, and disease characteristics of the IBD patients are depicted in Table 2. As seen in Table 1, 135/576 trips by control subjects were to the tropics compared with 97/523 trips by IBD patients (23.4% vs 18.5%, respectively; $P = .04$; odds ratio [OR], 1.3; 95% confidence interval [CI], 1–1.8), suggesting that IBD patients tend to refrain from traveling to the tropics compared with their healthy counterparts.

Table 2. Disease Characteristics of the IBD Patients

	IBD patients (n = 222)
Mean age of onset of IBD, *y*	26 ± 11
Mean duration of IBD, *y*	11 ± 9
Previous surgery for IBD	58 (26)
Extraintestinal manifestations	49 (22)
Ulcerative colitis	70 (32)
Proctitis	4 (6)
Left sided	43 (61)
Extensive	23 (33)
Crohn's disease	153
Ileal	77 (50)
Colonic	27 (18)
Ileocolonic	49 (32)
Crohn's phenotype[a]	
Inflammatory	80 (52)
Penetrating	32 (22)
Obstructive	49 (32)

NOTE. Data are presented as mean ± SD, or n (%).
[a]Percentage out of the available data.

Illness occurred in 79 of 523 trips by IBD patients compared with 63/576 in control subjects (15.1% vs 10.9%, respectively; OR, 1.44; 95% CI, 1.01–2; $P = .04$). However, this risk was mostly due to increased rate of illness during travel to developed countries among IBD patients compared with control subjects, whereas the risks of illness while traveling to developing countries or specifically while at the tropic regions were not different between the IBD and control groups (Figure 1). Within the IBD traveler group, illness occurred in 34 of 200 trips (17%) to developing countries versus 45/323 (13.9%) in developed countries (OR, 1.22; CI, 0.78–2.1; $P = .32$), whereas the control group was affected by illness in 52 of 243 trips (21.4%) to developing countries compared with merely 11/333 (3.3%) in developed countries (OR, 6.6; 95% CI, 3.2–12.2; $P = .0001$). Similarly, the risk of illness during trips to tropic regions of the world was modestly increased for IBD patients compared with their trips to developed countries (23/97 vs 45/323, respectively; OR, 1.9; 95% CI, 1.1–3.3; $P = .02$), but was

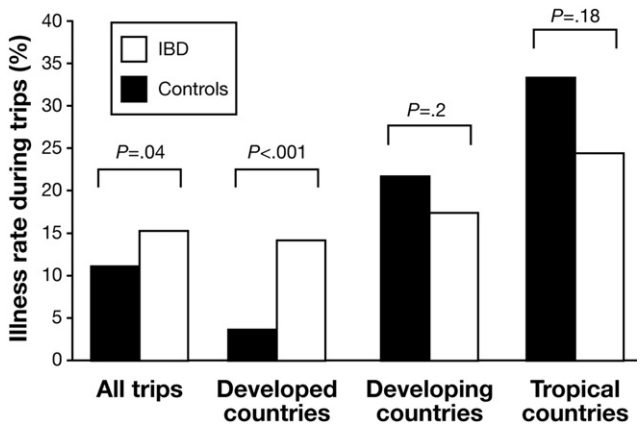

Figure 1. The rate of illness during trips in the IBD and healthy control populations, stratified by countries of destinations. By definition, developing countries also include tropical countries, but the latter are also shown separately in the *bars on the right* for finer data presentation.

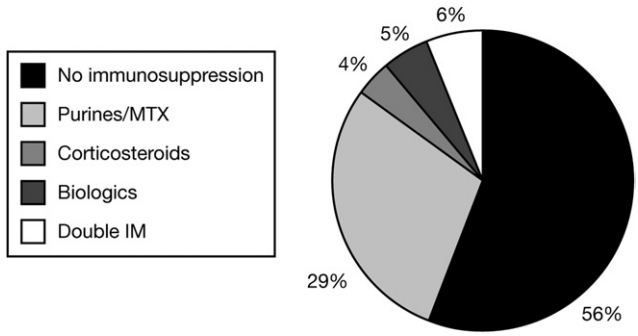

Figure 2. The distribution of the immunomodulating drugs used regularly during the trips by IBD patients.

strikingly accentuated in control subjects who were inflicted with illness in the tropics much more than when traveling in the industrialized countries (43/135, 33.3% vs 11/333, 3%, respectively; OR, 13.6; 95% CI, 6.7–27.6; $P < .001$).

The vast majority (92%) of illness abroad was related to abdominal symptoms in both the IBD and control groups, and most were mild to moderate and resolved within a few days. Only 5 IBD patients experienced severe travel-related illness requiring hospital admission (1 with dehydration in South America, 1 drainage of perianal abscess in the USA, 1 malaria in India, 1 partial small bowel obstruction in Germany, 1 disease flare in Italy). Four control travelers required hospital admission abroad: 1 with syncope in Cyprus, 1 with salmonella dysentery in South America, 1 with malaria in Ghana, and 1 with leg abscess in Thailand.

Effect of Immunosuppression and Other Factors on Travel-Related Risk

Nearly 45% of trips by IBD patients were undertaken during treatment with an immunomodulator (IM) and/or corticosteroids. The distribution of the different IMs used by the IBD travelers during their trips is shown in Figure 2. To explore the effect of IM treatment and other factors on the risk for travel-related illness, a comparison was performed between uneventful and illness-stricken trips of IBD patients (Table 3).

This comparison showed that the predominant effect on the risk for falling ill while traveling was related to factors of underlying IBD severity (Table 3). The risk of travel-illness stratified by immunosuppressed and immunocompetent status and compared with healthy controls is shown in Supplementary Figure 1. Notably, immunosuppressed IBD patients had similar risk of illness in the tropics as healthy individuals (Supplementary Figure 1).

In line with this pattern, when a multivariate analysis was performed, the independent effect of immunomodulators was nullified (Table 4). The only factors which retained an independent association with the risk of travel-related illness in IBD patients were prior hospitalization for IBD, number of flares, and being in remission for at least 3 months before traveling, which conferred a strong protective effect (Table 4). Indeed, the risk of illness in IBD patients setting out to travel after 3 months remission was 49/398 trips, which was not increased compared with 63/576 trips in healthy control subjects (12% vs 10.9%, respectively; OR, 1.1; 95% CI, 0.8–1.7; $P = .5$).

Table 3. A Comparison of Disease-Afflicted Trips and Uneventful Trips Among the IBD Population

	Illness-afflicted trips (n = 79)	Uneventful trips (n = 444)	*P* value
Mean age	32 ± 11	35 ± 13	.06
Females	30 (38)	186 (42)	.5
BMI	19.8 ± 3.3	20.6 ± 4	.06
Smokers	11 (14)	92 (21)	.16
Comorbidities	23 (29)	122 (27)	.8
Number of trips per person	2.7 ± 1.2	3.1 ± 1.7	.18
Crohn's disease	55 (70)	315 (71)	.8
Duration of disease, *y*	9.7 ± 8	10.5 ± 9	.4
Complicated Crohn's disease[a]	27 (49)	140 (44)	.5
Ever hospitalized for IBD	71 (90)	322 (73)	.002
Number of hospitalizations	5 ± 7.3	3.4 ± 5	.06
Number of flares since IBD onset	15 ± 16	9.5 ± 13	.007
Ever treatment with IM	70 (89)	346 (78)	.03
Prior intestinal surgery	27 (30)	119 (27)	.9
IM during the trip	46 (58)	181 (41)	.004
Steroids during trip	11 (14)	25 (6)	.01
Purine/MTX during trips	27 (34)	138 (31)	.5
Biologics	9 (11)	30 (7)	.15
Remission before trip	49 (62)	352 (79)	.001
Consulted GI physician before trip	27 (34)	85 (19)	.003
Developing countries	33 (42)	167 (38)	.4

NOTE. Data are presented as mean ± SD, or n (%).
GI, gastrointestinal; MTX, methotrexate.
[a]Percentage out of the available data.

Normalized Risk per Trip Duration

Because the duration of the trip may affect the probability of illness during travel, we also analyzed illness rate according to the numbers of days spent by each traveler abroad. IBD patients experienced 79 events during 11,203 days abroad comprising a risk of 7% per 10 days of traveling, compared with 63 disease events during 12,597 days abroad (5% risk per 10 days of traveling) in healthy individuals (OR, 1.4; 95% CI, 1.01–1.96; $P = .04$). Importantly, the analysis of risk per 10 days of traveling stratified to developing and developed regions of the world reproduced the results of the nonnormalized analyses and showed lack of increased risk for illness in IBD traveling to developing or tropic areas of the world (data not shown).

Table 4. Multivariate Analysis of Risk Factors for Illness During Traveling Among the IBD Population

Parameter	Odds ratio	Confidence interval	*P* value
Age (quartiles)	1.62	0.9–2.8	.1
BMI (quartiles)	1.3	0.7–2.5	.3
Developed country	0.8	0.5–1.5	.6
Ever treated with IM	1.2	0.5–3.1	.7
Number of flares (quartiles)	1.9	1.1–3.4	.02
Ever hospitalized	3.5	1.3–9.3	.01
IM during the trip	1.1	0.8–1.6	.5
Remission for >3 mo before traveling	0.3	0.16–0.5	<.001

Disease Flares and Infections After Travel

Disease flares were experienced within 3 months of returning to Israel in 85 out of the 523 trips (16%) by IBD travelers. Of these, 34 flares occurred after 79 illness-inflicted trips compared with 51 flares that occurred after the 440 uneventful trips (43% vs 11.6%, respectively; OR, 7.4; 95% CI, 4.2–12.9; $P < .001$). In 16 of the 34 flares (47%), respondents specifically noted that the flare in Israel was, in their opinion, a direct continuation of the flare started while traveling.

Discussion

The present study evaluated travel-associated risks among the IBD population.

International travel is increasingly prevalent for both leisure and business purposes with more than 1 billion people traveling abroad from their native country each year,[4] and numbers are rising rapidly. Not only does traveling increase in prevalence, it is also increasingly recognized as an important aspect of individual well-being and quality of life. Thus, in a recent Australian survey more than 60% of IBD patients noted restrictions on traveling as having a major detrimental effect on their perceived quality of life,[7] and a smaller-scale study confirmed these results.[8] Such restrictions may be self-imposed stemming from fears of disease flares or from concerns of other travel-related health hazards. In addition, such restrictions are also often mediated by physicians advising against traveling, especially to developing and tropic regions of the world. Indeed, the present study documents for the first time that IBD patients often refrain from traveling to certain destinations as they were significantly less likely to have traveled to tropic and subtropic

regions of the world compared with their healthy counterparts (Table 1).

Despite the significant impact on patients' quality of life, there are hitherto no studies investigating the incidence of travel-associated illness among IBD patients, although a small-scale study reported that IBD onset may occur during traveling abroad in some patients.[9] The present study indicates that while there is greater risk of illness while traveling in IBD patients compared with control subjects, there is similar risk in the 2 populations when traveling to developing countries. Because traveler diarrhea and other enteric infectious diseases predominately afflict travelers to developing countries, this unexpected observation suggests that IBD travelers as a whole do not stand a higher risk of contracting infections while traveling compared with the non-IBD population. Indeed, it is possible to infer from these results that most travel-associated illness in IBD patients is due to flares of underlying IBD.

In line with this, the relative rate of travel illness among IBD patients compared with control subjects was most pronounced during trips to developed industrialized countries but diminished when traveling to developing countries, and strikingly reversed when in tropic areas. Moreover, this phenomenon of a reduction in relative risk during trips to the tropics was observed also when specifically analyzing immunosuppressed IBD patients versus the control population (Supplementary Figure 1). Many patients noted in writing or during their interview that "when traveling in the tropics, my IBD felt the best ever." Although the reasons for these counterintuitive observations were not specifically investigated by the study, several possible explanations may come to mind. Because IBD flares may occur sporadically in industrialized countries, whereas control subjects are rarely ill in these countries and often sick in developing countries, this may partly account for the apparent difference of illness incidence while traveling in developed but not developing countries. An alternative explanation for the reduced risk of illness while in tropic areas of the world may intriguingly relate to mechanisms of IBD pathogenesis. For instance, a Th2 cytokine milieu has been postulated to be protective against development of Crohn's disease, and treatment with intestinal harmless worms has shown preliminary promising results in ameliorating Crohn's disease exacerbations.[10–12] Thus, the Th2 milieu in the developing and tropic countries may be hypothesized to confer a protective effect on flares of underlying IBD and mediate the relative risk reduction for IBD travelers to these countries. A possible additional explanation for the relative risk reduction for IBD patients in developing countries may stem from a more cautious dietary behavior by such travelers compared with travelers without underlying intestinal disease. Finally, stress and other psychological factors have been shown by some works, albeit not all,[13] to affect the course of IBD. Hence, these findings may be speculated to show that psychological factors involved in traveling, especially on long trips to the tropics, could potentially influence the incidence of abdominal symptoms during the trip.

Patients in clinical remission of more than 3 months stood a similar risk of travel-associated illness as the healthy population. This observation is important for the practical aspect of clinical counseling of IBD patients before travel regarding infectious and IBD flare risks. Documenting the incidence of travel-related illness is also important for providing observational risk estimates in order to allow insurance companies to formulate their policy rationally. In turn, the availability of insurance programs may further ease some of the bureaucratic obstacles confronted by the traveling IBD patient.

Several limitations of our study should be acknowledged. As any retrospective study, recollection bias could skew the results in unpredictable directions. However, we attempted to limit this bias by restricting the study to trips taken within the last 5 years. Moreover, similar results were observed when we subanalyzed only trips taken within the last year, for which recollection bias may be negligible. Thus, illness affected 20/121 last-year trips to industrialized countries in IBD patients compared with 4/182 trips in controls (OR, 8.8; 95% CI, 3–26; $P < .001$), whereas the risk was similar for IBD and controls during last-year trips to developing regions (10/44 vs 18/82, respectively; OR, 1.04; 95% CI, 0.4–2.5; $P = .9$), and the risk trended to reverse during trips to the tropics (4/17 vs 14/45, respectively; OR, 0.6; 95% CI, 0.2–2.4; $P = .5$).

An important word of caution is mandatory as this study was not powered to detect differences in risks of contracting rare opportunistic infections such as Strongyloides stercoralis, tuberculosis, or other organisms anecdotally reported to affect immunosuppressed IBD patients following traveling or residing in an endemic area.[3,14] Thus, larger scale studies are required to estimate patients' risk for travel-acquired rare opportunistic infections. Undoubtedly, one should also consider the fact that live attenuated vaccines such as yellow fever are contraindicated in immunosuppressed patients and be cognizant of this fact when counseling patients before travel.

An additional limitation stems from the fact that the study encompassed travelers from a single country, ie, Israel. The United Nations HDI classifies Israel as 1 of the 38 highly-developed countries, being in the 28th place in 2009 when the study was initiated. However, further studies are warranted to test whether these findings can be generalized to travelers from other developed countries, as well as to IBD travelers from developing countries. Finally, the reason for travel was unavailable and could possibly impact the rate of illness during business versus tourist trips.

In conclusion, IBD travelers have an increased risk of illness during trips abroad. However, most of this increased risk manifests during trips to developed rather than to developing countries, suggesting that most illness results from flares of IBD and not from contraction of enteric infections. Moreover, the absolute risk increase is small, and most episodes were mild, thereby providing important reassurance for IBD patients and their caregivers when considering trips outside their resident country. Traveling while in clinical remission of at least 3 months should be strongly advocated as it significantly reduces the risk for illness during traveling.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2011.10.025.

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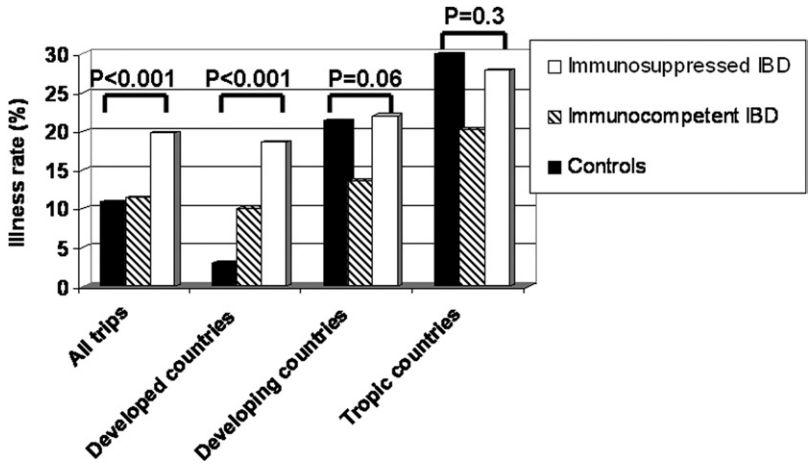
Conflicts of interest

This author discloses the following: Dr Ben-Horin has received consultancy fees from Schering-Plough and Abbot Laboratories. The remaining authors disclose no conflicts.

Funding

Supported in part by the "Talpiot" Medical Leadership program of the Sheba Medical Center (to SBH). The work was independent of the funding program.



Supplementary Figure 1. The rate of illness during travel in the immunosuppressed or immunocompetent IBD and healthy control populations.