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Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

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ABSTRACT

BACKGROUND

Approximately 8 percent of travelers to the developing world require medical care during or after travel. Current understanding of morbidity profiles among ill returned travelers is based on limited data from the 1980s.

METHODS

Thirty GeoSentinel sites, which are specialized travel or tropical-medicine clinics on six continents, contributed clinician-based sentinel surveillance data for 17,353 ill returned travelers. We compared the frequency of occurrence of each diagnosis among travelers returning from six developing regions of the world.

RESULTS

Significant regional differences in proportionate morbidity were detected in 16 of 21 broad syndromic categories. Among travelers presenting to GeoSentinel sites, systemic febrile illness without localizing findings occurred disproportionately among those returning from sub-Saharan Africa or Southeast Asia, acute diarrhea among those returning from south central Asia, and dermatologic problems among those returning from the Caribbean or Central or South America. With respect to specific diagnoses, malaria was one of the three most frequent causes of systemic febrile illness among travelers from every region, although travelers from every region except sub-Saharan Africa and Central America had confirmed or probable dengue more frequently than malaria. Among travelers returning from sub-Saharan Africa, rickettsial infection, primarily tick-borne spotted fever, occurred more frequently than typhoid or dengue. Travelers from all regions except Southeast Asia presented with parasite-induced diarrhea more often than with bacterial diarrhea.

CONCLUSIONS

When patients present to specialized clinics after travel to the developing world, travel destinations are associated with the probability of the diagnosis of certain diseases. Diagnostic approaches and empiric therapies can be guided by these destination-specific differences.

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† Members of the GeoSentinel Surveillance Network (GeoSentinel — The Global Surveillance Network of the International Society of Travel Medicine and the Centers for Disease Control and Prevention) are listed in the Appendix.

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Health problems are self-reported by 22 to 64 percent of travelers to the developing world[1]; most of these problems are mild, self-limited illnesses such as diarrhea, respiratory infections, and skin disorders. More importantly, each year, up to 8 percent of the more than 50 million travelers to these regions, or 4 million persons, are ill enough to seek health care either while abroad or on returning home.[1-3]

Much of the current understanding of morbidity profiles among ill returned travelers is based on data that were collected in the 1980s.[1-4] Although some morbidity studies have been designed to examine individual diseases,[5-9] specific high-risk destinations,[10] and certain types of travelers,[11-13] a comprehensive, multicenter comparison of the spectrum of illnesses acquired by a broad range of travelers returning from developing regions on all continents has been lacking.[14]

GeoSentinel sites are specialized travel or tropical-medicine clinics on six continents that collect clinician-based surveillance data on travel-related diseases. These data include a broad sample of travel destinations and of morbidity among persons who have become ill while traveling. We used the GeoSentinel database to verify the assumption that the destination of travel is associated with the probability of each diagnosis among travelers returning from the developing world.

METHODS

GEOSENTINEL SITES

The 30 current GeoSentinel sites are specialized travel or tropical-medicine clinics on six continents. They are recruited, on the basis of demonstrated training and experience and a record of publication in travel or tropical medicine, to contribute clinician-based sentinel surveillance data on all ill returned travelers seen (as detailed by the International Society of Travel Medicine, at www.istm.org, and by Freedman et al.[15]). The sites accounting for the majority of patients seen are within academic centers; several smaller-volume sites (almost all with a current academic affiliation) are in freestanding locations. Intake at the sites reflects a mixed population of patients requiring tertiary care and self-referred patients. Some sites are restricted to outpatient care, and at no site is practice limited to the care of ill travelers.

DATA COLLECTION

Criteria for Entry into the GeoSentinel Database

Patients must have crossed an international border within 10 years before presentation and have sought medical advice for a presumed travel-related illness. Anonymous surveillance data (including travel history) that could not be linked back to an individual patient were entered into a database at a central data center. Final diagnoses were assigned codes by the treating clinician from a standardized list of 524 possible individual diagnoses that were also categorized under 21 broad syndromes. (Diagnosis codes grouped according to syndrome are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) All sites used the best available reference diagnostic test in their own country. Patients were assigned as many diagnosis codes as needed. Since most infections are associated with fever, diagnoses predominantly localized to one organ system were included in that organ-system syndrome category and were not attributed to the broader category of systemic febrile disease.

The GeoSentinel data-collection protocol was reviewed by the institutional review board officer at the National Center for Infectious Diseases at the Centers for Disease Control and Prevention and classified as public health surveillance and not as human-subjects research requiring submission to institutional review boards.

Eligibility for Analysis

All travelers who presented to a GeoSentinel site after travel to the developing world were eligible for analysis. Patients with diagnoses that were either laboratory-confirmed or deemed probable were included in the analysis. Eligible patients who were ultimately found after medical assessment to have no underlying disease (1942 patients) and those found to have final diagnoses that were not confirmed or probable (1518 patients) were excluded.

COMPARATIVE MORBIDITY ACCORDING TO TRAVEL DESTINATION

We analyzed the six developing regions of the world where the majority of these illnesses were acquired (Fig. 1). Recent, temporally clustered travel to more than one country within a region often makes it difficult to attribute the illness to a spe-

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cific country. The place of exposure during travel was therefore determined to be the single region visited or, for travelers who entered more than one region, was determined according to the data field for "most likely place of exposure" if that information could be designated as certain by the clinician by virtue of incubation period or known patterns of endemicity (Fig. 1). To calculate a cumulative morbidity profile for all ill returned travelers, data from patients for whom a single region of exposure could be determined were grouped and then combined with data for ill travelers to multiple regions in whom ascertainment of the relevant place of exposure was impossible.

STATISTICAL ANALYSIS

The data analysis was performed with the use of SAS software, version 8 (SAS Institute). The primary variable analyzed was proportionate morbidity, calculated as the number of patients with a specific diagnosis or group of diagnoses as a proportion of all ill travelers returning from a developing region. All results are given in terms of the number of patients per 1000 patients in the group. Analyses of specific etiologic organisms according to region were performed only within an individual syndrome group. This analytic approach prevented a very frequent diagnosis within a region, such as malaria among travelers to sub-Saharan Africa, from overwhelming the contributions of various causes associated with other syndrome groups, such as diarrhea, that supplied proportionately fewer cases. Chi-square tests were used to compare these proportions among regions. Because of the large numbers of statistical tests performed, a conservative two-sided significance level of $P<0.01$ was chosen.

RESULTS

OVERALL MORBIDITY

The characteristics of 17,353 patients whose data were reported to GeoSentinel from June 1996 through August 2004 and who met the inclusion criteria are shown in Table 1. These patients, with travel exposures in 230 countries, presented to GeoSentinel sites located in Europe (49 percent), the United States or Canada (33 percent), Israel (8 percent), Australia or New Zealand (8 percent), and other sites (3 percent). More than 50 percent of the ill travelers had obtained documented advice from a medical provider before traveling. Diagnoses for 67.0 percent of all the returned travelers fell into 4 of 21 major syndrome categories:

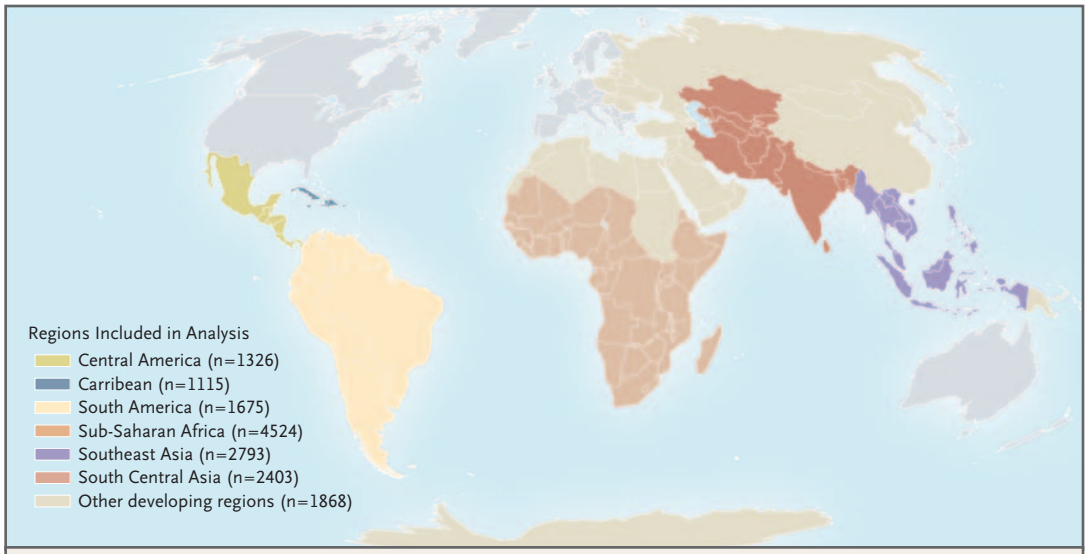

Figure 1. Regions of Travel Exposure among Ill Travelers Returning from the Developing World.

Data for 17,353 patients who presented to a GeoSentinel site were analyzed. (Ascertainment of exposure within a single developing region was not possible for 1649 travelers.) Other developing regions were West Asia, Northeast Asia, eastern Europe, Oceania, North Africa, and Antarctica.

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Table 1. **Characteristics of Ill Travelers Returning from the Developing World, According to Region Visited.***

Variable	All Regions	Caribbean	Central America	South America	Sub-Saharan Africa	South Central Asia	Southeast Asia	Other or Multiple Regions†
No. of travelers	17,353	1115	1326	1675	4524	2403	2793	3517
Age (yr)								
Median	33	37	32	30	34	32	32	35
Interquartile range	26–45	27–50	24–45	23–42	27–45	25–45	25–42	27–49
Duration of most recent travel (days)								
Median	23	14	18	35	28	30	24	18
Interquartile range	14–60	7–19	9–42	20–120	14–61	17–70	15–42	10–49
Time from travel to presentation at clinic (% of travelers)‡								
≤1 mo	64	59	61	61	70	71	72	52
>1–2 mo	11	14	12	13	10	9	9	11
>2–6 mo	15	19	19	17	13	13	12	20
>6 mo	10	8	8	9	7	8	7	17
Female sex (% of travelers)‡	48	54	52	45	44	50	47	51
Reason for travel (% of travelers)‡								
Tourism	59	75	66	56	43	67	74	59
Business	14	8	8	11	17	13	11	19
Research or education	4	1	6	4	6	3	3	4
Missionary or volunteer purpose	8	4	11	15	11	3	5	7
Visit to friends or relatives	15	12	8	14	24	14	8	12
Documented pretravel health advice (% of travelers)‡	55	30	48	62	59	61	62	46
Inpatient care (% of travelers)‡	11	5	4	6	18	10	11	11

* Percentages may not total 100 because of rounding.
† This category includes travel to West Asia, Northeast Asia, eastern Europe, Oceania, North Africa, or Antarctica (1868 travelers) or to multiple developing regions, for which ascertainment of exposure was impossible (1649 travelers).
‡ P<0.01 for the comparison among regions.

systemic febrile illness, acute diarrhea, dermatologic disorders, and chronic diarrhea (Table 2). The median duration of the most recent trip ranged from 14 days for the Caribbean to 35 days for South America. Although most of the patients (64 percent) were seen within a month after travel, 10 percent had indolent diseases or diseases with a long incubation period and were not seen until more than six months after travel (Table 1). The effects of pretravel care were not measured.

In this study, diagnoses were classified as confirmed at the following rates: malaria, 98.2 percent; campylobacter infection, 98.1 percent; shigella infection, 100 percent; cyclospora infection, 100 percent; dengue, 82.6 percent; and tickborne rickettsial disease, 62.6 percent. Overall, for specific infectious causes, 90.3 percent were classified as confirmed, suggesting appropriate rigor in the use of the "probable" classification.

DESTINATION ANALYSIS

For 13,836 of the ill returned travelers (80 percent), the relevant place of exposure could be determined to be one of the six major regions that receive travelers in the developing world. Most of the patients had traveled as tourists, except for travelers to sub-Saharan Africa, which had the highest proportions of business travelers and travelers visiting friends and relatives (Table 1). Unlike those returning from all other regions, less than a third of ill persons returning from the Caribbean had received advice before traveling.

Significant differences in proportionate morbidity (P<0.01) were seen among the travel regions

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Table 2. **Diagnosis According to Syndrome Group and Travel Region among Ill Travelers Returning from the Developing World.***

Diagnosis	All Regions (N=17,353)	Caribbean (N=1115)	Central America (N=1326)	South America (N=1675)	Sub-Saharan Africa (N=4524)	South Central Asia (N=2403)	Southeast Asia (N=2793)	Other or Multiple Regions (N=3517)†
	number of cases per 1000 patients							
Systemic febrile illness‡	226	166	153	143	371	171	248	145
Acute diarrhea‡	222	196	234	219	167	327	210	238
Dermatologic disorder‡	170	261	225	264	127	130	212	125
Chronic diarrhea‡	113	132	173	130	57	129	97	149
Nondiarrheal gastrointestinal disorder‡	82	87	75	82	70	74	58	121
Respiratory disorder‡	77	45	49	50	77	89	97	86
Nonspecific symptoms or signs‡	70	53	51	59	75	85	63	77
Genitourinary disorder‡	35	29	11	27	51	25	29	40
Asymptomatic parasitic infection‡	30	15	26	33	29	44	30	24
Underlying chronic disease‡	19	14	23	18	20	14	13	27
Injury‡	14	23	11	14	7	15	14	21
Neurologic disorder‡	15	23	24	16	10	15	10	16
Adverse drug or vaccine reaction‡	12	4	5	5	26	12	8	8
Psychological disorder‡	12	8	20	15	8	12	10	18
Tissue parasite‡	10	5	5	11	22	4	3	7
Cardiovascular disorder	8	12	7	5	8	7	5	10
Obstetrical or gynecologic disorder	3	3	2	2	4	3	3	3
Ophthalmologic disorder	2	2	2	2	2	1	1	2
Dental problem	1	1	1	1	1	0	2	1
Death	1	1	0	0	1	3	0	1
Loss to follow-up‡	8	9	12	9	8	5	4	13

* Diagnoses included in each syndrome category are listed in the Supplementary Appendix. Numbers may not total 1000 because patients may have had more than one diagnosis.
† This category includes travel to West Asia, Northeast Asia, eastern Europe, Oceania, North Africa, or Antarctica (1868 travelers) or to multiple developing regions, for which ascertainment of exposure was impossible (1649 travelers).
‡ P<0.01 for the comparison among regions.

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for 16 of the 21 syndrome categories (Table 2). In particular, systemic febrile illness was found disproportionately among patients presenting to GeoSentinel sites after travel to sub-Saharan Africa or Southeast Asia and acute diarrhea among those presenting after travel to south central Asia. Dermatologic disorders were seen disproportionately less commonly among travelers returning from sub-Saharan Africa or south central Asia. Diagnoses contributing to death included severe and complicated malaria, pulmonary embolism, pneumonia, and pyogenic abscess.

REGIONAL MORBIDITY ACCORDING TO SPECIFIC DIAGNOSIS

Destination-specific variations in the proportionate morbidity associated with etiologic diagnoses within each of the top four syndromic categories are presented in Table 3. Etiologic diagnoses were not commonly ascertained for chronic diarrhea, so they are not listed.

Overall, malaria was the most frequent cause of systemic febrile illness without localizing organ-system findings among ill travelers returning from the developing world (Table 3). In addition, for each of the six geographic regions, malaria was one of the three most frequent specific causes of systemic febrile illness among travelers, and it was the predominant cause of systemic febrile illness among those presenting after travel to sub-Saharan Africa. Travelers with dengue presented more frequently than did those with malaria for every region except sub-Saharan Africa and Central America. Rickettsial infections, primarily tick-borne spotted fever, appeared almost exclusively among travelers returning from sub-Saharan Africa, and typhoid fever was a primary contributor to systemic febrile illness among travelers returning from south central Asia.

For all regions except Southeast Asia, parasite-induced diarrhea was more common among ill returned travelers than was bacterial diarrhea. Patients with bacterial diarrhea presented most commonly after travel in Southeast Asia; campylobacter was the predominant cause. Of the parasitic causes, giardiasis was reported disproportionately among travelers returning from south central Asia.

Overall, insect bites were the most common cause of dermatologic problems, followed by cutaneous larva migrans, allergic reactions, and skin abscesses. However, cutaneous larva migrans was the most common dermatologic disorder among patients presenting after travel to the Caribbean, among whom it was seen much more commonly than among those returning from sub-Saharan Africa, south central Asia, or Central or South America. Bacterial skin infections, including skin abscesses, were found more commonly among patients returning from sub-Saharan Africa, south central Asia, or Southeast Asia than among those returning from the other three regions. Leishmaniasis was found mostly among patients who had traveled to South America or, to a lesser extent, Central America. Myiasis was reported most frequently among patients who had traveled to South America or Central America.

Travelers returning from each of the regions presented with intestinal nematode infestations, primarily involving ascaris and intestinal strongyloides. Of all ill returned travelers who presented with nondiarrheal gastrointestinal diagnoses, 40 per 1000 seen at our sites were reported to have acute hepatitis A, 20 per 1000 hepatitis B, 6 per 1000 hepatitis C, 13 per 1000 hepatitis E, and 36 per 1000 unspecified hepatitis. The sample size was too small to allow us to assess regional differences for hepatitis. Schistosomiasis (due to *Schistosoma mansoni* or *S. haematobium*) was seen predominantly among travelers returning from sub-Saharan Africa (196 per 1000). Acute brucellosis, leptospirosis, cysticercosis, filariasis, histoplasmosis, and echinococcosis occurred too infrequently to allow comparison among regions.

RARE DIAGNOSES

Clinicians evaluating returned travelers frequently entertain rare or exotic diagnoses. Travel-related cases of Ebola virus disease, Japanese encephalitis, rabies, tetanus, diphtheria, plague, tularemia, murine typhus, Rift Valley fever, poliomyelitis, primary amebic meningoencephalitis, anthrax, or yellow fever are reported sporadically in the literature. No cases of any of these diagnoses occurred among the 17,353 travelers whose data were analyzed in this study or among any of the 25,023 patients whose records were included in any category in our database but were excluded from this study. Among the 17,353 patients in our cohort, each of the following diagnoses occurred only once: *Angiostrongylus cantonensis* infestation, *A. costaricensis* infestation, hantavirus infection, cholera, melioidosis, Ross River virus

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infection, African trypanosomiasis, legionellosis, and meningococcal meningitis.

PROPORTIONATE MORBIDITY ACCORDING TO REGION

A summary profile of proportionate morbidity among ill returned travelers according to diagnosis or diagnosis group, expressed in terms of the proportion per 1000 ill returned travelers, is presented in Figure 2. Shown is the proportion, not the incidence rate, of each of the top 22 specific diagnoses among all ill returned travelers and among travelers returning from each of the regions.

DISCUSSION

Our database represents a large sample of ill travelers returning from the developing world. GeoSentinel sites are located primarily within academic centers, so some of the patients seen at each site present on the basis of consultations or outside referrals. Patients with imported illnesses that are neither self-limited nor mild are generally seen at such practices at some point during their care. At the same time, these practices are also the initial point of entry for many returned travelers who had pretravel medical preparation at the same clinic or for those who are affiliated with corporations, religious organizations, aid agencies, or governmental entities with which the clinic has an ongoing relationship or contractual arrangement. With significant growth in international travel, a travel or tropical-medicine clinic or infectious-diseases practice generally emerges in a community as the local specialized resource for providers and as the primary entry point for increasingly sophisticated travelers. Our data provide a reference for likely diagnoses, stratified according to destination, among travelers seeking care at or referred to such practices.

The data do not represent a comprehensive epidemiologic analysis of all illness in all travelers. Similarly, they do not represent a sample of illnesses in returned travelers such as those who would be seen at a nonspecialized, primary care practice, where mild or self-limited conditions would occur with higher frequency. Diagnoses with frequencies that may be underrepresented in GeoSentinel include diseases with a short incubation period, such as dengue; many cases of such diseases manifest during travel, so cases reported in returned travelers represent those acquired at the end of a trip. Finally, the small proportion of returned travelers with severe acute disease who need immediate hospitalization and are initially admitted through an emergency department may be underrepresented if the diagnosis is not considered related to travel or if care was sought outside the network. Travelers to destinations self-perceived to be particularly risky may present to a specialized unit earlier or with milder illness than travelers to more familiar destinations. Our data do not allow us to estimate incidence rates or to provide numerical risk for travel to particular destinations.

On an aggregate basis, the GeoSentinel database is a sample of illnesses acquired during exposure in 230 countries by sentinel travelers presenting in 13 countries for care. Nevertheless, biases for certain behavior-related diagnoses probably exist because of the geographic distribution and proportionate contributions of the individual sites. Patient intake at each site reflects local or national differences in the makeup of the traveling population, the distribution of travel destinations, and access to medical care. In addition, accommodations, eating habits, and other risk behaviors at a given destination may reflect the national and cultural background of the traveler. European travelers are more heavily represented in the sample than are North Americans (49 percent vs. 33 percent), and those from other regions (18 percent) are relatively underrepresented. Travel-related sexually transmitted diseases (proportionate morbidity, 8 per 1000 patients) and infections with the human immunodeficiency virus (2 per 1000 patients) were reported, but they are probably underrepresented in tropical-disease units; persons with self-recognized risk exposures or characteristic genitourinary symptoms may seek care in other settings.

At the same time, the benefit of a multicenter perspective over smaller, single-site studies, which have often reflected local patterns of travel, is demonstrated by the analysis of dermatologic disease. The most widely cited study of dermatologic disorders in travelers included 269 persons returning to France.[16] In that study, more than 60 percent of the patients had returned from travel to francophone countries of the Caribbean (Martinique and Guadeloupe), from French Guiana, and from sub-Saharan Africa. The finding that cutaneous larva migrans, pyodermas, and arthropod bites were among the top diagnoses agrees with

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Table 3. **Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region.***

Syndrome and Cause	All Regions	Caribbean	Central America	South America	Sub-Saharan Africa	South Central Asia	Southeast Asia	Other or Multiple Regions†
	number of cases per 1000 patients with syndrome							
Systemic febrile illness (n=3907)								
Specific pathogen or cause reported‡	594	459	527	446	718	522	547	454
Malaria‡	352	65	133	133	622	139	130	234
Dengue‡	104	238	123	138	7	142	315	35
Mononucleosis (due to Epstein–Barr virus or cytomegalovirus)‡	32	70	69	79	10	17	32	63
Rickettsial infection‡	31	0	0	0	56	10	16	24
Salmonella typhi or *S. paratyphi* infection‡	29	22	25	17	7	141	26	24
No specific cause reported‡	406	541	473	554	282	478	453	546
Acute diarrhea (n=3859)								
Parasitic diarrhea‡	354	283	403	368	353	453	262	323
Giardiasis‡	173	132	136	158	177	286	118	132
Amebiasis‡	120	105	155	142	138	103	74	135
Presumptive parasitic cause‡	35	9	45	52	33	55	33	13
Bacterial diarrhea‡	268	260	190	253	250	294	369	227
Campylobacter infection‡	85	46	32	90	73	87	180	57
Shigella infection	41	37	26	41	46	61	26	34
Nontyphoidal salmonella infection‡	27	27	13	14	29	12	56	30
Presumptive bacterial cause	110	132	94	106	99	136	116	95
Viral diarrhea‡§	9	23	32	5	7	4	5	7
Unspecified acute diarrhea‡	385	457	377	376	397	289	393	451

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Dermatologic disorder (n=2947)								
Insect bite, with or without superinfection	187	192	235	156	194	201	179	166
Cutaneous larva migrans‡	129	299	134	122	86	64	171	68
Allergic rash or reaction	113	148	128	97	105	112	93	132
Skin abscess‡	97	34	47	50	136	144	122	105
Rash of unknown cause	66	55	74	75	66	48	49	96
Mycosis, superficial	56	45	30	36	65	64	61	77
Animal bite requiring rabies postexposure prophylaxis‡	47	3	13	25	9	90	124	4
Leishmaniasis‡	38	0	64	143	14	19	0	36
Myiasis‡	35	0	101	100	40	0	0	14
Swimmer's itch‡§	28	3	0	2	117	3	9	14
Impetigo or erysipelas§	27	31	20	9	31	45	22	34
Mite infestation (e.g., scabies)§	22	21	37	39	12	29	17	14
Nondiarrheal gastrointestinal disorder (n=1421)								
Intestinal nematode infestation‡	239	278	273	256	307	202	344	141
Strongyloidiasis, simple intestinal‡	96	124	141	102	148	45	160	37
Ascaris infestation§	52	52	30	66	60	84	18	46
Gastritis or peptic ulcer disease‡	131	258	91	168	85	101	104	156
Helicobacter pylori status unknown	76	124	51	73	60	62	74	91
Positive for *H. pylori*‡§	47	103	40	80	22	28	25	60
Acute hepatitis‡	115	62	91	102	76	214	61	144
Hemorrhoids or constipation‡	89	124	192	117	54	84	74	84

* Numbers may not total 1000 because patients may have had more than one diagnosis. The most common diagnoses are listed for each category.
† This category includes travel to West Asia, Northeast Asia, eastern Europe, Oceania, North Africa, or Antarctica (1868 travelers) or ascertainment of exposure impossible subsequent to travel to multiple developing regions (1649 travelers).
‡ P<0.01 for the comparison among regions.
§ This diagnosis was listed in fewer than 100 reports.

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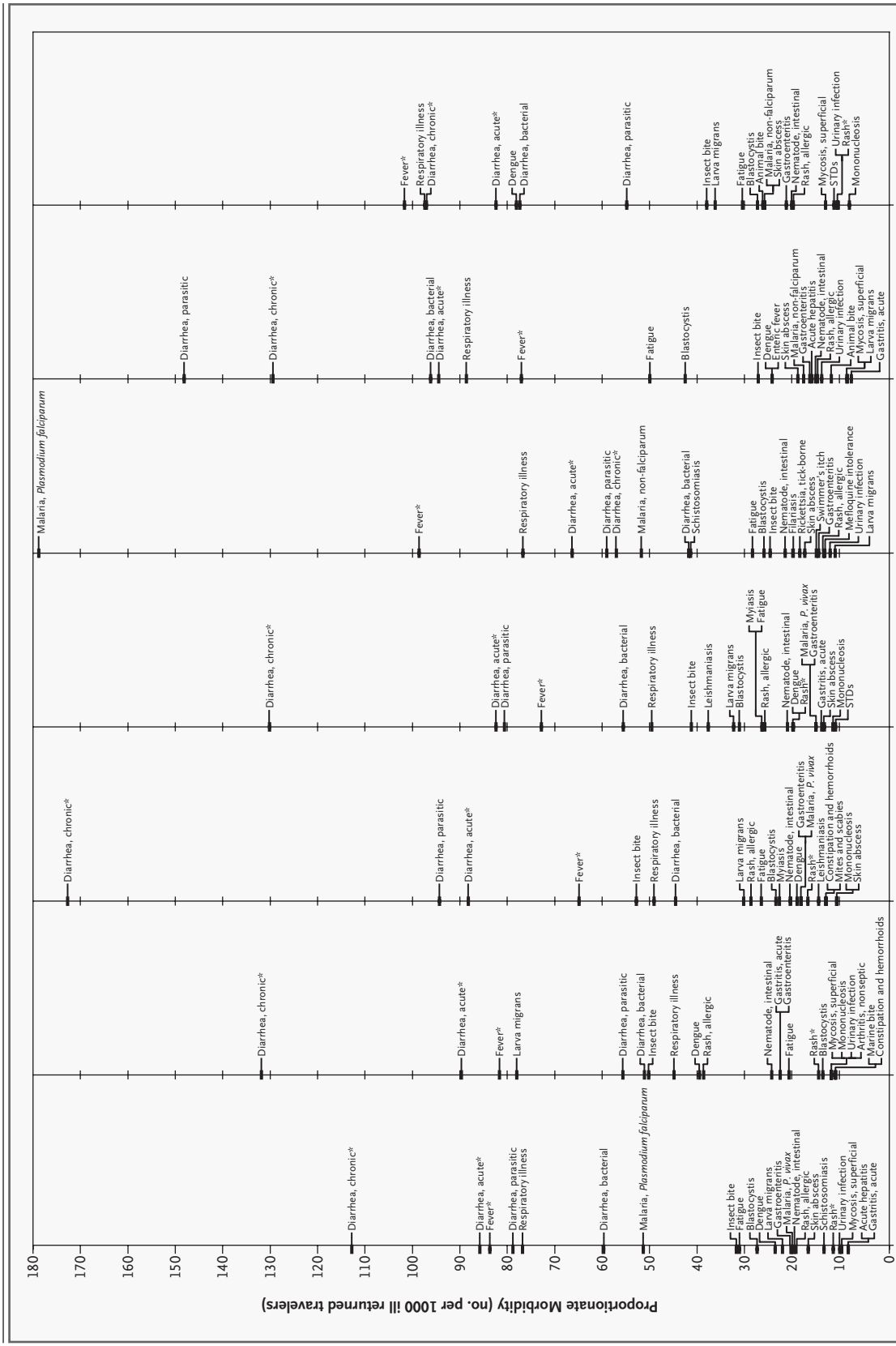

Figure 2. Proportionate Morbidity among Ill Travelers Returning from the Developing World, According to Region of Travel.

The proportions are shown, not incidence rates, of each of the top 22 specific diagnoses for all ill returned travelers within each of the regions. STD denotes sexually transmitted disease. Asterisks indicate syndromic diagnoses for which specific etiologic diagnoses could not be assigned.

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our own overall findings in all ill travelers. However, the significant destination-specific differences that we are able to describe for conditions such as cutaneous larva migrans, leishmaniasis, myiasis, swimmer's itch, and animal bites were not assessed in the earlier study.

The geographic dispersion of our sites, the full range of possible diagnoses, and the range of diagnostic tests necessary to identify the causes of tropical diseases preclude centralized laboratory testing for all patients. We used the best available national reference diagnostics for confirmed diagnoses. Probable diagnoses were restricted to patients who had an indisputable physical finding (e.g., tickborne rickettsiosis, cutaneous larva migrans, myiasis, or tungiasis), a response to a highly specific therapeutic agent, or a classic clinical presentation and exposure history, with other possible causes definitively ruled out by laboratory analysis. The last situation is particularly applicable to dengue, for which results of serologic tests are often difficult to obtain immediately and are often negative during the acute illness at the time of clinical presentation; in addition, patients with dengue often do not return for follow-up when faced with the cost of expensive diagnostic evaluation of a self-limited illness, particularly when the symptoms have resolved.

Codes available for a full range of syndromic diagnoses were used to classify patients consistently when a specific etiologic diagnosis was not assignable. Reasons included the frequency of self-limited acute infections and the effectiveness of empiric treatment or self-treatment for many syndromes, as compared with the expense and difficulty of diagnostic evaluation for exotic agents. For the syndromic groups of acute diarrhea and systemic febrile illness, specific etiologic diagnoses were not made in 40 percent or more of cases. Other studies have also found similarly high rates of undiagnosed fever[17,18] and diarrhea[19] in similar patients. Nonetheless, the clinicians in our study are experienced in disease recognition and diagnosis and have access to usually available diagnostic methods; the treatable causes of illness that are routinely sought in an initial clinic visit would probably not have been missed.

Our data on diarrheal illness illustrate important differences among studies that evaluate illness occurring during travel as compared with that seen after travel. All etiologic studies of travelers' diarrhea performed in the visited country during travel have shown a predominance of bacterial causes and a relative paucity of parasitic causes.[19-21] With respect to post-travel illness seen at our sites, diarrhea caused by parasites predominated over bacterial diarrhea in the overall analysis of ill returned travelers and in the analysis of every individual region except Southeast Asia. The likely explanation is that parasite-induced diarrhea tends to have a longer incubation period than bacterial diarrhea and to be more chronic and less treatable by the empirical antibiotic agents carried by travelers or prescribed at an initial medical encounter. Similar considerations most likely apply to other syndrome groups as well.

The high frequency of rickettsial disease reflects the emergence of *Rickettsia africae* in recent years in southern Africa, as has been reported in several single-site studies.[22] Dengue in travelers is well reported in studies from the 1980s onward, but in contrast to earlier data, it now appears to occur more frequently than malaria among travelers returning from any region except Africa and Central America. This change may reflect the use of effective antimalarial chemoprophylaxis by travelers. The proportionate morbidity associated with dengue is especially high among travelers returning from Southeast Asia and the Caribbean.

The current data provide a reference for likely diagnoses in returned travelers, with stratification according to destination but not according to prophylaxis designed before travel. The profile of proportionate morbidity generated by these data is important for guiding post-travel diagnosis and empiric therapy as well as for prioritizing pretravel intervention strategies.

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Dr. Freedman reports having received consulting fees from Shoreland, Sanofi Pasteur, GlaxoSmithKline, and Salix Pharmaceuticals and owning equity in Shoreland. Dr. Weld reports owning equity in Amgen and Chiron. Dr. Kozarsky reports having received consulting fees from Berna Products and lecture fees from GlaxoSmithKline. Dr. Keystone reports having received consulting fees from Sanofi Pasteur and GlaxoSmithKline and speaking fees from Roche and GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

The views expressed in this article are those of the authors and do not necessarily represent those of the CDC.

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APPENDIX

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REFERENCES

1. Steffen R, deBernardis C, Banos A. Travel epidemiology — a global perspective. Int J Antimicrob Agents 2003;21:89-95.

2. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. J Infect Dis 1987;156:84-91.

3. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. J Travel Med 2000;7:259-66.

4. Reid D, Cossar JH. Epidemiology of travel. Br Med Bull 1993;49:257-68.

5. Caumes E, Ehya N, Nguyen J, Bricaire F. Typhoid and paratyphoid fever: a 10-year retrospective study of 41 cases in a Parisian hospital. J Travel Med 2001;8:293-7.

6. Shah S, Filler S, Causer LM, et al. Malaria surveillance — United States, 2002. MMWR Surveill Summ 2004;53:21-34.

7. Raoult D, Fournier PE, Fenollar F, et al. Rickettsia africae, a tick-borne pathogen in travelers to sub-Saharan Africa. N Engl J Med 2001;344:1504-10.

8. Whitty CJ, Mabey DC, Armstrong M, Wright SG, Chiodini PL. Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country. Trans R Soc Trop Med Hyg 2000; 94:531-4.

9. Jelinek T. Dengue fever in international travelers. Clin Infect Dis 2000;31:144-7.

10. Taylor DN, Houston R, Shlim DR, Bhaibulaya M, Ungar BL, Echeverria P. Etiology of diarrhea among travelers and foreign residents in Nepal. JAMA 1988;260: 1245-8.

11. Liese B, Mundt KA, Dell LD, Nagy L, Demure B. Medical insurance claims associated with international business travel. Occup Environ Med 1997;54:499-503.

12. Herwaldt BL, de Arroyave KR, Roberts JM, Juranek DD. A multiyear prospective study of the risk factors for and incidence of diarrheal illness in a cohort of Peace Corps volunteers in Guatemala. Ann Intern Med 2000;132:982-8.

13. Patel D, Easmon CJ, Dow C, Snashall DC, Seed PT. Medical repatriation of British diplomats resident overseas. J Travel Med 2000;7:64-9.

14. Ryan ET, Wilson ME, Kain KC. Illness after international travel. N Engl J Med 2002;347:505-16.

15. Freedman DO, Kozarsky PE, Weld LH, Cetron MS. GeoSentinel: the global emerging infections sentinel network of the International Society of Travel Medicine. J Travel Med 1999;6:94-8.

16. Caumes E, Carriere J, Guermonprez G, Bricaire F, Danis M, Gentilini M. Dermatoses associated with travel to tropical countries: a prospective study of the diagnosis and management of 269 patients presenting to a tropical disease unit. Clin Infect Dis 1995;20:542-8.

17. Doherty JF, Grant AD, Bryceson AD. Fever as the presenting complaint of travellers returning from the tropics. QJM 1995;88:277-81.

18. Humar A, Keystone J. Evaluating fever in travellers returning from tropical countries. BMJ 1996;312:953-6.

19. Steffen R, Collard F, Tornieporth N, et al. Epidemiology, etiology, and impact of traveler's diarrhea in Jamaica. JAMA 1999; 281:811-7.

20. Hoge CW, Shlim DR, Echeverria P, Rajah R, Herrmann JE, Cross JH. Epidemiology of diarrhea among expatriate residents living in a highly endemic environment. JAMA 1996;275:533-8.

21. DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. N Engl J Med 1993;328:1821-7.

22. Jensenius M, Fournier PE, Vene S, et al. African tick bite fever in travelers to rural sub-Equatorial Africa. Clin Infect Dis 2003; 36:1411-7.

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CORRECTION

Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers . In Table 3 on page 127, the value for Sub-Saharan Africa for the ``Swimmer's itch´´ row should have been <1 per 1000, not 117 per 1000 as printed. This change so reduced the cumulative number of cases that the entire row should be deleted from the table. In Figure 2 on page 128, in the column labeled Sub-Saharan Africa, ``Swimmer's itch´´ should be deleted, and the value for ``Schistosomiasis´´ should be 55.6 per 1000, not 41.1 per 1000 as printed.

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