Am. J. Trop. Med. Hyg., 94(6), 2016, pp. 1385–1391
doi:10.4269/ajtmh.15-0920

Lymphocytosis and Lymphopenia Induced by Imported Infectious Diseases: A Controlled Cross-Sectional Study of 17,229 Diseased German Travelers Returning from the Tropics and Subtropics

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Abstract. The present controlled cross-sectional study aimed to assess relative and absolute lymphocytosis and lymphopenia induced by imported infectious diseases (IDs) seen among patients consulting the Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich (1999–2014) after being in the tropics and subtropics. The analysis investigated data sets from 17,229 diseased German travelers returning from Latin America (3,238), Africa (5,467), and Asia (8,524), and from 1,774 healthy controls who had not recently traveled. Among the cases, the proportion of those with relative lymphopenia (10.5%) and absolute lymphopenia (8.0%) was significantly higher than among controls (3.2% and 3.6%, respectively), whereas relative lymphocytosis was significantly lower among cases (6.1%) than among controls (8.0%). The study identified IDs with significantly larger proportions of relative lymphocytosis (cytomegalovirus [CMV] infection [56%], infectious mononucleosis [51%], and dengue fever [11%]); absolute lymphocytosis (infectious mononucleosis [70%] and CMV infection [63%]); relative lymphopenia (streptococcal pharyngitis [56%], malaria [34%], *Campylobacter* infection [19%], salmonellosis [18%], and shigellosis [17%]); and of absolute lymphopenia (human immunodeficiency virus infection [53%], malaria [45%], dengue fever [40%], salmonellosis [16%], and *Campylobacter* infection [11%]). This study demonstrates that relative and absolute lymphocytosis and lymphopenia are useful laboratory findings for travelers returning from the tropics and subtropics, as they are typically caused by imported viral, bacterial, and protozoan IDs.

INTRODUCTION

Lymphocytosis and lymphopenia (or lymphocytopenia) are frequent laboratory findings in clinical medicine that can be caused by a large number of congenital and acquired diseases, including infectious diseases (IDs).[1] Relative lymphocytosis and relative lymphopenia are defined as proportions of lymphocytes elevated or reduced, respectively, of the total number of leukocytes assessed during differential blood count, expressed as percentages (%). Absolute lymphocytosis and absolute lymphopenia are defined as the number of lymphocytes per volume of blood, which are elevated or reduced respectively, and generally expressed per microliter (μL). As these hematological parameters depend on the age of a patient and the test method used, normal ranges provided for different age groups can differ depending on the laboratory and test technology. Nevertheless, the generally used normal ranges for adults are approximately 20–40% and 1,500–4,500 or 1,000–5,000 lymphocytes/μL, respectively.[1,2] Furthermore, there are no reported differences between adult males and nonpregnant females.[3]

Lymphocytosis is not only seen in patients with viral IDs (e.g., infectious mononucleosis, infection with human cytomegalovirus [CMV], viral hepatitis, influenza, measles, mumps, rubella, and varicella), but also in those with bacterial (e.g., syphilis, brucellosis, and pertussis) and protozoan (particularly toxoplasmosis) IDs.[1,2] Generally, acute viral infections lead to relative lymphocytosis. Lymphopenia is more frequently diagnosed in patients with advanced human immunodeficiency virus (HIV) infection, after influenza infection, and with tuberculosis, especially military tuberculosis,[1,2] and to a greater extent, in patients with malaria[4] and with bacteremia.[5]

As the majority of these IDs are endemic to tropical and subtropical regions, travelers going to such destinations are particularly at risk of acquiring these IDs.[1] Data on this subject are rare, and no systematic study on infection-induced lymphocytosis and lymphopenia among travelers has been reported to date, despite the immense increase in international mobility. The number of international travels worldwide has increased from 25 million in 1950, to 626 million in 1999, and to 1,133 million in 2014. In addition to the traditional favorite destinations of Europe and North America, many new destinations have emerged, especially in tropical and subtropical countries.[6] Between 2005 and 2014, the average annual growth in international travels worldwide was 4.4%, with highest growth in south Asia (8.6%), in southeast Asia (7.9%), and in sub-Saharan Africa (6.2%). In 2014, about 18.2 million individuals traveled from Germany to destinations outside Europe. Of them, 1.5 million traveled to Latin America, 2.8 million to Africa, and 7.8 million to Asia.[7]

The aim of this controlled cross-sectional study was to assess the validity of the laboratory findings for lymphocytosis and lymphopenia induced by imported IDs. The study was performed using data from a large number of patients who consulted the Division of Infectious Diseases and Tropical Medicine (DITM) at the University of Munich, between 1999 and 2014 after being in the tropics and subtropics. These 17,299 diseased returned travelers (cases) were diagnosed and treated at a single study site, with an additional sample of 1,774 healthy individuals of German origin who had not recently traveled to the tropics and subtropics (controls). Consequently, all cases and controls were subject to the same standardized process, allowing for maximal comparability of the data.

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MATERIALS AND METHODS

Database. The DITM has been collecting data on sociodemographics (gender, age, origin, and profession), travel (duration, destination, and type of travel), clinical history and symptoms, diagnostics, and—if applicable—diagnosis data of individuals consulting its outpatient department for treatment or medical checkup. From January 1999 to December 2014, DITM registered 38,059 individuals with complete data sets. Of them, 22,588 (59.35%) individuals had symptoms after traveling to the tropics/subtropics (Latin America, Africa, or Asia), 7,514 (19.74%) individuals did not have symptoms and had not recently traveled to the tropics/subtropics, 4,810 (12.64%) individuals had symptoms but had not recently traveled to the tropics/subtropics, and 3,147 (8.27%) individuals did not have symptoms after traveling to the tropics/subtropics. The symptoms presented here are those from patients' first consultation at DITM after being in the tropics/subtropics.

Study population: cases and controls. Of the 22,588 patients returning from traveling in the tropics/subtropics, 19,581 (86.69%) were of German origin (defined as born in Germany). Among them, 17,229 (87.99%) patients had full data sets available on cell count, including leukocytes and proportion of lymphocytes, and were thereby defined as cases. Of the 7,514 healthy individuals who consulted the DITM for medical checkup before travel and had not recently traveled to the tropics/subtropics, 6,481 (86.25%) were of German origin. Among these healthy individuals, 1,774 (27.37%) had full data sets available on cell count, including leukocytes and proportion of lymphocytes, and were thereby defined as controls (Table 1).

Study design. In this study, all patients consulted the DITM, at which time the independent variables (exposure as sociodemographics and travel) and dependent variables (outcomes as symptoms, diagnostics, and diagnosis) were assessed simultaneously: transversal study or cross-sectional study. The dependent variables were not influenced by the study design: noninterventional or observant study. The descriptive part of the study compared the prevalence of relative and absolute lymphocytosis and of relative and absolute lymphopenia of imported IDs among cases and controls: prevalence study. The analytical part of the study compared these prevalences among cases with certain IDs and further with those of the controls: controlled study.

Laboratory analysis. Blood samples were taken from all individuals at first visit to the DITM before any therapeutic drug administration. They were collected in ethylenediaminetetraacetic acid coated tubes and analyzed with a Sysmex KX-21N (Sysmex Digitana AG, Horgen, Switzerland) without previous storage or freezing.

Reference range. The reference ranges of these hematological parameters were defined according to in-house standards of the DITM.[8] Reference ranges for leukocytes: 5,000–21,000/μL (age of individual: 8–30 days); 5,500–18,000/μL (1–11 months); 6,000–17,000/μL (1–3 years); 5,500–15,500/μL (4–7 years); 4,500–13,500/μL (8–13 years); and 4,000–10,000/μL (> 13 years). Values of leukocytes above the reference range were defined as absolute leukocytosis and below as absolute leukopenia.

Reference ranges for proportion of lymphocytes within differential blood count of leukocytes: 18–65% (age of individual: 15 days to 5 months), 18–60% (6–23 months), 13–55% (2–5 years), 13–50% (6–11 years), 13–45% (12–17 years), and 17–47% (> 17 years). Proportions of lymphocytes above the reference range were defined as relative lymphocytosis and below as relative lymphopenia.

Values for absolute number of lymphocytes were calculated by multiplication of total number of leukocytes and proportion of lymphocytes within differential blood count of leukocytes. Reference ranges for absolute number of lymphocytes: 2,000–8,000/μL (age of individual: 15 days to 5 months), 1,600–7,000/μL (6–23 months), 1,500–4,500/μL (2–5 years), 1,200–3,600/μL (6–11 years), 1,000–3,200/μL (12–17 years), and 1,000–2,900/μL (> 17 years). Values of lymphocytes above the reference range were defined as absolute lymphocytosis and below as absolute lymphopenia.

Infectious diseases. The study detected 36 imported IDs, which occurred in more than seven cases: nine viral, nine bacterial, nine protozoan, six helminthic, and three ectoparasitic IDs. These 36 IDs comprised 3,970 laboratory-confirmed cases with complete data sets. Only IDs with exact laboratory confirmation were considered in this study. Clinically suspected or probable cases were not included (Table 1).

Data analyses. The database of the DITM was the source of all data analyzed in this study. The descriptive analysis was performed by Excel Worksheet (Microsoft, Redmond, WA). The proportions of lymphocytosis and lymphopenia with 95% confidence intervals were used to assess significant differences between cases and controls and between cases with certain IDs. Bivariate approximative tests (χ^2 tests) and exact test (Fisher's tests) were conducted using EpiInfo, version 3.3.2. (Centers for Disease Control and Prevention, Atlanta, GA) and Stata software, version 9.0. (Stata Corporation, College Station, TX). Significant differences were defined as P values below 0.05 (Table 1).

Ethical considerations. Ethical clearance for the study protocol was provided by the Ethical Committee of the Medical Faculty at the University of Munich, Germany. Clinical and laboratory data were only used from patients who provided written informed consent, or in the case of minors, had general written informed consent from the legal caretakers.

RESULTS

Demographic data of cases and controls. Data from 17,229 cases and 1,774 controls fulfilled the inclusion criteria. Among the cases, 52.38% (9,025) were female, with this proportion being significantly ($P < 0.01$) lower than among the controls (39.29% [697]). Of the cases, the age range was 5 months to 92 years, with a median of 34.5 years, and an interquartile range (IQR) of 27.0–47.1 years. Of the controls, the age range was 1–92 years, with a median age of 37.7 years, and an IQR of 28.5–49.1 years. Grouped into the age groups of 0–19, 20–64, and 65–92 years, the corresponding proportions among the cases were 5.08% (876), 89.65% (15,446), and 5.26% (907), respectively, and among controls were 8.57% (152), 85.91% (1,524), and 5.52% (98), respectively (Supplemental Table 1).

Hematological values among cases and controls. The proportions of normal values for leukocytes and normal relative and absolute values for lymphocytes were significantly higher among controls (92.33%, 88.84%, and 88.56%, respectively) than among cases (85.21%, 83.49%, and 83.51%,

TABLE 1

Lymphocytosis and lymphopenia induced by imported IDs analyzed among 17,229 diseased German travelers returning from the tropics and subtropics (cases)

Blood cells	Leukocytes			Lymphocytes						
Blood cell count	Absolute			Relative			Absolute			
Value of blood cell count	Reduced	Normal	Elevated	Reduced	Normal	Elevated	Reduced	Normal	Elevated	
Laboratory diagnosis	Leukopenia	–	Leukocytosis	Relative lymphopenia	–	Relative lymphocytosis	Absolute lymphopenia	–	Absolute lymphocytosis	Total (%)
Controls	86	1,638	50	56	1,576	142	64	1,571	139	1,774
(%)	(4.85)	(92.33)	(2.82)	(3.16)	(88.84)	(8.00)	(3.61)	(88.56)	(7.84)	(100)
(95% CI)	(3.85–5.85)	(91.10–93.57)	(2.05–3.59)	(2.34–3.97)	(87.37–90.30)	(6.74–9.27)	(2.74–4.48)	(87.08–90.04)	(6.58–9.09)	–
Cases	1,061	14,681	1,487	1,801	14,384	1,044	1,379	14,388	1,462	17,229
(%)	(6.16)	(85.21)	(8.63)	(10.45)	(83.49)	(6.06)	(8.00)	(83.51)	(8.49)	(100)
(95% CI)	(5.80–6.52)	(84.68–85.74)	(8.21–9.05)	(10–10.91)	(82.93–84.04)	(5.70–6.42)	(7.60–8.41)	(82.96–84.06)	(8.07–8.90)	–
Among cases:	333	3,240	397	485	3,266	219	454	3,184	332	3,970
36 IDs (%)	(8.39)	(81.61)	(10)	(12.22)	(82.27)	(5.52)	(11.44)	(80.20)	(8.36)	(100)
(95% CI)	(7.53–9.25)	(80.41–82.82)	(9.07–10.93)	(11.20–13.24)	(81.08–83.46)	(4.81–6.23)	(10.45–12.43)	(78.96–81.44)	(7.50–9.22)	–
Number of IDs with significantly lager proportions compared with those of all cases	3	NA	4	5	NA	3	5	NA	2	NA
IDs with significantly lager proportions compared with those of all cases (%)	Dengue fever (48.01)	NA	Steptococcal pharyngitis (77.78)	Steptococcal pharyngitis (55.56)	NA	CMV inf. (55.56)	HIV inf. (52.63)	NA	Infectious mononucleosis (69.81)	NA
	HIV inf. (31.58)	NA	Infectious mononucleosis (32.08)	Malaria (34.23)	NA	Infectious mononucleosis (50.94)	Malaria (45.05)	NA	CMV inf. (62.96)	NA
	Malaria (27.03)	NA	Giardiasis (15.49)	*Campylobacter* inf. (18.83)	NA	Dengue fever (10.83)	Dengue fever (39.71)	NA	–	NA
	–	NA	*Campylobacter* inf. (12.33)	Salmonellosis (18.42)	NA	–	Salmonellosis (15.79)	NA	–	NA
	–	NA	–	Shigellosis (17.18)	NA	–	*Campylobacter* inf. (11.33)	NA	–	NA

CI = confidence interval; CMV = human cytomegalovirus; HIV = human immunodeficiency virus; IDs = infectious diseases; inf. = infection; NA = not applicable. In the present controlled cross-sectional study, 1,774 healthy Germans who had not recently traveled to the tropics and subtropics served as controls.

respectively). Among cases, the proportions of absolute leukocytosis (8.63%), relative lymphopenia (10.45%), and absolute lymphopenia (8.00%) were significantly higher than among controls, whereas the proportion of relative lymphocytosis (8.00%) was significantly higher among controls (Table 1 and Supplemental Table 1).

Hematological values and demographic data. Among female cases, the proportions of relative lymphocytosis (6.88%) and absolute lymphocytosis (9.87%) were significantly higher than among male cases (5.16% and 6.96%, respectively), whereas the proportions of relative lymphopenia (12.81%) and absolute lymphopenia (9.96%) were significantly higher among male cases than those among female cases (8.31% and 6.23%, respectively). Among controls, no significantly different hematological values were found between females and males.

Among cases of age group 0–19 years, the proportions of absolute leukopenia (11.42%), relative lymphocytosis (13.47%), and absolute lymphocytosis (10.05%) were significantly higher than those among cases of age group 65–92 years (4.63%, 3.31%, and 4.85%, respectively), whereas the proportions of absolute leukocytosis (11.03%) and relative lymphopenia (16.98%) were significantly higher among cases of age group 65–92 years than those among cases of age group 0–19 years (6.51% and 6.39%, respectively).

Regardless the lower sample size of controls, the proportion of relative lymphocytosis (19.08%) was also found to be significantly higher among controls of age group 0–19 years than among controls of age group 65–92 years (5.10%), whereas the proportions of relative lymphopenia (10.20%) and absolute lymphopenia (8.16%) were significantly higher among controls of age group 65–92 years than among cases of age group 0–19 years (0% each) (Supplemental Table 1).

Hematological values and travel data. Among the 17,229 diseased German travelers returning from the tropics/subtropics, the range of travel duration was 1 day to 50 years, with a median of 21 days, and an IQR of 14–35 days. Among cases with travel duration of 1–14 and 15–30 days, the proportions of relative lymphopenia (11.77% and 11.46%, respectively) and absolute lymphopenia (9.18% and 8.92%, respectively) were significantly higher than those among cases with travel duration of > 30 days (7.49% and 5.34%, respectively), whereas the proportion of absolute lymphocytosis (10.29%) was significantly higher among cases with travel duration of > 30 days than that among cases with travel duration of 1–14 or 15–30 days (7.39% and 8.13%, respectively).

Among cases with a travel destination in Latin America, the proportions of relative lymphocytosis (7.50%) and absolute lymphocytosis (10.44%) were significantly higher than among cases with a travel destination in Africa (5.52% and 7.85%, respectively) or Asia (5.85% and 8.15%, respectively), whereas the proportions of relative lymphopenia for those with a travel destination in Africa (11.32%) or Asia (10.62%) was significantly higher than those with a travel destination in Latin America (8.55%). Furthermore, the proportion of absolute lymphopenia for those with travel a destination in Africa (8.40%) or Asia (8.25%) was significantly higher than those with a travel destination in Latin America (6.70%).

Among cases who traveled as backpackers, the proportion of absolute lymphocytosis (8.78%) was significantly higher than among cases who traveled as all-inclusive travelers (7.11%). No other significantly different hematological values were found among business travelers, all-inclusive travelers, or backpackers (Supplemental Table 1).

Hematological values and symptoms. In the database, 15 different symptoms were registered systematically. The most documented symptoms were diarrhea (42.0%), fever (30.4%), nausea (19.5%), skin disorders (16.5%), and arthralgia (12.3%).

Among cases with fever and arthralgia, the proportions of absolute leukocytosis (13.08% and 12.49%, respectively), absolute leukopenia (10.41% and 9.00%, respectively), relative lymphopenia (20.84% and 17.62%, respectively), and absolute lymphopenia (17.51% and 15.27%, respectively) were significantly higher than among cases with diarrhea, fever, skin disorders, or any other symptoms (Supplemental Table 1).

Frequently imported IDs. In the study population, 36 IDs had at least seven laboratory-confirmed cases with known values of leukocytes and lymphocytes. Thirteen IDs had more than 50 cases each, and among them, six were intestinal infections, with *Blastocystis* (964), *Giardia* (736), *Campylobacter* (600), *Shigella* (227), *Salmonella* (190), and *Entamoeba* (137) spp. The remaining seven frequently documented IDs were dengue fever (277), malaria (111), cutaneous larva migrans (111), rickettsiosis (85), infectious mononucleosis (53), cryptosporidiosis (53), and schistosomiasis (52) (Supplemental Table 1).

IDs with highest proportions of lymphocytosis and lymphopenia. Compared with the mean proportions of all 17,229 cases, this study identified IDs with significantly larger proportions of absolute leukocytosis (streptococcal pharyngitis [77.78%], infectious mononucleosis [32.08%], giardiasis [15.49%], and intestinal infections with *Campylobacter* spp. [12.33%]), absolute leukopenia (dengue fever [48.01%], HIV infection [31.58%], and malaria [27.03%]), relative lymphocytosis (CMV infection [55.56%], infectious mononucleosis [50.94%], and dengue fever [10.83%]), relative lymphopenia (streptococcal pharyngitis [55.56%], malaria [34.23%], intestinal infections with *Campylobacter* spp. [18.83%], salmonellosis [18.42%], and shigellosis [17.18%]), absolute lymphocytosis (infectious mononucleosis [69.81%] and CMV infections [62.96%]), and absolute lymphopenia (HIV infection [52.63%], malaria [45.05%], dengue fever [39.71%], salmonellosis [15.79%], and intestinal infections with *Campylobacter* spp. [11.33%]). None of the proportions for leukocytes or lymphocytes of any helminthic IDs (cutaneous larva migrans, schistosomiasis, hookworm [*Necator* and *Ancylostoma* spp.] infections, trichuriasis, ascariasis, and oxyuriasis) or any ectoparasitic IDs (scabies, myiasis, and tungiasis) considered in this study were significantly elevated compared with the mean proportions of all 17,229 cases (Table 1).

IDs with highest number of lymphocytosis and lymphopenia. This study assessed imported IDs with a high number of cases of absolute leukocytosis (giardiasis [114], intestinal infections with *Campylobacter* spp. [74] and with *Blastocystis hominis* [61], shigellosis [26], and salmonellosis [20]); absolute leukopenia (dengue fever [133], intestinal infections with *B. hominis* [68], malaria [30], intestinal infections with *Campylobacter* spp. [25], and salmonellosis [11]); relative lymphocytosis (intestinal infections with *B. hominis* [51], dengue fever [30], infectious mononucleosis [27], intestinal infections with *Campylobacter* spp. [25], and giardiasis [17]); relative

lymphopenia (intestinal infections with *Campylobacter* spp. [113], giardiasis [86], intestinal infections with *B. hominis* [80], malaria [78], and shigellosis [39]); absolute lymphocytosis (giardiasis [78], intestinal infections with *B. hominis* [66], infectious mononucleosis [37], intestinal infections with *Campylobacter* spp. [29], and CMV infections [17]); and absolute lymphopenia (dengue fever [110], intestinal infections with *Campylobacter* spp. [68] and with *B. hominis* [61], malaria [50], giardiasis [30], and salmonellosis [30]) (Supplemental Table 1).

DISCUSSION

This study is the largest controlled cross-sectional study assessing the validity of the laboratory findings of relative and absolute lymphocytosis as well as relative and absolute lymphopenia induced by imported IDs. The study was performed with data from 17,229 patients who consulted the Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich between 1999 and 2014, after being in the tropics and subtropics.

The overall results of the study showed larger proportions of normal absolute values for leukocytes and lymphocytes and of normal relative values for lymphocytes among controls compared with cases. This finding was expected, as several of the identified imported IDs cause significantly larger proportions of absolute leukocytosis, absolute leukopenia, relative lymphopenia, and absolute lymphopenia. As absolute leukocytosis was found more often among cases and relative lymphocytosis more often among controls, the proportion of absolute lymphocytosis was nearly the same among cases and controls. Although the proportion of females was significantly higher among cases than among controls, after stratification into gender and age groups, no relevant differences were seen in these hematological parameters between cases and controls.

Gender-related differences concerning leukocytes and lymphocytes are not known, and consequently, their normal ranges are effective for both genders, as used in this study.[1,8] Age-related differences concerning leukocytes and lymphocytes are known, and therefore the age-based normal ranges were used in this study.[8] This study found significant associations between these independent variables (gender, age) and the presented hematological parameters, but these results were confounded by several IDs.

The overall results of this study showed that relative and absolute lymphocytosis were found more frequently among females, those of younger age and those who had traveled to Latin America. These associations were confounded by infectious mononucleosis and CMV infection. Females comprised 52.38% of all cases and accounted for a significantly greater proportion of CMV infections (62.96%). The proportion of cases in age group 0–19 years was found to be 5.08%, and this age group accounted for a significantly larger proportions of cases with infectious mononucleosis (22.64%). The proportion of cases with travel destinations in Latin America was 18.79%, and this group accounted for significantly greater proportion of cases with CMV infection (29.63%).

Absolute lymphocytosis was found more frequently among travelers with long travel duration (> 30 days) and backpackers. These associations were confounded by infectious mononucleosis and CMV infection. The proportion of travelers with a travel duration of > 30 days was 28.04%, and this group accounted for a significantly larger proportion among cases with infectious mononucleosis (41.51%). The proportion of backpackers among all cases was 53.49%, accounting for a significantly larger proportions of cases with infectious mononucleosis (67.92%) and CMV infection (62.96%).

In addition, relative and absolute lymphopenia were found more frequently among males, those of advanced age, those with travel destinations in Africa and Asia, travelers with short travel duration, all-inclusive travelers, and those with fever and arthralgia. All except for one (all-inclusive travelers) of these associations were confounded by several imported IDs, which often cause lymphopenia. The proportion of males was 47.62% in all cases, with males accounting for a significantly greater proportion of cases with HIV infection (89.47%), malaria (73.87%), intestinal infections with *Campylobacter* spp. (53.33%), and salmonellosis (53.16%). The proportion of cases in age group 65–92 years was found to be 5.26%, with this age group accounting for a significantly greater proportion of malaria cases (9.91%). The proportion of cases with travel destinations in Africa was 31.73%, with cases from this region accounting for significantly larger proportions of malaria (79.28%), HIV infection (78.95%), and streptococcal pharyngitis (66.67%). The proportion of cases with travel destinations in Asia was 49.47%, with cases from this region accounting for significantly larger proportions of dengue fever (74.37%), intestinal infections with *Campylobacter* spp. (68.33%), and salmonellosis (57.89%). The proportion of travelers with travel duration of < 30 days was 71.96%, with this group accounting for significantly larger proportions of HIV infection (84.21%), shigellosis (81.06%), dengue fever (80.14%), intestinal infections with *Campylobacter* spp. (78.67%), and salmonellosis (75.34%). The proportion of all-inclusive travelers among all cases was 20.17%, but no confounding by any ID was identified. The proportion of cases with fever among all cases was 30.39%, which was found in significantly larger proportions in cases with malaria (92.79%), dengue fever (81.95%), streptococcal pharyngitis (77.78%), salmonellosis (57.08%), intestinal infections with *Campylobacter* spp. (41.33%), and shigellosis (36.56%). The proportion of cases with arthralgia among all cases was 12.32%, with these cases accounting for significantly larger proportions proportions among those with dengue fever (41.88%) and malaria (19.82%).

In this study, four imported IDs were identified with significantly larger proportions of absolute leukocytosis: streptococcal pharyngitis, infectious mononucleosis, giardiasis, and intestinal infections with *Campylobacter* spp. The significant association between absolute leukocytosis and giardiasis was highly confounded by intestinal coinfections with *Escherichia* spp., whereas absolute leukocytosis is typical for the other three IDs. *Escherichia* spp. are the main enteropathogens for diarrhea. As shown in another study from DITM, more than 70% of patients with travelers' diarrhea had enteroaggregative *Escherichia coli*, enterotoxigenic *E. coli* producing heat-labile and heat-stable enterotoxin, found in stool samples.[9] Furthermore, intestinal coinfections were found in more than 60% of patients with travelers' diarrhea. More than 70% of patients with giardiasis and more than 90% of patients with intestinal *B. hominis* infections were found to have intestinal coinfections, not only caused by

E. coli but also with other bacteria such as *Campylobacter* spp., *Shigella* spp., or *Salmonella* spp. Although *B. hominis* may only serve a complement of other enteric pathogens by causing diarrhea, its intestinal detection can be used as an indicator for hygienic conditions of a traveler's or immigrant's environment.[8]

In this study, three imported IDs were found to cause significantly more cases of absolute leukopenia: dengue fever, HIV infection, and malaria. Of the total 17,229 cases, 1,061 (6.16%) were diagnosed with absolute leukopenia and 1,379 (8.00%) with absolute lymphopenia. Dengue fever alone caused 110 (7.98%) cases with absolute lymphopenia. Of the cases with absolute lymphopenia, 703 (50.98%) had recently been to Asia. Among them, 88 (12.52%) cases were diagnosed with dengue fever.

As already described in another study from DITM, malaria is an imported ID causing absolute leukopenia, relative lymphopenia, and absolute lymphopenia.[10] In this study, 1,379 cases presented absolute lymphopenia, of which 50 (3.63%) were diagnosed with malaria. Of them, 265 male cases with absolute lymphopenia had recently been in Africa. Among them, 34 (12.83%) cases were diagnosed with malaria.

This study has some limitations. It has a cross-sectional design, and as such, all data on independent (e.g., travel) and dependent (e.g., ID) variables were collected at the same day of consultation. Consequently, only limited data on the clinical status before travel were available through patient interviews. In addition, no follow-up data, such as duration of IDs, which developed after consultation, could be collected. Furthermore, the data analysis assessed associations between independent and dependent variables, but their causal interpretation was limited. Finally, no absolute data on the number of travelers were available, so no exact calculations on relative risk are provided in this study.

However, in contrast to the other studies with large numbers of patients, which were multicentric, this study provides a uniformity in patient referral patterns, consistency in coding of diagnoses by clinicians and central laboratory reference facilities. As all patients were subject to the same standardized process, maximal comparability of the data was possible. In addition, the study population was restricted to travelers of German origin, as hematological values may vary immensely between international populations, especially those living in endemic region for certain IDs.[11] Consequently, the conclusions taken from this study are restricted to German travelers only. Finally, the great majority of cases presented here were diagnosed during routine work at the outpatient travel clinic of the DITM, so extensive laboratory tests were not performed when not clinically relevant. For example, biomolecular testing of norovirus, rotavirus, or *Escherichia* spp. among patients with diarrhea were not routinely performed, as an exact diagnosis had not consequence for treatment.

CONCLUSION

This study has shown that there is high validity for the laboratory findings of relative and absolute lymphocytosis and relative and absolute lymphopenia induced by imported IDs among travelers returning for the tropics and subtropics. These hematological parameters were significantly associated with several variables concerning demographics (gender, age), travel (duration, destination, and type of travel), and symptoms of patients. However, these associations were highly confounded by various IDs, imported by diseased German travelers from the tropics/subtropics.

Several IDs were identified with significantly larger proportions of relative lymphocytosis (CMV infection, infectious mononucleosis, and dengue fever), absolute lymphocytosis (infectious mononucleosis, CMV infection), relative lymphopenia (streptococcal pharyngitis, malaria, intestinal infections with *Campylobacter* spp., salmonellosis, and shigellosis), and absolute lymphopenia (HIV infection, malaria, dengue fever, salmonellosis, and intestinal infections with *Campylobacter* spp.). For helminthic and ectoparasitic IDs, no significant associations with these hematological parameters were identified. This study demonstrates that relative and absolute lymphocytosis as well as relative and absolute lymphopenia are useful laboratory findings for travelers returning from the tropics and subtropics, as they are typically caused by imported viral, bacterial, and protozoan IDs.

Received December 23, 2015. Accepted for publication March 6, 2016.

Published online April 11, 2016.

Note: Supplemental table appears at www.ajtmh.org

Acknowledgments: We thank all participants of the study and all colleagues of the DITM who are not mentioned as authors. Because of their contribution all the analyzed data could have been generated and served as source for this study.

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