Fever in Returned Travelers: Review of Hospital Admissions for a 3-Year Period

Daniel O'Brien,[1] Sean Tobin,[2] Graham V. Brown,[1,3] and Joseph Torresi[1]

[1]Victorian Infectious Diseases Service, and Departments of [2]Clinical Epidemiology, and [3]Medicine, University of Melbourne, Royal Melbourne Hospital, Victoria, Australia

We reviewed 232 consecutive patients admitted to a tertiary-care hospital under the care of an infectious diseases unit for management of febrile illness acquired overseas. A total of 53% presented to hospital within 1 week of return and 96% within 6 months. Malaria was the most common diagnosis (27% of patients), followed by respiratory tract infection (24%), gastroenteritis (14%), dengue fever (8%), and bacterial pneumonia (6%). Pretravel vaccination may have prevented a number of admissions, including influenza (n = 11), typhoid fever (n = 8) and hepatitis A (n = 6). Compared to those who had not traveled to Africa, those who had were 6 times more likely to present with falciparum than nonfalciparum malaria. An itinerary that included Asia was associated with a 13-fold increased risk of dengue, but a lower risk of malaria. Palpable splenomegaly was associated with an 8-fold risk of malaria and hepatomegaly with a 4-fold risk of malaria. As a cause of fever, bacterial pneumonia was ⩾5 times more likely in those who were aged >40 years.

An estimated 30 million people from industrialized countries visit developing countries annually [1]. In 1992, 4.8 million people arrived in Australia after international travel [2]. In Australia, doctors are frequently faced with returned travelers who have acquired infections abroad, especially in Southeast Asia, and some of these infections are potentially life-threatening. When the illness is associated with fever, patients are often admitted to the hospital [3]. Although much has been written about infections in returned travelers [4–9], there have been few studies on fever in the returned traveler [10, 11], and none of these studies is from Australia, where travel destinations and the spectrum of clinical presentations may be very different from that reported in other studies.

The evaluation of a febrile illness in a returned traveler requires an understanding of the common etiologies, their epidemiology, and their modes of presentation. Therefore, we undertook a study to describe the causes of fever in returned travelers admitted to the Victorian Infectious Diseases Service (VIDS) at Royal Melbourne Hospital, Victoria, Australia.

METHODS

Study patients were either admitted directly or referred to VIDS at the Royal Melbourne Hospital, a 400-bed tertiary-care referral center. Data were collected prospectively during the 18-month period from 1 July 1998 to 31 December 1999. Retrospective data were collected by review of medical records for the previous 18 months (1 January 1997 to 30 June 1998). To be included, patients had to fulfill the following criteria: (1) their illness was acquired outside Australia, (2) they were admitted to the hospital from 1 January 1997 to 31 December 1999, and (3) they were febrile. Immigrants or refugees whose illnesses were not related to further travel outside Australia after immigration were excluded.

Patient classification. Patients were defined as "expatriates," "travelers," or "visitors." We defined an "expatriate" as an Australian resident whose illness was

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Reprints or correspondence: Dr. Joseph Torresi, Victorian Infectious Diseases Service, Royal Melbourne Hospital, Victoria 3050, Australia (Joseph.Torresi@mh.org.au).

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acquired while living outside Australia in a single country for the purpose of work or education for >1 month. A "traveler" was an Australian resident whose illness was acquired during recent overseas travel but not as an expatriate. A "visitor" was a non-Australian resident traveling to Australia whose illness was acquired before arrival.

Regions. Countries were assigned the following broad regional classification if they were situated within the following areas: Asia (Southeast Asia and the Indian subcontinent), Africa (the African continent), the Pacific (in the Pacific Ocean east of Australia, including New Zealand and Papua New Guinea but excluding Hawaii), and Latin America, (Central and South America).

Diagnosis. Diagnoses were established by demonstration of a microorganism in a clinically relevant specimen or by seroconversion to an infectious agent that was probably acquired overseas and that was considered to be responsible for the patient's clinical illness. If a specific causative organism could not be identified, a clinical diagnosis was assigned. Presumptive diagnoses were based on epidemiologic and clinical features, supporting laboratory investigations, and a response to appropriate treatment. Diagnoses were assigned by the authors of this study or by the specialist infectious diseases physicians of VIDS.

Information was entered into the Microsoft Access database program and analyzed by Epi Info, version 6 (Centers for Disease Control and Prevention). Statistical significance was determined by use of the χ^2 test for 2×2 tables for each of the categorical values.

RESULTS

Epidemiology. There were a total of 232 patients; 149 (65%) were men and 82 (34%) were women. Fifty-six patients were admitted in 1997, 80 in 1998, and 96 in 1999. A total of 182 patients (78%) were travelers, 30 (13%) were expatriates, and 20 (9%) were visitors. The median age of patients was 30 years (32 years for men and 28 years for women). The largest proportion of illness occurred in travelers aged 20–29 years (42%). Geographical regions to which the patient had traveled recently or had visited from during the time that the patient's illness was probably acquired included Asia (61%), the Pacific (20%), Africa (15%), and Latin America (2%). Only 4 patients (2%) had not spent time in a developing country.

Pretravel advice. For 173 (75%) of 231 of patients, it was possible to determine whether pretravel advice had been obtained. Only 104 (61%) of the 173 patients had received advice, and of these, the source of advice could be ascertained in 56. Thirty-five (63%) of the 56 patients obtained advice from their general practitioner, 19 (34%) from a specialist travel clinic, and 2 (4%) from other sources.

Pretravel vaccinations that our patients received included vaccinations for hepatitis A (77 patients [33%]), typhoid fever (68 [29%]), diphtheria-tetanus (41 [18%]), hepatitis B (38 [16%]), polio (33 [14%]), *Meningococcus* (17 [7%]) yellow fever (13 [6%]), rabies (4 [2%]), influenza (3 [1.3%]), Japanese encephalitis (2 [0.8%]), and cholera (2 [0.8%]).

Information on antimalarial prophylaxis was available for 201 patients (87%). Doxycycline was prescribed for 44 (22%), 20 patients (10%) received mefloquine, 6 patients (3%) received chloroquine alone, 4 patients (2%) received chloroquine-proguanil, and 2 patients (1%) received doxycycline-chloroquine.

Clinical features. The interval between the return to Australia and admission to the hospital could only be determined for 142 patients (62%). The median interval was 6.5 days (range, 1–590 days). Most patients presented soon after their return, with 28 (19%) presenting within 1 day of return, 77 (53%) within 1 week, 117 (81%) within 1 month, 129 (90%) within 3 months, 138 (96%) within 6 months, and 141 (98%) within 1 year. All patients who presented ⩾6 months after return had malaria.

The patient temperatures recorded during admissions to the hospital were 37°C–37.9°C for 83 (36%) of patients, 38°C–38.9°C for 74 (32%) of patients, and ⩾39°C for 75 (32%) of patients. When patients with a temperature of >38.9°C were compared with those whose temperature was ⩽38.9°C, malaria was the only diagnosis significantly more likely to be associated with a temperature >38.9°C (OR, 3.2; 95% CI, 1.7–6.1; $P < .001$). Most patients presented with nonspecific symptoms (table 1), and localizing symptoms were present in one-third or fewer of patients. The frequency of presenting symptoms is summarized in table 1.

Seventeen patients (7%) had splenomegaly, and 12 of these patients had malaria. Compared with patients without sple-

Table 1. Frequency of presenting symptoms in febrile returned travelers.

Symptom	No. (%) of patients
Fever	232 (100)
Headache	145 (63)
Myalgia	93 (40)
Cough	74 (32)
Diarrhea	71 (31)
Nausea	64 (27)
Abdominal pain	55 (24)
Vomiting	52 (22)
Arthralgia	40 (17)
Rash	29 (13)
Skin lesion	12 (5)
Dyspnea	11 (5)
Hemoptysis	2 (1)

Table 2. Etiology and frequency of illnesses that resulted in fever in returned travelers.

Diagnosis	No. (%) of patients	Cases confirmed microbiologically, %
Malaria (*Plasmodium* species)	62 (27)	100
P. vivax	38 (61)	
P. falciparum	14 (23)	
P. ovale	5 (8)	
P. vivax + *P. falciparum*	2 (3)	
P. ovale + *P. falciparum*	2 (3)	
Species unspecified	1 (2)	
Respiratory tract infection	56 (24)	
URTI	28 (12)	25
Bacterial pneumonia	14 (6)	50
Influenza	11 (5)	100
Pertussis[a]	1 (0.4)	
Tropical pulmonary eosinophilia[a]	1 (0.4)	
Tuberculosis[a]	1 (0.4)	
Gastroenteritis	33 (14)	40
Febrile illness, no confirmed diagnosis	22 (9)	
Dengue fever	18 (8)	47
Typhoid fever	8 (3)	87.5
Hepatitis A	6 (3)	100
Rickettsial infection	5 (2)	100
Tropical ulcer	5 (2)	
Connective tissue disease	4 (2)	
Acute encephalitis	3 (1)	
Pyelonephritis	3 (1)	
Amoebiasis, *Entamoeba histolytica*[a]	2 (1)	
Herpes simplex[a]	2 (1)	
Deep tissue abscess	2 (1)	
Meningitis	2 (1)	
Urinary tract infection	2 (1)	
Bacteremia[a]	1 (0.4)	
Cellulitis	1 (0.4)	
Clonorchiasis[a]	1 (0.4)	
Disseminated aspergillus[a]	1 (0.4)	
Acute Epstein-Barr virus[a]	1 (0.4)	
Melioidosis[a]	1 (0.4)	
Erythema nodosum	1 (0.4)	
Thyrotoxicosis[a]	1 (0.4)	
HIV-AIDS[a]	1 (0.4)	

NOTE. URTI, upper respiratory tract infection.

[a] Diagnoses with <5 cases that were microbiologically confirmed.

nomegaly, those with splenomegaly were 8 times more likely to have malaria (OR, 7.9; 95% CI, 2.4–27.3; $P < .001$). Palpable hepatomegaly was found in 16 patients (7%), and of these, 9 had malaria. Malaria was 4 times more likely to be the cause of fever in patients with hepatomegaly than it was in patients without hepatomegaly (OR, 4.0; 95% CI, 1.3–12.5; $P = .006$).

Confirmed diagnoses. A total of 245 diagnoses were obtained for 232 patients in this study (table 2). Malaria, respiratory tract infection, gastroenteritis, and dengue fever were the most common causes of fever in our patients. A diagnosis could not be made in only 22 patients (9%), although viral illnesses were thought to be responsible for most of the cases in this group of patients. Final diagnoses were categorized according to the mode of transmission (figure 1). Categories included vectorborne, respiratory, foodborne and waterborne, cutaneous, genitourinary, CNS, and bloodborne viral infection.

Vectorborne diseases. Infections resulting from mosquito bites accounted for 40% of our febrile patients. Malaria was the most common vectorborne infection, affecting 62 patients (figure 1). A total of 26 (42%) of infections were acquired in the Pacific region, 21 (43%) in Africa, 19 (31%) in Asia, and 2 (3%) in Latin America. Febrile patients who returned from the Pacific region and Africa were significantly more likely to present with malaria (OR, 5.4; 95% CI, 2.6–11.4; $P < .001$, for travelers to the Pacific and OR, 6.2; 95% CI, 2.7–14.4; $P < .001$, for travelers to Africa).

Of the patients who returned from Africa, 11 (52%) had infection with *Plasmodium falciparum,* and when compared with those who had not traveled to Africa, these patients were 6 times more likely to present with falciparum than nonfalciparum malaria (OR, 6.13; 95% CI, 1.7–23.8; $P = .001$). In contrast, patients who returned from the Pacific region were 4 times more likely to have nonfalciparum malaria than were patients who had traveled to regions other than the Pacific (OR, 4.4; 95% CI, 1.01–22.16; $P = .02$). Although the majority of patients who returned from the Pacific region with malaria had *Plasmodium vivax, P. falciparum* infection occurred in 4 patients (22%), reinforcing the need to promptly exclude *P. falciparum* as the cause of infection.

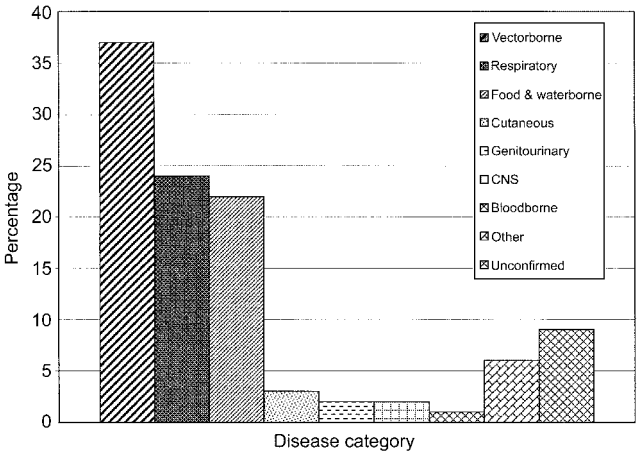

Figure 1. Grouping of diseases according to mode of transmission

Of the 62 patients with malaria, reliable information on antimalarial prophylaxis advice had been provided to 55 travelers. Of these travelers, 33 (60%) had been given antimalarial prophylaxis, but 15 (45%) of these patients reported incomplete with prophylactic medications. Overall, only 18 (33%) of these patients who had presented with malaria had taken and correctly adhered to antimalarial prophylaxis. Of these patients who had *P. falciparum* malaria diagnosed, 11 (69%) had commenced a course of prophylaxis, but of these, 9 (82%) reported incomplete adherence with their medications. Therefore, only 2 (11%) of these patients who had *P. falciparum* malaria diagnosed had adhered to their prescribed antimalarial prophylaxis regimen.

Dengue fever was the second most common vectorborne cause of fever. There were no cases of dengue hemorrhagic fever or shock syndrome. Seventeen patients acquired their illness in Asia and 1 acquired illness in the Pacific region. Eleven (61%) of 18 patients acquired their infection in Thailand. Febrile patients who had traveled to Asia were 13 times more likely to have acquired dengue fever than were patients returning from other destinations (OR, 13.2; 95% CI, 1.8–269.6; $P = .01$). The most common presenting symptoms for dengue fever included fever (18 patients [100%]), myalgia (11 patients [61%]), widespread generalized maculopapular rash (10 [55%]), and headache (11 [61%]). The diagnosis was confirmed serologically in 8 (44%) of 18 patients, and a presumptive diagnosis was made for the remainder.

Rickettsial diseases were the third most common vectorborne infections. Five patients had this diagnosis, all of which were confirmed with positive serological results. Three had African tick-bite fever *(Rickettsia africae)* acquired in South Africa and Zimbabwe, 1 patient was infected with the spotted fever group acquired in Papua New Guinea, and 1 patient was infected with the typhus group acquired in Bali.

Respiratory infections. Respiratory tract infections were the second most common cause of fever in returned travelers admitted to VIDS (figure 1). Bacterial pneumonia was not uncommon, accounting for 14 (25%) of respiratory admissions. A total of 8 patients (57%) acquired their illness in Southeast Asia, 4 (29%) in the Pacific region, and 2 (14%) in Africa. The median age of patients was 45 years, and, in comparison with other diagnoses, bacterial pneumonia was more common in patients aged ⩾40 years compared with patients aged <40 years (OR, 5.5; 95% CI, 1.5–21; $P = .002$).

A microbiological diagnosis was established in 50% of patients with pneumonia and included 1 infection each due to *Staphylococcus aureus, Streptococcus pneumonia, Haemophilus influenzae, Legionella pneumophila, Acinetobacter baumanii, Mycoplasma pneumoniae,* and *Klebsiella pneumoniae.*

Influenza accounted for 11 (20%) of 56 of the respiratory admissions. The mean age for patients was 36 years, and 8 infections (73%) were acquired in Asia, with 4 (80%) of 5 infections from Southeast Asia acquired from December through March. The diagnosis was established by detection of viral antigen in nasopharyngeal aspirates in 8 patients (73%); in the remaining patients, diagnosis was established by demonstrating antibody seroconversion. Only 1 patient had received an influenza vaccination, although 7 others had also sought pretravel advice from a medical practitioner.

Upper respiratory tract infections were common; these accounted for 28 respiratory admissions (50%). Nine patients had tonsillitis-pharyngitis, and of these, 7 had group A *Streptococcus* isolated from throat swabs.

Foodborne and waterborne infections. Gastroenteritis was the most common foodborne and waterborne infection in our study. Bacterial diagnoses were made for 13 (40%) of 33 patients admitted in the hospital with gastroenteritis. Of the bacterial isolates, 62% were *Campylobacter* species, 23% were *Shigella* species, and 15% were nontyphoidal salmonella.

Typhoid fever accounted for 8 (3.5%) of 232 of the patients (table 2) and was more common in patients who returned from Asia (table 3). The diagnosis was established by positive blood culture results in 4 of 8 patients and positive fecal culture results in 3 of 8 of patients, with the remaining patient diagnosed presumptively with typhoid fever. Only 1 patient had received pretravel advice from his general practitioner, and none had been vaccinated against typhoid. In comparison with other patients in this study, typhoid fever was 10 times more likely if patients had not sought pretravel advice from a medical practitioner (OR, 9.8; 95% CI, 1.1–221.2; $P = .01$).

Hepatitis A virus infection was uncommon (table 2). None of the 6 patients had been vaccinated against hepatitis A before travel, although 2 had received pretravel advice from a medical practitioner.

The frequency of the common diagnosis according to travel destination is shown in table 3. Infections were most frequently acquired in Asia and the Pacific region, although this most likely reflects the more frequent travel to these regions by Australian tourists. Dengue fever and typhoid fever were both more common in patients who had traveled to Asia than they were in those who had traveled to the Pacific region.

DISCUSSION

It has been estimated that 15%–37% of short-term travelers experience a health problem in relation to overseas travel [1, 9, 11], and a febrile illness occurs in up to 11% of returned travelers [1]. We were unable to determine the incidence of febrile illnesses in all returned travelers because we only reviewed patients admitted to the hospital with a medical problem. Instead, we have described the causes that most frequently

Table 3. Frequency of diagnoses according to region of travel.

Diagnosis	Asia	Pacific	Africa	Middle East	Latin America
Bacterial pneumonia	8 (57)	4 (29)	2 (14)	0	0
Dengue fever	17 (95)	1 (5)	0	0	0
Malaria	18 (32)	26 (38)	21 (32)	0	2 (3)
Hepatitis A	3 (50)	4 (67)	0	0	0
Typhoid fever	7 (88)	0	1 (13)	1 (13)	0

NOTE. Data are no. (%) of patients.

lead to hospital admission in travelers returning to Australia with a febrile illness acquired overseas.

In this study of returned travelers from developing countries admitted with fever, 53% presented within 1 week of return. Malaria accounted for all infections in patients who present ⩾6 months after return. In addition, a heightened suspicion of malaria is warranted in patients with fevers (temperature >39°C) and with hepatomegaly, splenomegaly, or both.

Malaria was the most common diagnosis in our study; it accounted for 28% of admissions. The risk of acquiring malaria is highest in the Pacific region and sub-Saharan Africa (1 in 50 to 1 in 1000), followed by the Indian subcontinent (1 in 1000 to 1 in 12,000); it is lowest in Southeast Asia and South America (<1 in 50,000) [12]. Most patients in our study acquired malaria in Papua New Guinea, although travel to Africa was associated with a substantial risk of acquiring *P. falciparum* malaria.

It is concerning that compliance with antimalarial prophylaxis was poor in patients admitted with malaria. In reported studies, up to 25% of travelers have blood drug levels that are inconsistent with their stated level of drug use [13], and only half of travelers adhere to malaria preventative recommendations [14]. In our study, two-thirds of all patients with malaria, and 89% of patients with *P. falciparum* malaria, had not adhered to antimalarial prophylaxis, despite some traveling to East Africa, where the incidence of infection with *P. falciparum* is 1.2% per month in those who were not using chemoprophylaxis [15]. Although resistance to mefloquine has been reported from sub-Saharan Africa [16], poor compliance with antimalarial prophylaxis is likely to pose a more significant risk factor for travelers.

Respiratory tract infections followed malaria as the next most frequent cause of fever in our patients. Respiratory tract infections are not infrequent in travelers [5, 17], and the associated etiologies of some are potentially life-threatening [18].

The occurrence of influenza in travelers may be underestimated, and this may be a common vaccine-preventable disease for travelers [19]. Influenza was the cause of fever in 11 patients (5%) we saw, most of whom acquired the infection in East Asia. Only 1 of our patients with influenza had received influenza vaccination. The majority of Australian travelers would not routinely be considered for influenza vaccination [20]. However, travelers acquiring influenza overseas may introduce this infection into Australia and provide a source of infection for the segment of the population likely to develop more severe complications. Therefore, influenza vaccination should be considered during pretravel health discussions.

Gastrointestinal illnesses are the most commonly reported disorders in travelers [1, 9, 11, 21], with up to 70% of travelers affected with diarrhea having symptoms severe enough to interfere with daily activities [22]. In our patients, gastroenteritis was the third most common cause of fever.

Dengue fever was the fourth most frequent diagnosis in our patients and the second most common vectorborne infection. Our findings reinforce the importance of dengue fever as a cause of fever in travelers [23, 24]. In developing countries, the fatality rate of dengue hemorrhagic fever is 5%, with most of these cases occurring among children [23, 25]. Dengue fever may therefore pose a serious health threat to children traveling or living for extended periods in countries where dengue is endemic.

A disturbing finding involved 1 patient who presented with HIV seroconversion after travel to northern Africa. This highlights the importance of providing pretravel advice regarding safe sexual practices and harm reduction for travelers and maintaining a high index of suspicion for HIV in travelers with a history of risk exposures.

Doherty et al. [10] also focused on travelers returning from developing countries who were admitted to the hospital with a febrile illness. Travelers were mostly male in both our study (65%) and that of Doherty et al. (64%; [10]). The majority of our patients were young travelers, with 97 (42%) between the ages of 20–29 years and 153 (69%) aged <40 years, which is similar to findings in other studies that examined all illnesses

Table 4. Comparison of common diagnoses in febrile returned travelers.

Diagnosis	Percentage of diagnoses in	
	Present study (n = 232)	Doherty et al. [10] (n = 195)
Malaria	27	42
Gastroenteritis	14	7
Upper respiratory tract infection	12	3
Bacterial pneumonia	6	4
Influenza	5	—
Fever, no diagnosis	9	25
Dengue fever	8	6
Typhoid fever	3	2
Hepatitis A	3	3
Rickettsial infection	2	1

in overseas travelers [9]. This probably reflects the greater likelihood that young travelers will travel to developing countries where the risk of acquiring a significant illness or infection is high.

The study by Doherty et al. [10] differed from ours in 3 main areas: (1) immigrants and refugees who had not traveled recently were included; (2) some infections may have been acquired locally; and (3) the travel destinations for the travelers were different. The frequency of travel to Africa, Asia, and the Pacific region reported by these investigators was 60%, 41%, and <9%, respectively, compared with 15%, 61%, and 20%, respectively, in ours. Therefore, our study helps define the spectrum of travel-related febrile illnesses acquired in Southeast Asia and the Pacific region. Malaria constituted a higher proportion of cases in the study by Doherty et al. [10], although the proportion of patients with respiratory tract infections was higher in our study. A comparison of the most frequent diagnoses from our study and that of Doherty et al. [10] is shown in table 4.

It is of concern that hepatitis A and typhoid fever are still among the 10 most common diagnoses in admitted febrile returned travelers (table 4). Study patients with these diagnoses had not been vaccinated for these preventable diseases before travel. Ten of these patients had failed to consult a medical practitioner before departure, and 3 patients had sought pretravel advice from a medical practitioner but were not vaccinated. Symptomatic hepatitis A infection occurs in 3–6 travelers per 1000 per month of stay in resort areas and increases to 20 per 1000 per month of stay for those traveling to rural areas of endemic countries [17]. The hepatitis A vaccine is safe and highly efficacious, with seroconversion rates of up to 100% [26]. Vaccination should be administered to all travelers, including short-term travelers, who travel to these destinations [5]. Typhoid vaccine is less efficacious than the hepatitis A vaccine [27–29], but the risks of acquiring typhoid fever is lower than the risk of acquiring hepatitis A [5]. The risk of acquiring typhoid fever is 1–10 in 30,000 per month of stay in developing countries [12]. In our study, none of the patients with typhoid fever had been vaccinated. All travelers who plan to spend ⩾2 weeks in countries where infection is endemic and where sanitation and hygiene conditions are likely to be poor should receive typhoid vaccination [19, 27]. This is especially important for travelers to Southeast Asia, where typhoid fever and multidrug-resistant *Salmonella typhi* are common [30].

In the nonimmigrant population, we have defined the spectrum of diseases in travelers returning from the Pacific region and Southeast Asia with fever. Malaria remains the most frequent cause of a febrile illness in returned travelers and therefore requires prompt exclusion. Respiratory tract infections constituted the second most frequent group, and of these, influenza could be prevented by vaccination. A significant proportion of illness is potentially preventable if appropriate pretravel advice is given and followed, including vaccination, prophylaxis, food and water precautions, and insect avoidance measures.

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