# Internal Medicine Grand Rounds

# Fever in the Returned Traveler

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## Case Presentation 1

A healthy 55 year-old physician presents with a chief complaint of "I think I have malaria" because he had experienced periodic fever for about 9 days. The reason that he thought he had malaria was that he had returned about a month ago from a trip where he was hiking in the jungles of West Papua on the same island as Papua New Guinea. He had gotten pre-travel vaccinations that included injectable typhoid vaccine and hepatitis A. He took doxycycline as malaria prophylaxis while in PNG but discontinued it early after return home. His fevers occurred in the morning at intervals of 48 hours and were characterized by rigors, myalgias, headache during each febrile episode, and fatigue after each episode, but he had no rash and no arthralgias. His past medical and social histories were unremarkable. He had no drug allergies and was not on any medications. He was afebrile with normal vital signs, and his physical exam was normal. His WBC was 6,400 with 90% PMNs; he was anemic with a hematocrit of 35.1, and his platelet count was 35. His chemistry panel was normal except for a bilirubin of 3.2 and a blood glucose level of 171. Blood cultures were negative. His blood smear had Dohle bodies and toxic granulations, and his malaria smear had forms consistent with *Plasmodium vivax*. His G6PD was normal. Due to his location of his trip, he received quinine and doxycycline followed by primaquine for radical cure.

## Case presentation 2

A healthy 36 year-old physician with a history of asthma presents with a chief complaint of fever that has lasted a week. He had returned a month before the onset of fever from visiting friends and relatives (VFR) in India. He travels to India regularly and usually spends about three weeks. He has not taken any precautions and not received any travel-related vaccinations. While in India, he developed an episode of "Delhi belly" that was characterized by non-bloody diarrhea with fever. He took 7 days of ciprofloxacin and recovered, but his fevers recurred after an interval of about 5 weeks later. He has no focal complaints and no complaints other than fever and profound fatigue. His temperature was 103°F. His exam was normal. His WBC was 5900 with 67% PMNs. His liver function tests revealed an AST of 153, and an ALT of 199 with normal bilirubin and alkaline phosphatase. Serological test for hepatitis were negative except for evidence of past immunization with hepatitis B vaccine. A CT scan of his chest, abdomen, and pelvis only revealed mild splenomegaly. A malaria smear was negative, but blood cultures grew *Salmonella paratyphi* A that was resistant to nalidixic acid but sensitive to cephalosporins. He was treated with a 4-week course of ceftriaxone and azithromycin.

**Introduction to Travel Medicine as Specialty**

Travel medicine has historically been a part of the field of tropical medicine and developed during the period of colonialism and imperialism by European and American governments because physicians in the far reaches of their empires needed to treat disease that developed in their soldiers and citizens within the colonies and many of these disease were unlike any that were familiar in the home countries. However, travel medicine is not simply tropical medicine. International travel often still involves travel to the tropics, but most US travelers travel either within the US or to Europe, which are not tropical countries. Further, travel and migration also occur from "South to North". Furthermore, infections constitute only a small proportion of the problems that affect travelers. Other issues such as traffic accidents, assaults, and environmental exposures are actually of greater significance to travelers and affect travel even within advanced industrial societies than many of the infectious diseases that are traditionally within the purview of infectious diseases and tropical medicine.

The International Society of Travel Medicine (www.istm.org) formed in 1971 and now has about 2900 members in around 90 countries with the purpose of promoting healthy and safe travel. It is a multidisciplinary society because the field is interdisciplinary and draws practitioners from many of the traditional subspecialties within medicine but also from fields such as preventive medicine, epidemiology, and public health.

"Travel medicine is an interdisciplinary specialty concerned with the prevention, management, and research of health problems associated with travel." Most practitioners are physicians, but physician assistants or nurse practitioners who have an interest in travelers' health run many travel medicine clinics.

Travel is increasing rapidly. As a comparison, the world population has increased 2.5 billion to an estimated 6.6 billion from 1950 to 2007, which is a 2.6-fold increase. At the same time, international travel arrivals have increased 35-fold in the same time period from 23.5 to 903 million using data from International Air Transport Association [1, 2] Most of the destinations for international travel are to Europe, but the fastest growing travel destination is East Africa. Most short-term travel is still for pleasure and vacation. Travel to Visit Friends and Relatives is the second-largest category and has special relevance [3]. Reasons for travel include:

| | |
|---|---|
| Leisure | 51% |
| VFR | 27% |
| Business | 16% |
| Other | 6% |

In addition to short-term destination travel, longer-term travel or migration of populations from one country to another country is also increasing rapidly. Migration

has increased from 40 million in 1975 to 175 million in 2000, and projections suggest that the number will increase to 230 million by 2050 (www.world-tourism.org/facts).

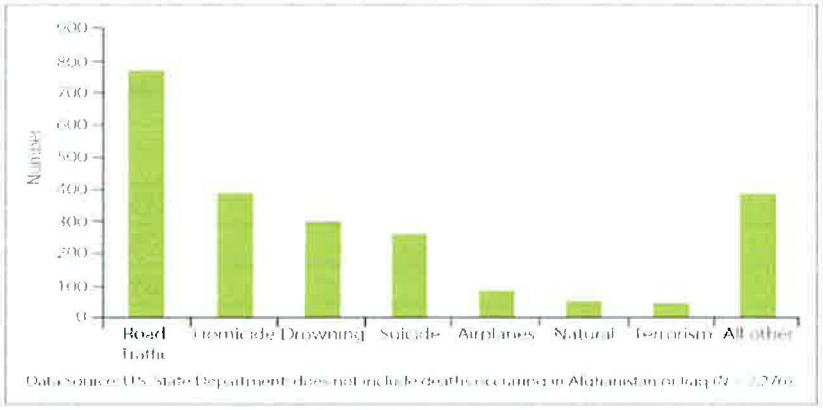
| Mode of Travel | 1990 | 2006 |
|---|---|---|
| Air | 39% | 46% |
| Road | 47% | 43% |
| Water | 8% | 7% |
| Rail | 6% | 4% |

(www.world-tourism.org/facts)

Travel can be thought of as a loop. The traveler will leave home, spend time in an unfamiliar location in contact with a large diverse group of people in shared sequential environments and then return home with souvenirs, many of them acquired unintentionally. As a result, the traveler then has a number of unintended public health roles. These include that of the victim, a sentinel of disease, a courier of disease, a processor of information, and a transmitter of disease to others [2, 3].

Travel can be hazardous. Data gathered by the ISTM indicate that 50% of all travelers will develop a health problem during travel, 8% will seek advice from a physician, 5% will be confined to bed for at least one day, 1% will be incapacitated either during or after travel, 0.3% will be hospitalized either abroad or at home, 0.05% will require medical evacuation, and 0.001% will die [4].

Despite common perception, infectious diseases are not the primary causes of death in travelers to developing countries; cardiovascular events are [5]. However, the specific cause of mortality depends partly depends upon age and destination. For instance, rates of cardiovascular disease are actually the highest among cruise ship passengers, who are primarily from North America and elderly. Homicide is the primary cause of death in international aid workers, accounting for 55%. Motor vehicle accidents account for the majority of deaths in Americans traveling to or living in developing countries [2, 5].




www.cdc.gov

There are a large number of reasons why road fatalities are generally higher in developing countries than in developed countries, including due to a large number of factors including the presence of a large number of poorly maintained vehicles on the road, bad poorly maintained roads, crowded roads, mixed use of roads with animals and other entities other than cars and trucks on the road, a large number of first generation drivers, more vulnerable road users, limited access to emergency vehicles, and less access to emergency medical care.

There are environmental risks as well that might be greater than at the travelers' homes. There may be a higher risk of animal bites from wild or feral animals, assaults including sexual assaults, civil unrest, natural disasters and environmental hazards.

Of course, there are also infectious disease risks, which include threats to safety from exposure to blood and body fluids though unprotected sex, tattoos, shaves, dental care and medical care including transfusions, and the use of illicit drugs as well as risks from contaminated food and water and arthropod-borne diseases.

**The Role of Pre-Travel Counseling**

Pre-travel counseling should seek to minimize these risks and generally has five components. This include an individualized risk assessment, the provision of advice on methods to reduce risk of illness or injury, the administration of vaccines, the provision of chemoprophylaxis for certain travel-related conditions, the provision of advice to for self-treatment for certain conditions, and instructions about when to seek medical care for either dangerous conditions or when self-treatment fails [2, 3].

Risk assessment must be individualized because each traveler is an individual with a unique medical history and unique travel plans. The risk assessment begins with consideration of the specific itinerary for the traveler. Risks will differ for the casual tourist to a plush resort compared risks for the long-term trekker. A detailed itinerary is more useful than a general one and should address reasons for travel, the duration of travel, the style of travel, and the season in the destination [2, 3].

The necessary general information includes general medical and psychiatric history, immunization history, and allergies. There are certain patient groups that have require special consideration and have special health needs. Last, there are considerations specific to travel such as the such as food and water precautions, insect and animal bite avoidance, immunizations, malaria preventions, sexually-transmitted disease prevention, air transportation issues, environmental risks, safety and security considerations, the need to buy travel insurance, and issues of sensitivity to differences between the travelers' cultures and the culture of the destination population [2, 3].

The typical travel advice applies to the general healthy individual. The recommendations usually need modification for specific groups of travelers because of unique susceptibilities in the age group, the presence of a pre-existing medical

condition, or the need to alter dosages or medical treatments as a function of the particular group of interest. Travelers with special health needs include pregnant and breast-feeding patients, neonates and pediatric travelers, the elderly, the disabled, those with pre-existing diseases, immunocompromised patients including transplant patients and those with HIV. Other groups like long-term expatriates also have unique needs. The medical needs of international migrants and of international adoptees also fall within the purview of travel medicine [2, 3].

The topic areas that are included within travel medicine are much more extensive than those devoted to infectious diseases. These areas include expedition medicine, assessment and treatment of conditions associated with marine and water exposure, including dive medicine and exposure to marine hazards, conditions associated with ascent to high altitude (including acute mountain sickness, high altitude pulmonary edema and high altitude cerebral edema), exposure to envenomations by bites and stings, conditions associated with air travel such as jet lag, deep venous thrombosis and pulmonary emboli, issues of exposure to environmental extremes of cold, heat, and sun, and exposure to environmental pollutants such as air pollution.

Of course, for pre-travel counseling to be effective, people have to seek it and then follow it. This is often not the case. In one study of Canadian travelers who contracted hepatitis A while traveling, only 20% had pre-travel counseling and only 15% had visited travel clinic [6]. Another study showed that although most travelers returning to North America with laboratory-confirmed cases of malaria had sought advice from a travel medicine physician but that only 11% used the recommended prophylaxis and only 17% used insect protection measures. Further, the diagnosis was missed in about 60% of cases with average delays in instituting appropriate therapy of 7.6 days for falciparum and 5.1 days for vivax malaria [6].

**Visiting Friends and Relatives: the VFR**

This constitutes a special category of traveler. The original definition of a VFR is "an immigrant, ethnically and racially distinct form the majority population of the country for residence (usually a higher-income country), who returns to his or her homeland (lower income) to visit friends and relatives" [7]. The definition has since expanded to include spouses and children born in country of residence [8, 9]. This group is important because they travel more often and experience greater morbidity and mortality than natives of their adopted country. Of residents of the US and Canada, 12% are foreign-born, they comprise 38% of overseas travelers. In addition, the patterns of migration have changed so that recent immigrants come from Asia and Latin America than from Europe as in the past. Returning to the home country exposes them to pathogens that are generally absent in their adopted countries [7, 10].

VFR travelers contract >50% of travel-related malaria and are 8 times more likely to contract the disease than are non-VFR travelers [2]. 75% of the typhoid and 90% of the paratyphoid cases imported into the US involve VFR travelers to South Asia and

Latin America [11, 12]. Imported cholera and tuberculosis are also more frequent in this group as are GI diseases, seafood-borne diseases, schistosomiasis and other helminthic disease, blood-and vector-borne diseases, zoonotic disease, bites and envenomations, and dengue fever.

Part of the reason for his is that VFR travelers are less likely to seek pretravel advice with rates of less than 30%. In general they travel to more remote locations away from tourist destinations, travel more often at the last minute, and stay for longer periods of time. There is also a lack of awareness of the risk. The are more likely to believe that they are immune to diseases at home, beliefs which are reinforced by their family and by the ignorance of their doctors. Last, there may be a number of barriers to seeking advice including financial, language, and cultural barriers with a lack of trust of physicians in their adopted country. They are also more likely to purchase medications in their country of origin where the medications are cheaper but also more likely to be counterfeit (30-50%) or drugs that are no longer effective like chloroquine, proguanil, or pyrimethamine [2].

**Vaccines as prevention**

Administration of vaccines is part of the pre-travel care. There are three categories of travel vaccines: routine, required, and recommended [2, 13, 14]. The routine vaccinations include tetanus, diphtheria, pertussis, Hib, polio, MMR, hepatitis B, hepatitis A, influenza, pneumococcal, HPV, rotavirus, varicella and zoster, meningococcal, and tick-borne encephalitis vaccines. These vaccines are often given beginning in childhood although now there are schedules for immunizations through adulthood. The specific recommendations for administration of routine vaccines vary from country to country. These vaccines are all very efficacious (>95%) if vaccine series is completed. The rationale for administering these vaccines before travel is, first, to complete the series within the country of origin, and, second, to protect those who travel to countries where universal vaccination is not the norm [2, 13, 14].

In the second category, the required vaccinations include only two vaccines: yellow fever and meningococcal vaccines for travelers to Mecca for either the Haj or Umrah pilgrimages. The World Health Organization published the second edition of the International Health Regulations in 2005 [15]. The World Health Assembly published the first edition, which was an update of the World Sanitary Regulations in 1969 and characterized three diseases, plague, cholera, and yellow fever as "quarantinable." The most recent update has the goal of providing guidelines regarding health efforts that member countries can implement "to prevent, protect against, and control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade." The updated regulations expanded the number of diseases to cover emerging disease, e.g., SARS. It also provides the mechanism by which countries can require certain vaccinations for entrance into those countries. The required vaccinations fall into this category of health policy. The

rationale for the yellow fever vaccination is the prevent the spread of virus from countries with disease activity to countries without disease but which have mosquito vectors that are competent to transmit disease. Epidemics of meningococcal meningitis among travelers to Mecca prompted the government of Saudi Arabia to require the vaccine for entrance into the country.

The third category contains the recommended vaccines [2, 13, 14]. These will vary from traveler to traveler and according to the destination, itinerary, and health needs of the individual tourist. These include hepatitis A and B, Japanese encephalitis, typhoid, cholera, poliomyelitis, meningococcal meningitis, rabies, and tick-borne encephalitis vaccines.

**Putting Travel Medicine on a Data-driven Basis**

Perhaps, 20 years ago most travel medicine recommendations were based primarily on the opinion of experts in the field. In 1995, the ISTM in collaboration with the CDC established GeoSentinel (www.istm.org/geosentinel) as a data collection tool to monitor travelers' health [16, 17]. GeoSentinel has 49 different sites, of which only 15 are in the US, on all continents that monitor traveler exposures in 237 countries and territories. The site monitors over 500 diagnoses, which are tracked by region, precise location, and time of exposure, and risk group with monthly tracking of 60 key diagnoses. As of the first week of July 2010, the data set contained more than 97,000 patient records with over 125,000 diagnoses. There are other similar organizations that have similar activities; these include TropNetEurop, EuroTravNet, and Global TravEpiNet.

**The General Approach to the Evaluation of Fever in the Returned Traveler**

Although there are certain diseases that physicians commonly associate with travel, such as malaria, most studies indicate that the most infectious disease illnesses in returned travelers are common syndromes that can easily be present in non-travelers. Diarrheal disease is the most common syndrome associated with travel and respiratory illnesses, predominantly upper respiratory illnesses but including pneumonia, as the second most common syndrome. In 2000, Hill described a series of 784 returned travelers, of whom 64% became ill during their trip. Infections were a significant proportion with diarrheal illnesses comprising 46%, respiratory illnesses comprising 26% and febrile episodes 3% [2, 4].

A compilation of several studies gives the following ranges: Diarrhea 20-60%, Acute respiratory infection 5-20%, Malaria 2%, Dengue 0.1%, Hepatitis 0.03 – 0.3 %, and animal bites with rabies risk 0.3% [18]. The specific prevalence differs by region [13].

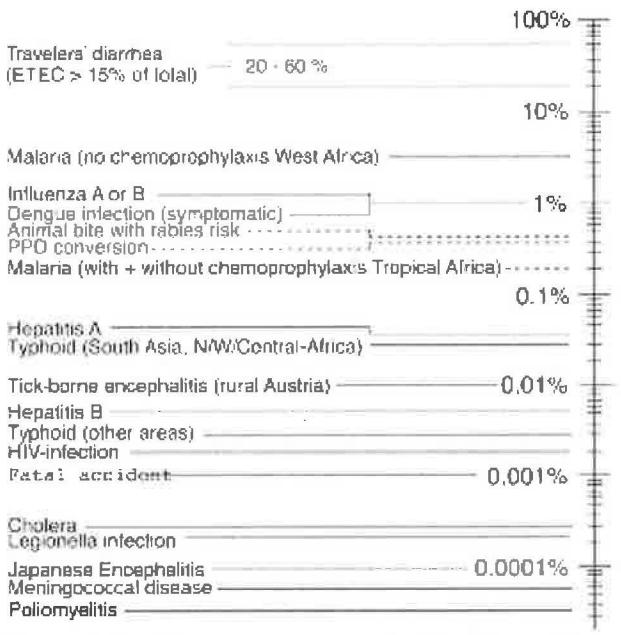



**Figure 1** Incidence rate per month of health problems during a stay in developing countries—2008.

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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 | 13 |
| 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 | 1 | 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.

Fever in a returned traveler can signal an illness that can be serious and sometimes lethal. One must remember that severe illness and mild, self-resolving illness can have similar initial appearances. The initial approach should identify 1) those diseases that are potentially rapidly progressive and lethal but treatable and 2) those diseases that are transmissible with the attendant public health consequences. The high case-fatality rate of falciparum malaria, especially in patients where diagnosis and treatment are either delayed or inappropriate, has determined much of the approach to diagnosis and management of acute febrile illnesses in returned travelers [2, 13].

For travelers, one needs to inquire about the geographic destination of travel because it will determine the risk of both the types of infecting organisms and the relative distribution of organisms. For instance, the geographic range of yellow fever is Africa and Latin America, so this diagnosis is not in the differential for a traveler to Southeast Asia while Japanese encephalitis is. The physician must further ask about specific activities that the traveler did during travel, such as animal bites, fresh water exposures in schistosomiasis-endemic areas, and sexual activities for example. Pre-travel vaccines, such as typhoid vaccine, will decrease but not necessarily eliminate the possibility of some disorders [2, 13]

Knowledge of typical incubation periods and major manifestations of the common diseases should allow the clinician to exclude some infections from the differential diagnosis. Most serious febrile infections are apparent in the first month after return although some may occur long after return. For example, most dengue will occur in the first week after return because the incubation time is about 3 to 7 days. Further, more than 90% of reported cases of *falciparum* malaria present within 30 days of return, but almost half of cases of *vivax* present more than 30 days after return. A history of prior travel and residence should be an integral part of every medical history; a history of use of physicians and health services in other countries is also important since many febrile travelers will be empirically treated for malaria simply because they have a fever [2, 12, 17, 18].

Certain signs or symptoms should prompt rapid evaluation. These include fever with hemorrhage or persistent bruising, neurological impairment including altered level of consciousness or paralysis of recent onset, jaundice, persistent diarrhea, persistent vomiting, skin rash, respiratory distress or a persistent cough. It is important to remember that there are noninfectious causes of fever. Although making a proper diagnosis is important for the welfare of the individual patient, one needs to remember that these infections can have public health implications if the infected traveler acts as a source for autochthonous transmission [2].

The basic laboratory workup should consist of a complete blood count with differential, a comprehensive metabolic panel with emphasis on liver function tests, urinalysis, blood cultures (before antibiotics), a chest radiograph, and thick and thin

smears for malaria. More specific studies are necessary if the history and physical exam suggest specific focal findings [2, 13]

Finally, one should remember that disease patterns change and evolve over time. Some of these changes will be discussed today.

**Specific Diseases**

There are many infectious diseases and many causes of fever that a person can acquire while traveling.

The remainder of this syllabus will cover malaria, yellow fever, dengue, Chikungunya, African tick bite fever, leptospirosis, and the enteric fevers caused by *Salmonella* with an emphasis of new developments in the field.

**Malaria**

Malaria is probably the most common blood-borne parasitic infection worldwide and is a major cause of mortality. The WHO estimates that there are between 350-500 million infections and about 1 to 3 million deaths annually [2]. The disease is distributed widely in a belt across the tropical latitudes with endemicity in more than 100 countries, but the historical distribution was much larger. As recently as 100 years ago, malaria occurred in temperate environments like North America and Northern Europe as far north as Ontario and the British Isles.

Malaria is caused by apicomplexan sporozoan protozoan parasites in the genus *Plasmodium*. There are only four species that are strict human pathogens in that transmission and maintenance involves a human-mosquito-human cycle without the existence of other mammalian host species. Transmission occurs almost exclusively through the bite of an infected female *Anopheles* mosquito although other mechanisms such as transfusion have occurred. The four human parasites are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Of these, *P. falciparum* is the most dangerous with the highest lethality and is the cause of malignant tertian malaria; the other species are usually considered "benign" although recent data strongly suggests that this is not true. Specifically, there are been reports of increasingly severe and lethal vivax malaria [2, 19, 20] and chloroquine-resistant *P vivax* [2, 21, 22] More recently, a fifth plasmodial species, *P. knowlesi* has been described as a pathogen in humans in a series of cases in Borneo, Sumatra, Malaysia, Singapore, and Thailand [2, 23]. The reservoir for this plasmodial species is a monkey, and transmission to humans is zoonotic [2, 23]. It raises the possibility of possibility of spread of other primate malarial species as humans encroach on previously undisturbed habitat.

The risk of contracting malaria for travelers differs widely between geographic regions and even within countries within a single geographic region. There is also much seasonal variation with more transmission within or just after the rainy season. Malaria is more common in rural areas than in the middle of large megacities, except for in

Africa where transmission occurs in urban areas. The highest risk is among travelers to West Africa and Oceania followed by other parts of Africa, South Asia, and South America. From 1997 to 2006, there were 10,745 cases of imported malaria in US residents. Almost 60% were acquired in sub-Saharan Africa with 14% and 13% in Asia and Latin America, respectively. *P. falciparum* caused the majority (85%) of fatal infections [2].

There are a large number of organizations, both national and international, that formulate guidelines for prevention and treatment. Some of these organizations include the WHO, the EU, the CDC, and the Canadian CATMAT. The guidelines are broadly similar but have small differences.

There are two main strategies to prevent malaria: mosquito avoidance measures and chemoprophylaxis. Although the use of these will decrease the probability of acquiring malaria, none are 100% effective.

Mosquito avoidance measures consist of the using of insect repellents, wearing clothing that cover most of the body, using bed nets, pretreating clothing and bed nets with pyrethroids (permethrin and deltamethrin), staying in screened or air-conditioned accommodations, and remaining indoors in the evening and at night when the *Anopheles* mosquito is active. The best repellent continues to be DEET (N, N-dimethyl-m-toluamide), which is safe and effective for those older than 2 months of age. DEET solutions with a concentration of 33% or greater offer 5-6 hours of protection. [24]. Picaridin is a newly approved repellent that is lasts almost as long as DEET [2].Oil of lemon eucalyptus also works but for a much shorter time. Other methods such as garlic, vitamin B, and ultrasound and magnets are completely ineffective. There is quinine in the tonic used to make gin and tonic; the concentration is so low that it is not possible to drink enough tonic water to be useful [25].

In addition pyrethroids, DEET can be used to impregnate clothing but only if the clothing are made of natural fibers. Indoor residual spraying with DDT-based insecticides and large scale outdoor spraying are public health measures but do not apply to the individual traveler. Insect avoidance measures alone may be appropriate if the risk of transmission is low. Chemoprophylaxis with antimalarial drugs is also effective in preventing malaria [2].The choice of the drug will depend upon a number of factors, including the traveler's age and medical conditions but most importantly upon the geographic destination and the activities at the destination. In general, prophylaxis starts before travel and during travel and for a period of time after return. Chloroquine was the old standby regimen, but its utility has decreased with the evolution of chloroquine resistance in *P. falciparum*. Currently, the utility of chloroquine and hydroxychloroquine is limited geographically to some areas such as the Caribbean and Central America located north of the Panama Canal and some areas in the Middle East. As chloroquine resistance rose, mefloquine use increased. It is still widely considered the drug of choice worldwide because of its ease of administration. However, there are now areas on Southeast Asia, specifically along the Thai-Myanmar border, the Thai-

Cambodian border, and the Cambodian-Vietnamese border, where mefloquine-resistance had evolved. Doxycycline and Malarone, which is a fixed dose combination of atovaquone and proguanil, can be used in areas of mefloquine resistance. The main use of primaquine is to kill the hypnozoites or the liver stage of *P. vivax* in "terminal prophylaxis", but primaquine is also useful for prophylaxis, especially if the *P vivax* is the predominant malarial species in an area [13]. One needs to check a G6PD level first.

Artemisinin, a drug derived from the *Artemisia annua* or the annual wormwood, has become the mainstay of treatment for severe malaria across the tropics. The drug Coartem, which is a combination of artemether and lumefantrine, recently received FDA approval for use within the US. Recently, however, there have been reports of treatment failures in Southeast Asia, which appears to be due to true drug resistance [21, 26]. Much of the evolution probably derives from use of subtherapeutic concentrations in counterfeit drugs [27-30].

Malaria usually develops 14 days after return but can be earlier depending upon duration of travel. The main symptoms are that of a nonfocal fever syndrome with fever, chills, headache, jaundice, anemia, myalgias, and malaise. The fever can be intermittent but is not always especially with falciparum malaria; diarrhea is common in severe malaria. Severe malaria is most common in falciparum malaria and can present with cerebral malaria, seizures, confusion, kidney failure, ARDS, and coma. Death is most common in children under 5, in pregnancy, and in the very old.

Malaria should be the first consideration in a febrile returning patient due to the high mortality associated with delays in treatment of falciparum malaria. The gold standard for diagnosis is smear microscopy, which is best performed on capillary blood at the bedside, because one can evaluate the species and the degree of parasitemia. Rapid diagnostic tests based upon lateral flow technology are available and obviate the need for a trained microscopist; one assay, BinaxNow has received FDA licensure within the US.

An educated and motivated traveler can take medications for self-treatment under certain conditions. Self-treatment is termed "presumptive self-treatment" or emergency stand-by treatment and is generally reserved for people who will be in an area at great risk for malaria and is more than > 24 hours from treatment. Generally, Malarone and Coartem are the drugs of choice, but one should use a different drug than is used for prophylaxis.

The CDC has a 24-hour hotline for advice with all aspects of malaria management.

**Yellow fever**

Yellow fever is a zoonotic arboviral disease caused by the yellow fever virus, which is a single-stranded positive-sense RNA virus in the flavivirus family. The virus is

related evolutionarily to dengue, Japanese encephalitis virus, West Nile Virus, and tick-borne encephalitis virus among others. Mosquitoes of the *Aedes* or *Haemogogus* genera transmit the virus. The current distribution of yellow fever is Africa and South America, but epidemics occurred as far north as Philadelphia in the late 1700s with the last epidemic in the US around 1900. Carlos Finlay and Walter Reed worked out the life cycle and transmission. Nonhuman primates are the primary reservoir although humans can become a reservoir if an urban infection cycle becomes established. There are three main cycles of transmission: a sylvatic (jungle) cycle, a savannah or intermittent cycle and an urban cycle. Most cases occur with rural exposure. The primary vector in urban epidemics is the *Aedes aegypti* mosquito. The risk is currently greatest in rural West Africa and throughout sub-Saharan Africa and tropical South America, and the risk is highest at the end of the rainy season. Aggressive vector control efforts in the 1970s had decreased the incidence of both dengue and yellow fever in tropical America but cessation of these efforts led to re-invasion of the continent by *A. aegypti* and reemergence of these two diseases. South America has had recent epidemics in Brazil, Bolivia, Venezuela, Paraguay, and Peru. There is evidence of increasing immunity with age, and a majority of cases are probably asymptomatic [2].

**Table. Countries with risk of yellow fever transmission**

| Africa | | | Central and South America |
|---|---|---|---|
| Angola<br>Benin<br>Burkina Faso<br>Burundi<br>Cameroon<br>Central African Republic<br>Chad[2]<br>Congo, Republic of the<br>Côte d'Ivoire<br>Democratic Republic of the Congo<br>Equatorial Guinea | Ethiopia<br>Gabon<br>The Gambia<br>Ghana<br>Guinea<br>Guinea-Bissau<br>Kenya<br>Liberia<br>Mali[2]<br>Mauritania[2]<br>Niger[2] | Nigeria<br>Rwanda<br>Sierra Leone<br>São Tomé and Principe<br>Senegal<br>Somalia<br>Sudan[2]<br>Tanzania<br>Togo<br>Uganda | Argentina[2]<br>Bolivia[2]<br>Brazil[2]<br>Colombia<br>Ecuador[2]<br>French Guiana<br>Guyana<br>Panama[2]<br>Paraguay<br>Peru[2]<br>Suriname<br>Trinidad and Tobago[2]<br>Venezuela[2] |

The risk in travelers depends upon destination and exposure to the vector. Fortunately, yellow fever is quite rate. The CDC reports only 9 cases in US and European travelers since 1979 to 2002; 8 of the 9 were fatal and all occurred in unvaccinated individuals. This is probably an underestimate of true cases. Current risk estimates are 10-50 per 100,000 travelers in a two-week period for West Africa and 1-5 for South America [2].

Infected patients are viremic on days 3 to 5 after inoculation by an infected mosquito. Disease develops after an incubation period of 3 to 6 days and presents as a nonfocal fever syndrome with fever, chills, headache, myalgias, prostration, nausea and vomiting. There is often a period of improvement after which about 15% or patients

progress to a severe toxic form of disease characterized by jaundice, hemorrhage, shock and multisystem failure. In severe cases the case fatality rate can approach 20-50%.

The diagnosis of yellow fever is mostly a serological diagnosis using assays that test for IgM and IgG antibodies. IgM antibodies will be positive in acute disease; IgG antibodies in the absence of IgM antibodies represent either immunization, past infection, or cross-reaction with other flaviviruses. Further testing can distinguish between yellow fever virus and other cross-reacting viruses. PCR-based tests on blood can be positive during the incubation period but are generally negative by the time a person develops disease. Definitive diagnosis can be done with culture or with histopathology and immunohistochemistry, but this is usually restricted to state health labs and the CDC.

There is no specific antiviral therapy. Management is supportive and symptomatic with rest, fluids, and the provision of analgesics and antipyretics, avoiding NSAIDS due to the risk of bleeding.

There are no chemoprophylactic drugs. Travelers should try to avoid mosquito bites using the same methods as for malaria. Since the mosquito vector breeds in small volumes of standing water near houses, one should empty water sources like flowerpots, buckets, barrels, bird feeders, and car tires.

For yellow fever, there is a safe and effective vaccine. The vaccine is a live attenuated virus vaccine that uses the 17D strain and was developed in the 1930s. One injection is usually sufficient to give long-lasting immunity. Although the IHR generally require reimmunization every 10 years, immunity is measurable for as long as 28 years after vaccination.

In general the vaccine is safe. A minority of patients has mild side effects such as muscle aches and headache, but less than 1% has severe enough side effects that they need to curtail normal activities. Immediate sensitivity reactions do occur but are also rare.

The most important recent development is the recognition of two classes of vaccine-associated side effects, yellow fever vaccine-associated neurologic disease (YFV-AND) and yellow fever vaccine-associated viscerotropic disease (YFV-AVD)[2, 31-34]. The most common syndromes associated with neurologic disease include meningoencephalitis, acute disseminated encephalomyelitis, bulbar palsies, Bell's palsy, and Guillain-Barre syndrome. It usually occurs in neonates and in those above the age of 60 and seems to be restricted to first-time vaccinees. The rate is about 0.8 per 100,000 vaccinees; recovery is usually complete, and very few fatalities have occurred.

Yellow fever vaccine-associated viscerotropic disease has a clinical appearance that is similar to natural disease with vaccine virus isolated from ill patients. About 40 cases have been described with onset averaging 3.5 days after vaccination. In contrast

to neurotropic disease, the case fatality rate is about 50%. Most disease occurs in first-time vaccinees above the age of 60 [33, 34].

Infants below 9 months of age and people either with true egg allergies or a history of immediate hypersensitivity to the vaccine should not receive it. Providers should exercise caution in the elderly. Immunocompromised patients usually do not receive the vaccine because it is a live virus vaccine. The vaccine appears to be safe in pregnancy and during breast-feeding [2].

Many travelers will require the "International Certificate of Vaccination or Prophylaxis" to enter specific countries. IHR allow countries to require proof of vaccination for all persons entering either into the country or from travelers coming from yellow fever endemic countries, even if only in transit [2, 15]The WHO issued a new certificate form in 2007. Physicians who possess a "Uniform Stamp" can only issue these certificates or facilities; state health departments or the CDC issue the stamps. Practicing travel medicine specialist can write a waiver, which must carry the stamp, for those with medical contraindications to the vaccine. Unwillingness to be vaccinated is not a valid reason for a waiver. The waiver letter does not guarantee the destination country will accept it [2].

**Table of Countries that require proof of yellow fever vaccination for all arriving travelers[1]**

| | |
|---|---|
| Angola | French Guiana |
| Benin | Gabon |
| Bolivia (or signed affidavit at point of entry) | Ghana |
| Burkina Faso | Liberia |
| Burundi | Mali |
| Cameroon | Niger |
| Central African Republic | Rwanda |
| Congo, Republic of the | São Tomé and Príncipe |
| Côte d'Ivoire | Sierra Leone |
| Democratic Republic of Congo | Togo |

**Dengue Fever**

Dengue fever results from infection with one of four serotypes, DENV-1 through DENV-4, of the dengue fever virus [35]. Dengue fever is a reemerging disease with more than 100 million cases estimated to occur annually and distributed across a wide swath of the tropical world in >100 countries. Like with yellow fever, aggressive mosquito control methods had nearly eradicated dengue from the Western hemisphere, but the disease has since reappeared after these efforts stopped. As with yellow fever, the vectors are day-biting mosquitoes of the genus *Aedes*, which are peridomestic mosquitoes with a limited flight range. The vector is present in the continental United States. Dengue is transmitted readily in urban settings unlike malaria. Increases in urbanization with the growth of third world megacities with poor housing, poor water supplies and poor housing are all factors in the reemergence. For travelers it is the

second-leading cause of fever in returned travelers, affecting 2-8% of travelers, and the second-leading cause of hospitalization in those returning from the Caribbean, South America, South Central and Southeast Asia [36],[37]. Like yellow fever, dengue was once prevalent in the United States, especially in the Southeastern states and Texas. There have been recent epidemics in Haiti and the Dominican Republic [38, 39] There are periodic reintroductions with autochthonous spread in Florida [40], Hawaii [41, 42], and Texas [43][34][44][45].

The major syndromes are dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The incubation period is from 4 to 7 days and most infections are asymptomatic. When symptoms occur, they are usually are mild with a nonfocal fever syndrome, headache, retro-orbital pain, a generalized maculopapular blanching rash that lasts about 3 days, leukopenia, myalgia and severe joint and bone pain ("break-bone fever"). About 1% of symptomatic patients have DHF, which is characterized by severe thrombocytopenia, evidence of vascular leak, and hemorrhage. DHS has the highest mortality and is characterized by hypotension or shock [35].

Lifelong immunity to specific to the infecting serotype with short-lived heterologous immunity; second and third infections with other serotypes can occur, and there is some indication that this leads to more severe disease. The mechanism is unclear.

The diagnosis is made serologically by measuring the presence of IgM and IgG antibodies to the virus. As with yellow fever, there is cross-reactivity to other flaviviruses but neutralization assays can help distinguish between the two.

There is no vaccine, but otherwise, the methods of prevention and treatment are the same as for yellow fever.

**Chikungunya**

Chikungunya virus was a fairly obscure virus with a distribution limited to Eastern Africa in the area of the Makonde plateau in Tanzania and Mozambique until 2004 when a large epidemic began that spread to Reunion Island in 2005 and 2006 and other islands off of the coast of Africa with further spread to across the Indian Ocean to India and to the Indonesia Archipelago [46-49]. French and Italian tourists on holiday on the resort beaches returned home with infections that brought the disease to Europe where a focus of autochthonous transmission occurred in Emilia Romagna in Italy [50-52]. Chikungunya virus (CHIKV) is a single-stranded positive-sense RNA virus that belongs Alphavirus genus of the to the family Togavirus family and is related to the O'nyong'nyong virus, the Ross River virus, and the Western and Eastern Equine Encephalitis virus, the last two of which are present in the United States. Both *Aedes aegypti* and *Aedes albopictus* (the Asian tiger mosquito) mosquitoes, both of which are peridomestic daytime-biting insects, spread the virus. The virus has nonhuman primate reservoir. Although this is an arboviral infection, there have been reports of blood-borne

transmission (transfusion). Transmission has occurred during parturition if the mother is viremic at time of delivery 49%; there has been no transmission through breast milk [47]. 52 cases occurred in US travelers in 2006 and 2007 [53].

The clinical presentation of dengue has been described as that of dengue with the addition of severe arthritis. Chikungunya derives from a Kimakonde word that means "that which bends up" and describes the results of the prominent joint symptoms. The disease characteristics are fever, headache, fatigue, nausea and vomiting, and rash. The joint pain is really a severe tenosynovitis. The incubation period is about a week. Only about 3-25% are symptomatic with severe disease in only a small percentage. The case-fatality rate in Reunion Island was less than 0.1%, but many of those with symptoms will suffer from severe fatigue and joint pain for long periods of time, meaning up to a year or more, after resolution of the acute infection [54-56].

There is no vaccine, and there are no chemoprophylactic regimens. The only effective prevention methods are the insect avoidance methods that are used for yellow fever and dengue.

There are no specific antiviral therapies. Management is supportive and symptomatic with rest, fluids, and provision of analgesics and antipyretics for treatment of pain and fever (with the exception of aspirin to avoid Reye's syndrome).

Diagnosis suggested by a compatible clinical syndrome in a person with appropriate exposure through dates of travel and activities. Diagnostic testing is not commonly available but is primarily serological. PCR-based testing and viral isolation are available, mostly through the CDC and state health departments.

| **Countries where people have become infected with Chikungunya virus.** | |
|---|---|
| Benin | Mauritius |
| Burundi | Mayotte |
| Cambodia | Myanmar |
| Cameroon | Nigeria |
| Central African Republic | Pakistan |
| Comoros | Philippines |
| Congo, DRC | Reunion |
| East Timor | Senegal |
| Equatorial Guinea | Seychelles |
| Guinea | Singapore |
| India | South Africa |
| Indonesia | Sudan |
| Italy | Taiwan |
| Kenya | Tanzania |
| Laos | Thailand |
| Madagascar | Uganda |
| Malawi | Vietnam |
| Malaysia | Zimbabwe |
| Maldives | |

[b] This list does not include countries where only imported cases have

**African tick-bite fever**

Rickettsial diseases also occur frequently in travelers [57]. There are a large number of species in 5 related genera, *Rickettsia*, *Orientia*, *Neorickettsia*, *Ehrlichia*, and *Anaplasma.* The genus Rickettsia contains two groups, the typhus group and spotted fever group. They are all arthropod-borne, but the vectors, which can be ticks, fleas, mites, or lice, are specific to the rickettsial species. There are a large number of species, probably more than thirty, each with a different geographic distribution, a slightly different presentations, and geographically distinct names. Texas has two endemic diseases: Rocky Mountain spotted fever and scrub typhus [58]. Rickettsial diseases are common worldwide but have attracted attention due to the occurrence in big-game hunters who travel to rural South Africa. Data indicate that the risk of acquiring African tick bite fever, which is caused by *R. africae*, is four to five times the greater than the risk for acquiring malaria [59, 60]. The disease occurs 1-2 weeks after exposure and is characterized by fever, headache, malaise with a mild rash and an eschar or tache noir at the site of the tick bite.

Diagnosis of rickettsial disease is usually retrospective and serological using acute and convalescent sera. Biopsy of lesions with immunohistochemistry, PCR techniques or isolation of the organism provides a definitive diagnosis.

The drug of choice for all rickettsial diseases is tetracycline, which should generally be started before obtaining a laboratory diagnosis. Chloramphenicol, fluoroquinolones, azithromycin, and rifampin are second-line agents.

There are no preventive vaccines or drug regimens. Preventive strategies are designed to avoid tick bites.

**Leptospirosis**

Obligately aerobic spirochetes of the genus *Leptospira* are the cause of this disease. It has a worldwide distribution with the highest prevalence in the tropics although outbreaks in temperate environments have been described [61, 62]. Humans acquire the bacteria through contact of skin and mucous membranes with water that is contaminated with the urine of reservoir animals like rats, dogs, and cattle [61, 63]. These animals have chronic carriage of the bacteria in the tubules. New evidence indicates that there may be prolonged human shedding as well [64]. There are increases in cases after floods. There have been epidemics after floods and other natural disasters, and clusters of cases have been reported in travelers after large-scale water exposures following white-water rafting, triathlons, and eco-challenges [65]. Recent data suggest that it is a major cause of fever and death in the Peruvian Amazon [66].

The incubation period is typically 2 to 3 weeks and the typical presentation is of a nonfocal fever syndrome characterized by recovery in a week even in the absence of

treatment. A second "icteric" form called Weil's disease develops in 5-10% of patients and is characterized by jaundice, renal failure, pulmonary hemorrhage, arrhythmia, and hemodynamic collapse with a mortality in this is 5-15% [61, 66].

Diagnostic techniques are poor. The gold standard is the microagglutination test (MAT) but is usually restricted to reference laboratories. Rapid diagnostic tests using group antigens are often used in the field but could use improvement. The diagnosis is often missed because no one considers it.

There is no vaccine, but weekly doxycycline is effective as chemoprophylaxis.

Treatment needs to be empiric and started early. Doxycycline is useful for mild to moderate disease, and ceftriaxone is therapy of choice for severe disease. Jarisch - Herxheimer reactions can occur.

**Typhoid and Paratyphoid**

*Salmonella typhi* and *Salmonella paratyphi* A, B, or C are the causes typhoid fever and paratyphoid fever, the enteric fevers. Typhoid and paratyphoid fever are common causes of fever in returned travelers. There are an estimated 22 million cases of typhoid and 6 million cases of paratyphoid worldwide each year with an estimated 200,000 deaths from typhoid fever [67]. According to the CDC, there are about 400 cases of typhoid and 150 cases of paratyphoid annually. The risk is highest in South Asia with rates 6-30 times higher than other locations; risk is nonexistent in travel within the US or to Europe. This is much more common among VFR travelers than among others. As humans are the only known reservoir, transmission requires ingestion of food or water contaminated with human feces. Transmission is more common with longer stays but can occur within one week [11].

The typical incubation period is between 6 and 30 days, and the gradual onset of fever over a 3 to 4 day period with peaks of 102-104, headache, malaise, anorexia, hepatosplenomegaly, and a transient rash with "rose-colored" spots characterize the clinical syndrome. Untreated disease can last a month and then resolve although mortality can be significant. The most dreaded complication is intestinal hemorrhage or perforation [68].

The primary significance of this disease derives from the high rates of antibiotic resistance. Nalidixic acid resistance, which is a predictor of fluoroquinolone resistance, is high and the rates of multidrug resistance are also increasing. Fluoroquinolone resistance is common enough in India that 3$^{rd}$ generation cephalosporins have become the drug of choice [69].

Blood cultures are positive in 50% of cases; bone marrow biopsy is more sensitive at 80%. Stool cultures are generally negative. The Widal test is available in a lot of developing countries because it is cheap, but is not very useful [68].

Enteric fever is preventable with food and water precautions; only typhoid has vaccines, of which there are two, an oral vaccine containing the live attenuated Ty21 strain and the injectable vaccine that contains the capsular polysaccharide Vi antigen. Both vaccines are about 50-80% effect for about a 2 to 3 year period [11]

In a related area, travelers' diarrhea is the most common infectious disease problem associated with travel although it is rarely a cause of fever. Studies show that 20-60% of travelers develop diarrhea during their trip, 25% alter their itinerary, 15% are in bed for a day, and 3% have persistent GI symptoms upon return. The primary causes are bacterial with *Escherichia coli*, *Shigella*, *Salmonella*, and *Campylobacter* accounting for 60-80% of disease [70, 71]. These are usually acute presentations and resolve even without treatment even though therapy can decrease the duration of disease. Symptomatic treatment and maintenance of proper hydration is also important. The major problem in the field is the evolution of resistance to antibiotics. Fluoroquinolones have long been the mainstay of treatment of travelers' diarrhea but rates of fluoroquinolone-resistance in *Campylobacter* in the Indian subcontinent preclude its empiric use [72]. For this reason, azithromycin is replacing it for use in this geographic area [73]. The use of rifaximin for prophylaxis is increasing [70].

**References and Resources**

There are a large number of organizations that publish statistics, information, data, and recommendations regarding travel. Some of these are listed below:

**Resources**

www.istm.org/ International Society of Travel Medicine
www.slamvi.org La Sociedad Latinoamericana de Medicina del Viajero
www.astmh.org American Society of Tropical Medicine and Hygiene
www.isid.org International Society for Infectious Diseases
www.wms.org Wilderness Medical Society
www.cdc.gov/travel Center for Disease Control and Prevention
www.who.int World Health Organization
www.state.gov US State Department
www.cia.gov Central Intelligence Agency

**Reference Books**

Health Information for International Travel CDC 2010 (the Yellow Book) CDC
International Travel and Health (Green Book) WHO 2010
Epidemiology and Prevention of Vaccine Preventable Diseases (the Pink Book) CDC 2009
The AAP Red Book or 2009 Report of the Committee on Infectious Diseases (the Red Book) American Academy of Pediatrics 2009

**Textbooks**

Travel Medicine, 2nd edition. JS Keystone, PE Kozarsky, DO Freedman, HD Nothdurft, BA Connor (Eds). 2008. Mosby.

Manson's Tropical Medicine, 22nd Edition, GC Cook and AI Zumla (Eds). 2009. Saunders.

Tropical Infectious Diseases: Principles, Pathogens, and Practice, 2nd Edition. RL Guerrant, DH Walker, and PF Weller (Eds). 2006. Churchill-Livingston.

**Handbooks**

The Travel and Tropical Medicine Manual, 4th Edition. E Jong and C Sanford (Eds). 2008. Saunders Elsevier.

Manual of Travel Medicine and Health, 3rd Edition. R Steffen, HL Dupont, and A Wilder-Smith. 2007. BC Decker.

Infectious and Tropical Diseases: A Handbook for Primary Care. TSC Kwan-Gett, C Kemp, and C Kovarik (Eds). 2006. Elsevier.

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