



eLITERATURE REVIEW

eInfections Review

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October 2007: VOLUME 1, NUMBER 4

Illness in the Returned Traveler

In this Issue...

As the number of travelers expands, clinicians are more likely to encounter the illnesses these travelers develop. Knowing the rates of diagnoses according to region visited, as well as the time since travel was completed, can help practitioners focus on the most likely diagnoses for a particular traveler.

To that end, in this issue we review data from a variety of international sources, presenting current information on illnesses endemic to specific travel destinations. In addition, we present updates on 3 prominent systemic febrile illnesses: non-*falciparum* malaria, dengue, and Chikungunya virus infection, which recently erupted in the Indian Ocean Islands and is spreading into India.

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Length of Activity

1.0 hours Physicians

Expiration Date

September 27, 2009

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Identify the most common illnesses in travelers returning from different regions of the world
- Describe the difficulties in diagnosing non-*falciparum* malaria
- Discuss the clinical manifestations of dengue and Chikungunya virus infections in travelers

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COMMENTARY

Faced with an ill traveler, a clinician may narrow the long list of possible diagnoses by focusing on those that are most common for the region visited. Since studies from one center, or even one country, cannot adequately represent the tremendous number of travelers worldwide, networks have been established to collect data from clinics around the globe. With information from over 20,000 ill travelers, the GeoSentinel network provides data for two of the articles reviewed in this issue. Dr. Freedman's *NEJM* paper provides diagnoses by region visited for 17,000 travelers, while Dr. Wilson discusses 7,000 travelers with fever as a chief complaint, emphasizing region of exposure and length of incubation as two important diagnostic clues. Malaria, found in one-fifth of all febrile travelers, must be ruled out in every febrile traveler who has visited an endemic area; the disease is especially common in those who have visited sub-Saharan Africa or the Pacific Islands. On the other hand, dengue is more common than malaria after travel to Southeast Asia,

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and enteric fever (typhoid and paratyphoid fever) occurs frequently in travelers from south-central Asia. Timing—in regard to onset of symptoms—is also an important diagnostic clue. For example: dengue has a short incubation of 5-10 days and, therefore, does not develop more than 2 weeks after return; 65% of *falciparum* malaria infections present within 2 weeks of travel; but one-half of *vivax* cases and one-third of hepatitis cases present more than 6 weeks after return.

In the US, almost one-third of the 1500 malaria cases diagnosed annually are caused by *P. vivax* or *ovale*. While *P. falciparum* causes about 85% of cases in travelers to Africa, *P. vivax* is the most common species in travelers to Asia, the Americas, and the Middle East. As the article by Bottieau points out, hypnozoites (latent liver forms) of *P. vivax* or *ovale* are not prevented by most approved malaria prophylaxis regimens. In fact, these medications may delay the presentation of malaria, making diagnosis more difficult. In the US and Israel, more than one-third of malaria cases present more than two months after travel. Most of these late cases are *P. vivax* or *ovale* infections in persons who have taken standard prophylaxis.¹ Therefore, all travelers should be educated about malaria symptoms and reminded that these symptoms may develop months after travel. For some travelers with expected heavy *vivax* exposure, primaquine can be considered for primary prophylaxis or for post-exposure treatment prophylaxis to prevent relapses. Bottieau also describes a high relapse rate after treatment for *P. vivax* or *ovale*. Currently, the CDC recommends primaquine 30 mg of base per day for 14 days to overlap with standard treatment with a schizonticide such as chloroquine.² Since relapses often occur after poor adherence, clinicians should stress the importance of compliance with the full regimen.

Two additional articles give us a snapshot of illnesses that are common and devastating in the countries where they are endemic. Dengue virus causes 100 million cases of dengue fever and 250,000 cases of dengue hemorrhagic fever each year. Dengue has been the subject of intensified surveillance over several years by TropNetEurop, a large European network that studies illness in travelers. The Wichmann article points out that for travelers, as for children in endemic areas, severe illness is more common after secondary infections. In the Makonde (African) language, "Chikungunya" means "that which bends", describing the posture of those infected by this mosquito-borne virus which recently swept through the Reunion Island, infecting one-third of its 770,000 people. Simon describes the fever, arthritis, and other manifestations of this illness in travelers returning from the Indian Ocean Islands.



References

1. Schwartz E, Parise M, Kozarsky P, Cetron M. [Delayed onset of malaria - implications for chemoprophylaxis in travelers](#). *N Engl J Med* 2003;349:1510-6.
2. Griffith KS, Lewis LS, Mali S, Parise ME. [Treatment of malaria in the United States, a systemic review](#). *JAMA* 2007;297:2264-77.

THE SPECTRUM OF ILLNESS IN TRAVELERS FROM ALL REGIONS OF THE WORLD



Wilson ME, Weld LH, Boggild A. **Fever in returned travelers: results from the GeoSentinel Surveillance network**. *Clin Infect Dis* 2007;44:1560-8.

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Freedman DO, Weld LH, Kozarsky PE, et al. **Spectrum of disease and relation to place of exposure among ill returned travelers**. *N Engl J Med* 2006;354:119-30.

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These two articles describe illness in about 20,000 returned travelers who were seen at GeoSentinel clinics. The GeoSentinel Surveillance Network consists of 30 travel or tropical-medicine clinics on six continents. Clinicians at these sites obtain information from all ill travelers and enter it into a large database. Illnesses are reported by categories, such as systemic febrile illness, diarrheal illness, respiratory illness, and, when possible, by specific diagnosis.

In the first article, Wilson et al describe the causes of fever in returned travelers. From March 1997 to March 2006, approximately 25,000 persons were seen after travel for illnesses that were confirmed or considered probable. Among these, almost 7000 reported fever as a chief reason for seeking care. Overall, systemic febrile illness was the largest category, accounting for one-third of all febrile illness; diarrheal disease and respiratory illness together caused another third. Malaria, the most common specific illness, was diagnosed in 20% of all febrile travelers; dengue was diagnosed in 6%. The most common vaccine-preventable illnesses were typhoid fever, hepatitis A, and influenza A. The researchers reported that more than 70% of typhoid fever was acquired in south-central and southeast Asia. Furthermore, as compared to other groups of travelers, those visiting friends and relatives were more likely to have vaccine-preventable causes of fever and less likely to have received pre-travel medical advice.

In the second article, Freedman et al compare the frequency of all travel-related illnesses—febrile and nonfebrile—by region of exposure in 17,000 travelers seen from 1996 to 2004, highlighting the important regional differences in the categories of illnesses and specific diagnoses. For travelers to sub-Saharan Africa and Southeast Asia, systemic febrile illness was the most common category. For Africa, the most frequent illness in this category by far was malaria, with tick-borne rickettsial infection a distant second, and dengue a rare diagnosis. For Southeast Asia, dengue was 2 to 3 times more common than malaria. Travelers returning from south-central Asia, on the other hand, were seen more often for acute diarrhea than for systemic febrile illness. Of note, however, enteric fever (typhoid and paratyphoid illness) was found much more commonly in south-central Asia than in any other region, and was diagnosed at the same rate as dengue and malaria. In South America, Central America and the Caribbean, skin conditions and acute diarrhea were the most common categories. Insect bites with or without infections, cutaneous larva migrans, and allergic reactions occurred frequently in all three regions. The researchers also reported that travelers to South America, and to a lesser extent to Central America, acquired cutaneous leishmaniasis, and that travelers to both regions developed myiasis, infestation with larvae of certain flies (maggots). Overall, parasites, especially giardiasis and amebiasis, were more common than bacteria as causes of diarrhea - the exception being Southeast Asia, where campylobacter was the predominant cause. Other commonly diagnosed gastrointestinal illnesses included strongyloidiasis, ascariasis, gastritis, peptic ulcer disease, and acute hepatitis.

Whereas previous articles have described much smaller numbers of travelers often from fewer regions, these articles describe the illnesses of a large number of travelers visiting all regions. Certain caveats, however, must be considered. Many of the GeoSentinel sites are referral centers, which often see travelers with illnesses that are more difficult to diagnose or more severe than those seen at primary care centers. Also, infections with short incubations or those which are self-treated may be under-represented. While bacterial pathogens are a more common cause of travelers' diarrhea than parasites, bacteria were reported less frequently in this study probably because they cause diarrhea that is brief or responsive to self-treatment. Furthermore, infections with a shorter incubation period, such as dengue and rickettsial infections, may develop during travel and resolve or improve before return home. It should also be noted that a large number of cases, as in many series, did not have specific diagnoses. For about 40% of systemic febrile illnesses and acute diarrhea, no specific etiology was identified.

PITFALLS IN THE PROPHYLAXIS, DIAGNOSIS, AND TREATMENT OF NON-FALCIPARUM MALARIA

Bottieau E, Clerinx J, Van den Enden, E, et al. **Imported Non-Plasmodium falciparum malaria: a five-year prospective study in a European referral center.** *Am J Trop Med Hyg* 2006;75:133-38.

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There are 4 species of malaria that cause illness in humans. *Plasmodium falciparum* is the deadliest, but the non-falciparum species, *P. vivax*, *ovale*, and *malariae*, are often more difficult to diagnose. They infect a smaller percentage of erythrocytes and are, therefore, harder to see on peripheral blood smears. Also, they may present months, or even years, after exposure. *P. vivax* and *ovale* are the only species which develop a dormant hypnozoite phase in the liver. *P. malariae*, on the other hand, may produce a low-level, chronic parasitemia unrecognized until recrudescence after a long latent period. In this article, Bottieau et al describe 98 cases of non-falciparum malaria diagnosed by blood smear from 2000 to 2005 at a referral center for tropical diseases in Belgium.

Among these 98 cases, the median time from leaving the endemic area to the onset of fever was two months; however, 18% of patients became symptomatic more than 6 months after exposure, and 5% after more than a year. Eighty episodes were first attacks of malaria, with 21 occurring in persons who reported adherence to malaria prophylaxis. These 21 had a longer time from exposure to onset of fever (median 91 days vs. 40 days for those who didn't take prophylaxis). Eighteen episodes (3 of the 34 *P. ovale* cases and 15 of the 48 *P. vivax* cases) were relapses following previous treatment of malaria: 7 of these relapses were in patients who had not taken primaquine, either because it was not prescribed (5) or they were non-adherent (2), and 10 occurred after treatment with low-dose primaquine (15 mg of base daily for 14 days). These 10 were then successfully treated with a higher dose of primaquine (0.5 mg/kg daily for 14 days). One patient infected with *P. vivax* in Indonesia relapsed after 3 courses of primaquine, the third course being at the higher dose.

This article demonstrates some of the pitfalls in diagnosing and treating non-falciparum malaria. Since primaquine is the only approved drug which prevents or eradicates the dormant liver stage of *P. vivax* and *ovale*, symptoms of infection with these species may present in anyone who was exposed and did not receive primaquine, including travelers who adhered strictly to the commonly recommended prophylactic medications. In fact, these prophylactic medications may actually obscure the diagnosis by prolonging the time to development of symptoms. For eradication of hypnozoites in the liver and prevention of relapse, patients with *P. vivax* and *ovale* infections should take primaquine. The recommended dose is now 0.5 mg/kg (maximum dose 30 mg) per day for 14 days to all non-pregnant patients who are not glucose-6-phosphate dehydrogenase (G6PD) deficient.

MALARIA DIAGNOSED IN THE US IN 2005

Thwing J, Skarbinski J, Newman RD, et al. **Malaria Surveillance - United States, 2005.** *MMWR* 2007;56:23-38.

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In 2005, 1,528 cases of malaria were reported to the CDC. All cases were confirmed by blood smear or PCR. To determine rates for individual countries, the number of cases acquired in a specific country was divided by the World Tourism

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Organization estimate of the annual number of U.S. travelers to that country.

Among these 1,528 cases, 1180 had a species identified: 63% were *falciparum* malaria, 29% were *vivax*, 5% *malariae*, and 3% *ovale*. About two-thirds of all cases were acquired in Africa, and two-thirds of African cases were acquired in West Africa. Most of the remaining cases came from Asia (with India providing the majority of Asian cases) and the Americas (predominantly Central America and the Caribbean). Among individual countries, Nigeria had the highest number of cases and the highest rate. High rates were also seen in travelers returning from other West and Central African countries, Papua New Guinea, and Vanuatu. Honduras, India, and Haiti had intermediate rates. The country with the lowest rate was China; Mexico, the Philippines, Thailand, and Costa Rica also had low rates. Eighty-three percent of African cases were *falciparum* malaria; in every other country except Haiti, *vivax* malaria predominated. More than half of the malaria cases in U.S. civilians occurred in persons who had visited friends and relatives; among these civilian cases, only 20% had taken recommended prophylaxis. All 7 deaths were caused by *P. falciparum*; none of these 7 patients had taken prophylaxis, and all had delays before diagnosis was made and/or treatment was given. Two congenitally acquired cases were reported, both *vivax* infections. The mothers had emigrated from Honduras and India 10 months and 2 years earlier.

This article illustrates the critical importance of taking a travel history from all febrile patients. As the two congenital cases demonstrate, even a history of remote travel may be important for diagnosing cases of non-*falciparum* malaria. Furthermore, travelers who visited friends or relatives accounted for the majority of cases of malaria in the U.S. Those born in endemic regions should be instructed that immunity to malaria wanes quickly after leaving a malarious area, and prophylaxis is needed for protection when returning to these areas.

SEVERE DENGUE IN TRAVELERS

Wichmann O, Gascon J, Schunk M, et al. **Severe dengue virus infection in travelers: risk factors and laboratory indicators.** *J Infect Dis* 2007;195:1089-96.

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Dengue virus is a flavivirus spread by mosquitoes in most tropical countries. Residents of these countries and travelers to endemic areas may develop asymptomatic infection or a systemic febrile illness. Four serotypes of dengue virus cause infection. While infection with one of the 4 serotypes protects against subsequent infection with that specific serotype, it predisposes to severe illness from secondary infection (infection with a different serotype). In endemic areas, children with secondary infections may develop severe dengue illness, including dengue hemorrhagic fever. In travelers, however, severe infection has not been well characterized. Wichmann and colleagues describe dengue illness in subjects seen between 2003 and 2005 at 14 referral centers in the European Network on Surveillance of Imported Infectious Diseases. They determined how many met all 4 WHO criteria for dengue hemorrhagic fever: fever, platelet count <100,000 cells/mm³, capillary leak (20% increase in the hematocrit, pleural effusion, ascites, or hypoproteinemia), and hemorrhagic tendency (spontaneous bleeding, petechiae, or a positive tourniquet test). The authors also described other severe manifestations and the risk factors for severe illness.

A total of 219 patients were reported. The median age was 32 years (range, 11-70 years). Most patients were European, but 17 were born in endemic areas and had immigrated to or were visiting Europe. Sixty-five percent of patients acquired the infection in Asia, with India and Thailand topping the list of individual countries. About 20% had traveled to Central America, and the remainder to South America, the Caribbean, and Africa. Almost two-thirds of patients had visited dengue-endemic countries before. Dengue infection was confirmed in 133 patients: 115 had a rise in antibody titers in paired sera, and 18 had positive PCR results with or without an antibody increase. The remaining 86 had a probable diagnosis based on



IgM antibodies in a single serum sample. One-fourth of patients were considered to have secondary infections diagnosed by a high IgG titer in the presence of IgM antibodies. After 13 patients were excluded for potentially confounding flavivirus vaccination (yellow fever, tick-borne encephalitis, Japanese encephalitis), 27 cases (17%) remained as the group of secondary infections. Overall, 93% of patients with dengue had fever and 69% had headache. One-half of subjects reported rash, myalgia, and retroorbital pain. Petechiae occurred in 13%, and spontaneous bleeding, most often from the nose or gums, in 8%. Most patients had leukopenia and thrombocytopenia, usually presenting within the first 3 to 6 days. Elevated transaminases and LDH were common but often occurred later. Forty-four percent had a positive tourniquet test (≥ 20 petechiae per square inch on the forearm after inflation of a blood pressure cuff between the diastolic and systolic pressures for 5 minutes). Only 2 (1%) fulfilled the 4 WHO criteria for dengue hemorrhagic fever. Twenty-three patients (11%) had one or more of the following severe manifestations: internal hemorrhage, plasma leak, shock, and platelet count $< 50,000$. Those with severe manifestations, compared to those without, had lower nadir WBC and platelets counts, higher ALT and AST increases, and a higher rate of secondary immune responses (44% vs. 13%, $p < 0.05$); however, 8 of these patients with severe manifestations had visited a dengue-endemic country for the first time. A positive tourniquet test did not predict severe infection or spontaneous bleeding. Overall, 51 patients (23%) were hospitalized.

This report provides clinical and laboratory data for a large number of travelers with dengue. While dengue hemorrhagic fever diagnosed by WHO criteria was rare, severe manifestations occurred in 11% of subjects. Severe disease was more likely to occur in those with secondary infection but also occurred in some travelers with primary infection. For travelers to endemic areas, mosquito precautions are important for prevention of dengue and other infections.

CHIKUNGUNYA INFECTION CAUSES FEVER AND ARTHRITIS IN TRAVELERS TO THE INDIAN OCEAN ISLANDS

Simon F, Parola P, Grandadam M. **Chikungunya infection, an emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases.** *Medicine* 2007;86:123-37.

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Chikungunya, a mosquito-transmitted infection, discovered in the 1950s in Africa, was little known until recently, when an outbreak exploded in the Indian Ocean Islands. This epidemic has already reached India and Malaysia, and may continue to spread, producing fever and arthritis in both the indigenous population and travelers. Simon and colleagues provide a comprehensive description of this dramatic illness in 47 travelers seen at two referral centers for tropical and travel-related illness in Marseilles, France. The diagnosis was suspected in persons with fever and/or arthralgia who had traveled to the Indian Ocean Islands - Reunion Island, the Comoros Archipelago, the Seychelles, or Mauritius. The diagnosis was confirmed by serology, PCR, or isolation of the virus from blood.

The 47 patients comprised 22 females and 25 males, with a mean age of 45 (range 0.5-73 years). The majority were tourists, although 17 were born in the islands and had either migrated to or were visiting France. Simon describes a biphasic illness with fever and arthralgia/arthritis in the initial phase. Fever lasted a mean of 4 days (range 2-9 days). One half of the patients had a transient rash for 1-4 days in the early phase, consisting of macules, papules, or erythema mainly on the face, trunk and extremities. Arthritis was commonly symmetrical and peripheral, involving distal fingers, wrists, toes, and ankles, but arthralgia extended to knees, hips, shoulders, and elbows. Edema of the face and pruritus of the rash were common. Leukopenia occurred in 75% of patients and thrombocytopenia and elevation of liver and muscle

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enzymes in 50%. All patients improved in 7 to 10 days, but the majority (83%) had persistent or recurrent joint pain, often debilitating, marking the second phase of the illness. Common findings were swelling of proximal finger joints, tenosynovitis, carpal/tarsal/cubital tunnel syndrome, and Raynaud's phenomenon. At 1, 3, and 6 months after disease onset, 88%, 86% and 48% of patients were still symptomatic.

As often happens, travelers brought an epidemic illness into the spotlight. Since this illness is spreading rapidly, physicians in Western countries are likely to see more patients with this previously little-known illness. For any traveler to the Indian Ocean islands or India presenting with fever and arthralgia/arthritis, Chikungunya infection must be considered. Unfortunately, there is no specific treatment, and the disabling joint disease often persists for months. Prevention of mosquito bites is the key to preventing infection.

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- Describe the difficulties in diagnosing non-*falciparum* malaria
- Discuss the clinical manifestations of dengue and Chikungunya virus infections in travelers

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- **John G. Bartlett, MD** has disclosed that he has served on the HIV Advisory Board for GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Pfizer and Tibotec. He is also on the Policy Board for Johnson & Johnson.
- **Paul G. Auwaerter, MD** has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme. He is on the Speakers' Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson & Johnson.
- **Sara E. Cosgrove, MD, MS** has disclosed that as a co-investigator, she has received grants or research support from Merck and served on the Advisory Boards for Ortho-McNeil and Cadence Pharmaceuticals.

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