TRAVEL MEDICINE ADVISOR

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AHC Media

Murine Typhus in Returned Travelers

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Drs. Barry and Blackburn report no financial relationships to this field of study.

Synopsis: *Murine typhus, caused by* Rickettsia typhi *and transmitted by the rat flea, has emerged as an etiologic agent of undifferentiated febrile illness in returned travelers. This retrospective study found that most cases of murine typhus at a well-known reference center in France were diagnosed in travelers returning from Africa or Southeast Asia.*

Source: Walter G, Botelho-Nevers E, Socolovschi C, et. al. Murine Typhus in Returned Travelers: A Report of Thirty-Two Cases. *Am J Trop Med Hyg* 2012;86:1049-53.

Murine typhus is an acute zoonotic infection caused by *Rickettsia typhi*, an obligate-intracellular Gram-negative bacterium belonging to the typhus group of rickettsiae. *R. typhi* infections occur worldwide, particularly in warm, humid coastal environments of the tropics; in the U.S., autochthonous transmission also occasionally occurs in Hawaii, Texas, and California. The rat flea, *Xenopsylla cheopis* is generally considered the primary vector. Humans are infected when rickettsia-laden flea feces are scratched into pruritic flea bite excoriations. The peri-domestic Rattus species is the critical vertebrate host that transmits the infection to fleas, although the rats do not usually show signs of illness even with high-level rickettsemia.

The authors at the World Health Organization Collaborative Center for Rickettsial Diseases in Marseilles, France retrospectively analyzed the epidemiological, clinical and biological characteristics of 32 patients with murine typhus who were diagnosed there during a three-year period (January 2008 to December 2010). A case was defined as a patient whose microimmunofluorescence serology was positive (single serum with IgM titer > 1:64 and/or IgG antibody titer > 1:128, or a >4-fold increase in titers between acute and convalescent sera). If cross-reactions were observed with other *Rickettsia* agents, a Western blot and cross-adsorption test were used to discriminate the species.

During the three-year study, 32 confirmed cases of murine typhus were discovered, and all were in returned travelers. During that time 42,276 sera were sent for evaluation to this reference laboratory for suspected rickettsial diseases from France and other countries. Thirteen (41%) of the 32 patients acquired murine typhus in Africa (Tunisia, Morocco, Ivory Coast, Central African Republic, Madagascar or Chad), and twelve (38%) acquired it in Southeast Asia (Indonesia, Philippines, Thailand, Cambodia, Vietnam, Myanmar or Laos). Tunisia and Indonesia were the two most common countries of exposure.

The classic triad of fever, headache and rash was seen in only four patients, although a rash was present in 15 patients (47%). Elevated serum transaminases were found in over half the patients and represented the most common laboratory abnormalities. Cytopenias were observed in 12 (38%) of the 32 patients, and renal failure in three (9%) patients. Contact with rodents was rarely reported (n=2 of 32), and almost half of the cases were diagnosed in August or September, which seemed to correlate with flea abundance in endemic areas as well as a time of increased travel for Europeans. Fever was found in all patients for whom data were available (31 of 31).

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Two patients had life-threatening illnesses, and three developed the hemophagocytic syndrome. All 32 patients recovered. The authors concluded that murine typhus should be considered a possible cause of febrile, undifferentiated illness in returning travelers.

■ COMMENTARY

Rickettsial diseases are increasingly being recognized among international travelers. In a Geosentinel study of almost 7,000 ill returnees with fever as a chief complaint, rickettsial disease was seen in 2%.[1] The taxonomy of *Rickettsia* species is fairly complex, but there are two species pathogenic for humans in the typhus group: *R. prowazekii* (epidemic louse-borne typhus) and *R. typhi* (murine typhus). Murine typhus, unlike African tick bite fever (caused by the spotted fever group rickettsia, *R. africae* - a relatively common cause of febrile illness in travelers returning from Southern Africa), does not present with a tell-tale eschar. Indeed, murine typhus is notoriously non-specific with fever, headache and an often poorly visible maculopapular exanthem; gastrointestinal symptoms appear to be common in children. The primary pathological lesion of *R. typhi* infection is an inflammatory vasculitis characterized by perivascular infiltration of lymphocytes, mast cells and macrophages. Thrombocytopenia and transaminitis are common. A recent report from Taiwan emphasized that fever with transaminitis is a clue to the diagnosis.2 The incubation period of murine typhus is 8 to 16 days, and rash occurs near the end of the first week of illness - beginning on the trunk and spreading peripherally, sparing the palms and soles. The majority of patients experience mild illness, although, as reported in this article, illness can be severe. One patient presented with septic shock and another with myocarditis. As in other rickettsial diseases, the presence of G6PD deficiency, hemoglobinopathies such as thalassemia, and advanced age can be associated with severe or even fatal disease. Although spontaneous recovery can occur without treatment, the drug of choice for murine typhus remains doxycycline, to hasten recovery.

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Travel Infections: FoodNet Casts Doubt on Residual Immunity in VFR Travelers

By Lin H. Chen, MD

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Dr. Chen has reviewed research grants from the Centers for Disease Control and Prevention and Xcellerex.

Synopsis: *Travel was associated with 13% of the enteric infections reported to FoodNet, and the most commonly identified pathogens were Campylobacter, nontyphoidal Salmonella, and Shigella species. Precautions to avoid consuming contaminated food and water remains highly relevant in advising travelers.*

Source: Kendall ME, et al. Travel-associated enteric infections diagnosed after return to the United States, Foodborne Diseases Active Surveillance Network (FoodNet), 2004-2009. *Clin Infect Dis* 2012;54(S5):S480-7.

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FoodNet is an active surveillance program that collects data on 9 laboratory-confirmed pathogens from 10 sites in the United States: 7 states (Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee) and certain counties in California, Colorado, and New York. Kendall et al analyzed infections reported in this network from 2004-2009 that were considered to be travel-associated and compared them to infections in non-travelers; they also estimated risks according to travel destination. The authors defined travel associations based on the intervals between return date and illness onset: <30 days for *Listeria, Salmonella* (typhoid and paratyphoid), <15 days for *Cryptosporidium* and *Cyclospora*, and <7 days for all other enteric pathogens.

Approximately 13% (8270/64,039) of reported enteric infections that also contained travel information were considered travel-associated. Travel-associated cases had a mean age of 33.1 years, older than nontravelers (mean age 25.5 years), especially within the group aged 18-44 years. Travel-associated cases were more likely to be Asian, less likely to be black., and less likely to be hospitalized. Five deaths were reported for travel-associated cases, attributed to Listeria (n=1), *Vibrio vulnificus* (n=1), and nontyphoidal *Salmonella* (n=3).

The most frequently identified pathogens in travelers was Campylobacter (42%), followed by nontyphoidal Salmonella (32%) and Shigella infections(13%). These organisms were also the most common and top 3 for nontravelers, although nontyphoidal *Salmonella* was more common in nontravelers (47% of infections), and Campylobacter was less common (27% of infections). All 3 cases of cholera were travel-associated, as well as high proportions of typhoidal and paratyphoidal Salmonella (68% and 50%, respectively). *Shigella dysenteriae, S. boydii*, and *S. flexneri* were also often travel-associated (56%, 44%, and 24%, respectively), whereas non-cholera *Vibrio, Yersinia*, Shiga toxin-producing *Escherichia coli* (STEC), and *Listeria* occurred more commonly in nontravelers.

The most common countries for travel-associated infections were Mexico, India, Peru, Dominican Republic, and Jamaica, and account for half of the travel-associated cases. Furthermore, race and ethnicity correlated with travel destinations. For example, 85% of Asian travelers reported travel to Asia, 95% of Hispanic travelers reported travel to Latin America and the Caribbean [LAC], and 58% of black travelers reported travel to Africa.

The authors estimated risk for each pathogen based on travel region. Africa had the highest risk for travel-associated infection (76 cases/100,000 travelers), followed by Asia (23 cases/100,000 travelers), and LAC (20 cases/100,000 travelers). Within LAC, South America had the highest rate of *Campylobacter* (26.4 cases/100,000 travelers). The Caribbean had the highest rate of nontyphoidal *Salmonella* (8.6 cases/100,000 travelers), and Central America had the highest rates of *Shigella*, *Cryptosporidium*, and STEC (8.6, 2.8, and 1.0 cases/100,000 travelers, respectively).

Europe had the lowest overall risk, and *Campylobacter* was the most common infection associated with Europe and Oceania.

■ COMMENTARY

Travelers' diarrhea (TD) is the most common ailment encountered by travelers, affecting 20-60% of travelers visiting developing countries.[1] Hygiene standards at the travel destination are the usual predictors for development of TD. Ciprofloxacin continues to be effective for self-treatment of TD in many areas, but azithromycin is the drug of choice for travelers to areas where there is a high risk of fluoroquinolone-resistant Campylobacter, particularly in South and Southeast Asia.[2]

A GeoSentinel analysis of 6,086 travelers with gastrointestinal infections seen during 2000-2005 found highest risk to be associated with travel to South Asia, sub-Saharan Africa and South America.[3] Kendall et al show similar patterns in this FoodNet analysis. Health Protection Scotland also analyzed data gathered from 2003-2007 on possible imported infectious intestinal diseases in Scotland and estimated an overall occurrence of 1.3 infections/100,000 visitors abroad, with Egypt having the highest rate at 46.7/100,000 visitors.[4]

Most studies to date have found enterotoxigenic *Escherichia coli*, enteroaggregative *E. coli*, and *Campylobacter* to be the most frequently identified pathogens, although recent studies on infections acquired in Mexico, Guatemala, and India have identified enterotoxigenic *Bacteroides fragilis* and Arcobacteria to be common causes of TD.[5]

Noroviruses are also increasingly recognized worldwide as important causes of gastroenteritis, and their prevalence as a cause of TD is beginning to be elucidated. Koo et al studied 3 cohorts of international travelers who acquired TD in Mexico, Guatemala, and India, and identified noroviruses by RT-PCR in 10.2% of cases; this was only second to E. coli in frequency.*7* The prevalence of noroviruses appeared to vary by geographic location and by time of study.

The FoodNet finding that 13% of reported enteric infections were travel-related provides useful information on predicting the risk of acquiring TD as well as the etiology of TD. With a large number of travelers to Mexico, it was the most common country of acquisition although travel to Africa had the highest risk due to the relatively lower numbers of travelers to Africa. Another relevant finding is that race and ethnicity correlated with travel destinations, which suggests that many of the reported cases might have been Visiting Friends and Relatives (VFR) travelers. This refutes the general impressions and misconceptions among some VFR travelers that they may have residual immunity due to past residence in the destination country.

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Case Study: Risk Assessment and Potential Interventions for Tuberculosis in Travelers

By Anisha P. Kamath, Vamsi K. Kantamaneni and Maria D. Mileno, MD

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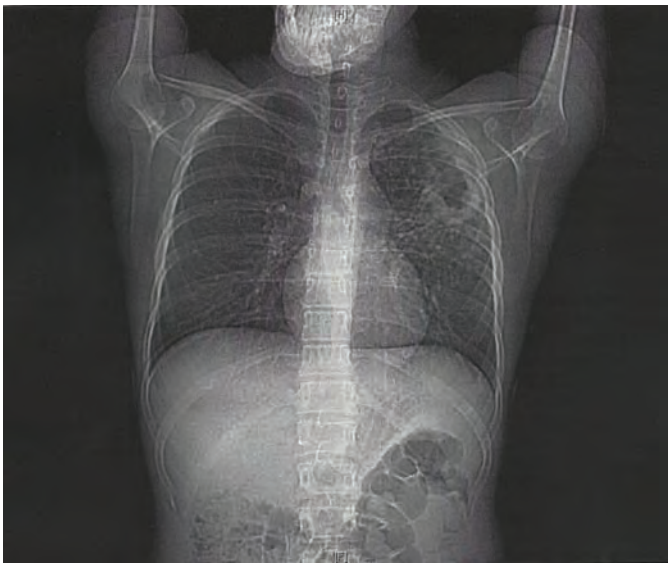
The authors report no financial relationships to this field of study.

Synopsis: *We describe a recent case of cavitary tuberculosis (TB) occurring in a Rhode Island resident along with a review of various approaches to travelers who are at high risk of exposure and infection from TB. Travel medicine advisors and their travelers must be aware of effective and appropriate tuberculosis prevention and screening methods.*

Source: Tuberculosis Prevention in travellers by Amy Neilson and Cora A Mayer reprinted from *Australian Family Physician* Vol.39. No.10, October 2010.

A 23-YEAR-OLD WOMAN WITH A PAST MEDICAL HISTORY OF CHILDHOOD asthma presented to our emergency room with cough, fever, chills and recent 5 lb. weight loss. Cough was productive of green, yellow and brown sputum for three weeks. She reported a single episode of hemoptysis (1/4-1/2 cup of bright red blood) 3 weeks previously. She smoked 10 cigarettes/day with occasional use of marijuana. Chest imaging showed cavitary lesions in the left upper lobe. (*Figure 1*) Sputum acid fast stains and cultures showed *Mycobacterium tuberculosis* complex. When asked about possible TB contacts, she mentioned that she had visited her family in South Korea 2 years ago, and noted that her uncle had a "chronic coughing illness" while she was there. She had no other known potential TB contacts. (*See figures 2 and 3, Chest CTs with contrast showing a cavitating lesion in the left upper lobe, page 46;47.)*

Figure 1



Tuberculosis transmission occurs when a contagious patient coughs, sneezes, or otherwise spreads infectious mycobacteria through droplets that can remain suspended in air for hours. Bovine TB, caused by closely related *Mycobacterium bovis*, can be transmitted by consumption of contaminated, unpasteurized dairy products obtained from infected cattle. Travel to Mexico represents a potential source of this infection in the western hemisphere.[2]

TB is a disease with worldwide prevalence, morbidity and mortality. The WHO estimates that one-third of world's population is infected with TB.[4] Latent TB infection (LTBI) may progress to active TB, and untreated disease can be fatal. CDC (2012) estimates TB incidence at more than 9 million new cases globally, and nearly 2 million TB-related deaths each year.[2] In the United States, the annual incidence is approximately 4 per 100,000, but in some countries in sub-Saharan Africa and Asia, the annual incidence is several hundred per 100,000.2 Many factors have hampered efforts to reduce TB transmission worldwide and they include Multi-Drug Resistance [MDR], Extensively Drug Resistant [EDR] strains, poverty, co-endemic human immunodeficiency virus infections, long standing inability of public health systems in developing countries to deal effectively with the disease, and ever increasing rates of global travel.[1]

MDR and XDR-TB are of particular concern among HIV-infected and other immunocompromised individuals. Nearly 500,000 new cases of MDR-TB are diagnosed each year, and in some countries the proportions are as high as 20% of TB cases.[2] As of early 2010, XDR-TB had been reported in 58 countries.[2] Travel medicine advisors may warn about the risks of TB in various countries, but travelers may not seek evaluation unless illness actually occurs. Tuberculosis is a worldwide disease and travelers also must be made aware of the incidence rates of TB, MDR-TB and XDR-TB in the countries they travel to.

■ COMMENTARY

Risk Assessment and tools available to ameliorate the risk of TB in travelers[1]

The risk of TB infection increases with length of travel, extent of exposure to the local population, and also among health care workers, refugees and prisoners. Travelers to highly endemic countries are at substantial risk, of similar magnitude to the average risk for the local population.[6]

TB Risk Assessment Issues[1]	Potential Tools[1]
Destination(s)	Personal protective equipment
Duration of travel	BCG Vaccine
Type of Travel	Tuberculin skin testing or Interferon gamma release assays [IGRAs]
Age of traveler	Prophylactic therapy
Health of traveler	Referral to travel, pulmonary and infectious disease clinics

In the Australia guidelines BCG vaccination is recommended for those whose **destination** is to a high risk country, which is defined as a yearly TB incidence varying from >40/100, 000 (UK recommendation) to >100/100,000[1] BCG vaccine is not routinely utilized in the US.

In terms of **duration of travel** the risk of latent infection [LTBI] in long-term travelers (3-12 months) to highly endemic areas is calculated from pre- and post-travel tuberculin skin testing [TST].[1] It has been found that the risk of infection for longer term travelers approximated that of the local population. Healthcare workers in such geographic areas experience an even higher risk.

Type of Travel and Potential Contacts: No cases of active TB resulting from transmission during air travel have been reported thus far.[7,8,9] Long distance aircraft generally have high efficacy particulate air filtration systems which reduce risk by filtering bacteria larger than 0.3 microns thereby removing *Mycobacterium tuberculosis*.[7] Also, aircraft cabins undergo air exchanges in excess of 15 times per hour - more than are employed in negative pressure isolation rooms for MDR-TB cases.[7] The WHO recommends that passengers known to have infectious TB avoid travel.[7,8,9]

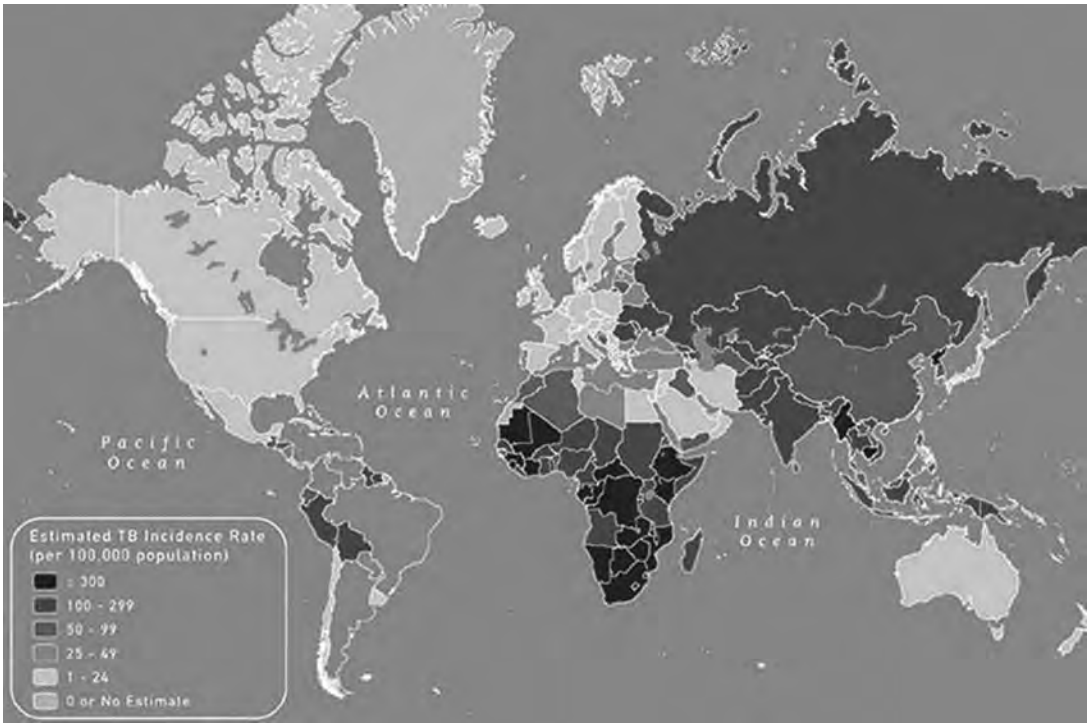
One modeling study estimated the risk of infection, given a potential source, to be 1 in 1000. [7] The probability that a person transmits tuberculosis is determined by a number of factors including sputum-smear status, duration and nature of contact, shared air space or ventilation, susceptibility of exposed people and the infectiveness of the traveler with TB.[7]

The latest WHO international guidelines for the control of tuberculosis in relation to air travel require—after a risk assessment—tracing of passengers who sat for longer than 8 hours in nearby rows adjacent to people with pulmonary tuberculosis who were either smear positive or smear negative.[8,9] These guidelines are based on limited research about risk of TB associated with air travel. Also, the true benefit of tracing and screening passengers and crew members is currently unknown.[9] A further recommendation is that all commercial air travel should be prohibited until the infected person has two consecutive negative sputum smears for drug-susceptible tuberculosis or two consecutive cultures for multidrug-resistant tuberculosis.[8] Ibrahim Abubakar, from the University of East Anglia, chaired the European Centre for Disease Prevention and Control (ECDC) working group on tuberculosis and air travel. He reviewed the evidence from thirty-nine studies looking at transmission of tuberculosis during commercial air travel, to verify if current international recommendations are justifiable.[8,9] In all, thirteen studies involving more than 4,328 passengers from 6 countries were analysed. The majority of studies found no evidence of TB transmission. Only two studies reported reliable evidence of transmission.[8,9] Contrary to the latest WHO guidelines, for the control of tuberculosis in relation to air travel, a recent study published in The Lancet, March 2010 has reported little risk of tuberculosis transmission via air travel.[8,9] The analysis suggests that there is reason to doubt the value of actively screening air passengers for infection with *Mycobacterium tuberculosis* and that the resources used might be better spent addressing other priorities for the control of tuberculosis.[8,9]

Societal factors that affect TB transmission include: poverty, urbanization, overcrowding, high population density, migration, reduced health literacy, less autonomy to act upon health recommendations, reduced access to health services, malnutrition and exposure to indoor air pollution. Personal infectivity is dependent upon the number of bacilli present in sputum, the intensity and frequency of coughing and existence of cavitation on chest radiography.

Infants and children less than 4 years of age are at greatest risk of developing active disease following primary tuberculosis. Risk then declines between the ages 5-10 years, before climbing during adolescence (age 15-19 years) to a second peak at 20-30 years of age. The elderly are at even higher risk.

Map 3-15. Estimated TB incidence rates, 2009[2]

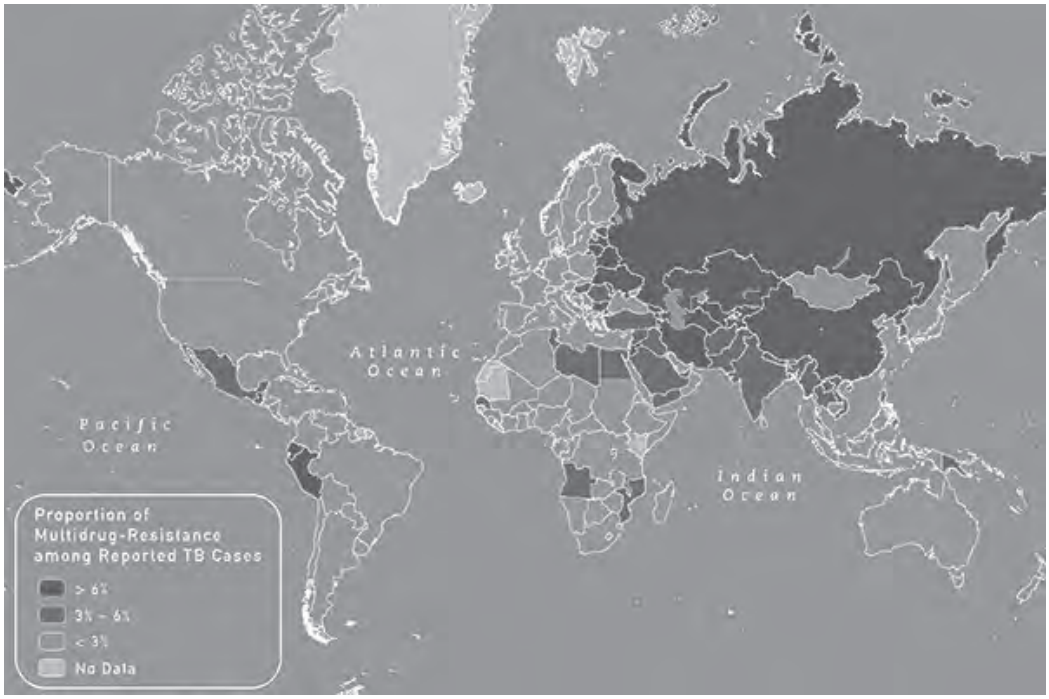


[1]Data from World Health Organization. Global tuberculosis control: WHO report 2010. Geneva: World Health Organization; 2010.

Health factors that significantly increase the risk of developing active TB include poor nutrition, smoking, diabetes, alcohol misuse, silicosis, malignant disease, chronic systemic illnesses and immunosuppressive therapy. HIV is an important risk factor for acquiring TB infection. Hence the general underlying health of the traveler may impact their risk of infection.

Personal Protective Equipment (PPE) equipment is recommended for travelers who are at higher risk of exposure to patients

Map 3-16. Proportion of MDR-TB among new TB cases, 2009[2]



with active TB, such as healthcare workers. CDC guidelines recommend professionally fitted N-95 respirators with appropriate training regarding their use. WHO advises particular caution during procedures with high risk of TB transmission such as bronchoscopy or sputum induction, and when providing healthcare to patients who may have MDR- or XDR-TB.1 There are no studies to suggest that travelers in planes or buses derive any benefit from PPE.[1]

BCG Vaccine is used in countries where TB is endemic. The principal use of BCG vaccine is for the prevention of the severe consequences of active TB in young children.[2] The vaccines have variable protective efficacy1 (0-80%) with estimate of 50% for BCG vaccines across all age groups. Factors that contribute to this variability are:

a) Host factors: age at vaccination, nutrition status, genetics, HIV status.

b) Vaccine factors: different strains of vaccine, including both phenotype and genotype.

c) Geographical factors: latitude

d) Epidemiological factors: local prevalence of non-tuberculous mycobacteria.

Issues for BCG Vaccination:[5]

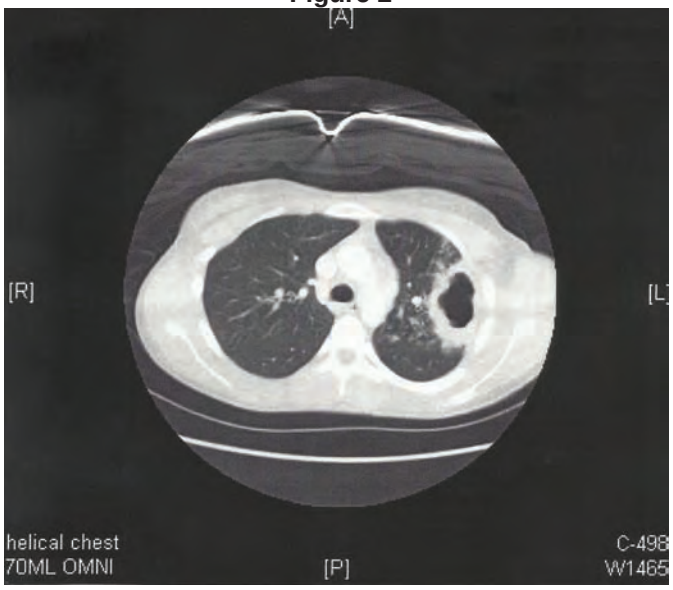
Contraindications: HIV infection, pregnancy, serious illness, impaired immunity, generalized skin diseases with potential for sepsis, previous history of TB or >5 mm tuberculin reaction, significant febrile illness in the preceding month.[1]

Tuberculin Skin Testing (TST) versus Interferon Gamma Release Assays (IGRAs):[6]

IGRA (Interferon Gamma Release Assay)[3] is an important addition to the diagnosis and control of TB. Interferon gamma is released in response to *in vitro* stimulation of sensitised T-cells with specific *Mycobacterium tuberculosis* antigens. These antigens are absent in BCG vaccine strains and most other Mycobacterial species except *M.kansasii*, *marinum* and *szulgai*. CDC recommends TST (and/or QFT-G) testing 8-10 weeks post travel.[1] The BMC (Biomedcentral) states that available studies on cost-effectiveness provide strong evidence in support of use of IGRAs in screening high risk groups. In general, the higher unit cost of the IGRAs compared to the TST is compensated for by cost savings through the more targeted performance of chest radiographs and chemoprevention. If increasing evidence that IGRA-positive subjects have a higher probability of progression to active TB holds

Advantages	Disadvantages
Limited protection against active TB (50% in adults,80% in children)	Large, unsightly and sore vaccination scars can occur
Simple and available	Swollen lymph nodes lasting weeks
Inexpensive	Abscess may occur at injection site
Quickly and relatively easily administered	Very rare but serious reactions, such as disseminated infection, may occur with vaccine strains.
Protection lasts for 10 years and no booster doses are recommended. No evidence that booster vaccination improves protection, so no more than one BCG is recommended in a lifetime.[5]	TST interpretation becomes difficult due to skin test positivity resulting from BCG vaccinations.

Figure 2



true, the IGRA-only screening strategy may prove to be a more cost-effective test.

Updated Guidelines for Nucleic Acid Amplification (NAA) Tests for the diagnosis of TB: [10]

These tests reliably detect *Mycobacterium tuberculosis* in specimens one or more weeks earlier than do cultures. Earlier laboratory confirmation of TB can lead to earlier treatment initiation, improved patient outcomes, increased opportunities to interrupt transmission and more effective public health interventions. These are confirmatory tests. CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered, but has not yet been established, and also for those in whom the test result would alter case management or TB control activities, such as contact investigation.

Map 3-17. Distribution of countries and territories reporting at least one case of XDR- TB as of 2010[2]

Prophylaxis and Treatment for Converters include:

Chemoprophylaxis with 12 months of isoniazid is recommended for those who convert to a positive TB test. WHO recommends preventive therapy with isoniazid for people with HIV who are at risk of TB. They may also benefit from early Highly Active Antiretroviral Therapy (HAART) and close post-travel TST or IGRA testing.[1]

American Thoracic Society (ATS)/CDC Guidelines for treatment of LTBI2 recommend 9 months of isoniazid as the preferred treatment and 4 months of Rifampin as an alternative. Active TB is treated with a variety of regimens dependent upon the potential for MDR- or XDR-TB in a patient who acquires TB during travel, and whether pregnancy is an issue. For active TB during pregnancy, isoniazid, rifampin and ethambutol are given for 9 months with close monitoring for hepatotoxicity during pregnancy and 3 months postpartum.

TST	IGRAs
Requires two visits. Results available in 2-3 days. Less expensive test.	Requires only one visit, results available next day. More expensive.
Affected by previous BCG vaccination. False positive responses in 20-40% cases.	Unaffected by BCG vaccination.
False positive responses due to non-tuberculous mycobacterial infections.	Unaffected by most non-tuberculosis mycobacterial infections or prior positive test.
Test reading is subjective: large discrepancies between readers, different cut-offs employed depending on perceived risks, induration difficult to measure.	Objective results: eliminates inter-reader variability in interpretation of results.
Lack of privacy.	Privacy maintained, since test performed in a laboratory.

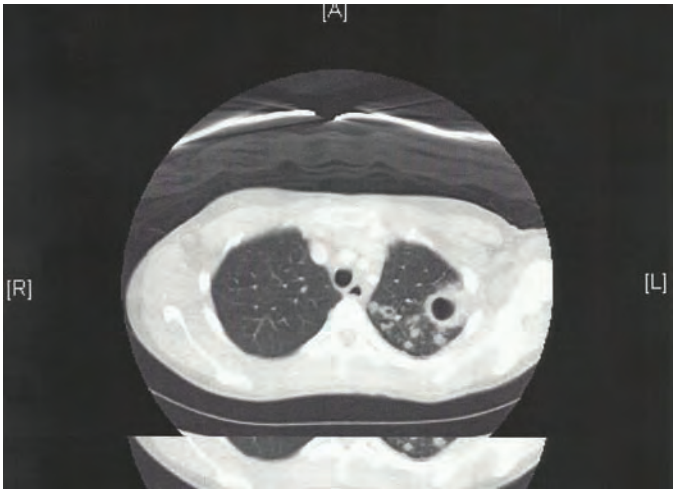
Education about TB should be included in a pre-travel visit and travelers can be invited back for post-travel screening.

Eight to ten weeks after travel represents a good time frame for post-travel screening. Travel clinics should also consider annual screening TB among regular travelers whose risk factors warrant it.

What travelers should be tested for TB?[6]

• Corporate travelers and expatriates traveling to endemic regions for >3months.

Figure 3



• Healthcare workers, including students, working or volunteering in high TB prevalence areas.

• Individuals working in high-risk situations such as refugee and transit camps.

• Individuals with travel-related TB exposure such as known exposures at health facilities.

• Long term tourists and travelers (>3months) who work or reside in regions with a high prevalence of TB.

• International visa requirements: many countries require testing for refugees, immigrants and asylum seekers.

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CME Objectives & Instructions

Upon completion of this educational activity, participants should be able to:

- discuss the latest data regarding the diagnosis and treatment of various travel-related diseases;
- explain new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world;
- implement strategies in the practice setting to inform patients of disease outbreaks and epidemics relevant to their travel plans.

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
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CME Questions

1. Murine typhus is a disease:
   A. Caused by a Rickettsia transmitted by rat bites or exposure to rodent urine.
   B. Often presenting with septic shock following evolution of a fever and rash.
   C. That can be contracted by travel in Indonesia and Africa.
   D. Is common in travelers to the Caribbean and Africa returning with fever of unknown origin.

2. Which of the following organisms is a commonly identified cause of travel-associated enteric infection in the US:
   A. *Vibrio cholera*
   B. Shiga toxin-producing *E. coli*
   C. *Campylobacter*
   D. *Yersinia*

3. Which of the following is NOT a correct statement regarding interferon gamma release assays [IGRAs]?
   A. Requires single visit, results are available next day.
   B. Patient privacy is maintained.
   C. False positive results due to previous BCG vaccination occur.
   D. This test eliminates inter-reader variability.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

FDA Approves First New Anti-Obesity Drug in Years

In this issue: Lorcaserin for weight loss; statins and fatigue; treatment-resistant gonorrhea; hydrocodone classification changes; USPSTF recommendations; and FDA actions.

Magic bullet for weight management?

The FDA has approved lorcaserin, the first new weight loss medication in more than a decade. The drug is approved for chronic weight management in adults with a body mass index of 30 or greater, or 27 or greater in those with weight-related conditions such as high blood pressure, type 2 diabetes, or hypercholesterolemia. Lorcaserin works by activating the serotonin 2C receptor in the brain, which promotes satiety. Approval was based on the results of three randomized, placebo-controlled trials of nearly 8000 obese and overweight patients with and without type 2 diabetes. All participants received lifestyle modification and reduced-calorie diets as well as exercise counseling. Lorcaserin was associated with an average weight loss of 3-3.7% compared to placebo over 1 year. Those with type 2 diabetes experienced favorable changes in glycemic control. There is no evidence of valvulopathy associated with the drug; although serotonin syndrome is a concern, especially when the locaserin is taken with an SSRI or some migraine drugs. The most common side effects include headache, dizziness, fatigue, nausea, dry mouth, and constipation as well as hypoglycemia in diabetic patients. Lorcaserin will be marketed by Arena Pharmaceuticals as Belviq. ■

Do statins cause fatigue?

Statins may be associated with fatigue and exertional intolerance, according to a small study from UC San Diego. Researchers randomized just over 1000 patients (692 men and 324 women) to simvastatin 20 mg (lipophilic statin), pravastatin 40 mg (hydrophilic statin), or placebo for 6 months. The outcomes were self-ratings of change in baseline in "energy" and "fatigue with exertion." Statin users were more likely to report worsening energy and fatigue compared to placebo ($P = 0.002$) Fatigue and exertional intolerance was worse with simvastatin compared to pravastatin (simvastatin, $P = 0.03$; pravastatin, $P = 0.01$). Women were more severely affected than men. The authors acknowledge that these findings are based on small numbers and findings are provisional. However, they also state that "this is the first randomized evidence of affirming unfavorable statin effects on energy and exertional fatigue." They further suggest that these effects "germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected morbidity/mortality benefit." (*Arch Intern Med* published online June 11, 2012. doi: 10.1001/archinternmed.2012.2171). The study also raises the potential issue of increased adverse effects of lipophilic statins such as simvastatin. The various risks and benefits of lipophilicity have been debated for years. It is clear that highly lipophilic statins, such as the now removed cerivastatin (Baycol), may have more muscle toxicity, and may have more CNS adverse effects as well. Of currently marketed statins, simvastatin is the most lipophilic, while pravastatin and rosuvastatin are the least. ■

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Call to action for resistant gonorrhea

The World Health Organization (WHO) is calling for urgent action to prevent the spread of "untreatable gonorrhea" around the world. The concern is based on reports from several countries, including Japan, United Kingdom, Australia, France, Sweden, and Norway, of gonorrhea that is resistant to cephalosporin antibiotics — the last remaining treatment option. According to WHO, more than 100 million people are infected with gonorrhea annually, and the world is faced with "dwindling treatment options." WHO is calling for greater vigilance on the correct use of antibiotics and more research into alternative treatment regimens for gonococcal infections. The agency also calls for increased monitoring and reporting of resistant strains as well as better prevention, diagnosis, and control of gonococcal infections. Single-dose treatment to assure adherence is also important as is the treatment of partners. WHO also stresses education and prevention, with special attention to high-risk groups such as sex workers and men who have sex with men. Cephalosporin-resistant gonorrhea has not been reported in the United States yet, but surveillance systems are in place. According to a recent CDC editorial in the *New England Journal of Medicine,* "It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense..." (*N Engl J Med* 2012; 366:485-487). ■

Changes on horizon for hydrocodone drugs

Could Vicodin soon be a Schedule II drug? The answer may be yes depending on congressional action this summer. The U.S. Senate recently passed The FDA Safety and Innovation Act (S 3187) with an amendment to classify all hydrocodone-containing products from Schedule III to Schedule II. The House of Representative's version of the bill did not contain similar language, and the proposal is under consideration for the final bill to be sent to the President for signature later this summer. Meanwhile, lawmakers in New York are moving forward with legislation that would make all hydrocodone-containing drugs Schedule II. If enacted, these laws would categorize hydrocodone containing drugs, such as Vicodin and Norco, in the same group with morphine, oxycodone, and methadone. Schedule II drugs cannot be phoned in, and patients are required to receive a new prescription for each refill. The proposed tightened regulations are in response to the explosion of prescription opioid abuse nationwide. Meanwhile, pharmacy groups, such as the American Pharmacists Association, are opposed to the legislation and are actively lobbying against it, arguing that it is unnecessarily restrictive to patients who legitimately need access to these drugs. ■

Vitamin D and calcium supplements

The U.S. Preventive Services Task Force (USPSTF) has now recommended that vitamin D and calcium supplements above the usual recommended daily allowances are of no benefit to help prevent bone fractures in healthy older women, and may actually cause harm. In a draft recommendation statement issued in early June, the USPSTF concluded that there is insufficient evidence to recommend vitamin D for prevention of cancer or combined vitamin D and calcium for the prevention of fractures in postmenopausal women or men. They further recommend against daily supplementation of more than 400 IU of vitamin D and 1000 mg of calcium carbonate. Older adults who are at risk for falls may continue to take vitamin D (www.uspreventiveserviestaskforce.org/draftrec3.htm). The draft recommendation was issued just after a study was published showing calcium plus vitamin D supplements appear to be associated with lower mortality in older individuals. In a large meta-analysis, patients receiving both calcium and vitamin D had a 9% reduction in mortality (hazard ratio, 0.91; 95% confidence interval, 0.84-0.98), although vitamin D alone did not affect mortality (*J Clin Endocrinol Metab* published online May 17, 2012, doi: 10.1210/jc.2011-3328). ■

FDA actions

The FDA has issued opinions on two oral novel anticoagulants. The agency turned down Janssen's application for approval of rivaroxaban (Xarelto) for the treatment of acute coronary syndrome, at least for now. The FDA did not release the reasons for the decision, but speculation is they want more information from the ATLAS-ACS trial. Rivaroxaban was approved last year for prevention of venous thromboembolism after hip or knee replacement surgery, and also for stroke prevention in patients with non-valvular atrial fibrillation (AF). The FDA also delayed the approval of apixaban (which would represent the third novel oral anticoagulant along with dabigatran and rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular AF. It had been widely speculated that the drug would be approved this spring, especially given that the FDA had granted a priority review for apixaban last November. The delay is similarly due to the need for additional information from the ARISTOTLE trial. Once approved apixaban will be marketed by Bristol-Myers Squibb as Eliquis. ■