TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media LLC

INSIDE

Volume 18, No. 10
October 2008

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, and peer reviewer Philip Fischer, MD, report no financial relationships relevant to this field of study.

2008 Prevention of Influenza Guidelines: Changes You Should Consider

ABSTRACT AND COMMENTARY

By Mary-Louise Scully, MD

Dr. Scully is Director, Travel and Tropical Medicine Center, Sansum Clinic, Santa Barbara, CA.

Dr. Scully reports no financial relationships relevant to this field of study.

Synopsis: *The new influenza guidelines now recommend annual vaccination of children ages 5-18 years in addition to the previous recommendation of children ages 6 months to 5 years. To meet the anticipated vaccine demand, the FDA has released 113 lots of the 2008-2009 Northern Hemisphere influenza vaccine produced by 6 different manufacturers.*

Source: Fiore AE, et al. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR* 2008; 57 (RR-7):1-60.

This report updates the 2007 recommendations by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) with regard to the use of influenza vaccine and antiviral agents. The important changes include: 1) a new recommendation that annual vaccination be administered to all children ages 5-18 years beginning in the 2008-2009 influenza season, if feasible, but no later than the 2009-2010 season; 2) a recommendation that annual vaccination of all children ages 6 months through 59 months continue the to be a primary focus of vaccination efforts since these children are at higher risk of influenza complications; 3) a new recommendation that either trivalent inactivated influenza vaccine (TIV) or live, attenuated influenza vaccine (LAIV) be used when vaccinating healthy persons ages 2-49 years (the previous recommendation was to administer LAIV to persons only between 5-49 years); 4) a recommendation that vaccines containing the 2008-2009 trivalent vaccine virus strains A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens be used.

The recommendation remains that children ages 6 months to 8 years should receive 2 doses of influenza vaccine (doses separated by $\geq$ 4 weeks) if they have not been vaccinated previously at any time with either LAIV or TIV because 2 doses are needed for protection in these children. Two doses also should be given to children ages 6 months to 8 years who received only one dose in their first year of vaccination. In children < 5 years with asthma or reactive airways disease the LAIV should be avoided. Since LAIV is a live, attenuated

vaccine, it is contraindicated in immunosuppressed individuals. Patients with a history of hypersensitivity to eggs and a history of Guillian-Barré after influenza vaccination should not be vaccinated with either LAIV or TIV.

Annual recommendations for adults have not changed and essentially encourage vaccination for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting influenza to others. Persons older than 50 years; pregnant women; patients with chronic pulmonary, cardiac, or renal conditions; diabetic patients; immunosuppressed patients; nursing home patients; health care workers; and caregivers of young children remain a focus of adult vaccination programs.

Other inactivated vaccines can be administered simultaneously with either TIV or LAIV. Among children 12-15 months of age, the concurrent use of LAIV with measles, mumps, rubella (MMR) alone and MMR and varicella vaccine has been examined and no interference in immune response was observed. In addition, based on available safety and immunogenicity data, it is acceptable to administer TIV with zoster vaccine for adults older than 50 years.

As resistance to both amantadine and rimantidine has increased rapidly in the past several years, oseltamivir and zanamivir remain the only antiviral medications recommended for influenza treatment or prophylaxis in the United States. Unfortunately, in 2007-2008, increased resistance to oseltamivir was reported in many countries among influenza A (H1N1) viruses. In the United States during the 2007-2008 influenza season, about 10% of influenza A (H1N1) viruses were found resistant to oseltamivir, but none of the influenza A (H3N2) or influenza B viruses were found to be resistant (overall percentage of influenza A and B viruses resistant to oseltamivir was < 5%). However, antiviral recommendations may change during the 2008-2009 season, and clinicians can keep up to date with information available on the CDC's web site (http://www.cdc.gov/flu/professionals/antivirals/index.htm).

COMMENTARY

The influenza vaccine supply is projected to be abundant this year, with 113 lots of Northern Hemisphere vaccine released by the FDA to meet the expected demand for implementation of the new pediatric recommendations. In addition, the vaccine antigens have been changed to reflect the predominant strains of last year's season.

Success ultimately will depend upon both health care providers' endorsement of the implementation and, even more, the endorsement from parents and caregivers of children. The LAIV and the single-dose vials or syringes of TIV are considered thimersol-free (0 or < 1.0 mcg per 0.5 mL dose) and, therefore, preferred for infants and pregnant women. All multi-dose vials still contain about 25 mcg mercury per 0.5 mL dose. In 2001, the U.S. Public Health Service and other organizations recommended that efforts be made to remove or reduce the thimersol content from vaccines as part of an overall plan to reduce mercury exposures from all sources.[1] Each year, it is expected that the number of influenza vaccines that do not contain thimersol will continue to grow.

Respiratory infections are second after gastrointestinal infections as a cause of illness in travelers, and influenza accounts for 5-6% of respiratory illness reported in travelers.[2] Influenza virus is spread by direct contact or

Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Travel Medicine Advisor***, PO Box 740059, Atlanta, GA 30374-9815.

Subscription Information: Customer Service: (800) 688-2421 or fax (800) 284-3291. Hours of operation: 8:30am-6pm Monday-Thursday; 8:30am-4:30pm Friday ET. Email: customerservice@ahcmedia.com Website: www.ahcmedia.com. Subscription rates: USA, one year (12 issues) $449. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

aerosol (fine droplet), and the traveler's world of crowded airports, buses, museums, and churches poses a perfect setting for influenza transmission. Outbreaks have occurred on cruise ships, an increasingly favored way of traveling for many, and which are especially conducive to influenza transmission.[3] Moreover, influenza circulates at low levels year round in the tropics—a frequent destination of travelers and cruise ships. Cruise ships often have a mixture of passengers and crew from both hemispheres and, although the available vaccine in the country of departure may not be matched optimally for the circulating strains in the opposite hemisphere, it is always preferable to vaccinate than to let the individual travel without any vaccine protection at all.[4] ■

References

1. CDC. Summary of the Joint Statement on Thimersol in Vaccines. *MMWR* 2000; 49:622-631.
2. Leder K, et al. Respiratory tract infections in travelers: A review of the GeoSentinel Surveillance Network. *Clin Infect Dis* 2003; 36:399-406.
3. Miller JM, et al. Cruise ships: High risk passengers and the global spread of new influenza viruses. *Clin Infect Dis* 2000:31:433-438.
4. Freedman DO, Leder K. Influenza: Changing approaches to prevention and treatment in travelers. *J Travel Med* 2005; 12:36-44.

Travelers and Eosinophilia

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD

Dr. Mileno is Director, Travel Medicine, The Miriam Hospital, Associate Professor of Medicine, Brown University, Providence, RI.

Dr. Mileno reports no financial relationships relevant to this field of study.

Synopsis: *Travelers returning from tropical countries may have significant exposures to helminths, yet there is no established clinical approach to identify and treat those who are both infected and presenting with eosinophilia. An approach to cases of eosinophilia in which schistosomiasis in returning travelers had been excluded is outlined in this recent publication.*

Source: Meltzer E, Percik R, Shatzkes J, et al. Eosinophilia among returning travelers: A practical approach. *Am J Trop Med Hyg* 2008;78(5):702-709.

There is a broad differential diagnosis for eosinophilia, defined as an absolute eosinophil count of > 500 cells/µl, yet cases due to helminthic disease probably occur more often in routine travelers than in the general population. There is a high index of suspicion concerning potential eosinophilia in immigrants and refugees. Schistosomiasis is an important cause of eosinophilia, followed by filariasis, primarily in persons residing in Africa, and is not rare in travelers returning from endemic areas.

This retrospective case series from Israel looked at travelers (excluding expatriates and immigrants) who returned from developing countries between January 1994 and June 2006. Eosinophilia was defined as total eosinophil count > 500/µl or > 6% on differential counts. All patients had a CBC, chemistry panel including liver function tests, and one or more stool samples for ova/parasites. Travelers to schistosomiasis-endemic areas were also tested for Schistosoma ova in urine and received a serologic test for schistosomiasis.

Other travelers underwent serologic tests for additional helminth infections such as strongyloidiasis and Toxocara infections performed at the Laboratory for Parasitic Diseases at the Centers for Disease Control (CDC), Atlanta, GA. Testing such as imaging or biopsies were performed according to clinical judgment. Patients diagnosed with schistosomiasis were treated with praziquantel 60 mg/kg for one day divided into two doses. Diagnosed cases of acute schistosomiasis received repeated dosing within three months. Other cases with eosinophilia were treated with albendazole 400 mg twice each day for 3 to 5 days. Symptoms and eosinophil count were evaluated.

Of 995 post-travel patients evaluated, 82 (8.6%) had eosinophilia, 44 (53.7%) of these had schistosomiasis-associated eosinophilia (SAE) and 38 (46.3%) had post-travel non-schistosomal eosinophilia (NSE).

Age, travel duration, and male/female ratio were not significantly different between NSE and SAE cases. Geographically, SAE were almost exclusively acquired through travel to Africa (95%). Most NSE cases had traveled to Asia (65.7%), with Southeast Asia and India being primary areas of transmission. Acute schistosomiasis occurred in 21 of 44 SAE cases and particularly presented with fever, rash, and respiratory symptoms. Sixteen of 44 (36.6%) were asymptomatic fellow travelers of a diagnosed index case and were identified through screening. Only 7 (16.9%) presented with chronic schistosomiasis, usually genitourinary.

At presentation, 94.7% of persons with NSE were symptomatic, with abdominal pain and protracted diarrhea as leading symptoms followed by dermatologic findings (rash or pruritis) and respiratory symptoms, mainly dry cough. Symptoms occurred in isolation or in

combination. Two patients presented with only symptoms of fatigue. Symptoms began in most cases during travel and were already present for several weeks on presentation to the clinic. Median time to presentation was six weeks (range from 1 day to > 1 year).

NSE had a median initial eosinophil count of 1700 cells/µl compared to SAE cases who had 1400 cells/µl (P=0.067). Mildly abnormal liver function tests occurred in 5.3% of NSE cases and 13.0% of SAE cases—not a statistically significantly difference. Serologic testing was positive in all 44 SAE cases. Diagnosis by observation of ova was made in 22.7% of cases. Only a smattering of NSE cases had diagnostic findings. Two cases had hookworm alone documented, and one case had hookworm and Ascaris. *Blastocystis hominis* and *Entamoeba histolytica/dispar* were found alone or with helminths in four cases. One patient had hookworms noted in a sputum sample. Five tests for strongyloidiasis were positive. No tests for toxocariasis, filariasis, or trichinosis were positive. In fact, definitive parasitologic diagnosis was achieved in only 9 NSE cases (23.7%). Two patients had non-infectious causes of eosinophilia, one with drug allergy; another with positive Strongyloides serology had increasing lymphadenopathy and, ultimately, B-cell lymphoma was diagnosed.

In terms of treatment, all persons with SAE tolerated praziquantel with no documented treatment failure. Thirty-seven NSE patients were offered empiric therapy with albendazole. One declined and four others were lost to follow up. Of 30 treated patients available for evaluation of clinical response, 90% (27/30) showed a favorable response to treatment; 76.7% had complete remission of symptoms; 13.3% had significant improvement; 3 cases (10%) had no response. One had lymphoma, one had eosinophilic gastroenteritis, and one remained without a specific diagnosis but responded to corticosteroid treatment as did the patient with eosinophilic gastroenteritis.

COMMENTARY

This study showed that NSE is certainly not rare and represented 4% of all referrals to this post-travel clinic. Some forms of travel pose even higher risks; the incidence of NSE reported in military personnel actively screened after deployment to a developing country has been 50%. What lessons can we learn from this study, and from what we know about refugees and immigrants? Although diagnostic yields were low, responses to treatment were high. Screening for eosinophilia in travelers returning from Africa may have an important impact for the immediate and future health of these individuals. Knowing about significant levels of eosinophilia would provide an important clue to the potential diagnosis and treatment of strongyloidiasis and schistosomiasis.

Young healthy travelers to developing countries who develop eosinophilia should be evaluated first and foremost for helminth infections. Strongyloidiasis and schistosomiasis have the strongest associations with eosinophilia. Other infectious diseases may be associated with eosinophilia, including cocoidioidomycosis, aspergillosis, isosporiasis, *Dientamoeba fragilis*, *Mycobacterium leprae,* and chronic *Mycobacterium tuberculosis* infections, although the diagnostic yields are quite low when based solely upon the finding of eosinophilia.

Schistosomiasis is an important and frequent cause of eosinophilia, and this diagnosis should be pursued using serology and attempted ova detection. Identified cases, and arguably individuals with known exposure or fellow travelers of index cases, should be treated with praziquantel.

Hookworm and strongyloides are the most prevalent helminthic infections. In some groups, strongyloides seroprevalence reached 77%. Canine hookworms have recently been shown to occasionally cause NSE and eosinophilic gastroenteritis. A case can be made that empiric therapy is most sensible, rather than an extensive diagnostic workup in travelers returning from regions of such high endemicity. Universal treatment with albendazole, a broad spectrum antihelminthic, is highly effective in populations with high incidence of helminthic infection, such as refugees and immigrants, and has an excellent safety record.

One algorithm for travelers returning from Africa with eosinophilia might include empiric treatment for schistosomiasis with praziquantel followed by albendazole. Travelers with NSE might have an evaluation that includes a thorough history and physical examination, stool samples for ova and parasites, and a therapeutic trial of albendazole. If a strongyloides serology is positive, treatment with ivermectin would be administered. Further testing should be reserved for individuals who remain symptomatic.

In summary, eosinophilia that is associated with schistosomiasis is uncommon but not rare. NSE is more a more common scenario. Travelers with NSE are often symptomatic, and eosinophilia is most probably associated with helminthic infection(s). A better methodology is still needed to evaluate persons with eosinophilia for potential parasitic infection. Empiric albendazole results in resolution of symptoms and eosinophilia in most cases, with further treatment reserved for the few cases that do not respond to initial empiric treatment. Lastly, consideration of the noninfectious causes of eosinophilia including allergic disorders, medications, toxins, autoimmune diseases, and endocrine disorders such as Addison's disease may yield the diagnosis. ■

Plasmodium falciparum Malaria in a Man with Sickle Cell Disease, Four Years After Exposure

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP

Dr. Barry is a Professor of Medicine and Public Health; Director of International Health Program, Department of Medicine, Yale University School of Medicine, New Haven, CT.

Dr. Barry reports no financial relationships relevant to this study.

Synopsis: *A case of symptomatic Plasmodium falciparum malaria manifested itself 4 years after a visit to an area of malaria endemicity in an 18-year-old male with sickle cell disease. The exceptionally long incubation period raises questions of how and where P. falciparum parasites could reside for several years before causing disease.*

Source: Greenwood T, Vikerfors T, Sjoberg M, et al. *Plasmodium falciparum* malaria 4 years after exposure in a man with sickle cell disease. *Clin Infect Dis* 2008 ;47 :e39-41.

An 18-year-old man from Togo was admitted to a hospital in Sweden with a 3-day history of chest, stomach, and back pain with recurrent episodes of sweating and fever. He was known to have hemoglobin SC disease and splenomegaly; he was admitted for presumed sickle cell crisis. Fever continued despite intravenous antibiotics and fluids. Results of bacterial cultures of blood, nasopharynx, urine, and stool specimens were normal as were results of serological tests for Epstein-Barr virus and cytomegalovirus. A blood smear revealed *P. falciparum* in < 0.01% of erythrocytes with largely ring forms noted on the peripheral smear, but also with a few trophozoites, schizonts, and gametocytes. PCR analysis performed by two methods confirmed the presence of *P. falciparum*. A species specific PCR test detected only one clone of *P. falciparum*. The patient was treated successfully over 3 days with oral atovaquone/proguanil.

The patient was born in Togo but had lived for the past 14 years in Sweden. His last visit to Togo was 4 years prior to hospital admission. The patient had taken mefloquine prophylaxis weekly during this visit, but he recalled one episode of fever during which he was treated with a different antimalarial, and then continued taking mefloquine again. He had not received blood transfusions, visited an airport, nor been living close to anyone in Sweden with malaria. Blood smear specimens saved as part of a routine hematologic exam four years before the trip to Togo were reanalyzed and found to be negative for parasites. The authors postulate that this case demonstrates clinical symptoms that can develop from a chronic infection with *P. falciparum*.

COMMENTARY

This is a very unusual case! In contrast to *P. vivax* and *P. ovale*, *P. falciparum* and *P. malariae* infections do not have dormant liver hypnozoite stages in their life cycles. *P. malariae* infections may have very long incubation periods—as long as several decades—but it is not clearly understood where the parasites reside. *P. falciparum* associated malaria usually presents in > 95% of cases within 2 months after exposure.[1] Resistance to malaria associated with sickle cell trait (genotype AS) has been offered as an example of genetic selection for more than half a century. Nevertheless, the mechanism of malaria resistance remains the subject of considerable debate. Abnormal hemoglobins (S, C, E) lead to a "balanced polymorphism" within malaria-endemic areas, in that they are associated both with a reduction in the number of homozygous individuals whose life expectancy is limited by vaso-occlusive crisis or infections and with an extension of the duration of life of heterozygous individuals due to protection against severe malaria. Individuals in malaria endemic areas who have sickle cell anemia or sickle cell trait have reduced levels of parasitemia when compared to individuals with normal AA hemoglobin.[2,3] Longitudinal cohorts of children followed with sickle cell trait have revealed that levels of parasitemia are lower in AS individuals during the first 2 years of life, and AA children are more often hospitalized with malaria.[3] This differential protection by sickle cell trait against malaria is most marked in the first 5 years of life.[4]

The mechanism by which HbS trait or Hb SS disease protects is not fully understood but involves both impaired parasite growth or parasite death within sickle trait erythrocytes. Carriers of sickle cell trait have a dramatic acceleration of sickling rates in parasitized cells, followed by subsequent clearance of the parasite. Recent studies also suggest enhanced innate immunity among individuals with sickle cell disease or trait may also be playing a role in reducing malaria mortality and morbidity in young children.[2]

A recent study has shown that individuals with sickle cell anemia and malaria also have deformed red blood cells that are unable to develop adequate sticky knobs that adhere to endothelial cells in blood vessels, one mechanism felt to be responsible for the severity of *P. falciparum* malaria.[5] Overall, it has been postulated that hemoglobin S trait in early childhood provides 90% pro-

tection against severe or cerebral malaria, and 60% protection against malaria that is not severe.[4] Hemoglobin C also protects against malaria through the inhibition of parasite growth.

This case is particularly interesting in that light microscopic examination detected not only ring forms but also trophozoites and schizonts, despite a low percentage of infected erythrocytes on peripheral smear. This finding perhaps signifies the inability of sticky knobs to form on this patient's red blood cells, which usually causes sequestration of the more mature schizonts and trophozoites. One might also postulate that splenic dysfunction, which can occur in SC disease associated with splenomegaly, resulted in an inability to clear late stage parasites.

This case really challenges the standard teaching that *P. falciparum* rears its head within the life-span of an erythrocyte, i.e., 120 days. Many questions are raised. Had these parasites been multiplying in the blood and remained at subpatent levels? Does *P. falciparum* have a dormant stage in splenic or lymphoid tissue? Was this patient's admission really only precipitated by a sickle crisis, and the malarial parasites found on smear reflect an incidental persistent low-level parasitemia? Did *P. falciparum* malaria trigger a sickle crisis or did a sickle crisis cause a chronic subpatent parasitemia to develop into clinical malaria by overwhelming splenic function? There have been isolated case reports of acute *P. falciparum* malaria following splenectomy for lymphoma after prolonged absence from endemic areas, as well as recrudescence in cases after removal of the spleen for misdiagnosed tropical splenomegaly syndrome.[6,7] Did splenic dysfunction in this patient, which can occur despite splenomegaly, precipitate malaria parasitemia? Whatever mechanism, this case report should alert clinicians to the possibility of malaria in patients from endemic areas who present in sickle crisis even if there is a history of a prolonged time period since clear exposures to the parasite. ■

References

1. Centers for Disease Control. Malaria Surveillance-United States, 2006. *MMWR* 2008;57(SS05):24
2. Williams TN, Mwangi TW, Roberts DJ, et al. An immune basis for malaria protection by the sickle cell trait. *PLoS Med* 2005;2(5):e128. http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020128. Accessed 9/2/08.
3. Yves Le Hesran J, Personne I, Personne P, et al. Longitudinal study of *Plasmodium falciparum* infection and immune responses in infants with or without the sickle cell trait. *Int J Epidemiol* 1999;28:793.
4. Greenwood B, Marsh K, Snow R. Why do some African children develop severe malaria? *Parasitology Today* 1991;7(10):277.
5. Cholera R, Brittain NJ, Gillrie MR, et al. Impaired cytoadherence of *Plasmodium falciparum*-infected erythrocytes containing sickle hemoglobin. *PNAS* 2008;105(3):991.
6. Bidegain F, Berry A, Alvarez M, et al. Acute Plasmodium falciparum malaria following splenectomy for suspected lymphoma in 2 patients. Clin Infec Dis 2005;40:e97-100.
7. David PH, Hommel M, Miller LH, et al. Parasite sequestration in Plasmodium falciparum malaria: Spleen and antibody modulation of cytoadherence of infected erythrocytes. Proc Natl AcadSci USA 1983;89:5075-5079.

Tuberculosis Among Foreign-born Persons in the United States

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

Dr. Chen is Assistant Clinical Professor, Harvard Medical School, Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA.

Dr. Chen reports no financial relationships related to this field of study.

Synopsis: *In the United States, tuberculosis (TB) case rates and drug resistance are much higher in foreign-born persons. The greatest risk of active TB is associated with individuals from sub-Saharan Africa and southeast Asia, and those of older age at arrival. Although risk is higher in persons who arrived recently in the U.S., the majority of TB cases have occurred in foreign-born persons who have lived in the U.S. for more than 2 years.*

Source: Cain KP, et al. Tuberculosis among foreign-born persons in the United States. *JAMA* 2008;300(4):405-412.

The authors analyzed the cases of tuberculosis that occurred in the United States among foreign-born persons from 2001 through 2006. During this period, 46,970 cases of TB were reported among foreign-born persons, of whom 28% were recent entrants who were within 2 years of entry to the United States, and 69% were not recent entrants. TB case rates were highest in recent entrants. When analyzed by country of birth, case rates in recent entrants were 3-7 times higher than among non-recent entrants. Recent entrants born in sub-

Saharan Africa and Southeast Asia had annual case rates > 250/100,000 persons. Cases in persons born in sub-Saharan Africa and southeast Asia account for 53% of all TB cases in foreign-born individuals, although people born in these regions account for only 22% of the foreign-born population in the United States. Recent entrants from Central America, Eastern Europe, the Pacific Islands, and South, East, and Central Asia had annual case rates of > 100/100,000 persons.

Moreover, TB rates among foreign-born persons remained at > 10/100,000 persons even among those who have lived in the United States for more than 2 decades, 4 times higher than among U.S.-born persons. When analyzed by age at arrival to the United States, TB rates rose with increased age at arrival. In recent entrants, annual case rates increased from 25-30/100,000 persons in those who arrived at age < 5 years, to > 100/100,000 persons in those who arrived at age > 50 years. Similarly, in non-recent entrants, the annual case rates were increased from 5/100,000 persons in those who arrived at age < 5 years, to > 60/100,000 persons in those who arrived at age > 60 years.

Drug resistance is another problem in foreign-born persons with tuberculosis, occurring in 10-11% of bacterial isolates compared to 4% in U.S.-born persons. INH-resistance was highest in recent entrants from Vietnam (20%), Peru (18%), the Philippines (17%), and China (16%). Multidrug-resistant TB occurred in 6% of recent entrants from Peru and China, compared to 0.6% among U.S.-born persons.

The authors assessed pre-arrival screening, which currently includes chest radiography in persons aged 15 year or older, plus sputum smear if found to have abnormal radiograph. They found that 4499 foreign-born persons were reported with TB within 3 months of arrival to the United States, with 91% having pulmonary disease. Abnormal chest radiographs and positive sputum smears were found in 1211, which could have been identified by current overseas screening. Another 1502 had an abnormal chest radiograph, negative sputum, but positive sputum culture. Screening with CXR, sputum smear and culture would identify the latter group of individuals, 46% of whom are from Vietnam or the Philippines.

COMMENTARY

Mycobacterium tuberculosis infects about 30% of the world's population.[1] In 2006, there were 9.2 million new TB infections and 1.7 million deaths attributed to TB.[2] In the United States, the majority of TB cases occur in foreign-born persons and racial/ethnic minorities.[3] In 2007, foreign-born persons in the United States had a TB rate that was 9.7 times higher than in U.S.-born persons.[3] The CDC found TB rates to be much higher among Hispanics, blacks, and Asians (7.4, 8.3, and 22.9 times higher, respectively) than in non-Hispanic whites; foreign-born persons comprised the vast majority of TB cases among Hispanics (77.2%) and among Asians (96.1%).[3]

From October 1998 to October 1999, the CDC assessed the ability of overseas screening with chest radiographs, plus 3 AFB sputum smears for those with abnormal chest radiographs, to detect pulmonary TB among U.S.-bound immigrants. At that time, overseas screening in Vietnam found that among 1179 adult immigration applicants with abnormal chest radiographs, 82 (7.0%) had positive acid-fast bacilli smears, and 183 (15.5%) had positive *Mycobacterium tuberculosis* cultures.[4] The sensitivity of chest radiographs plus AFB smears was only 34% and inadequate to control tuberculosis among foreign-born persons.[4]

In 2007, the CDC initiated additional TB screening for U.S.-bound immigrant applicants, which included: targeted tuberculin skin testing of children 2-14 years old who live in countries with high TB incidence (i.e., WHO-estimated rates of > 20 cases per 100,000 population) and all known TB contacts; and adding cultures and drug-susceptibility testing for persons with suspected TB.[3] These new initiatives were started in 2007 in Mexico, Nepal, the Philippines, and Thailand, and are being expanded in 2008 to Vietnam and some African countries.[3]

The report by Cain, et al., substantiates data from past TB analyses, and highlights the following:

- Foreign-born individuals who arrived in the United States within 2 years are 3-7 times more likely to have active TB infection than non-recent entrants.
- Persons born in sub-Saharan Africa and Southeast Asia have the highest risk of having been infected with TB.
- Older age at arrival to the United States is associated with increased case rates.
- TB drug resistance is more common in foreign-born persons compared to U.S.-born persons.
- Pre-arrival TB culture in addition to chest radiograph and sputum smear should be useful for screening persons born in Vietnam or the Philippines.
- Non-recent entrants comprised the majority (69%) of the TB cases in foreign-born persons, clearly an important group to target for diagnosis and treatment.

The great proportion of TB among foreign-born persons underscores the importance to screen persons born in high-incidence countries for TB. Screening for latent TB is even more important in foreign-born persons who came to the United States before the enhanced overseas screening was instituted. A model of lifetime TB reactivation estimated the risk to be at least 20% among most persons with ≥ 10 mm of PPD induration who have either evidence of old healed TB or are HIV infected.[5]

The lifetime risk is estimated to be 10-20% among persons with recent tuberculin skin test conversion, among persons younger than 35 years of age who are on infliximab treatment and have ≥ 15 mm of induration, and in children ≤ 5 years of age with ≥ 10 mm induration.[5]

The development of whole-blood interferon-γ release assays holds promise as alternative TB screening tools. These tests avoid the cross reactivity due to immunization with BCG, which has plagued the interpretation of tuberculin skin tests in the past. The tests have recently been approved by the FDA, and wider use is anticipated in the near future.[6,7]

Travel medicine practitioners can contribute to the TB control efforts through the screening of travelers who were born in high-risk countries for TB (sub-Saharan Africa and Southeast Asia in particular, but also Central America, Eastern Europe, the Pacific Islands, and South, East, and Central Asia). Travelers who are visiting friends and relatives are especially at risk, even if prior TB screenings were negative, when they plan to spend time in countries with high risk for TB. The TB screening can be done when travelers present for pre-travel evaluations, or can be performed after the travelers return. If available, screening can utilize a interferon-γ release assay when there is concern about BCG-associated positivity contributing to the positive tuberculin skin test. ■

References

1. Corbett EL et al. The growing burden of tuberculosis. *Arch Intern Med* 2003;163:1009-1021.
2. WHO. Global tuberculosis control: Surveillance, planning, finance: WHO report 2008. Geneva, World Health Organization. Available at http://www.who.int/tb/publications/global_report/2008/pdf/fullreport.pdf. Accessed May 7, 2008.
3. CDC. Trends in tuberculosis—United States, 2007. *MMWR* 2008;57(11):281-285.
4. Maloney SA, et al. Assessing the performance of overseas tuberculosis screening programs: A study among US-bound immigrants in Vietnam. *Arch Intern Med* 2006 Jan 23;166(2):234-40.
5. Horsburgh CR. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004;350(20):2060-2067.
6. Mazurek GH, Weis SE. Prospective comparison of the tuberculin skin test and 2 whole-blood interferon-γ release assays in persons with suspected tuberculosis. *Clin Infect Dis* 2007;45:837-845.
7. Mazurek GH, et al. Detection of *Mycobacterium tuberculosis* infection in United States navy recruits using the tuberculin skin test or whole-blood interferon-γ release assays. *Clin Infect Dis* 2007;45:826-836.

CME Questions

15. Which of the following statements regarding influenza is *not* correct?

a. All influenza vaccines can be given concurrently with other inactivated vaccines.
b. Live, attenuated influenza vaccine can be given to persons ages 2-49 years.
c. In the United States during 2007-2008, the overall percentage of influenza A and B viruses resistant to oseltamivir was > 90%.
d. Oseltamivir and zanamivir are the only antiviral medications presently recommended for influenza treatment or prophylaxis in the United States.
e. Cruise ship travel has been associated with spread of influenza infections.

16. The approach to eosinophilia in returned travelers includes:

a. All such travelers should be initially screened for Addison's disease upon return from Africa.
b. Screen all travelers returning from Africa for eosinophilia as well as those returning from Asia who are ill.
c. Treat all returned travelers with albendazole alone.
d. Treat all returned travelers from Africa with albendazole and praziquantel.

17. Which of the following statements is true?

a. *P. falciparum* usually presents with higher levels of parasitemia in children due to asplenia caused by sickle cell disease.
b. *P. falciparum* is more likely to present as cerebral malaria in children with SS disease.
c. Hemoglobin C is only protective against malaria when coupled with hemoglobin S.
d. Low-grade, persistent *P. falciparum* parasitemia is often found in patients with sickle trait AS.

18. In recent years, *Mycobacterium tuberculosis* infection in the United States:

a. has affected mainly urban non-Hispanic whites.
b. occurred at much higher rates in foreign-born persons.
c. involves multidrug resistant strains only in foreign-born individuals.
d. has not been a concern in recent immigrants due to overseas screening.
e. became well-controlled and nearly eliminated.

Answers: 15. c; 16. b; 17. d; 18. b

PHARMACOLOGY WATCH

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

Gender Differences with Anticoagulation Discontinuation

In this issue: Some women with DVT may stop warfarin after six months; Vytorin and cancer; preventing recurrent stroke; and FDA news.

When is it safe to stop anticoagulation after an unprovoked venous thromboembolism? A new study suggests that women with minimal risk factors may safely stop anticoagulation after 6 months of therapy, although the same may not be true for men. Canadian researchers randomized 646 patients with a first, unprovoked major venous thromboembolism and followed them for 4 years. Data were collected for 69 potential predictors of recurrent venous thromboembolism while patients were taking oral anticoagulants and a multi-variable analysis of predictor variables was performed. Men had a 13.7% annual risk of recurrence after discontinuing oral anticoagulation and there was no combination of clinical predictors that could identify a low-risk subgroup of men. In women, 52% had zero or one of the following risk factors: hyperpigmentation, edema or redness of either leg, d-dimer ≥ 250 mcg/L while taking warfarin, body mass index ≥ 30 kg/m^2, or age ≥ 65 years. These women had an annual risk of recurrent thromboembolism of 1.6% (95% CI, 0.3% to 4.6%). Women who had two or more of these risk factors had an annual risk of 14.1%. The authors conclude that women with zero or one risk factor may safely discontinue oral anticoagulant therapy after 6 months of therapy following their first unprovoked venous thromboembolism; however, this conclusion does not apply to men (*CMAJ* 2008;179:417-426). An accompanying editorial points out that patients with the first episode of unprovoked venous thromboembolism have a high rate of recurrence if they stop anticoagulation therapy — about 10% in the first year. Current guidelines from the American College of Chest Physicians recommend lifetime therapy for patients with a first episode of proximal deep venous thrombosis or pulmonary embolism provided that good anticoagulant monitoring is achievable and indefinite treatment is consistent with patient preferences. This study identifies a large group of women who may safely stop anticoagulation after 6 months although the authors do recommend further validation (*CMAJ* 2008; 179:401-402).

FDA Announces Vytorin Investigation

The news keeps getting worse for Merck/Schering-Plough, the distributor of Vytorin®: The FDA has announced that it will investigate a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of the possible association between the use of Vytorin and increased incidence of cancer. The SEAS trial was designed to see if Vytorin, a combination of simvastatin and ezetimibe, would reduce cardiovascular events in patients with aortic stenosis. In a July press

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

release, the company reported on preliminary data which showed that the trial did not show benefit for the primary endpoint of aortic-valve related major cardiovascular events, but did show that a larger percent of subjects treated with Vytorin were diagnosed with, and died from, all types of cancer compared to placebo during the 5-year study. There was improvement in the secondary endpoint of ischemic events (15.7% vs 20%) but no benefit in other secondary endpoints. The number of cancers was 105 (11.1%) in the Vytorin group vs 70 (7.5%) in the control group (P = 0.01), and the number of cancer deaths was 39 (4.1%) in the Vytorin group vs 23 (2.5%) in the control group (HR 1.67; 95% CI, 1.00 to 2.79; P = 0.05). The FDA is also looking at interim data from two large ongoing trials of Vytorin, the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) which, so far, have not shown an increased risk of cancer associated with Vytorin. The SHARP trial should be completed in 2010, while the IMPROVE-IT trial should be finished in 2012. Initial data from the SEAS trial were presented in the recent news conference; full results were published at www.nejm.org (DOI: 10.1056/NEJMao0804602) on Sept. 2, 2008. The FDA says its investigation will take at least 6 months from the date of publication.

PRoFESS Trial Shows No Stroke Benefit

The recently published PRoFESS trial failed to show benefit of two strategies for preventing recurrent strokes. In the first arm of the study, the angiotensin-receptor blocker (ARB) telmisartan was compared to placebo in more than 20,000 patients with ischemic stroke. Patients were randomized to telmisartan 80 mg daily or placebo and followed for a mean follow-up of 2.5 years. Mean blood pressure was 3.8/2.0 mmHg lower in the telmisartan group; however, there was no difference in the rate of recurrent stroke (8.7% telmisartan vs 9.2% placebo [HR 0.95; 95% CI, 0.87 to 1.01; P = 0.11). The rate of new onset diabetes was 1.7% in the treatment group and 2.1% in the placebo group (P = 0.10). The authors conclude that therapy with telmisartan initiated soon after an ischemic stroke did not significantly lower the rate of recurrent stroke, diabetes, or major cardiovascular events. The second wing of the study compared aspirin plus 200 mg of extended release dipyridamole (Persantine®) twice daily vs clopidogrel (Plavix®) 75 mg daily in the same patient group. After a mean of 2.5 years of follow-up recurrent stroke occurred in 9% of patients receiving aspirin and dipyridamole and 8.8% of patients receiving clopidogrel (HR 1.01; 95% CI, 0.92 to 1.11). The secondary outcomes of stroke, myocardial infarction, or death from vascular causes occurred in 13.1% of both groups. The authors conclude that there is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke (*N Engl J Med*, published on-line at www.NEJM.org, Aug. 27, 2008).

FDA Actions

The FDA has issued a warning regarding the use of simvastatin in patients who are taking amiodarone. More than 20 mg of simvastatin plus amiodarone puts patient at higher risk for rhabdomyolysis since amiodarone inhibits CYP 3A4, one of the enzymes that metabolizes simvastatin. The simvastatin labeling has contained a warning regarding concomitant use with amiodarone since 2002; however, the FDA continues to receive reports of rhabdomyolysis associated with use of the two drugs. Physicians are also urged to tell their patients to report any unexplained muscle pain, tenderness, or weakness while taking the drugs. Other risks for rhabdomyolysis associated with statins include advanced age, uncontrolled hypothyroidism, and renal impairment.

There should be plenty of flu vaccine this fall. The FDA has announced the approval of six manufactures including GlaxoSmithKline, ID Biomedical, MedImmune, Novartis, Sanofi Pasteur, and CSL Limited. The vaccine will again be a trivalent vaccine comprised of two influenza A viruses and one influenza B virus. All three strains are new this year, an unusual occurrence as usually only one or two strains are updated each year.

The FDA issued an alert in October 2007 regarding exenatide (Byetta®) and the risk of acute pancreatitis. Since then, 6 more cases of hemorrhagic or necrotizing pancreatitis have been reported to the FDA associated with use of the drug, including two deaths. Exenatide is an injectable incretin mimetic used to treat type 2 diabetes. The FDA is recommending that exenatide should be stopped immediately if pancreatitis is suspected. Currently there is no patient profile which would predict increased risk of pancreatitis. Amylin Pharmaceuticals, the manufacture of exenatide, is working with the FDA on new labeling regarding the risk of hemorrhagic or necrotizing pancreatitis. ■