TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Volume 15, No. 4
April 2005

Travel Medicine Advisor® is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd. NE, Six Piedmont Center, Suite 400, Atlanta, GA 30305. Periodicals postage paid at Atlanta, GA. POSTMASTER: Send address changes to *Travel Medicine Advisor®*, P.O. Box 740059, Atlanta, GA 30374.
Customer Service:
1-800-688-2421.
Subscription Information:
Travel Medicine Advisor® Update is a bimonthly supplement to *Travel Medicine Advisor®* looseleaf service. Price: $429 (includes *Travel Medicine Advisor* looseleaf reference manual plus one-year subscription to *Travel Medicine Advisor® Update*.) To subscribe, **call 1-800-688-2421.**

History of Thymic Dysfunction and Yellow Fever Vaccination

Conference Coverage by Mary Louise Scully, MD

Synopsis: *New information provides updated guidance on assessing the risk of yellow fever vaccine-associated viscerotropic disease (YEL-AVD). Health care providers should carefully weigh the risks and benefits of the vaccine in elderly travelers or any patient, regardless of age, who has a history of thymus disorder or dysfunction, including myasthenia gravis, thymoma, thymectomy, or DiGeorge syndrome.*

Source: Barwick Eidex R. Thymus Disease as a Potential Risk Factor for Yellow Fever Vaccine-Associated Viscerotropic Disease. ASTMH Annual Meeting. Miami, FL: Nov 8, 2004; Barwick Eidex R. The Yellow Fever Vaccine Safety Working Group. History of Thymoma and Yellow Fever Vaccination (letter). *Lancet.* 2004;364:936.

At the 53rd meeting of the American Society of Tropical Medicine and Hygiene in Miami, FL, November 7-11, 2004, Rachel Barwick Eidex of the CDC presented the latest update on the history of thymic dysfunction and risks of yellow fever vaccination. This information was also published in a *Lancet* September 2004 letter. Yellow fever vaccine-associated viscerotropic (YEL-AVD) and neurotropic disease (YEL-AND) are the newer terms for post-vaccination multiple organ system failure and post-vaccinal encephalitis, respectively. YEL-AVD is a disease that both clinically and histologically, resembles naturally acquired yellow fever. It occurs in primary vaccinees 2-5 days after receiving 17D yellow fever vaccine. Patients develop fever, myalgias, arthalgias, lymphopenia, elevated liver enzymes, sometimes progressing to liver failure, thrombocytopenia, and DIC. Viral dissemination to organs such as liver, lung, spleen, lymph nodes, brain, and muscle has been documented in several cases. As of July 2004, 23 cases of YEL-AVD have been reported worldwide, of which 14 (61%) have been fatal. Advancing age appears to be associated with a higher risk of YEL-AVD, with individuals over 60 years being at greatest risk. In the United States, the reported incidence of YEL-AVD is about 3 cases per million civilian doses of yellow fever vaccine given. A similar incidence of YEL-AVD (2.5 per million doses distributed since 1996) was reported in a UK study.[1]

Attempts to identify risk factors associated with YEL-AVD are quite challenging because of its low incidence. Of the 23 vaccinees reported to have YEL-AVD, 4 (17%) were found to have a history of thymus disease, suggesting thymic dysfunction as a possible independent risk factor for development of YEL-AVD. The first case was a 67-year-old female from the United States with a malignant thymoma and thymectomy 2 years before vaccination, who subsequently developed fatal YEL-

AVD. A second patient, also from the United States, was a 70-year-old man with a history of myasthenia gravis and thymectomy for thymoma 20 years before vaccination who developed YEL-AVD and survived. A third patient from Switzerland had a thymectomy due to thymoma 8 years prior to vaccination and also developed YEL-AVD, but survived. The final patient was a 44-year-old man with a history of thymectomy for benign thymoma 2 years before yellow fever vaccination in Columbia. He developed YEL-AVD with fulminant hepatic failure and died.

The thymus, derived from the Greek word meaning mind, life-force, or soul, is important in the processing and maturation of T-lymphocytes and regulating the integrity of T-cell and B-cell function. At birth, the thymus weighs 12 to 15 grams. It reaches its maximum weight of 40 grams at puberty, then involutes and persists in an atrophic state into old age. These normal changes of the thymus with aging may in part explain the higher risk of YEL-AVD observed in the elderly. The incidence of thymoma is rare (0.15 cases per 100,000 person years), but increases with age older than 40 years up through the age of 80 years.[2] Thymic tumors are also associated with various autoimmune disorders, reduced numbers of circulating B lymphocytes, and hypogammaglobulinemia. It was also shown in an animal model that use of antithymocyte serum to induce immune suppression would potentiate lethal yellow fever 17-D infection.[3]

Yellow fever vaccination for travelers to endemic areas for yellow fever is is an essential role of travel medicine providers. It is estimated that 9 million travelers visit yellow fever endemic countries each year. The risk of illness and death due to yellow fever in an unvaccinated traveler for a 2 week trip to Africa are estimated to be 1:2000 and 1:10,000, respectively.[4] The risk of yellow fever will vary with the season of travel, length of exposure, the specific recreational or professional activities of the traveler, and the rate of yellow fever virus transmission at the time. The risk increases dramatically during epidemic periods. However, reporting of human yellow fever cases from endemic areas is often delayed and underestimated, adding to the challenge of assessing risk. The risk of yellow fever in a traveler to South America is less than that for a traveler to Africa, but cases do occur. Three of the 4 travelers from Europe and the United States who became ill with yellow fever during 1996-1999 had traveled to South America.[5,6] Proper use of the yellow fever vaccine remains the most effective means to decrease the risk of disease in travelers and residents of endemic countries.

In summary, new data point to thymic dysfunction as an independent risk factor for YEL-AVD. Health care providers should now specifically ask patients about a history of thymus disorder or dysfunction, irrespective of the patient's age. This should include any history of thymoma, thymectomy,

Travel Medicine Advisor is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd. NE, Six Piedmont Center, Suite 400, Atlanta, GA 30305.
POSTMASTER: Send address changes to *Travel Medicine Advisor,* P.O. Box 740059, Atlanta, GA 30374.
Customer Service: 1-800-688-2421.

Subscription Information: *Travel Medicine Advisor* is a monthly supplement to *Travel Medicine Advisor* looseleaf service. Price: $429 (includes *Travel Medicine Advisor* looseleaf reference manual plus one-year subscription to *Travel Medicine Advisor Update*.) To subscribe, **call 1-800-688-2421.**

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Bia is a consultant for GlaxoSmithKline and Bristol Myers Squibb. Dr. Barry is a consultant with the Ford Foundation. She and Dr. Bia receive funds from Johnson & Johnson for academic programs. Dr. Hill reports a speaker's bureau relationship with Chiron and Merck. Dr. Jong is a consultant with Berna-Vaccines, is on the speaker's bureau of Aventis and GlaxoSmithKline, and is involved in research with Merck. Dr. Keystone is a consultant for Merck, on the speaker's bureau of GlaxoSmithKline and is involved in research with Roche. Dr. Mileno is a consultant with GlaxoSmithKline and is involved in research with Merck. Dr. Chen, Dr. Fischer, Dr. Scully, and Ms. Hynes report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

myasthenia gravis, or DiGeorge syndrome (congenitalabsence of thymus and parathyroids). In these patients, yellow fever vaccine should be waived and, if travel to yellow fever endemic areas cannot be avoided, patients should be advised to use other protective measures such as insect repellents containing DEET and permethrin products to avoid mosquito bites. The CDC has updated the Vaccine Information Statement (VIS) for yellow fever vaccine to include a caution about vaccinating persons with a history of thymic disease and is available at www.cdc.gov/nip/publications/VIS/#yf. Physicians in the United States are urged to continue to report any possible adverse events to yellow fever vaccine to the United States Vaccine Adverse Event Reporting System (www.vaers.org) or by telephone, 1-800-822-7967. ■

References

1. Kitchener S. Viscerotropic and Neurotropic Disease Following Vaccination With the 17D Yellow Fever Vaccine, ARILVAX. *Vaccine*. 2004;22:2103-2105.
2. Kelleher P, et al. What is Good's Syndrome: Immunologic Abnormalities in Patients With Thymoma. *J Clin Path*. 2003;56:12-16.
3. Hirsch MS, et al. Effects of Antithymocyte Serum on 17-D Yellow Fever Infection in Adult Mice. *Nature*. 1967;216:179-180.
4. Monath T, et al. Prevention of Yellow Fever in Persons Traveling to the Tropics. *Clin Infect Dis*. 2002;34: 1369-1378.
5. World Health Organization. Yellow Fever 1998-1999. *Wkly Epidem Rec*. 2000;75:322-327.
6. World Health Organization. Yellow Fever 1996-1997. Part 1. *Wkly Epidem Rec*. 1998;73:354-359.

TB, BCG, PPD, and Travelers

ABSTRACT & COMMENTARY

Synopsis: *In low-risk populations, positive tuberculin skin tests (TST, purified protein derivative, PPD) might be due to previously received tuberculosis (TB) vaccine (Bacille Calmette-Guerin, BCG), rather than to latent tuberculosis infection. In travelers and other higher risk groups, however, positive tests should suggest infection.*

Source: Tissot F, et al. Influence of Bacille Calmette-Guerin Vaccination on Size of Tuberculin Skin Test Reaction: To What Size? *Clin Infect Dis.* 2005;40:211-217.

The interpretation of tuberculin skin tests is challenging and controversial, especially in the face of previously administered BCG vaccine. In Switzerland, a country where TB infection is not common but where BCG had previously been routinely given, Zysset and colleagues prospectively evaluated 2-step (second test done 8-15 days after the first for possible booster effect) TST results in 5117 hospital employees, in view of potential risk factors for TB infection.

On initial testing, 40% had TST results greater than or equal to 10 mm, and an additional 400 of the 2764, who initially had negative results, were positive on the second-step testing. Thus, a total of 48% had positive results. On multivariate analysis, the influence of BCG vaccination on TST results varied across age categories. Vaccination was the strongest predictor of a positive result up to age 40 years. The influence of BCG vaccination on TST results was less significant when only results of 18 mm or greater were considered. Having been subjected to 5 or more previous TSTs was also an independent risk factor for having a positive result. After careful, statistical analysis, Zysset et al conclude that "except for persons who have never been vaccinated, TST reactions of up to 18 mm in diameter in persons less than 40 years old are more likely to be the result of prior vaccination than of infection, and should not systematically lead to preventive chemotherapy." How do we view such a statement?

■ COMMENT BY PHILLIP R FISCHER, MD, DTM&H

BCG vaccine is effective in decreasing the risk of extra-pulmonary TB, but seems less effective in altering the risk of pulmonary disease.[1] The vaccine is nearly impossible to find in the United States, but immigrants from other countries have often been vaccinated. In fact, BCG vaccination is still routinely used in 161 countries.[2]

The interpretation of TST results is fraught with controversy. Several studies, particularly those done in children in areas of high TB prevalence, suggest that the influence of BCG on TST results is significant, but that it wanes over time.[3,4,5] In the United States, the Centers for Disease Control and Prevention advise that previous BCG vaccination history should not affect the interpretation of a TST result in someone who is at risk of recent infection.[6]

With this in mind, the Swiss data summarized above provide fuel for ongoing discussions. Positive reactions measuring between 10 and 18 mm in young adults seemed to be more likely due to BCG vaccination than to latent infection. Zysset et al's recommendation to limit treatment for latent tuberculosis among these positive individuals seems appropriately data-driven.

Nonetheless, American practitioners of travel medicine are seeing a patient population that is vastly differ-

ent from the group studied in Switzerland. Many of th Swiss subjects in the study had no history of travel to or from an area endemic for tuberculosis, or of exposure to a patient with TB; their only risk factors for positive TST were the BCG vaccination and previous TST. Travel medicine providers typically see patients who have emigrated from TB-endemic areas or who are traveling to and from areas wherein there is significant risk for tuberculosis exposure. Thus, travel medicine providers see individuals with clear-cut risk factors for TB, and attribution of a positive result to a past BCG vaccine would involve discounting the very real possibility of actual TB exposure and infection.

In the same issue of *Clinical Infectious Diseases,* in which the Swiss study appears, Dr. Laurie Miller reviews infectious disease issues relevant to international adoption.[7] She points out that there is no reliable method to distinguish positive TST reactions caused by BCG vaccination from those caused by infection, and reminds readers that experts agree prior vaccination should influence neither the interpretation of these reactions nor the decision of whether to treat the subject. The Swiss might reasonably discuss whether this is true for healthy young adults with no other risk factors, but their data should not change the application of current expert opinion and practice for immigrant children and adults, for international travelers, and for people potentially exposed to someone with active TB. At least in these populations, positive TST results should still prompt further evaluation for active TB and, if no active disease is found, consideration of therapy for latent TB infection, regardless of whether or not the individual received BCG vaccination. ■

References

1. Colditz GA, et al. Efficacy of BCG Vaccine in the Prevention of Tuberculosis: Meta-Analysis of the Published Literature. *JAMA.* 1994;271:698-702.
2. World Health Organization. Vaccines, Immunization, and Biologicals. www.who.int/vaccines/globalsummary/immunization/ScheduleResult.cfm, accessed 3-4-05.
3. Chee CBE, et al. Interpretation of the Tuberculin Skin Test in *Mycobacterium bovis* BCG-Vaccinated Singaporean Schoolchildren. *Am J Respir Crit Care Med.* 2001;164:958-961.
4. Lienhardt C, et al. Risk Factors for Tuberculosis Infection in Sub-Saharan Africa. *Am J Respir Crit Care Med.* 2003;168:448-455.
5. Wang L, et al. A Meta-Analysis of the Effect of Bacille Calmette Guerin Vaccination on Tuberculin Skin Test Measurements. *Thorax.* 2002;57:804-809.
6. American Thoracic Society, Centers for Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *Am J Respir Crit Care Med.* 2000;161:S221-247.
7. Miller LC. International Adoption: Infectious Disease Issues. *Clin Infect Dis.* 2005;40:286-293.

International Adoption in 2005

ABSTRACT & COMMENTARY

Synopsis: *A number of infectious diseases are of special concern to internationally adopted children and their adoptive families. These include infection with HIV, hepatitis B, tuberculosis, syphilis, intestinal parasites, or other pathogens, completion of childhood immunizations, and preparing for international travel.*

Source: Miller LC. International Adoption: Infectious Diseases Issues. *Clin Infect Dis.* 2005;40:186-193.

Dr. Laurie Miller, from New England Medical center in Boston, Massachusetts, reviewed many aspects of international adoption that specialists in infectious diseases and international adoption medicine may encounter. The pediatric infectious disease consultant may be asked to interpret pre-adoption medical and vaccination records, screen the adopted children after arrival, and care for the children when infectious diseases are suspected or diagnosed. Infectious disease consultants may also be asked to prepare families for their travel to meet the child.

Dr. Miller identified some common issues in reviewing pre-adoption medical records, pre-travel evaluations, post-arrival infectious disease screening, and management of immunizations, and highlighted some infectious diseases diagnosed after arrival in the United States (*see Table 1*).

■ COMMENT BY LIN H. CHEN, MD

Several studies have analyzed results of screening for infectious diseases in internationally adopted children. Dr. Miller's review sums up the data from these studies, and formulates clinically relevant approaches to these diseases. Dr. Miller's experience, from evaluating international adoptees, has led to some helpful reflections. For example, she noted that medical records from South Korea have been excellent, and immunization records are probably reliable; immunization records from Guatemala

Table 1

Infectious diseases in internationally adopted children after arrival in the United States.

Disease	Risk of disease in international adoptee	Recommendation
HIV	Risk: low. 0.16% of children evaluated in 17 international adoption clinics from 1990-2002 were infected.	Screen for HIV-1 and HIV-2 on arrival; consider repeat testing 6 months after arrival; consider PCR test for HIV DNA in children < 6 months old.
Hepatitis B	Risk: significant. 5% of international adoptees were infected; highest rates among Romanian adoptees.	Screen with hepatitis B surface antigen, core antibody, and surface antibody; retest 6 months later.
Hepatitis C	Risk: low. Tests may be inconclusive due to the presence of maternal antibodies, delayed seroconversion, and false-positive ELISAs.	Screen for hepatitis C antibodies by ELISA.
Hepatitis A	Risk: present	Screen to assess the need for hepatitis A immunization in children with hepatitis B or C.
Syphilis	Risk: significant. 15-20% pre-adoption records from former Soviet Union listed congenital syphilis. Undiagnosed, untreated congenital syphilis have been discovered in adoptees, most commonly from China and Central America.	Screen with RPR (+/- FTA). Repeat screening when 10-12 weeks old, for children adopted at < 3 months of age. Serial evaluations for children with a history of treated congenital syphilis until 12 months old.
Intestinal parasites	Risk: significant. 25% of internationally adopted children are found to have intestinal parasites after arrival, although South Korean children are rarely infected. *G. lamblia* is the most frequently identified, but *E. histolytica*, *D. fragilis*, *A. lumbricoides*, *T. trichiura*, hookworms, and *S. stercoralis* are also found often. Infection may be associated with growth delay and anemia.	Screen for ova and parasites with 3 stool samples. Follow-up samples after treatment. Retest if symptoms develop later.
Bacterial enteric pathogens and *H. pylori*	Risk: present. Increased risk for *H. pylori* in children from orphanages.	Evaluate gastrointestinal symptoms for enteric pathogens. Evaluate symptoms of dyspepsia, abdominal pain, growth delays, or anemia for *H. pylori* infection.
Tuberculosis	Risk: significant. 5-20% of international adoptees have positive Mantoux test at arrival. History of BCG vaccination should not influence the interpretation of Mantoux test results or the decision to treat.	Screen with Mantoux test at arrival. Consider retest 6 months later. If test result is ≥10 mm, obtain chest radiograph and evaluate for active tuberculosis. In children with known exposure or immunosuppresion, test result of ≥ 5 mm are considered positive.
Skin infections	Risk: present. mpetigo, molluscum contagiosum, and scabies are common.	Empiric treatment with topical permethrin can decrease household spread of scabies.
Others: malaria, *P. jiroveci* pneumonia, tungiasis, leprosy	Risk: uncommon	Evaluate if symptoms are present.

and India may also be acceptable. Similarly, adoptees from South Korea were rarely infected with intestinal parasites.

Dr. Miller recommends screening for hepatitis A to assess the need for immunization in children with hepatitis B or C. Medical providers should keep in mind that children may be asymptomatic shedders of hepatitis A virus, and most internationally adopted children come from intermediate to high endemicity regions for hepatitis A. One case report documented a probable transmission of hepatitis A from a child adopted from Russia to the adoptive father,[1] although screening for hepatitis A in newly arrived international adoptees is usually not necessary. Adoptive family members should be cautioned about hepatitis A, and preventive strategies including good hand hygiene and immunization.

Dr. Miller also summarized immunization issues in international adoptees. A number of studies have found low antibody levels against vaccine-preventable diseases, sometimes in spite of documented immunizations.[2-5] Many children have incomplete immunization records, especially adoptees from China as reported by Dr. Miller. On the other hand, some international adoptees have demonstrated adequate antibody levels to diphtheria and tetanus.[6] The decision to repeat immunizations versus testing for antibodies to vaccine-preventable diseases in international adoptees has been debated. The American Academy of Pediatrics has recommended using a combination of antibody testing and repeat immunizations.[7] Dr. Miller recommends testing for antibodies to diphtheria, tetanus, and poliovirus serotypes 1-3 to verify immunity. These strategies continue to be evaluated, and cost-effectiveness data should help to define the best approach to fulfill the recommended childhood immunizations in internationally adopted children. ■

References

1. Wilson ME, et al. Post-Travel Hepatitis A: Probable Acquisition From an Asymptomatic Adopted Child. *Clin Infect Dis.* 2001;33:1083-1085.
2. Hostetter MK, et al. Immunization Status of Adoptees From China, Russia, and Eastern Europe. *Pediatric Research* 1998;43:147a. Abstract #851.
3. Schulpen TWJ, et al. Immunisation Status of Children Adopted From China. *Lancet.* 2001;358:2131-2132.
4. Miller LC, et al. Immunization Status of Internationally Adopted Children. *Pediatrics.* 2001;108:1050-1051.
5. Miller LC. Internationally Adopted Children—Immunization Status [letter]. *Pediatrics.* 1999;103:1078.
6. Staat MA, et al. Immunization Verification in Internationally Adopted Children. *Pediatric Research.* 2001;49:468A. Abstract #2680.
7. American Academy of Pediatrics—2000 *Red Book*. Report of the Committee on Infectious Diseases. Pickering LK, et al. Elk Grove Village, IL; American Academy of Pediatrics. 2000.

2004 Resort Malaria in the Dominican Republic

ABSTRACT & COMMENTARY

Synopsis: *Until November 2004, urban and resort areas of the Dominican Republic had been considered free of malaria. Seventeen cases of* P. falciparum *malaria, including 3 US travelers described here, have led to an expansion of CDC malaria recommendations. Chloroquine prophylaxis is indicated for travel, not only to rural areas of the Dominican Republic, but also the far eastern region resort areas of La Altagracia province (ie Punta Cana) and Duarte Province.*

Source: Transmission of Malaria in Resort Areas—Dominican Republic, 2004. *MMWR.* 2005;53:1195-1198.

THE CENTERS FOR DISEASE CONTROL BEGAN RECEIVING reports of *P. falciparum* malaria in US travelers to the Dominican Republic during the third week of November 2004. All 3 US cases were characterized by severe disease, with need for ICU care. None of these individuals had traveled to areas considered malarious, and none had received blood transfusions in the previous year.

Case 1: A 47-year-old female was admitted to an ICU in the United States with multi-organ system failure, acute respiratory distress syndrome, and renal failure after a 6-day period of fever, chills, abdominal pain, headache, nausea, and vomiting. Symptoms began 24 hours after returning from a 1-week stay in an all-inclusive resort in Punta Cana, La Altagracia Province. Outpatient examinations were unrevealing, until 2 days prior to admission when she had jaundice. The patient was obtunded on admission, and a 35% *P. falciparum* parasitemia was detected, as well as anemia, leukocytosis, and profound thrombocytopenia (5000/dl). After 2 days of intravenous quinidine gluconate, the parasitemia cleared and, on day 5, quinidine was discontinued, as she was placed on doxycycline. She underwent hemodialysis for renal failure and improved. She was discharged to a rehabilitation center and remained there

as of December 30, 2004.

Case 2. A 71-year-old man presented to an emergency department in Canada, 10 days after returning from a week at a resort in Punta Cana, complaining of fever, myalgias, and malaise. He was diagnosed with viral syndrome, discharged, was also seen as an outpatient, and told he had a viral syndrome. On day 6 of symptoms, he was admitted with hypotension, hypoxia, acute renal failure, and respiratory failure requiring mechanical ventilation. Blood smears on day 2 of his admission showed a 9% *P. falciparum* parasitemia. He received intravenous quinidine gluconate and doxycycline and underwent hemodialysis. He reported no travel other than a day trip to Santo Domingo, and remained hospitalized as of December 30, 2004.

Case 3. A 39-year-old man was admitted to an ICU in Canada 12 days after he returned from a resort in Punta Cana, where he had stayed for 2 weeks. His course was complicated by anemia, acute respiratory distress syndrome, acute renal failure, and cerebral malaria. He underwent exchange transfusion.

P. falciparum parasitemia was 2% on day 2 of his admission, and he was treated with chloroquine and quinine. His course was complicated by anemia, acute respiratory distress syndrome, acute renal failure, and cerebral malaria. He underwent exchange transfusion.

COMMENT BY MARIA D. MILENO, MD

Plasmodium falciparum is the only malaria species present in the Dominican Republic. Although it is fortunate that it still remains sensitive to chloroquine, *P. falciparum* is rapidly fatal and warrants intensive education of travelers regarding prevention of insect exposures, chemoprophylaxis with chloroquine, and complete discussions on when to seek care. Given the severity of the cases reported above, it is also quite fortunate that no deaths resulted. Seventeen cases were reported in total, in 3 US, 6 Canadian, and 8 European travelers. Annually in the Dominican Republic there are an average of 1500-2500 malaria cases. This most recent outbreak in the resort areas is not the only one that has occurred there. Another outbreak occurred from July 1999 to March 2000 in the wake of hurricanes Mitch and George, at which time increased breeding patterns of *Anopheles albimanus* mosquitoes were noted. In September 2004, hurricane Jeanne struck the Dominican Republic with heavy rains that flooded Punta Cana and the Bavaro Zone, areas that have also utilized numerous malaria-infected migrant workers for construction projects.

This is one example of how environmental events can change the locations of known malaria transmission areas. It is possible and quite concerning that new areas of drug-resistant malaria transmission may develop in regions affected by the recent Asian tsunami, as mosquito-breeding patterns may have been altered. Effective surveillance systems and rapid communication among networks are crucial to detect and intervene in cases of malaria in areas previously deemed nonmalarious. ■

Efficacy of Oral Cholera Vaccine

ABSTRACT & COMMENTARY

Synopsis: *Orally administered cholera vaccines have offered the promise of controlling cholera epidemics during prior studies in Bangladesh.[1,2] However, the high prevalence of HIV co-infection in sub-Saharan Africa has raised doubts about the level of protection an oral cholera vaccine could generate in this setting.*

Source: Lucas M, et al.Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *N Engl J Med.* 2005; 352:757-767.

THIS ARTICLE EVALUATES A MASS IMMUNIZATION program with recombinant cholera-toxin B subunit, killed whole cell (rBS-WC) cholera vaccine in Beira, Mozambique, a city where seroprevalence of HIV infection is 20-30%. Lucas and colleagues, 5 of whom were associated with the Ministry of Health in Mozambique, were able to mass immunize (2-dose regimen) approximately 19,550 non-pregnant individuals over 2 years of age before the anticipated cholera outbreak that coincides with every rainy season. Seroprevalence for HIV amongst pregnant women in this area is known to be 20 -30%. Each dose of the rBS-WC vaccine (Dukoral, SBL Vaccines) consisted of recombinant cholera-toxin B subunit and approximately 1 x 10" inactivated whole cells of the classic and El Tor biotypes of Vibrio cholerae 01, serotypes of Inaba and Ogawa. Surveillance for cholera was then begun at the Cholera Treatment Center in Beira, where all cases of acute non-bloody diarrhea requiring medical care are referred. The total population of Beira is 450,000. A case-control study was conducted during the predicted outbreak of El Tor, Ogawa, for this particular year, by recruiting neighborhood controls of the same sex and age living next to the case subject's house. To estimate the level of vaccine protection, antecedent rates of vaccination were compared between persons with culture-confirmed cholera, severe enough to seek treatment, and age and sex-matched neighborhood controls without diarrhea. Receipt of 1 or more

doses of rBS-WC vaccine was associated with 78% protection (95 % CI, 39-92%; P = .004). The vaccine was equally effective in children younger than 5 years of age and in older persons.

COMMENT BY MICHELE BARRY, MD

This is an ambitious landmark study of a cholera vaccine that appears to be highly protective against a severe form of disease necessitating medical treatment in a highly impacted HIV area in sub-Saharan Africa. Here, periodic flooding, difficult access to safe water, and the common practice of open defecation and drainage of municipal waste into water supplies contribute to epidemic cholera. Although this study did not include HIV testing, and vaccine protection could not be directly evaluated in such a population, the seroprevalence rate for HIV infection of 20-30% of pregnant women in this area indicates that this vaccine likely offered significant protection for HIV-infected persons. In addition, the safety of this oral vaccine in an HIV population can be inferred. No clinically significant adverse reactions to the vaccine were reported during the mass immunization campaign. In prior trials in Sweden, Brazil, and Kenya, the vaccine was not associated with adverse reactions or progression of HIV disease, although a transient increase in HIV viremia was observed in one study.[3]

Of interest to travel medicine practitioners, a parallel case-control study was performed of non-choleraic diarrhea presenting for medical treatment. There was no evidence that the vaccine conferred any protection against non-choleraic diarrhea 3 months after oral cholera vaccination. This is an intriguing finding given that rBS-WC has been shown to provide cross-protection against heat-labile toxin producing *E. coli*, albeit only for a few months after vaccination.[4] However, no cultures were reported for ETEC, and all these cases were severe enough to be referred for medical treatment. Perhaps they simply do not reflect prevention of mild disease.

References

1. Clemens JD, et al. Field Trial of Oral Cholera Vaccines in Bangladesh. *Lancet.* 1986;2:124-127.
2. Clemens JD, et al. Field Trial of Oral Cholera Vaccines in Bangladesh: Results From 3-Year Follow-Up. *Lancet.* 1990;335:270-273.
3. Ortigao-de-Sampaio MB, et al. Increase in Plasma Viral Load After Oral Cholera Immunization of HIV-Infected Subjects. *AIDS.* 1998;12:F145-F150.
4. Peltola H, et al. Prevention of Travellers' Diarrhea By Oral B-Subunit/Whole-Cell Cholera Vaccine. *Lancet.* 1991;338-1285-1289.

CME Questions

3. Which one of the following statements regarding yellow fever is correct?

a. Yellow fever vaccine associated viscerotropic disease (YEL-AVD) occurs in approximately 1:2000 vaccine recipients.
b. Thymectomy or thymic dysfunction appears to be an independent risk factor for YEL-AVD.
c. YEL-AVD is always fatal.
d. Travel to South America is associated with a higher risk of yellow fever than travel to Africa.

4. In an immigrant or returned international traveler, tuberculin skin test results greater than 10 mm:

a. should be ignored if the individual received BCG vaccination.
b. should not stimulate further evaluation unless the result is > 18 mm.
c. are only worrisome if the individual is older than 40 years old.
d. should be interpreted without regard to BCG vaccination history.

5. The following statements regarding infectious diseases in internationally adopted children is correct:

a. Immunization records of international adoptees are usually accurate and reliable.
b. International adoptees should routinely be screened for tuberculosis, HIV-1, and HIV-2 at arrival.
c. International adoptees have been immunized against hepatitis B, therefore should be exempt from hepatitis B testing after arrival.

6. Which statement characterizes *P. falciparum* malaria in the Dominican Republic best?

a) It is a new endemic species, recently documented in the Dominican Republic.
b) It has less pathogenic potential, given that it is still sensitive to chloroquine.
c) It is currently located only in certain focal, rural areas of the Dominican Republic.
d) It is multi-drug-resistant in the Dominican Republic.
e) It is a fatal form of malaria found in both rural areas and resort areas; it remains chloroquine-sensitive.

7. Which one of the following statements regarding oral cholera vaccine is true?

a. Oral cholera vaccine provides herd protection for a population with a high seroprevalence of HIV in sub-Saharan Africa.
b. Oral cholera vaccine provides some protection for ETEC diarrhea, but only for 6 months after administration.
c. Oral cholera vaccine is effective in young children living in a high HIV impact area.
d. Oral cholera vaccine may revert to pathogenicity in areas where there is a high HIV prevalence.

Answers: 3. (b); 4. (d); 5. (b); 6. (e); 7. (c)

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.*

Preparing for the Possibility of a Bird Flu Pandemic

The possibility of a bird flu pandemic has health officials worldwide in a high state of alert. The highly pathogenic avian influenza A virus is responsible for the death of more than 100 million birds in Southeast Asia, but less than 100 cases have been documented in humans, and only 2 of those have been from human-to-human contact. Still, influenza A viruses are known to undergo an antigenic shift periodically, marking an abrupt change in the viral genome. It is the possibility of a mutation that has health officials concerned. If the virus suddenly became infectious in human populations, the resulting pandemic could kill millions, as similar avian influenza virus pandemics did in 1968, with one to four million deaths, and 1918, when the avian flu pandemic killed as many as 50 million people. The World Heath Organization is urging all countries to develop or update their influenza pandemic preparedness plans. From a pharmaceutical perspective, the WHO has singled out oseltamivir (Tamiflu) as the treatment of choice to reduce symptoms and prevent spread of avian influenza. Roche Holding AG, the makers of oseltamivir, recently announced that Britain and the United States are discussing large purchases of the drug, with the intent of stockpiling supplies for a potential avian influenza outbreak. Other governments around the world have been stockpiling the drug as well, and Roche is increasing its production capacity to meet the additional demand.

Amoxicillin-Clavulanate vs Ciprofloxacin

The search for effective antibiotics to treat common infections is a high priority, given increasing resistance patterns for many commonly used antibiotics. This was the basis for a new study by researchers at the University of Washington, in which they compared ciprofloxacin to amoxicillin-clavulanate in women with uncomplicated cystitis. The study was driven by an increasing rate of resistance to trimethoprim-sulfa and other antimicrobials among *E. coli* strains causing acute cystitis in women. While ciprofloxacin is a common alternative, amoxicillin-clavulanate has not been well studied. In a randomized, single-blinded trial, 370 women aged 18 to 45 with symptoms of acute uncomplicate cystitis with a positive urine culture were randomized to amoxicillin-clavulanate 500/125mg twice daily or ciprofloxacin to 250 mg twice daily for 3 days. Clinical cure was observed in 58% of women treated with amoxicillin-clavulanate, compared with 77% of women treated with ciprofloxacin ($P < .001$). Amoxicillin-clavulanate was not as effective as ciprofloxacin, even among women infected with *E. coli* strains suscepti-

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) 262-5416. E-mail: leslie.hamlin@ thomson.com.

ble to amoxicillin-clavulanate. At follow-up visits 2 weeks after treatment, 45% of women in the amoxicillin-clavulanate group had vaginal colonization with *E. coli*, compared to only 10% in the ciprofloxacin group ($P <$ .001). The authors point out that *E. coli* resistance is an increasing problem worldwide, especially with trimethoprim-sulfa. However, resistance is also been seen with fluoroquinolones including ciprofloxacin. Amoxicillin-clavulanate was chosen in the study in the hopes of finding an effective fluoroquinolone-sparing antibiotic for the treatment of uncomplicated cystitis. Unfortunately, amoxicillin-clavulanate is not a reliable option and alternatives will need to be found (*JAMA.* 2005;293:949-955).

AD Therapy and Cognitive Function

Men with prostate cancer who note worsening cognitive function in the early stages of androgen deprivation (AD) therapy should consider that the change is due to the treatment not the disease, according to new study published online in the "Early View" section of *Cancer*. Researchers from Finland followed 23 men undergoing AD for prostate cancer. Thirty-one cognitive tests were performed at baseline, 6 months, and 12 months into therapy. Testosterone and estradiol locals were followed throughout treatment. Visual memory of figures in recognition speed of numbers were significantly impaired at 6 months. Surprisingly, some men with the lowest change in estradiol levels had an improvement in verbal fluency and 12 months. The author suggests that cognition may be adversely affected during androgen deprivation (*Cancer*-published online 2/16/05).

LDL Lowering in CHD Patients

An LDL target in the 70s for CAD patients may become the standard, as evidence continues to mount for the benefit of intensive cholesterol lowering. The latest study from the "Treating to New Targets" or TNT investigators looked at 10,000 patients with stable coronary disease and LDL levels less than 130. Patients were randomized to atorvastatin 10 mg/day (low dose) or 80mg/day (high dose) and were followed for an average of 4 years. Mean LDL cholesterol was lowered to 101 mg/dL in the low-dose group and to 77 mg/dL in the high-dose group. Persistent elevations in liver enzymes was more common in the high-dose group (0.2% low dose, 1.2 % high dose [$P <$ .001]). The study end points were cardiovascular events including death from CHD, nonfatal MI, resuscitation after cardiac arrest, or stroke (fatal or nonfatal). A primary event occurred in 548 patients in the low-dose group (10.9%) and 434 patients in the high-dose group (8.7%) for a 2.2% absolute rate reduction (HR, 0.78; 95% CI, 0.69-0.89; $P <$ .001). There was a higher death rate from noncardiovascular causes in the high-dose treatment group, and no difference in overall mortality. There were no trends in the noncardiovascular deaths, specifically no higher rate of cancer or violent deaths. The authors conclude that aggressive LDL lowering is warranted in CHD patients (*N Engl J Med*-published online March 2005). An accompanying editorial suggests more caution, stating, "Patients and their physicians will need to carefully weigh the benefits or a reduction in the risk of cardiovascular events. . . against the uncertainty of an increase in the risk of death from noncardiovascular causes" (*N Engl J Med*-published online March 2005).

FDA Actions

The FDA and federal marshals from the Department of Justice have seized Paxil CR and Avandamet tablets manufactured by GlazxoSmithKline at its plants in Knoxville, TN, and Puerto Rico. The FDA stated that the seizures were prompted by violations of manufacturing standards that resulted in the production of poor quality drug products, including tablets that could split apart and tablets that had inaccurate doses of the active ingredient.

In late February, the FDA issued a public health advisory regarding nataluzimab (Tysabri), Biogen's recently approved drug for the treatment of relapsing forms of multiple sclerosis. Marketing of the drug has been suspended while the agency and the manufacturer evaluate 2 cases of progressive multifocal leukoencephalopathy in MS patients who were using the drug, one of which resulted in death. Nataluzimab received accelerated approval in November 2004, and 8000 patients have received the drug, including 3000 who received it during clinical trials. ■