TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media LLC

INSIDE

Volume 17, No. 10
October 2007

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson.Peer reviewers Mary-Louise Scully, MD, and Lin Chen, MD, report no financial relationships relevant to this field of study.

BinaxNOW Malaria Rapid Diagnostic Test

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

Assistant Clinical Professor, Harvard Medical School; Director Travel Resource Center, Mount Auburn Hospital, Cambridge, MA

Dr. Lin H. Chen reports no financial relationship relevant to this field of study.

Synopsis: *The US FDA approved the BinaxNOW Malaria Test, making it the first rapid diagnostic test for malaria available in the United States.*

Source: http://www.binax.com/NOWmalaria.shtml, http://binax.com/uploads/binaxnowmalaria-productinsert6_2007.pdf.

THE DIAGNOSIS OF MALARIA HAS TRADITIONALLY RELIED UPON microscopy. However, microscopic diagnosis is labor intensive, somewhat subjective, and assurance of quality standards can be difficult at best. The BinaxNOW Malaria Test is an immunochromatographic assay that uses monoclonal antibodies to detect malaria antigens, including both the aldolase enzyme present in all Plasmodium species and more specifically the histadine-rich protein 2 (HRP-2) of *Plasmodium falciparum.* The test requires whole blood obtained by either venipuncture or fingerstick, and must be performed immediately following sample collection, although blood can be refrigerated for up to 3 days. The test kit contains a dipstick card to which the blood sample is applied (about 15µl), followed by the addition of a reagent, and it is read after 15 minutes. The appearance of lines indicates the adequacy of test, presence of *P. falciparum*, or presence of other plasmodial species.

The manufacturer reports overall test sensitivity to be 99.7% for *P. falciparum* and 93.5% for *P. vivax*, and specificity to be 94.2% for *P. falciparum* and 99.8% for *P. vivax*. In an endemic population, a comparison of the BinaxNow Malaria Test against microscopy has demonstrated sensitivities of 99%-100%: 99.7% for *P. falciparum* and 81-82% for *P. vivax*, and specificities of 90%-95% for *P. falciparum* and 99%-100% for *P. vivax*. In a non-endemic population, the test demonstrated a 100% sensitivity and specificity for *P .falciparum* and 99% sensitivity and specificity for *P. vivax*. The test shows cross-reactivity with rheumatoid factor and human anti-mouse antibody (HAMA).

COMMENTARY

Rapid diagnostic tests (RDTs) for malaria have been advocated for use as field tests,[1] and some tests have been available for use in hospitals and laboratories in Europe. A number of RDTs based on assays for HRP-2 and/or parasite

LDH have been evaluated in the diagnosis of febrile returning travelers.[2-6] One study that tested the NOW Malaria Test demonstrated sensitivity and specificity of 96.4% and 97%, respectively in returned travelers in France.[6] Other investigators found that the test had better sensitivity when used in a microbiology laboratory than at bedside.[7] A study on non-European immigrants and travelers found that the NOW Malaria rapid test was both sensitive (100%) and specific (100%) in detecting *P. falciparum* infections; however, it was less specific (93.1%) and sensitive (90.7%) for identifying the other Plasmodium species.[8]

One significant drawback of the RDTs is that the parasite HRP-2 persists in the circulation for some time.[9] Following effective treatment for malaria, a significant proportion of RDTs were false-positive at day 14 (98.2%), day 21 (94.6%), day 28 (92.0%), and day 35 (73.5%).[10] The persistence of these positive results would limit its use in evaluating patients who have had recent malaria infections. Some test results cannot be interpreted because of interfering antibodies, which are known to occur in the presence of rheumatoid arthritis and human anti-mouse antibodies (HAMA), and possibly with other, yet unidentified, inhibitors.[11] Additionally, there is concern that RDTs may need to be stored in cool conditions, and storage in the tropics may affect test reliability.[12] The manufacturer states that BinaxNow Malaria Tests stored at 2° - 37° Celsius remain stable until their date of expiration.

Some investigators have also evaluated RDTs for self-diagnosis of malaria by travelers.[13-15] One study found 20.6% of tests were incorrectly interpreted with 14.1% false negative interpretations.[13] Other investigators found high false-negative interpretations on samples with high parasitemia (>2% parasitemia) tested with 2 different RDTs (MalaQuick and ParaSight), where 96.8% and 33.8% of tests, respectively, were correct interpretations.[14] Both tests were associated with high levels of false-negative interpretations. One study had promising data to support self-diagnosis, but still showed 9% failure to perform test accurately.[15] Such tests are *not* currently indicated for use by travelers. For now, RDTs can be a useful diagnostic tool for field work, and also in practices that do not have reliable microscopy. ■

References:

1. Murray CK, et al. Rapid diagnostic testing for malaria. *Trop Med Int Health*. 2003 Oct;8(10):876-883.
2. Uguen C, et al. ParaSight-F rapid manual diagnostic test of *Plasmodium falciparum* infection. *Bull World Health Organ*. 1995;73(5):643-649.
3. Humar A, et al. Parasight F test compared with the polymerase chain reaction and microscopy for the diagnosis of *Plasmodium falciparum* malaria in travelers. *Am J Trop Med Hyg*. 1997 Jan;56(1):44-48.
4. Ricci L, et al. Evaluation of OptiMAL Assay test to detect imported malaria in Italy. *New Microbiol*. 2000 Oct;23(4):391-398.
5. Palmer CJ, et al Multicenter study to evaluate the OptiMAL test for rapid diagnosis of malaria in U.S. hospitals. *J Clin Microbiol*. 2003 Nov;41(11):5178-5182.
6. Durand F, et al. Performance of the Now Malaria rapid diagnostic test with returned travellers: a 2-year retrospective study in a French teaching hospital. *Clin*

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. Application to mail at periodicals postage rates is pending at Atlanta, GA 30304. 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 $9.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions. For pricing information, call Tria Kreutzer at (404) 262-5482.

Microbiol Infect. 2005 Nov;11(11):903-907.
7. Wiese L, et al. Bedside diagnosis of imported malaria using the Binax Now malaria antigen detection test. *Scand J Infect Dis.* 2006;38(11-12):1063-1068.
8. Gatti S, et al. A comparison of three diagnostic techniques for malaria: a rapid diagnostic test (NOW Malaria), PCR and microscopy. *Ann Trop Med Parasitol*. 2007 Apr;101(3):195-204.
9. Grobusch MP, et al. Comparison of three antigen detection tests for diagnosis and follow-up of falciparum malaria in travellers returning to Berlin, Germany. *Parasitol Res*. 2003;89:354-357.
10. Swarthout TD, et al. Paracheck-Pf accuracy and recently treated Plasmodium falciparum infections: is there a risk of over-diagnosis? *Malar J*. 2007 May 16;6:58.
11, Durand F, et al. Invalid result of *Plasmodium falciparum* malaria detection with the BinaxNOW Malaria rapid diagnostic test. *J Med Microbiol* 54 (2005), 1115
12. Jorgensen P, et al. Malaria rapid diagnostic tests in tropical climates: the need for a cool chain. *Am J Trop Med Hyg*. 2006 May;74(5):750-754.
13. Trachsler M, et al. Feasibility of a rapid dipstick antigen-capture assay for self-testing of travellers' malaria. *Trop Med Int Health.* 1999 Jun;4(6):442-447.
14. Funk M, et al. MalaQuick versus ParaSight F as a diagnostic aid in travellers' malaria. *Trans R Soc Trop Med Hyg*. 1999;93:268-272.
15. Whitty CJM, et al. Self-testing for falciparum malaria with antigen-capture cards by travelers with symptoms of malaria. *Am J Trop Med Hyg*. 2000;63:295-297.

Cholera Cases: Past, Present, and Future

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

Director, Travel and Tropical Medicine Center, Sansum Clinic, Santa Barbara, CA

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

Synopsis: *Although imported cholera cases in developed countries such as France may continue to decline, the global number of cholera cases continues to rise at an alarming rate. Orally administered cholera vaccine may hold promise in controlling cholera epidemics.*

Source: Tarantola A, et al. Retrospective analysis of the cholera cases imported to France from 1973 to 2005. *J Travel Med* 2007; 14(4):209-214.

THIS RETROSPECTIVE ANALYSIS REVIEWS DETAILS OF the 129 proven cholera cases imported to France between January 1, 1973, and December 31, 2005. All strains were identified as *Vibrio cholerae* serogroup 01. The peak years of activity were 1980-1989, when most patients acquired their illness while visiting Morocco and Algeria, likely as a result of immigrants returning to these countries to visit friends and relatives. This trend disappeared, resulting in no further cases from Morocco or Algeria after the year 2000, as these countries essentially became cholera free. Since 1996 the geographic sources of imported cholera acquisition in France have been travel to Africa, mostly West Africa, or Asia.

The mean age of patients was 35 years, but during 1980-1999 there was a relatively higher proportion of imported cases in the younger ages (0-15) and older patients (over 66). The majority of patients (82%, n = 57) required hospitalization and a total of 2 deaths occurred. There was a significant seasonality with 82% of cases being reported between May and September. Cholera cases were reported from a wide variety of regions in France, and not just the larger cities with significant immigrant populations, such as Paris, Lyon, or Marseilles. In addition, the diagnosis of imported cholera was increasingly made in the nonteaching hospitals of France.

COMMENTARY

The historical trend of imported cholera cases in French travelers, initially after travel to Morocco and Algeria, but more recently after travel to other areas of Africa and Asia, is consistent with the pattern for global cases reported to the World Health Organization (WHO). The number of imported cholera cases is small relative to the impressive numbers reported from endemic areas. In 2006, the number of cholera cases reported to the WHO soared to 236,896, up from 131,943 cases in 2005 (overall increase of 79%).[1] The majority of cases were from Africa (234,349 cases), followed by Asia (2,472), with India reporting most of the Asian cases (1,939 cases). A total of 33 countries in Africa reported cholera cases, but the African countries with the greatest burden of disease were Angola, Ethiopia, Sudan, and Democratic Republic of the Congo. Together, these 4 countries alone reported 186,928 cases with 4,988 deaths. The United Republic of Tanzania had an almost 5-fold increase in cases compared to 2005 with 14,297 cases. Malawi, Mozambique, Zambia, and Zimbabwe all reported increased numbers of cholera cases in 2006.

Despite these impressive numbers, the WHO estimates that cholera cases remain underreported. One reason is that not all countries consistently report cholera cases to the WHO. For example, several cholera outbreaks in 2004 on the Indian continent and Southeast Asia (Bangladesh, Myanmar, and Pakistan) occurred, yet they were not reported to the WHO.[2] Another reason for underestimation of cholera is that milder cases may not seek medical care, and a stool specimen may not be obtained. Lastly, the fear that negative publicity regarding a cholera outbreak will adversely affect the tourism industry in a developing country may also contribute to underreporting.

Orally administered cholera vaccine (OCV) offers some promise in controlling cholera epidemics. A mass immunization program using an oral, inactivated, whole cell, recombinant vaccine cholera toxin B subunit (WC-rBS)) for 19,550 non-pregnant individuals in Beira, Mozambique was associated with 78% protection.[3] The WHO has now prequalified this vaccine (Dukoral™) for use in the setting of cholera outbreaks. Two doses (3 doses for children ages 2-6) are given at least one week apart. Booster doses are given after 2 years for children older than 6 years and adults but children 2-6 years are given a booster after 6 months. This vaccine is also licensed for short-term protection (< 3 months) against diarrhea caused by ETEC (enterotoxigenic *Escherichia coli*). The vaccine is available in the UK, Canada, and many other countries such as Peru, Thailand, and Sweden, but is not yet available in the United States.

Countries without access to safe water and basics of adequate sanitation will remain at risk for epidemic cholera disease. The latest country to be added to the list is Iraq with 3,182 cases of watery diarrhea, suspected as cholera, 9 deaths, and 283 stool isolates of *Vibrio cholera* reported by health official from just 5 out of 11 districts of Sulaymaniyah Governate as of September 6, 2007.[4,5] The outbreaks are occurring in the Kurdish province of Sulaimaniyah and Kirkuk. Health officials in Iraq suspect the source of the outbreak is cracked water pipes that had allowed contamination by sewage. Unfortunately, the political instability of this war-torn country, the disruption of the existing infrastructure, the dwindling number of health care providers, and the lack of safe drinking water, are perfect ingredients for epidemic cholera disease. ■

References:

1. WHO. Cholera, 2006. *Wkly Epidemiol Rec*. 2007; 82:273-284.
2. Zuckerman JN, et al. The true burden and risk of cholera: implications for prevention and control. *Lancet Infect Dis*. 2007; 7:521-530.
3. Lucas ME, et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *N Eng J Med*. 2005; 352:757-767.
4. Major cholera outbreak hits northern Iraq. Reuters Health Information, August 29, 2007. http://www.reutershealth.com/archive/2007/08/29/eline/links/20070829elin012.html (accessed August 30.2007)
5. Cholera, Diarrhea and Dysentery Update 2007. ProMed-mail 2007; 10 Sept: 20070910.2989. http://promedmail.org. Accessed 10 September 2007.

Uncomfortable in Airplanes

ABSTRACT AND COMMENTARY

By Philip Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Division of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

Dr. Fischer reports no financial relationship relevant to this field of study.

Synopsis: *Seven percent of long-haul air travelers have symptoms compatible with acute mountain sickness, and others have significant atmospheric pressure-related discomfort. Mild decreases in oxygen saturation relate to some of the discomfort.*

Source: Muhm JM, et al. Effect of aircraft-cabin altitude on passenger discomfort. *N Engl J Med* 2007;357:18-27.

Acute mountain sickness occurs in travelers to high altitudes and consists of symptoms such as headache, nausea, malaise, loss of appetite, and poor sleep. The incidence of acute mountain sickness increases with rapid ascent. At higher altitudes, the severity of symptoms seems to relate with decreased oxygen saturations in a low-pressure, low-oxygen atmospheric environment.

Some travelers experience symptoms similar to those of acute mountain sickness during long commercial air flights, even though the aircraft cabins are pressurized to approximate altitudes of no more than 8,000 feet. A collaborative group of researchers, including some at the Boeing Company, studied the effects of barometric pressure on discomfort during simulated 20-hour flights.

A total of 502 adult subjects who had not experienced significant recent altitude or air travel exposures during the preceding month participated in the study. A hypobaric chamber simulated conditions during a 20-hour commercial flight (with meals, movies, and seating typical of an air trip). Some participants were randomly assigned to an exercise protocol, with 10 minutes of walking each hour during the first 9 "flight" hours. Symptoms were assessed using the

Environmental Symptoms Questionnaire IV, one of the standard measures of acute mountain sickness.

Oxygen saturations decreased with increasing simulated altitude with a 4.4% drop in the group simulating 8,000 feet altitude. Seven percent of subjects qualified for a diagnosis of acute mountain sickness, and this incidence did not vary between altitude groups (4,000, 6,000, 7,000, and 8,000 feet). Malaise, muscle discomfort, and fatigue were more common at 8,000 feet than at other simulated altitudes. Discomfort was inversely related to oxygen saturation. Women were more likely than men to report discomfort, and older individuals were least likely to report discomfort. Exercise was associated with a reduced prevalence of muscle discomfort, but it did not affect other symptomatic outcomes.

COMMENTARY

There are many mechanisms by which people feel uncomfortable during long air flights. The Boeing study summarized here suggests that acute "mountain" sickness might indeed be a source of discomfort on airline flights.

Acute mountain sickness occurs largely at very high altitudes. But, more than 20% of travelers are reported to have symptoms of this condition even at lower elevations (6,500 feet).[1] The data summarized here indicate that identical symptoms can develop with prolonged air travel, at least in a simulated setting. As at altitude, symptoms in aircraft are linked to oxygen desaturations occurring over time. It is likely that the physiology of acute mountain sickness combines both hypoxia and gradual pressure-related fluid shifts, Similar changes could take place in aircraft, as well as on the ground, at simulated altitudes.

Muscular discomfort was much more prevalent at 8,000 feet altitude (10%-15% at various times in the simulated flight) than at lower altitudes (4% - 6% at 7,000 feet). Maintaining a cabin "altitude" of 6,000 feet during long flights could greatly facilitate passenger comfort. Since walking periodically during the flight decreased the risk of muscle discomfort by more than half, it could be suggested that travelers prone to discomfort during long flights get up and move about the cabin regularly.

Even without acute mountain sickness and hypoxia-related myalgia, many passengers are uncomfortable during long commercial air flights. Deep vein thrombosis is an uncomfortable and dangerous risk for travelers. Passengers with risk factors for deep vein thrombosis (previous thromboembolism, malignancy, recent surgery, obesity, a Factor V Leiden heterozygote or homozygote, pregnancy or recently post-partum) traveling in aircraft for more than 6 hours should move their legs regularly, use compression stockings, and possibly consider prophylactic use of low molecular weight heparin.[2, 3]

Pressure changes in aircraft also hinder Eustachian tube function and cause ear pain. Up to 9% of adults [4,5] and 14% of children[6] are bothered by earaches during times of changing cabin pressure. Prophylactic pseudoephedrine is effective in adults with a history of air travel-associated ear pain (120 mg orally 30 minutes prior to take-off)[5,7] but is ineffective in children.[6]

Intestinal gas expands approximately 35% when transitioning from sea level to the 8,000 foot "altitude" of a pressured airplane cabin. Nausea and discomfort result. Meals containing high levels of fiber slow gastric emptying by 33% at altitude and further aggravate symptoms.[4]

There are, therefore, many reasons long-haul travelers can feel physically uncomfortable in airplanes. What's an airline to do? Perhaps adjusting cabin pressure to the equivalent of 6,000 feet (rather than 8,000 feet) would help. What's a traveler to do? Move about the cabin when possible. Exercise leg muscles, even when seated. Use compression stockings if there is a pre-existing personal risk for thromboembolism. Adults with a history of air-travel-associated earache can consider pre-flight use of pseudoephedrine. And, travelers with past feelings of bloating and dyspepsia during flight should choose low fiber meals just prior to and during the flight. ■

References:

1. Committee to Advise on Tropical Medicine and Travel. Statement on high altitude illnesses. *Canada Communicable Disease Report* 2007;33(ACS-5):1-20.
2. Philbrick JT, et al. Air travel and venous thromboembolism: a systematic review. *J Gen Intern Med* 2007;22:107-114.
3. Sohail MR, and Fischer PR. Health risks to air travelers. *Infect Dis Clin N Am* 2005;19:67-84.
4. Hinninghofen H, and Enck P. Passenger well-being in airplanes. *Auton Neurosci* 2006;129:80-85.
5. Csortan E, et al. Efficacy of pseudoephedrine for the prevention of barotrauma during air travel. *Ann Emerg Med* 1994;23:1324-1327.
6. Buchanan BJ, et al. Pseudoephedrine and air travel-associated ear pain in children. *Arch Pediatr Adolesc Med* 1999;153:466-468.
7. Jones JS, Sheffield W, White LJ, Bloom MA. A double-blind comparison between oral pseudoephedrine and topical oxymetazoline in the prevention of barotrauma during air travel. *Am J Emerg Med* 1998;16:262-264.

Quadrivalent Human Papillomavirus Vaccine as a Travel Vaccine

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP
Professor of Medicine and Global Health
Yale University School of Medicine

Dr. Barry receives no funding from any issue related to this commentary. She is a consultant for Ford Foundation and had received funding from Johnson and Johnson and Sanofi-Pasteur.

Synopsis: *In June, 2006, the FDA licensed the first human papillomavirus vaccine (HPV) to prevent cervical cancer and other HPV associated cancers: vaginal, urethral and oral tumors. Is this yet another travel vaccine for our patients?*

Source: Markowitz LE, et al. Quadrivalent human papillomavirus vaccine. Recommendations of the advisory committee on immunization practices. *MMWR* March 23, 2007;Vol.56/RR-2.

HPV IS THE MOST COMMON SEXUALLY TRANSMITTED infection in the United States; an estimated 6.2 million persons are newly infected every year. Although over 100 HPV types have been identified the quadrivalent vaccine Gardasil® made by Merck protects against 4 HPV types (6, 11, 16, 18). However, types 16 and 18 are responsible for 70% of cervical cancers and types 6 and 11 are associated with 90% of all genital warts. This prophylactic vaccine made from non-infectious HPV-derived particles is recommended for females ages 9 - 26 years. Ideally the vaccine should be administered before onset of sexual activity. Administration of the Merck vaccine, which has no thimerosal, the organomercury preservative, requires 2 booster doses (0.5 ml intramuscularly) at 2 and 4 months. Duration of efficacy thus far has only been demonstrated for 5 years — future booster doses may be needed. The vaccine is available in a single dose vial or a prefilled syringe. Storage is at 2° C - 8° C (36° F - 46° F) and it should not be frozen. Vaccination can be administered for women with abnormal pap smears who are HPV positive to protect against other HPV infections, but it will not help or change the medical course of these abnormal pap smears. The private sector list price of the vaccine is $119.75 per dose — $360 for the full 3 vaccine doses.

COMMENTARY

During these times of globalization, college and high school students are traveling the world and are inundating travel health clinics. Experience of freedom while being away from home and school leads to increased sexual activity sometimes called "situational disinhibition".[1] The travel clinic visit presents the perfect time to offer HPV vaccine as trips often coincide with increased sexual activity with new partners or travel companions. Unfortunately, the students' traveling schedules often do not allow enough time for full immunization, but certainly a first dose and educational materials about the benefits of full vaccination can be offered. Such educational materials can instruct the traveler that in addition to cervical cancer, HPV infection is also associated with anogenital cancers such as cancer of the vulva, vagina, penis and anus. Studies support a role for HPV also causing a subset of oral cavity and pharyngeal cancers. HPVs are non-enveloped double-stranded DNA viruses that are classified as "types" designated on the basis of nucleotide sequences with numbers assigned in order of their discovery.

Genital HPV infection is primarily transmitted soon after an individual's sexual activity begins. One study has shown that 14.3% of women aged 18-25 with one lifetime sex partner, 22.3% with 2 lifetime partners and 31% with more than 3 lifetime partners had HPV infection.[2] A 2002 National Survey in the United States revealed that 40% of females in the U.S. were sexually active by age 16 and 70% by age 18.[3] The majority of HPV infections are transient and asymptomatic and cause no clinical problems; 70% of new HPV infection clears within one year. Persistent infection with high-risk cancer-inducing types is one consequence of infection that vaccination may prevent.

The longest follow-up of the phase II trial of women vaccinated has been 5 years and reveals that antibody titers plateau by about 24 months but there is no evidence of waning efficacy in preventing cervical cancers at this point, ie, 95.8% efficacy (CI 83.8-99.5%) Follow-up studies by Merck to determine boosting intervals in the 5,500 women enrolled will be continued for at least 14 years by following Pap testing results and serologic testing linked to vaccine and cancer registries. Adverse effects to vaccination were mostly local pain, with reporting of fever in less than 5.0%. There were no reports of anaphylaxis. In the future, Cervarix® a GlaxoSmithKline HPV vaccine submitted to the FDA and pending approval has a different adjuvant and may require less boosting.

Wynia at the AMA has written an interesting article on how public health and public trust were affected by an aggressive stance and lobbying effort by Merck with release of Gardasil®.[4] His opinion is that a Merck donation of funds to Texas Governor Rick Perry, at the time of his state law mandating vaccination, was inappropriate and self-defeating. He contended that public health decisions should be delegated to the public health community, and public trust relies on a clear separation between those making money on vaccines and those making decisions about which vaccines to require or recommend.

The backlash against the Merck campaign will have seriously held back effective HPV vaccination should religious conservatives partner with patient advocacy groups and vaccine phobics to question how vaccines are required prior to school entry. Wynia ends by describing the lesson learned from this story: public trust relies upon the public health community making unbiased and fully disclosed decisions without lobbying or market pressures. For this associate editor and commentator, the take-home message from this event is that pharmaceutical companies should not be allowed to influence government in such public health decisions through either funding or lobbying. ■

References:

1. Apostopopoulos Y, et al. HIV-risk behaviours of American spring break vacationers: a case of situational disinhibition? *Int J STD AIDS*. 2002 Nov;13(11):733-43.
2. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15-44 years of age, United States, 2002. *Adv Data* 2006;362:1-55.
3. Abma JC, Martinez GM, Mosher WD, Dawson BS. Teenagers in the United States: sexual activity, contraceptive use, and childbearing, 2002. Vital Health Stat 2004;24:1-48.
4. Wynia MK. Public health, public trust and lobbying. *Am J Bioeth*. 2007; 7(6):4-7.

Zika in Yap

SPECIAL REPORT

By Stan Deresinski, MD

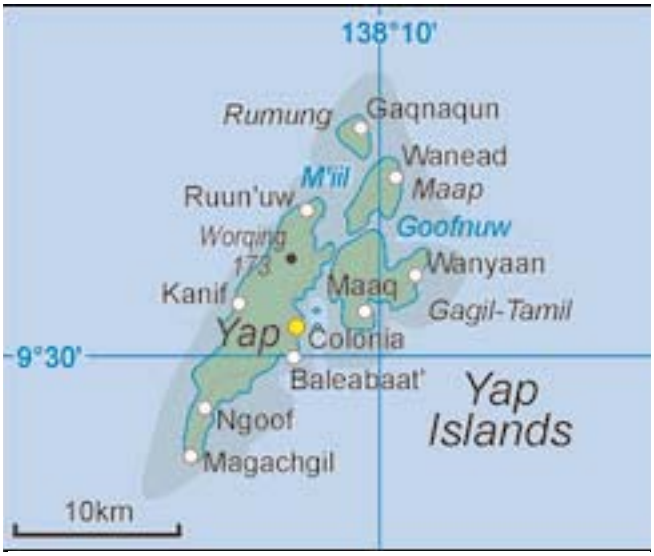
This article originally appeared in the September issue of Infectious Disease Alert.. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD.* Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Source: www.cdc.gov/news/2007/06/zika_yapislands.html

Synopsis: An outbreak of mild dengue-like illness on the Pacific island of Yap was due to a flavivirus, the Zika virus.

AN OUTBREAK OF DENGUE-LIKE ILLNESS THAT began in May, 2007, on Yap, one of the Carolina islands of the Federated States of Micronesia, proved to be due to Zika virus. As of early August, 99 confirmed and 54 probable cases had been identified, with the most recent case dating from July 17th. Additional probable cases have been seen on neighboring islands. The cause of the outbreak was determined by the Arbovirus Diagnostic Laboratory of the CDC.

Dengue is a mosquito-borne flavivirus first identified in 1947 in a sentinel rhesus monkey stationed on a tree platform in the Zika forest, near Entebbe, Uganda and monkeys are presumed to be the natural reservoir of the virus. Symptoms and signs are generally relatively mild and consist of fever, conjunctivitis, arthralgias, and maculopapular rash. The illness lasts 2 to 7 days. Treatment is symptomatic. Serosurveys indicate that Zika virus infections occur in Africa, Southeast Asia, and Malaysia. For instance, a seroprevalence study found an incidence of 31% in several communities in the Nigerian state of Oyo between 1971 and 1975.[1] In addition, an outbreak occurred in Indonesia almost 3 decades ago.



*The Yap Islands, or Yap, composed of 4 continental islands located in the Caroline Islands of the Federated States of Indonesia in the western Pacific Ocean. (*Image by Aotearoa from Poland, GNU FDL from www.cdc.gov/news/2007/06/zika_yapislands.html).

With the assistance of 2 Epidemiologic Service Officers of the CDC, control measures are aimed at reducing peridomestic mosquito breeding sites in open water containers, aerial spraying, and personal protective measures aimed at prevention of mosquito bites.[2] ■

References:
1. Fagbami AH. Zika virus infections in Nigeria: virological and seroepidemiological investigations in Oyo State. *J Hyg* 1979; 83:213-219.
2. http://www.cdc.gov/news/2007/06/zika_yapislands.html

CME Objectives

• To present the latest data regarding the diagnosis and treatment of various travel-related diseases;
• To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world; and
• To alert the readers to recent disease outbreaks and epidemics. ■

CME Questions

14. Which of the following statements is correct regarding rapid diagnostic tests (RDTs) for malaria:

a. RDTs are currently recommended for use by travelers for self-diagnosis.
b. BinaxNow Malaria Test is more sensitive and specific for P. vivax infections.
c. Rapid diagnostic tests aid clinicians evaluating febrile returning travelers.
d. BinaxNow Malaria Test can differentiate between *P. malariae* and *P. vivax*.

15. Choose the correct statement (s)

a. The greatest numbers of cholera cases reported to the WHO in 2006 were from Africa and Asia.
b. Worldwide the number of cholera cases is on the decline.
c. An oral, inactivated, recombinant cholera vaccine also may provide short term protection against enterotoxigenic *E. coli.*
d. All of the above
e. A and C are correct.

16. Muscle discomfort during long flights in commercial aircraft:

a. is due to acute mountain sickness
b. is related to relative hypoxia
c. is most common in older men
d. is not related to cabin pressure

17. HPV vaccination

a. is equally protective against both cervical cancer and genital warts.
b. is a series of 3 intramuscular shots given on a monthly schedule for 3 months.
c. will boost the immune response in women with in situ cervical cancer; a small percentage of abnormal pap smears will revert to normal.
d. is somewhat protective against tumors of the oral cavity as well as cervical cancer.

Answers: 14.(c) 15.(e) 16.(b) 17.(d)

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.

Stopping Statins in At-Risk Patients — Just Too Risky

In this issue: *Make sure your patients don't stop statins after a stroke or surgery; MRSA is becoming more resistant to mupirocin; new asthma treatment guidelines; and FDA approvals and warnings.*

Stopping statins, even briefly, after stroke or cardiovascular surgery increases vascular complications according to 3 new studies. Spanish investigators looked at 89 patients who were on chronic statin therapy and were admitted with acute stroke. Half were randomized to statin withdrawal for the first 3 days after admission, while the other half immediately received atorvastatin 20 mg/day. After 4 days, the statin withdrawal group was also started on atorvastatin. The primary outcome was death or dependence after 3 months as defined by modified Rankin scale of 2 or more. After 3 months, 60% of those in the statin withdraw group were disabled to the point of dependence compared with 39% of those that continued statin therapy (P = 0.043). Early neurologic deterioration was also far greater in the statin withdrawal group (65.2% versus 20.9%; $P < 0.0001$). Statin withdrawal patients also had greater infarct volume (P = 0.002). The authors conclude that statin withdrawal in the first few days after stroke is associated with a markedly increased risk of death or dependency at 90 days; hence, treatment should continue the acute phase of an ischemic stroke (*Neurology* 2007; 69:904-910).

In another study, researchers in Italy looked at stroke patients who discontinued statins after discharge from the hospital. The study population included 631 stroke patients (322 men, 309 women) without evidence of heart disease. All patients were discharged on a statin, but 38.9% discontinued the drug within 12 months. In the 12 months of follow-up, 116 patients died. After adjustment for all confounders and interactions, the hazard ratio for mortality in patients who quit a statin was 2.78 (95%CI, 1.96-3.72; P = 0.003) or nearly 3 times higher risk of death (*Stroke* 2007, published online ahead of print 8/30/07).

Another study from the Netherlands looked at a brief interruption in statin therapy associated with major vascular surgery. Nearly 300 patients on statins underwent major vascular surgery, and statin therapy was interrupted in the perioperative period in 70 patients for mean duration of 3 days. An association was observed between statin discontinuation and an increase risk of postoperative troponin release (HR 4.6) and the combination of MI and cardiovascular death combined (HR 7.5). Because many surgical patients are NPO and unable to take oral statins, and there's no intravenous statin available, the only extended release statin was tried on a subset of patients preoperatively. Patients receiving extended-release fluvastatin had fewer perioperative cardiac events compared to other statins (*Am J Cardiol* 2007; 100:316-320). The message of these studies is that statin interruption, even for a brief period during hospitalization, may lead to serious adverse events in patients at risk.

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) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

Mupirocin Less Effective Against MRSA

Mupirocin (Bactroban) is becoming less and less effective against MRSA, even in hospitals with low levels of mupirocin use. Researchers from Washington University in St. Louis performed nasal swab cultures for MRSA in all patients admitted to their surgical intensive care unit (SICU) on admission, weekly during hospitalization, and at discharge. Of the 302 positive MRSA isolates, 13.2% were resistant to mupirocin, with 8.6% having high-level resistance. Patients with mupirocin-resistant MRSA were more likely to be older, have a history of a previous admission in last year, and had higher in-hospital mortality. The authors conclude that patients carrying mupirocin-resistant MRSA acquired it through contact with the health-care system; the strains were probably not acquired in the SICU (*Clin Infect Dis* 2007; 45:541-547). Mupirocin is commonly used to decolonize patients who are *staph aureus* carriers or have nasal colonization with MRSA. With resistance patterns increasing nationwide, this strategy may need to change.

New Guideline for Asthma Diagnosis/Management

The National Asthma Education and Prevention Program has issued an update to their clinical practice guidelines for diagnosis and management of asthma (Expert Panel Report 3 [EPR-3]). The new guideline emphasizes the importance of asthma control and highlights 4 areas of emphasis including assessment and monitoring, patient education, control of environmental factors and other asthma triggers, and pharmacotherapy. The new guideline recommends continued use of a stepwise approach to asthma control in which medication doses or types are stepped up or down as needed based on asthma control. Recommendations now are based on 3 age groups, 0-4 years, 5-11 years (a new category), and 12 years and older.. The new age group was added because of evidence that children respond differently to medications than adults. The entire guideline can be found at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf .

FDA Actions

The FDA announced on August 14 that manufacturers of rosiglitazone (Avandia) pioglitazone (Actos), and other combination medications containing the 2 drugs will be required to add a "black box" warning to their labeling to reflect the risk of heart failure associated with the 2 drugs. Both drugs have been associated with reports of significant weight gain and edema, and some cases continuation of therapy has lead to poor outcomes including death. The black box warning advises health-care professionals to carefully observe patients taking these drugs for signs and symptoms of heart failure including rapid weight gain, shortness of breath, edema. The warning also recommends not starting either drug in patients with a history of congestive heart failure. The agency continues to review rosiglitazone for the possible increase risk of myocardial infarction associated with use of the drug.

The FDA has approved a new indication for zoledronic acid (Reclast) as a once-a-year treatment for postmenopausal osteoporosis. Reclast is administered as an annual 15-minute intravenous infusion. The drug is a bisphosphonate similar to oral bisphosphonates such as alendronate and risedronate.

Anesiva has received approval to market lidocaine topical powder intradermal injection system (Zingo) to provide local analgesic prior to venipuncture or peripheral intravenous cannulation in children ages 3-18. Zingo is a single-use helium powered system that is administered 1-3 minutes prior to needle insertion. The system is also being studied in trials of adults.

The FDA has approved a new combination of carbidopa, levodopa, entacapone (50 mg/200 mg/200 mg) for the treatment of Parkinson's disease. The new preparation helps reduce the pill burden for Parkinson's patients on multiple medications. Carbidopa/levodopa/entacapone will be marketed by Orion Corporation as Stalevo.

Omrix Biopharmaceuticals has received approval to market human thrombin (Evithrom) to promote blood clotting and control bleeding during surgery. Evithrom is the first human thrombin approved since 1954 and the only product currently available for this indication. It is applied to the surface of bleeding tissue during surgery and may be used in conjunction with absorbable gelatin sponge. Other thrombins currently on the market are derived from cattle plasma.

Nursing mothers who were taking codeine may put their babies at risk of morphine overdose if they are "ultra-rapid metabolizers of codeine," a condition that may affect up to 28% of the population. Codeine is generally recommended for nursing mothers as a cough suppressant and pain medication; however, ultra-rapid metabolizers quickly convert codeine to morphine and excrete it in breast milk. At least one infant death has been associated with this condition. The FDA has issued warning regarding codeine use by nursing mothers, recommending that mothers observe their infants closely while taking the medication for signs of morphine overdose including sleepiness, difficulty breast feeding, breathing difficulties or limpness. ■