TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media

INSIDE

Volume 21, No. 4
April 2011

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, reports no financial relationship to this field of study. Peer reviewer, Lin Chen, MD, has received research grants from the Centers for Disease Control and Prevention and Xcellerex. Peer reviewer, Philip R. Fischer, MD, DTM&H, reports no financial relationship to this field of study. Executive Editor Gary Evans and Senior Managing Editor Paula Cousins report no financial relationship to this field of study.

ACIP 2010 Vaccine Updates: Meningococcal Conjugate Vaccines and Tdap

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

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

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

Synopsis: *New guidelines for the use of quadrivalent meningococcal conjugate vaccine (MCV4) and Tdap are now in place to eliminate breakthrough cases of meningococcal disease and to curb a rising tide of pertussis cases.*

Sources: Updated recommendations for use of meningococcal conjugate vaccines — Advisory Committee on Immunization Practices (ACIP), 2010. *Morb Mortal Wkly Rep* 2011;60:72-76; Updated Recommendations for the use of tetanus toxoid reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) from the ACIP. *Morb Mortal Wkly Rep* 2011;60:13-15.

On Oct. 27, 2010, the Advisory Committee on Immunization Practices (ACIP) approved updated recommendations for the use of quadrivalent (serogroup A, C, Y, and W-135) meningococcal conjugated vaccines (Menveo®, Novartis; and Menactra®, Sanofi Pasteur) for adolescents and persons with high risk for meningococcal disease. The two main recommendations are: 1) routine vaccination of adolescents, preferably at age 11 or 12 years, with the a booster dose at age 16 years and 2) a two-dose primary series administered 2 months apart for persons age 2-54 years with persistent complement component deficiency, functional or anatomic asplenia, and adolescents with human immunodeficiency virus (HIV) infection. The rationales for these changes were based on a review of additional data on bactericidal antibody persistence, vaccine effectiveness, current trends in meningococcal disease epidemiology, and immunogenicity in high-risk groups by the Meningococcal Vaccines Work Group of ACIP.

The goal of meningococcal immunization of adolescents is to protect persons age 16-21 years, since this is the time when rates of meningococcal disease peak. The original recommendation to vaccinate at the 11- or 12-year-old preventive care visit was, in part, because data show that as adolescents grow older, they are less likely to visit a health care provider. Also, it was initially expected that the vaccine would protect adolescents through age 21. However, in 2010, the Centers for Disease Control and Protection (CDC) received 12

reports of serogroup C or Y meningococcal disease among persons who had received a meningococcal conjugate vaccine. The mean age of these persons was 18.2 years and the mean time since vaccination was 3.25 years. Five of these 12 persons had an underlying condition that may have increased their risk of meningococcal disease (CDC, unpublished data).

In addition, a case control study evaluating the vaccine effectiveness (VE) of meningococcal vaccine showed that VE for persons vaccinated less than 1 year earlier was 95%, at 1 year was 91%, and for persons vaccinated 2-5 years earlier VE fell to 58%. Similarly, the Work Group looked at five studies of circulating bactericidal antibody levels and concluded that approximately 50% of persons vaccinated 5 years earlier had protective levels against meningococcal disease. This implies that 50% of persons given vaccine at age 11 or 12 might not be protected at the time they are at highest risk, that is, at age 16-21.

Therefore, for persons 11-18 years old, the primary series should be one dose, preferably at age 11 or 12 years. The booster dose should be at age 16 if the primary dose was at 11 or 12 years, and at ages 16 to 18 if the primary dose was at age 13-15. If the primary dose was given on or after age 16 years, no booster dose is needed.

The Work Group also reviewed the data supporting the need for a two-dose primary meningococcal vaccine series in persons with certain special medical conditions *(see table, pg. 19)*. They concluded that persons with persistent complement component deficiencies (e.g., components C5-C9, properidin, factor H, or factor D) and anatomic or functional asplenia should receive a two-dose primary series administered 2 months apart and then receive a booster dose every 5 years. For HIV-infected persons 11-18 years old, the primary series should also be two doses given 2 months apart, with the same booster schedule followed as in non-HIV infected adolescents. Other persons with HIV who are vaccinated should receive a two-dose primary series as well.

Additional ACIP recommendations were made with regard to tetanus toxoid reduced diphtheria toxoid and acellular pertussis vaccine (Tdap). These include: 1) use of Tdap regardless of the interval since the last tetanus- or diphtheria-containing vaccine, 2) use of Tdap in adults age 65 and older, and 3) the use of Tdap in under-vaccinated children age 7-10 years. Specifically, for all adults, including those age 65 years and older, a single dose of Tdap is recommended and can be given regardless of the interval since the last Td. This is especially important for those adults who have, or anticipate having, close contact with an infant younger than 12 months.

Persons age 7-10 years who are not fully vaccinated against pertussis should receive a single dose of Tdap. If additional doses of tetanus- and diphtheria-containing vaccine are needed (those never vaccinated or with unknown status), these patients should receive a series of three vaccinations preferably the first being Tdap, with subsequent doses of Td. For now, Tdap is recommended only for single-dose administration across all age groups.

■ COMMENTARY

The new quadrivalent meningococcal conjugate vaccine (MCV4) recommendations will likely cause some initial confusion with health care providers as well as parents. Yet the important goal of reducing breakthrough

Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media, a division of Thompson Media Group 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 105109, Atlanta, GA 30348.

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.

infections with this deadly disease more than justifies the changes. The idea, at its simplest, was to not let go of immunizing adolescents at 11-12 years, yet boost protection before the time of peak risk at age 16-21.

The addition of a two-dose MCV4 primary series for persons with a reduced response to a single-dose vaccine (asplenia, HIV, etc.) will ensure better protection as well. The ACIP recommends that these patients who have had only a one-dose primary series (which is everyone, as of now) receive a booster dose at the earliest opportunity and then every 5 years. Of note, the ACIP is not advocating at this time vaccinating all HIV-infected patients with MCV4; rather, if an HIV patient is going to receive the vaccine (i.e., traveling to the meningitis belt of Africa), then a two-dose primary series should be given.

All other persons at risk for meningococcal disease age 7-55 should receive a single dose of vaccine with subsequent dose after 5 years only if the person remains at increased risk (microbiologists or travelers to an endemic or highly endemic country). This interval should be shortened to 3 years for persons age 2-6 years. Refer to table 1 in the MMWR report as useful guide to the new MCV4 schedule.

Pertussis cases in the United States continue to rise with 20,127 provisional cases reported as of Dec. 18, 2010, up from 16,858 in 2009.[1] Despite the 2005 ACIP recommendations for use of Tdap in adolescents and adults, Tdap coverage is only 56% among adolescents and < 6% among adults.[2,3] These new recommendations to broaden the use of Tdap in children older than age 7 and older adults may help turn the tide on these rising numbers.

At the February 2011 ACIP meeting, there was discussion about recommending Tdap in pregnant woman, but this decision was deferred for the moment due to lack of available data (there are two studies ongoing in this area). For now, women of child bearing potential should be given Tdap prior to pregnancy or in the immediate postpartum period to reduce the risk of pertussis in the unimmunized newborn. Further guidelines on the use of Tdap in pregnancy may be forthcoming when the data from the studies in progress become available. ■

References

1. Centers for Disease Control and Prevention. Notifiable Diseases and Mortality Tables. *Morb Mortal Wkly Rep* 2010;59:1658-1671.
2. Centers for Disease Control and Prevention. National, state, and local area vaccination coverage among adolescents aged 13-17 years — United States, 2009. *Morb Mortal Wkly Rep* 2010;59:1018-1023.
3. Centers for Disease Control and Prevention. Tetanus and pertussis vaccination coverage among adults aged ≥18 years — United States, 1999 and 2008. *Morb Mortal Wkly Rep* 2010;59:1302-1306.

Table. Summary of meningococcal conjugate vaccine recommendations, by risk group — Advisory Committee on Immunization Practices (ACIP), 2010

Risk Group	Primary Series	Booster Dose
Persons age 11-18 years	1 dose, preferably at age 11 or 12 years	At age 16 years if primary dose at age 11 or 12 years At age 16-18 years if primary dose at age 13-15 years No booster needed if primary dose on or after age 16 years
HIV-infected persons in this age group	2 doses, 2 months apart	At age 16 if primary dose at age 11 or 12 years At age 16-18 years if primary dose at age 13-15 years No booster needed if primary dose on or after age 16 years
Persons age 2-55 with persistent complement component deficiency* or functional or anatomical asplenia	2 doses, 2 months apart	Every 5 years At the earliest opportunity if a 1-dose primary series administered, then every 5 years
Persons age 2-55 years with prolonged increased risk for exposure†	1 dose	Persons age 2-6 years: after 3 years Persons age 7 years or older: after 5 years§

Abbreviations: HIV = human immunodeficiency virus.

* Such as C5-C9, properidin, or factor D.

† Microbiologists routinely working with *Neisseria meningitidis* and travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic.

§ If the person remains at increased risk.

Source: Updated recommendations for use of meningococcal conjugate vaccines — Advisory Committee on Immunization Practices (ACIP), 2010. *Morb Mortal Wkly Rep* 2011;60:72-76.

Smartphones: Remote Point-of-care Diagnostics

ABSTRACT & COMMENTARY

By Brian G. Blackburn, MD, and Michele Barry, MD, FACP

Dr. Blackburn is a Clinical Assistant Professor in the Division of Infectious Diseases and Geographic Medicine at Stanford University School of Medicine; Dr. Barry is the Senior Associate Dean of Global Health at Stanford University School of Medicine

Dr. Barry is a retained consultant for the Ford Foundation and has received research or grant support from Johnson & Johnson Corporate Foundation, the Doris Duke Foundation, and the National Institutes of Health. Dr. Blackburn reports no financial relationship to this field of study.

Synopsis: *E-health, including mobile phone diagnostics, is a rapidly growing field, which may revolutionize point-of-care diagnostics for physicians.*

Source: Tice AD. Gram stains and smartphones. *Clin Infect Dis* 2011;52:278-279.

Although undeniably useful, Gram stains have become less accessible to physicians in an era when clinicians go to the laboratory infrequently to view specimens and hospital laboratories move off-site. This brief report describes a Honolulu hospital's approach to this problem. With the use of smartphones among physicians now widespread and the advent of low-cost digital cameras and microscopes, images of Gram stains can be uploaded in the laboratory and sent out as email or text message attachments to clinicians. Software applications can allow magnification and manipulation of the image while viewing on the phone. Similar technology is already in use in our institution for viewing radiologic and dermatologic images. Implementing systems that incorporate this type of technology could re-invigorate the use of Gram stains and perhaps bring first-hand visualization of such tools to a generation of physicians that would otherwise rarely see them, possibly improving the appropriate use of antimicrobials as a result.

■ COMMENTARY

Smartphones are now in widespread use and have the potential to revolutionize many aspects of health care delivery. While the developed world certainly will benefit, it is perhaps in resource-poor settings where smartphones may have their greatest impact. The use of smartphones to disseminate images of Gram stains more widely among the health care team in this report is an encouraging example of the potential of this emerging technology. But the real action is in point-of-care diagnostics. In the developing world, laboratory technicians often have insufficient training, and equipment for microscopy is either unavailable or not portable; yet, such settings are often well-served by mobile phone networks. Thus, mobile phones with cameras are a natural fit for diagnostic imaging and telemedicine.

One group has built a mobile phone-mounted light microscope and demonstrated its potential for clinical use by successfully imaging blood smears with malaria-infected red blood cells (RBCs) and sickled RBCs.[1] They also imaged sputum smears positive for *Mycobacterium tuberculosis* via fluorescence microscopy with the smartphone-microscope. Resolution was sufficient to detect blood cell and microorganism morphology, and with the tuberculosis samples, the authors were able to use automated image analysis software to quantify the number of mycobacteria.[1] Another group reported that microscopic images taken with a mobile phone's built-in camera (by simply opposing the mobile phone camera to the ocular of common optical microscopes, without an adaptor) resulted in images of sufficient quality for many diagnostic purposes. Because these image files were small, they could be sent via text message to distant reference centers for tele-diagnosis. Resolution above 0.8 megapixels resulted in images sufficient for diagnosis.[2]

Another recent development is smartphone-based lens-free digital microscopy. A lightweight, relatively inexpensive holographic microscope can be attached to the camera unit of a mobile phone, with samples loaded from the side.[3] Holographic signatures captured by the phone permit reconstruction of images through digital processing. Although this technology requires images to be uploaded to a computer for processing and then redownloaded to end-users, obviating the need for a traditional microscope may be beneficial in some settings.

A group in rural Thailand is using smartphones to improve malaria case management.[4] After patients are diagnosed with malaria, their information is entered into an electronic database and a schedule for clinical follow-up is generated, which is available on smartphones and usable by local health care workers. Follow-up home visits then are conducted in part with the assistance of mobile phones loaded with a follow-up software application geared toward ascertaining symptoms, treatment compliance, and the like. The program also generated summary statistics of malaria cases, which could be automatically sent to study personnel for real-time epidemiological monitoring. Compared to the paper-based system that was in use during the 4 years preceding implementation of this program, the rates of malaria patients appropriately completing follow-up 1 month after infection using the mobile phone-based platform increased from < 50% to 98%, adherence to antimalarial drug therapy was 94% for *P. falciparum*-infected

patients, and community health care personnel in these low resource settings were able to efficiently utilize the system to perform their work, even in remote areas. A modified version of this program currently is functioning in seven Thai provinces, a key part of an urgent containment program to halt the spread of multi-drug resistant malaria on the Thai-Cambodian border.[4]

Another group has pioneered wide-field fluorescent and darkfield imaging on a mobile phone with lightweight and relatively inexpensive optical components that are attached to the existing camera unit of the phone.[5] In resource-limited settings, this could provide an important tool for quantification of various mobile assays or chips/microarrays, which require the interpretation of fluorescence, such as CD4 counts or viral load measurements in HIV-infected patients.

Potential applications of smartphone technology extend well beyond even these ideas. Medication bottles with embedded wireless chips can remind patients on-the-spot when to take medications, and can then transmit additional reminders for patients and information about medication use/compliance to their doctors via smartphones. Unpublished data suggest this results in increased medication compliance.[6] Even the audio-recording capability of smartphones is being developed in one setting as a means of assisting with diagnostics based on heart sounds. Preliminary results indicate that accurate assessment of some components of the cardiac exam can result from acoustic recordings of heart sounds using only a cellphone and hands-free kit. Heart sound analysis software, which can run on a standard cellphone in real time, can detect S1 heart sounds with a sensitivity of 92%.[7]

Smartphones are clearly an emerging technology with great potential to aid in the development of diagnostics and other tools useful in global health settings. Even in resource-limited countries, the majority of the population in most settings lives within range of a cell phone tower and has a mobile phone. The range of possible applications seems limited only by the number of ideas which are put to the test. In our institution at Stanford, an innovative program called C-IDEA (the Consortium in Innovation, Design, Evaluation, and Action) aims to accelerate progress in the design of extremely affordable diagnostics, drugs, and devices for global health, and a class on Liberation Technology has student teams designing cell phone applications to impact health. As we watch applications such as Facebook and Twitter interface within the current political arena, we look forward to a similar revolution in cell phone diagnostics for health. ■

References

1. Breslauer DN, et al. Mobile phone based clinical microscopy for global health applications. *PLoS One* 2009;4:e6320.
2. Bellina L, Missoni E. Mobile cell-phones (M-phones) in telemicroscopy: Increasing connectivity of isolated laboratories. *Diagn Pathol* 2009;4:19.
3. Tseng D, et al. Lensfree microscopy on a cellphone. *Lab Chip* 2010;10:1787-1792.
4. Meankaew P, et al. Application of mobile-technology for disease and treatment monitoring of malaria in the "Better Border Healthcare Programme". *Malar J* 2010;9:237.
5. Zhu H, et al. Cost-effective and compact wide-field fluorescent imaging on a cell-phone. *Lab Chip* 2011; 11:315-322.
6. May M. Aiding adherence: Five approaches to following prescriptions. *Nat Med* 2010;16:504.
7. Chen T, et al. Intelligent Heartsound Diagnostics on a Cellphone using a Hands-free Kit. Association for the Advancement of Artificial Intelligence Spring Symposium Series; Palo Alto, CA; March 2010.

Getting the Lead Out

ABSTRACT & COMMENTARY

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

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

Synopsis: *Lead toxicity can compromise health and kill children anywhere in the world. With less lead-based paint and gasoline in the United States, lead toxicity is increasingly associated with oral ingestion of lead from imported jewelry and cosmetics.*

Source: Mann M, et al. Lead poisoning of a child associated with the use of a Cambodian amulet — New York City, 2009. *Morb Mortal Wkly Rep* 2011;60:69-71.

Routine lead screening of a 1-year-old U.S.-born son of Cambodian immigrants living in New York revealed an elevated blood lead level (10 mcg/dL). No lead paint or other identifiable risk for lead toxicity was identified during a home interview and inspection. Three months later, a follow-up lead level was 20 mcg/dL. The father then admitted that the child had been wearing a necklace as an amulet "to protect him" since the age of 3 months, and that the child had been seen mouthing the amulet. The metal beads on the amulet were tested and found to consist of 45% lead. Eight days after removing the amulet from the boy's home, his lead level had dropped to 14 mcg/dL, and 5 weeks after that, the lead

level was 10 mcg/dL. Five months after removing the amulet from the child's home, his lead level was 5 mcg/dL.

Interestingly, another young child in the same home had previously had a high lead level (17 mcg/dL), which also dropped to 7 mcg/dL 3 months after he stopped wearing a Cambodian amulet. A 10-year-old in the home who also wore a similar amulet (but presumably did not lick it or put it in her mouth) had a blood lead level of 4 mcg/dL.

■ COMMENTARY

Many children in southeast Asia wear "protective" strings around their necks, wrists, or waists. Often, the knotted strings include metal beads, and it has been suggested that the metal is often derived from lead bullets.

Lead toxicity usually results from oral ingestion of lead. When leaded paints were used in the United States, toxicity often occurred in children with pica. They either ate paint chips or played with paint chips and subsequently touched their fingers to their mouths. Lead toxicity also was associated with locations near high-volume road traffic, where soil in play areas was presumably contaminated with vehicle exhaust from cars and trucks burning leaded gasoline. As lead has been removed from commercial paints and gasoline, other sources of lead exposure deserve increased attention.[1-3]

In some parts of the world, parents use eye cosmetics on their children to line the eyelids with black and/or bluish pigment. Often called "kohl," these cosmetics sometimes contain high quantities of lead and they are often imported from India and the Middle East.[4,5] In Nigeria, lead toxicity has been associated both with the use of eye cosmetics and playing in yards where truck batteries are recycled, presumably contaminating the soil with leaded battery waste.[6] The current case reminds us that lead bead-containing amulets, even when imported from other countries, can serve as a source of lead toxicity in children.

While preparing this commentary for *Travel Medicine Advisor*, I visited a rural health center in Cambodia. Many patients came with amulets to prevent evil spirits from "landing on them" or otherwise influencing them. Some mothers carried scissors to medical visits to ward off evil spirits along the way. Interesting, though, I saw no amulet that was loose enough around the neck to allow oral contact or represent a choking hazard, and I did not see lead-containing amulets on wrists where children could get them into their mouths. Perhaps parents who insist on putting lead-containing amulets on their children could follow the practices of these Cambodian parents to keep the lead out of the mouths of their children.

Lead toxicity can be fatal, such as seen in a Minnesota child who swallowed a lead-laden charm.[7] Whatever the cause of lead toxicity, careful environmental evaluation and individualized case management are important; the Centers for Disease Control and Prevention offers guidelines.[8] ■

References

1. Jones RL, et al. Trends in blood lead levels and blood lead testing among US children aged 1 to 5 years, 1988-2004. *Pediatrics* 2009;123:e376-e385.
2. Nichani V, et al. Blood lead levels in children after phase-out of leaded gasoline in Bombay, India. *Sci Total Environ* 2006;363:95-106.
3. Nuwayhid I, et al. Blood lead concentrations in 1-3 year old Lebanese children: A cross-sectional study. *Environ Health* 2003;2:5.
4. De Caluwe JP. Lead poisoning caused by prolonged use of kohl, an underestimated cause in French-speaking countries. *J Fr Ophtalmol* 2009;32:459-463.
5. al-Hazzaa SA, Krahn PM. Kohl: A hazardous eyeliner. *Int Ophthalmol* 1995;19:83-88.
6. Wright NJ, et al. Causes of lead toxicity in a Nigerian city. *Arch Dis Child* 2005;90:262-266.
7. Centers for Disease Control and Prevention. Death of a child after ingestion of a metallic charm — Minnesota, 2006. *Morb Mortal Wkly Rep* 2006;55:340-341.
8. Centers for Disease Control and Prevention. Lead. Available at: www.cdc.gov/nceh/lead/. Accessed Feb. 19, 2011.

ASTMH Meeting Highlights 2010

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 has received research grants from the Centers for Disease Control and Prevention and Xcellerex.

At the 59th annual meeting of the American Society of Tropical Medicine and Hygiene held in Atlanta, GA, Nov. 3-7, 2011 *(see abstracts, pg 23)*, Dr. Paul Arguin, head of the Domestic Malaria Unit, presented Malaria Updates from the Centers for Disease Control and Prevention (CDC). For 2009, 1,490 cases of malaria were reported to the CDC. The most commonly reported reason for travel was visiting friends and relatives (61.7%), followed by missionary (9.5%), business (5.8%), and tourism (4.7%). The top exposure countries for all reported cases of malaria in the United States in 2009 were Nigeria, Ghana, India, Haiti, Sierra Leone, and Ivory Coast.

The most common exposure countries for U.S. residents included the same countries.

The reported malaria cases most frequently had exposure in West Africa (51.4%), as illustrated by the Nov. 5, 2010, issue of *Morbidity and Mortality Weekly Report*, which described four cases of *Plasmodium falciparum* in flight crew acquired in Accra, Ghana.[1] These cases showed the continued high transmission of malaria in west Africa even for brief stays, and emphasize the importance of mosquito avoidance measures as well as malaria chemoprophylaxis.

Malaria in Haiti has been a concern. Prior to the earthquake in 2009, the CDC received 59 reports of malaria acquired in Haiti, compared to 19 cases in 2008. For 2010, there have already been 35 cases reported, including eight severe cases.

Dr. Arguin reported some notable changes in malaria prevention guidelines because no malaria transmission has occurred in Iguassu Falls, Angkor Wat, Armenia, Bahamas, Syria, and Turkmenistan. Additionally, mosquito avoidance only is recommended for travelers to Cape Verde, Iraq, Quintana Roo, and Tabasco in Mexico, and all areas except Limon Province in Costa Rica. He emphasized that the recommendation of chemoprophylaxis should not be based on geography alone, but also requires individual risk assessment.

Dr. Gary Brunette, head of the Travelers' Health Branch, presented Travelers' Health Updates. Recent changes in vaccine recommendations include: 1) Ixiaro® is approved and available for persons age 17 and older to prevent Japanese encephalitis, whereas JE Vax® is only recommended now for persons age 1-16 years; 2) a four-dose rabies post-exposure prophylaxis is recommended in persons without pre-exposure prophylaxis and includes rabies immune globulin plus rabies vaccines given on days 0, 3, 7, 14 for normal hosts, but a fifth dose should be given on day 28 to immune-suppressed hosts; and 3) additional yellow fever vaccine precautions include age ≥ 60 years and HIV-positivity with CD4 of 200-499.

The Yellow Fever (YF) Vaccine Working Group

A NUMBER OF INTERESTING STUDIES WERE PRESENTED AT THE ASTMH annual meeting, including the following from the Clinical Tropical Medicine Scientific Session I.

• **Monath TP, et al.** Inactivated, cell-based yellow fever 17d vaccine — safety and immunogenicity in animal models and results of a phase 1 clinical trial.

An inactivated yellow fever vaccine has been developed using YF 17D RNA grown in Vero cells. Studies in mice, hamster, and monkeys have shown that a single dose led to antibody titers similar to the live-attenuated YF vaccine (antibody ≥ 20) by day 21. A randomized, double-blind phase 1 clinical trial found that two doses given on days 0 and 21 were safe, and compared a low-dose to a high-dose regimen. On day 21, low-dose regimen achieved 12.5% seroconversion and high-dose achieved 45% seroconversion. By day 31 (10 days after the second dose), 100% of subjects achieved seroconversion.

Inactivated YF vaccine appears promising in a phase 1 clinical trial, and we await results of additional trials.

• **D'Acremont V, et al.** Etiology of fever in children from urban and rural Tanzania.

The investigators analyzed 1,005 children age 2 months to 10 years (median, 18 months) with temperatures > 38º C, collected clinical information and test results, and derived levels of probability for the diagnoses. The children were recruited from Dar Es Salaam (n = 507) and Ifakara (n = 498). Acute respiratory infections (ARIs) accounted for 50%, malaria 10%, GI infections 9%, typhoid fever 3%. Among the ARIs, one-quarter were influenza, and both arenavirus and picornavirus also were prevalent. Those with unknown diagnoses were tested by PCR; dengue, chikungunya, Rift Valley fever, and West Nile fever were ruled out, but a high rate of HHV6 infection was detected.

Acute respiratory infections appear to be the most common cause of fevers among children in two Tanzanian communities. Malaria, GI infections, and typhoid also were identified. When evaluating febrile illnesses in children, clinicians working in similar communities should direct specific diagnostic testing to identify these common etiologies.

• **William T, et al.** A retrospective study of severe *Plasmodium knowlesi* infections at Queen Elizabeth Hospital, Sabah, Malaysia.

The investigators retrospectively reviewed clinical records of patients who were diagnosed with *P. knowlesi* at Queen Elizabeth Hospital, a tertiary referral center in Kota Kinabalu, Sabah, Malaysia. *P. knowlesi* accounted for 24% of all cases of malaria at QEH (78/324), and 34% of *P. knowlesi* cases had severe disease. The patients commonly had hematological abnormalities and hyperbilirubinemia, especially older individuals. Other studies including dengue virus were all negative. A high proportion had severe malaria, including 64% with respiratory distress and 59% with acute renal failure. Among 23 patients with severe disease, five died (22%). ACT is effective for treatment.

This series shows that P. knowlesi *can cause severe disease and is a major cause of severe malaria at QEH. Travel medicine providers should be aware of this recently identified strain of* Plasmodium *and evaluate febrile travelers appropriately.* ■

formed by the World Health Organization, Centers for Disease Control and Prevention, National Travel Health Network and Centre, and other experts are continuing to harmonize yellow fever country risks and vaccine recommendations. The new YF risk classification criteria will be stratified to four groups: endemic, transitional, low, and no risk; the risk maps will correspond to vaccination maps. The following countries in the African region will probably have changes in YF risk classification: Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Sao Tome, and Principe, Somalia, Tanzania, Zambia. In the Americas, changes probably will occur for Argentina, Brazil, Colombia, Ecuador, Panama, Paraguay, Peru, Trinidad and Tobago, and Venezuela. Until the new recommendations are formalized and published, travel medicine providers are advised to follow the current guidelines.

Additionally, the CDC has produced a YF Vaccine Course in collaboration with experts. It is an online module, is free, and offers CME, CNE, CPE, and CHES credits. Access to the module is via the CDC Travelers' Health Website. Finally, the Yellow Book 2012 will be available in spring 2011.

[Acknowledgement: The Associate Editor thanks Drs. Paul Arguin and Gary Brunette for sharing their ASTMH presentations and for reviewing this report.] ■

CME Objectives

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

• Discuss the latest data regarding the diagnosis and treatment of various travel-related diseases;

• Explain new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world;

• Implement strategies in the practice setting to inform patients of disease outbreaks and epidemics relevant to their travel plans.

Reference

1. Centers for Disease Control and Prevention. Malaria imported from West Africa by flight crews — Florida and Pennsylvania, 2010. *Morb Mortal Wkly Rep* 2010;59:1412.

CME Questions

1. All of the following statements about ACIP vaccine updates for MCV4 and Tdap are true *except*:
a. A two-dose primary series of conjugate meningococcal vaccine is recommended in adolescents with HIV.
b. Tdap can be given regardless of the interval from the last tetanus diphtheria toxoid-containing vaccine.
c. A booster series of Tdap vaccines given 2 months apart is recommended in unimmunized children.
d. Tdap is recommended in adults, especially if in contact with newborns or young children.
e. A microbiologist with ongoing risk of meningococcal exposure should be immunized with conjugate meningococcal vaccine every 5 years.

2. Mobile phone applications have been (or are being) developed which can assist with:
a. dissemination of gram stain images from the Clinical Microbiology lab to the clinical health care team.
b. reading blood smears for malaria or sputum smears for tuberculosis.
c. malaria case management in rural, developing world settings.
d. making diagnoses via assessment of the cardiac examination.
e. All of the above

3. Which of the following statements is *not* true?
a. Lead toxicity occurs after ingesting leaded paint chips.
b. Lead toxicity can be caused by licking jewelry.
c. Lead toxicity has been linked to swallowed charms.
d. Lead toxicity is most common among adolescents.

4. Which of the following statements is *correct*?
a. *P. knowlesi* infections are generally mild in severity and mimic those caused by *P. vivax*.
b. Inactivated YF vaccine did not appear promising in phase 1 clinical trials.
c. Acute respiratory infections appear to be the most common cause of fevers among children in two Tanzanian communities.
d. Malaria transmission has occurred recently in Iguassu Falls, Angkor Wat, Armenia, Bahamas, Syria, and Turkmenistan.

Answers: 1. c, 2. e, 3. d, 4. c.

PHARMACOLOGY WATCH

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

Apixaban and Rivaroxaban Near Approval for Nonvalvular AF

In this issue: Apixaban and rivaroxaban near approval for nonvalvular atrial fibrillation; fidaxomicin for *C. difficile* infections; guideline for intensive insulin therapy; and FDA Actions.

Dabigatran for stroke in patients with nonvalvular atrial fibrillation

Dabigatran, a direct thrombin inhibitor, recently was approved for prevention of stroke in patients with nonvalvular atrial fibrillation. The evidence for its benefit is strong enough that the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society recently upgraded their atrial fibrillation guidelines to include dabigatran (*Circulation* published online February 14, 2011). Meanwhile, the direct factor Xa inhibitor rivaroxaban is working its way through the FDA approval process for the same indication, with approval expected later this year. The latest player in the field is apixaban, also a direct factor Xa inhibitor. Apixaban was studied in a double-blind Phase 3 study of 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable. Patients were randomized to receive apixaban 5 mg twice daily or aspirin 81-324 mg per day with a mean follow-up of 1.1 years. The primary outcome was occurrence of stroke or systemic embolism. The study was terminated early because of a clear benefit in favor of apixaban. There were 51 events (1.6 % per year) in the apixaban group vs 113 events (3.7% per year) in the aspirin group (hazard ratio with apixaban 0.45, 95% confidence interval 0.32-0.62; P < 0.001). The death rate was 3.5% in the apixaban group vs 4.4% in the aspirin group (P = 0.07). The rates of major bleeding or intracranial hemorrhage were similar; however, the risk of first hospitalization for cardiovascular causes was significantly lower with apixaban. The authors suggest that apixaban is more effective than aspirin. In indirect comparisons, apixaban is more effective than aspirin plus clopidogrel and at least as effective as warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation (*N Engl J Med* published online February 10, 2011). Apixaban is currently being studied head-to-head with warfarin in the ARISTOTLE trial. If the data from that trial looks favorable, it is likely that both apixaban and rivaroxaban also will be approved for this indication in the not-too-distant future. Dabigatran and apixaban are both dosed bid while rivaroxaban is a once-a-day drug. The extent to which these drugs gain general usage at the expense of warfarin in large part will be due to patient preference and cost. ■

Fidaxomicin for *C. difficile* infections

A new option may soon be availiable for treating *Clostridia difficile* infections. Fidaxomicin (not yet approved in this country) is a non-systemic (poorly absorbed) narrow spectrum macrolide antibiotic that is bacteriocidal against *C. difficile* infections. It recently was compared to vancomycin in a head-to-head Phase 3 noninferiority study of 629 adults. Patients with a positive stool toxin test to *C. difficile* were randomized to

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) 262-5404. E-mail: neill.kimball@ahcmedia.com.

fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day. The primary endpoint was clinical cure and the secondary endpoint was recurrence within 4 weeks and global cure (no recurrence). Fidaxomicin was noninferior to vancomycin in both the intention-to-treat (88.2% cure rate with fidaxomicin vs 85.8% with vancomycin) and per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients had recurrence with fidaxomicin in both groups (15.4% vs 25.3%, $P = 0.005$ intention-to-treat, and 13.3% vs 24.0%, $P = 0.004$ per protocol) although the lower rate of recurrence was in the less virulent strains. For the more virulent strains, the recurrence rate was about 25% for both drugs. Fidaxomicin was associated with a higher rate of hyperuricemia and elevated transaminases (*N Engl J Med* 2011;364:422-431). An accompanying editorial points out that the incidence and virulence of *C. difficile* infections is increasing at an alarming rate in this country. Fidaxomicin inhibits vegetative forms of *C. difficile* while preseving intestinal flora, a combination that holds promise, and if borne out "this new agent could become a recommended therapy for *C. difficile* infection" (*N Engl J Med* 2011;364:473-475). ■

Guideline for intensive insulin therapy

A guideline from the American College of Physicians (ACP) recommends against aggressively controlling blood glucose in hospitalized patients. Intensive insulin therapy (IIT) is no longer recommended for patients in intensive care units, regardless of whether they have diabetes. Specifically, the ACP recommends not using IIT to strictly control blood glucose or even normalized blood sugar in surgical ICU or medical ICU patients, and recommends a target blood glucose level of 140-200 mg/dL if insulin therapy is used. The recommendation is based on multiple studies that show no reduction in mortality with a blood glucose target of 80-180 mg/dL compared with higher targets using a variety of intensive insulin regimens. This includes treatment of patients with myocardial infarction, stroke, acute brain injury, or those under perioperative care. The guideline further recommends that avoiding targets less than 140 mg/dL should be a priority because harm is likely with lower blood glucose targets (*Ann Intern Med* 2011;154:260-267).

FDA actions

The FDA is warning against the use of terbutaline for prevention or prolonged treatment of preterm labor in pregnant women. The drug, which is approved for treatment of asthma, has been used off label for treatment of preterm labor and uterine hyperstimulation; however, the agency has received postmarketing reports of serious adverse reactions, including heart problems, and even maternal deaths, associated with the drug. The FDA has added a Boxed Warning and Contraindication to the labeling of the drug warning against these uses. This extends to both the IV and oral forms of terbutaline.

The FDA has approved hydroxyprogesterone caporate injection to reduce the risk of preterm delivery before 37 weeks of pregnancy in a pregnant woman with a history of at least one spontaneous preterm birth. The drug is not intended for use in women with a multiple pregnancy, such as a twin pregnancy, or other risk factors for preterm birth. The drug was approved under the FDA's accelerated approval regulations, and, as such, additional studies will be required after approval to show that the drug does indeed have clinical benefit. Hydroxyprogesterone caproate is given once a week by injection into the hip beginning at week 16 and no later than week 21. The drug is marketed by Hologic Inc. as Makena.

The FDA has issued a drug safety alert regarding the risk of serious liver injury with dronedarone (Multaq). The drug — which is approved for prevention of atrial fibrillation/flutter — has been associated with multiple cases of severe liver injury, including two cases that required liver transplantation. Dronedarone previously was found to double the risk of death in patients with severe heart failure and was approved with a REMS designed to prevent its use in that patient population. Physicians are reminded to advise patients to contact a health care professional immediately with any signs of hepatic injury or toxicity. All patients on dronedarone should get periodic hepatic serum enzymes especially during the first 6 months of therapy.

The FDA has approved a new treatment for head lice. Spinosad is an insecticide originally derived from a naturally occurring soil bacterium. The 0.9% topical suspension was shown to be effective in two Phase 3 active-control, randomized studies in which 86% of patients treated with the active drug were lice free after 14 days compared to 44% of controls. The product should not be used in children under 6 months of age because it contains benzyl alcohol. Spinosad is applied as a single 10-minute application which may be repeated in one week if lice are seen. It will be marketed by ParaPro LLC as Natroba. ■