TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media

INSIDE

Volume 21, No. 10
October 2011

Financial Disclosure:
Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, reports no financial relationships relevant to this field of study. Peer reviewer Mary-Louise Scully, MD, peer reviewer Philip R. Fischer, MD, DTM&H, Executive Editor Gary Evans, and Senior Managing Editor Paula Cousins, BSN, report no financial relationships relevant to this field of study.

Fever in Travelers After Visiting Malaria-endemic Areas

ABSTRACT AND 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.

Synopsis: *Common specific causes of fever in Finnish returned travelers were* Campylobacter*, malaria, bacteremia, HIV, and influenza; they included a significant proportion of potentially life-threatening infections, and more than one diagnosis. Evaluation of such fevers should be systematic and thorough.*

Source: Siikamaki HM, Kivela PS, Sipila PN, et al. Fever in travelers returning from malaria-endemic areas: Don't look for malaria only. *J Travel Med* 2011;18:239-244.

AUTHORS FROM THE HELSINKI UNIVERSITY CENTRAL HOSPITAL, A TERTIARY HOSPITAL in Finland, retrospectively reviewed patient records from 2005 to 2009 to define the causes of fever in returned travelers and to evaluate the diagnostic approach. The 462 records were selected through requests for malaria smears in the emergency department.

The most common categories of diagnoses were acute diarrhea (27%), systemic febrile illness (21%), and respiratory illness (15%). Campylobacteriosis was the most common specific diagnosis (9%), while malaria was diagnosed in 4%. Bacteremia was identified in 5% of patients tested (21/428), and influenza was diagnosed in 8 patients. HIV antibodies were performed in 174 patients (38%) and 3% were positive. Non-infectious etiologies caused fever in 3%, and in 25% of the cases the etiology remained unknown.

Potentially life-threatening illnesses were diagnosed in 26% of the patients, and were associated with elevated C-reactive protein (CRP) ≥ 100 (odds ratio [OR], 3.6; 95% confidence interval [CI], 2.0-6.4) and thrombocytopenia (OR, 3.8; 95% CI, 2.0-7.3). One patient died of septicemia. Forty-five patients (10%) had more than one diagnosis.

■ COMMENTARY

A number of serious, life-threatening infections can cause fever in a returned traveler, and the evaluation may be challenging for clinicians unfamiliar with

the epidemiology at the destination countries. Data from studies on travelers are welcome to further strengthen work-ups for particular diagnoses.

A well-established network of specialized travel and tropical medicine clinics, GeoSentinel, analyzed fever in 24,920 returned travelers seen from March 1997 through March 2006 and found fever to be the main cause for seeking medical evaluation in 6,957 (28%).[1] In that analysis, 15% of the fever cases were due to diarrheal disease, 14% due to respiratory illness, and 35% had a febrile systemic illness. Malaria, found in 21% of febrile returned travelers, was the most common specific cause identified.[1] Etiologies for fever varied by region visited and by time of presentation after travel, and the most significant risk factors were travelers who visited sub-Saharan Africa, south-central Asia, and Latin America and whose reason for travel was visiting friends and relatives (VFR). Malaria caused 33% of the 12 deaths among febrile travelers.[1]

A number of centers have studied fever in their returned travelers. A prospective observational study from January 1997 to December 2001 on fever in returning travelers (n = 147) admitted to a university teaching hospital in Milan, Italy, found that malaria accounted for nearly half of admissions (47.6%), followed by presumed self-limiting viral infections (12%).[2] The most useful investigations at this center were blood smears and PCR for malaria, which were positive in 65% of cases for which they were performed. Serology was useful to identify hepatitis A and dengue virus infections.[2]

Investigators in Marseilles, France, also conducted a 5-year prospective observational study on the etiologies of fever in travelers returning from the tropics admitted to a university teaching hospital (n = 613).[3] Malaria was the most common diagnosis (75.2%), with most cases (62%) acquired by VFR travelers from the Comoros Islands; 8.2% of the patients remained unexplained.[3]

Bottieau et al from University Hospital Antwerp, Belgium, also analyzed the etiology of fever and diagnostic predictors from April 2000 to December 2005 in nearly 2,000 returned travelers.[4,5] Exposures occurred commonly in sub-Saharan Africa and Southeast Asia-Pacific (68% and 12%, respectively).[4] Tropical diseases accounted for 39% of the cases, cosmopolitan infections for 34%, and 24% remained unknown. Approximately one-quarter required hospitalization. The travel destinations were major determinants of tropical infections, with malaria and rickettsial infections as the leading diagnoses after a stay in Africa (35% and 4%, respectively); dengue, malaria, and enteric fever after travel to Asia (12%, 9%, and 4%, respectively); and dengue and malaria on return from Latin America (8% and 4%, respectively).[4]

Although malaria accounted for only 4% of the diagnoses in the study by Siikamaki et al, other European studies found malaria to be a more significant cause of morbidity,[1-5] and also a major cause of mortality.[1,4] Therefore, malaria remains one of the most important diagnoses to exclude when a returned traveler presents with fever. Some findings associated with malaria from these studies include splenomegaly, thrombocytopenia, lack of localizing symptoms, and hyperbilirubinemia.[5] Other key predictors of fever etiology include: skin rash and skin ulcer for rickettsial infection (mainly African tick bite fever); skin rash, thrombocytopenia, and leukopenia

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.

for dengue; eosinophilia for acute schistosomiasis; and splenomegaly and elevated serum alanine aminotransferase level for enteric fever.[5]

Siikamaki and colleagues reaffirm that a significant proportion of febrile returning travelers had a potentially life-threatening illness (about one-quarter). Bacteremia was as common as malaria. Also, the significant finding of several HIV cases warrants routine HIV testing. Both blood cultures and HIV tests should be considered in febrile travelers. Importantly, the high proportion of patients (10%) with more than one diagnosis highlights the need for careful systematic work-up. A hospital-based study of the causes of fever in adults on the Thai-Myanmar border found that dual diagnoses were common, especially malaria (25% of the diagnoses) and leptospirosis (17%).[6]

In summary, fever is common in ill returned travelers and often results in hospitalization. The time of presentation and geographic region of exposure provide key information to generate the differential diagnoses. Particular symptoms and findings suggest some specific diagnoses. Travel medicine specialists who evaluate febrile returned travelers should evaluate the patient systematically, and include studies for malaria, blood cultures, and HIV tests especially in cases where localizing symptoms are lacking. ■

References

1. Wilson ME, Weld LH, Boggild A, et al; GeoSentinel Surveillance Network. Fever in returned travelers: Results from the GeoSentinel Surveillance Network. *Clin Infect Dis* 2007;44:1560-1568.
2. Antinori S, Galimberti L, Gianelli E, et al. Prospective observational study of fever in hospitalized returning travelers and migrants from tropical areas, 1997-2001. *J Travel Med* 2004;11:135-142.
3. Parola P, Soula G, Gazin P, et al. Fever in travelers returning from tropical areas: Prospective observational study of 613 cases hospitalised in Marseilles, France, 1999-2003. *Travel Med Infect Dis* 2006;4:61-70.
4. Bottieau E, Clerinx J, Van den Enden E, et al. Fever after a stay in the tropics: Diagnostic predictors of the leading tropical conditions. *Medicine (Baltimore)* 2007;86:18-25.
5. Bottieau E, Clerinx J, Schrooten W, et al. Etiology and outcome of fever after a stay in the tropics. *Arch Intern Med* 2006;166:1642-1648.
6. Ellis RD, Fukuda MM, McDaniel P, et al. Causes of fever in adults on the Thai-Myanmar border. *Am J Trop Med Hyg* 2006;74:108-113.

New Dracunculiasis Cases in Chad: A Setback in Global Eradication

ABSTRACT AND COMMENTARY

By Mary-Louise Scully, MD

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

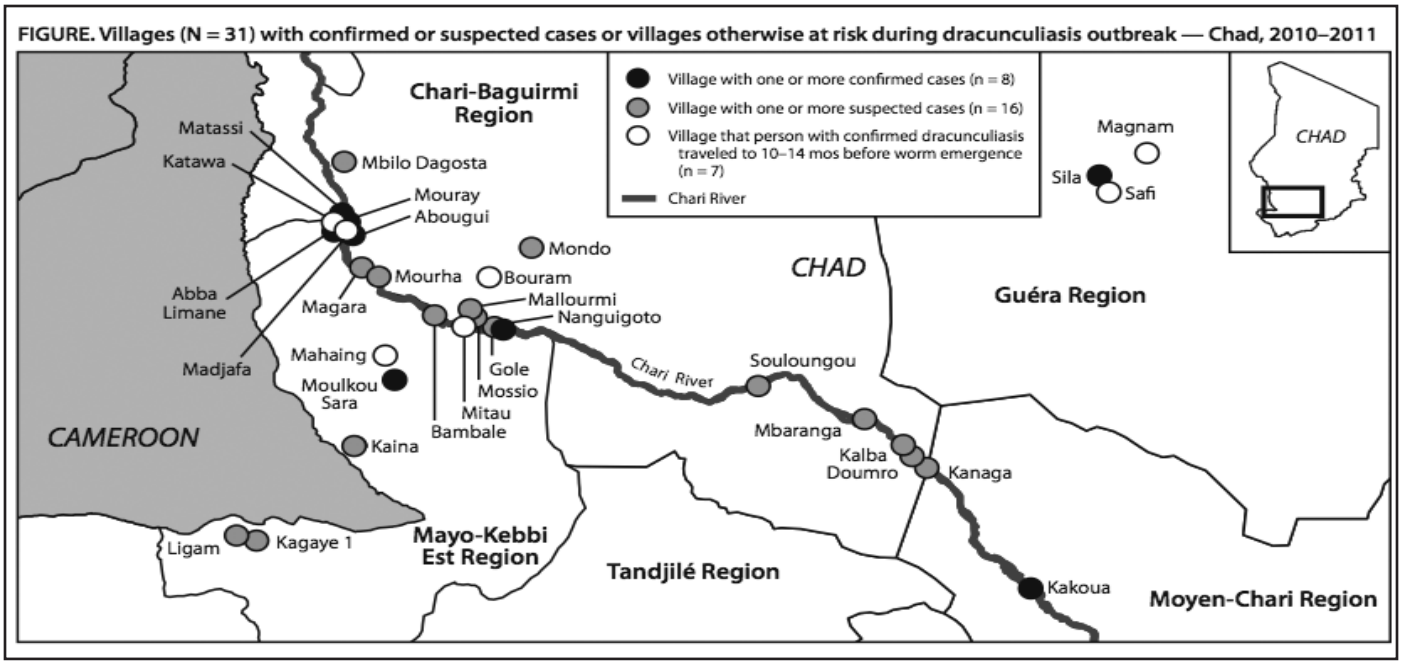
Dr. Scully reports no financial relationships to this field of study

Synopsis: *Immense efforts are ongoing toward the goal of worldwide elimination of dracunculiasis (Guinea worm disease). Ten new cases were reported in 2010 in Chad, a country where disease transmission had been interrupted since 2000.*

Source: Centers for Disease Control and Prevention. Renewed transmission of dracunculiasis — Chad, 2010. *MMWR Morb Mortal Wkly Rep* 2011;60:744-748.

During April-June of 2010, 2 new cases of dracunculiasis were confirmed by extracted worm identification of *Dracunculus medinensis* and polymerase chain reaction (PCR) in Chad, Africa. Chad's National Guinea Worm Eradication Program (NGWEP) initiated an outbreak investigation and with the help of the World Health Organization (WHO) uncovered 8 additional cases, all confirmed by worm collection. The 10 confirmed cases were located in eight different villages within four regions of Chad *(see Figure, page 56)*. Six of the eight villages were on the borders of the Chari River, which runs across southern Chad. This large river is a main transportation route in southern Chad, supports local fishing industry, and is crossed frequently by nomadic herdsman, who often travel through Chad to neighboring countries.

In December of 2010, the Centers for Disease Control and Prevention (CDC) joined with the Chad Ministry of Public Health and the WHO to conduct a dracunculiasis outbreak investigation and during January-February of 2011 a survey took place in 210 villages and 15 nomad camps. The results demonstrated that both villagers (55%) and nomads (87%) reported consuming water from unsafe sources, but the percentage of this risk activity among nomads was clearly much higher. Also, only 33% of the surveyed nomads knew about dracunculiasis (recognized a photo) vs. 75% of surveyed villagers. Nomadic populations regularly interact with the sedentary groups by sharing water sources or attending weekly markets. The lack of knowledge and the frequent inges-



tion of unsafe water make this nomadic population an important target group for prevention efforts. These efforts include filter distribution, education, and case containment, which includes efforts to prevent an infected patient from contaminating water sources.

With the late detection of cases in Chad, none of the 10 patients were prevented from potentially contaminating drinking water sources; therefore, 31 villages were classified as at-risk for further cases of dracunculiasis. Since this CDC investigation, 2 additional cases emerged in Chad in 2011, raising the number of at-risk villages to 36.

■ COMMENTARY

The presence of dracunculiasis, or Guinea worm, likely dates back in history to antiquity. It is believed that the "fiery serpent" mentioned in the Old Testament may be referring to Guinea worm. The existence of Guinea worm in Egyptian times was confirmed when the calcified remains of a male Guinea worm was found by radiography in the abdominal wall of a mummy as part of Britain's Manchester Mummy Research Project.[1] Carl Linnaeus often is credited with the first suggestion that the disease was indeed caused by a worm and the name "Guinea worm" was likely coined when 17th century Europeans saw the disease during travel to the Gulf of Guinea area of West Africa.

Humans are the only mammalian reservoir for this nematode and are therefore solely responsible for the persistence of the disease. When drinking water from sources contaminated with larvae-infected copepods (tiny "water fleas") is ingested by humans, the Guinea worm larvae are released, penetrate the gut wall, and mate in the retroperitoneal space. The male worm dies shortly after mating, but 10-14 months later the female migrates through subcutaneous tissues, often to the lower extremities, and creates a blister, which eventually ruptures forming a painful ulcer. If the lesion is immersed in water, which relieves the excruciating pain, the worm ejects its larvae into the water, which in turn are ingested by new copepods, perpetuating the life cycle.

There is no effective drug treatment or vaccine for this debilitating illness. The management involves removal of the 3-foot long worm slowly, by rolling it around a gauze or stick a few centimeters per day. This extraction is long and painful for the patient and secondary bacterial infections can complicate the process. In addition, an infected person does not develop any immunity to the disease.

In 1986 it was estimated that dracunculiasis affected 3.5 million people in 20 countries in Africa and Asia. Through the efforts of former President Jimmy Carter and his wife Rosalynn, the Carter Center has spearheaded the international Guinea worm eradication campaign, working with many other global partners. As a result of these efforts, Guinea worm cases have fallen to fewer than 1,800 cases worldwide, a reduction of more than 99% and another likely 79 million cases have been averted.[2] Perhaps even more impressive is that this was all accomplished without a drug or a vaccine, but rather with the old fashioned public health tactic of educating people about changing their behavior.[3]

There are three remaining countries with pockets of dracunculiasis — South Sudan, eastern Mali, and western Ethiopia. Between January and June of 2011, there have been 806 confirmed cases of dracunculiasis from 366 villages. The majority of cases are from South Sudan (793), with very low numbers from Mali (3), Ethiopia (8), and Chad (2).[4] Ghana has been declared free of disease

with no cases reported in 14 months. This outbreak in Chad, the first cases since 2000, is felt to represent a public health emergency and a setback for the Global Guinea Worm Eradication Program. Unfortunately, the resources needed for active surveillance in Chad are lacking, but any available resources will first be directed toward the 36 at-risk villages identified by this investigation. This outbreak also highlights the need for ongoing disease surveillance in formerly endemic areas after eradication programs end. In Chad, we recently have witnessed this type of setback in global disease eradication efforts with recrudescence of cases of onchocerciasis, polio, and now Guinea worm. ■

References

1. Archaeology. Under Wraps: Rosalie David in Conversation. Available at www.archaeology.org/online/features/mummies/. Accessed Sept. 4, 2011.
2. Guinea Worm Eradication Program. The Carter Center. Guinea worm Fact Sheet. Available at www.cartercenter.org/health/guinea_worm/mini_site/facts.html.
3. Barry M. The tail end of Guinea worm — global eradication without a drug or vaccine. *N Engl J Med* 2007;356:2561-2564.
4. World Health Organization Collaborating Center for Research, Training and Eradication of Dracunculiasis. Guinea worm wrap-up No. 206. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2011. Available at http://cartercenter.org/news/publications/health/guinea_worm_wrapup_english.html. Accessed Sept. 2, 2011.

Plasmodium knowlesi: The Newest Human Malaria Parasite

SPECIAL REPORT AND UPDATE

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

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

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

Synopsis: Plasmodium knowlesi*, typically a parasite of macaque monkeys, is rapidly emerging as a fifth species of malaria that causes disease in humans. Hundreds of human cases have now been reported from southeast Asia, including several fatalities.* P. knowlesi *may be more widely distributed than initially appreciated, and appears to cause more severe disease than the other non-falciparum malaria species.*

Source: Kantele A, Jokiranta TS. Review of cases with the emerging fifth human malaria parasite, *Plasmodium knowlesi*. *Clin Infect Dis* 2011;52:1356-1362.

Malaria continues to be a global scourge, causing more than 200 million annual symptomatic cases and nearly a million annual deaths worldwide.[1] For decades, human malaria has been classically attributed to four pathogens, *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. *P. falciparum* causes the most severe form of malaria, and is responsible for most of the morbidity and mortality on a global basis; *P. vivax* and *P. ovale* cause a generally less severe illness, but can cause late relapses; and *P. malariae* usually causes a low-grade illness and can occasionally persist for years, or even decades.

While more than two dozen *Plasmodium* species cause malaria in primates, the species specificity of these pathogens has generally been strict. Natural transmission of any *Plasmodium* species to humans, aside from the four classical "human" malaria species described above, has been quite rare.

P. knowlesi was first recognized in 1931, when it was observed to cause malaria in macaque monkeys; it causes malaria in other monkey species as well. Despite being less species-specific than other *Plasmodium* spp., it was presumed to infect only non-human primates in the wild. Although nosocomial infection of humans was reported in the 1930s, natural infection of humans with *P. knowlesi* was unknown until 1965, when a case was reported in a returned traveler who had been to peninsular Malaysia.[2]

Few naturally acquired *P. knowlesi* human infections were recognized until a 2004 study examined 208 patients with malaria in Malaysian Borneo who were thought to be infected with *P. malariae* based on microscopy, but for whom PCR testing for this species was negative. One hundred twenty (58%) of these patients had actually been infected with *P. knowlesi*, based on PCR testing with new primers specific for this species; the morphological similarities between these two species contribute to this common diagnostic error.[3] Multiple similar reports have followed, and retrospective analyses have shown that many cases of malaria, dating back many years in southeast Asia, were in fact due to *P. knowlesi*.

Transmission of *P. knowlesi* appears to be zoonotic;

cases of natural human-mosquito-human transmission have yet to be described. Although gametocytes (responsible for transmission of malaria from a human host to a mosquito) are formed in human *P. knowlesi* infections, this occurs only at low levels. In addition, the natural vector mosquitoes (*Anopheles leucosphyrus* group) for *P. knowlesi* are forest feeders. Importantly, at least one widely distributed urban vector (*Anopheles stephensi*) can transmit *P. knowlesi*,[4] suggesting that transmission could become widespread if human-mosquito-human transmission were to occur.

To date, *P. knowlesi* has been identified as the cause of human malaria in 573 cases within Malaysian Borneo, 90 cases in peninsular Malaysia, 33 cases in Burma, 11 cases in Thailand, 6 in the Philippines, 6 in Singapore, 5 in Vietnam, 2 in Indonesian Borneo, and 1 in Brunei. Of these 727 patients, 8 (1.1%) have been travelers, and 5 (0.7%) have died.

Clinically, *P. knowlesi* is similar to other malaria species. Non-specific fever and chills are common, as are headache, rigors, malaise, myalgia, cough, and thrombocytopenia; anemia has been uncommon. Overall, 7% of cases have been severe (as determined by WHO criteria), most commonly due to respiratory distress. A small number of patients have developed renal dysfunction, and neurological symptoms have been rare; cerebral malaria has not been reported.

Like *P. falciparum*, *P. knowlesi* can infect red blood cells of all ages, resulting in potentially high levels of parasitemia. Of the five species which cause malaria in humans, *P. knowlesi* has the shortest life cycle (24 hours), enabling potentially rapid progression of disease. Although *P. knowlesi* may be confused microscopically with *P. malariae* (the least virulent of the human malaria species), it can cause a severe illness like *P. falciparum*.

The diagnosis of *P. knowlesi* often is based on PCR. Although visible by light microscopy, the early trophozoites of *P. knowlesi* resemble the ring forms of *P. falciparum*, and its later stages mimic those of *P. malariae*. Thus, *P. knowlesi* infection often is misidentified microscopically as *P. malariae*, or less commonly, *P. falciparum*. Because *P. knowlesi* malaria can be life-threatening, this parasite should be suspected when microscopic examination suggests *P. malariae*, but the patient has either severe disease, high-grade parasitemia, or a recent history of travel to southeast Asian forests. Rapid diagnostic tests have not been validated for the diagnosis of *P. knowlesi* and currently should be regarded as unreliable for this purpose.

P. knowlesi appears to be susceptible to all antimalarials; current recommendations are for treatment with chloroquine if a patient is known to be infected with *P. knowlesi*.[5] Because *P. knowlesi* infection can rapidly become severe, it should be treated promptly, and with drugs appropriate for falciparum malaria if the species identification is based on microscopic examination alone or if co-infection with *P. falciparum* cannot be excluded with certainty. *P. knowlesi* does not appear to establish liver hypnozoites nor to cause late relapse based on this mechanism; primaquine treatment thus appears unnecessary.

P. knowlesi appears to be a natural parasite of macaques throughout southeast Asia. The wide distribution of human cases shows that *P. knowlesi* generally is able to infect humans, unlike the other malaria species that infect non-human primates. Although initially identified only in Malaysian Borneo (and with the majority of reported cases there), it seems likely that *P. knowlesi* is widely distributed throughout Borneo; the small number of cases reported from the Indonesian side of this island is likely the result of the poorer surveillance and public health capacity of Indonesia relative to Malaysia. The increasing number of recent *P. knowlesi* cases overall may be a result of ascertainment bias (given the increasing availability of PCR methods to detect *P. knowlesi*), or of decreasing numbers of other malaria species relative to *P. knowlesi*, or of increased transmission of *P. knowlesi* in recent years (although archival blood films argue against this latter possibility). While human-mosquito-human transmission has been reported in experimental settings, this has not yet been observed to occur naturally.[6] If natural human-mosquito-human transmission does occur, *P. knowlesi* could spread more widely in Asia, given that at least one vector species (*Anopheles latens*) is widely distributed in southeast Asia and the southern Indian subcontinent; another species (*An. stephensi*) is widely distributed in urban centers and could result in spread to cities. *P. knowlesi* could become a major human pathogen in such a circumstance, and probably is already more widespread than has been appreciated to date. This emerging infection, perhaps the second-most virulent of what are now five human malaria species, will be important to monitor as cases continue to be reported in the coming years. ■

References

1. World Health Organization: World Malaria Report: 2010. Available at: www.who.int/malaria/world_malaria_report_2010/en/index.html. Accessed Sept. 5, 2011.
2. Chin W, Contacos PG, Coatney GR, et al. A naturally acquired quotidian-type malaria in man transferable to monkeys. *Science* 1965;149:865.
3. Singh B, Kim Sung L, Matusop A, et al. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet* 2004;363:1017-1024.
4. Coatney GR, Collins WE, Warren M, et al. The primate

malarias [original book published 1971] [CD-ROM]. Atlanta, GA: Centers for Disease Control and Prevention; 2003.
5. Centers for Disease Control and Prevention. Guidelines for Treatment of Malaria in the United States (updated May 18, 2009). Available at: www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf. Accessed Aug. 30, 2011.
6. Chin W, Contacos PG, Collins WE, et al. Experimental mosquito-transmission of *Plasmodium knowlesi* to man and monkey. *Am J Trop Med Hyg* 1968;17:355-358.

Imported Pediatric Malaria

ABSTRACT AND COMMENTARY

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is 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: *A retrospective survey shows that imported pediatric malaria continues to occur. Children most at risk are those traveling to visit friends and relatives, especially in West Africa, without being provided effective chemoprophylaxis.*

Source: Hickey PW, Cape KE, Masuoka P, et al. A local, regional, and national assessment of pediatric malaria in the United States. *J Travel Med* 2011;18:153-160.

A RETROSPECTIVE REVIEW OF PEDIATRIC MALARIA AT A Washington, DC, children's hospital identified 98 cases over 8 years from 1999 to 2006. Their mean age was 9.6 years. Approximately half of the children were long-term U.S. residents who had visited friends or relatives in their country of origin, and most of the others were recent immigrants. Eighty-five percent of these children had been exposed to malaria in West Africa. Only 6% reported having been properly adherent to an effective malaria chemoprophylaxis regimen. Seventeen of the children were initially diagnosed with something other than malaria, but 82% of patients were accurately diagnosed as having malaria on the day they presented for care. The mean duration of symptoms prior to diagnosis was 5 days (range 1-30). One child recovered following cardiac arrest, 19% required intensive care, and all survived.

The authors then reviewed the Pediatric Health Information System database and identified 306 children with malaria at 40 large American children's hospitals from January 2003 to June 2008. *P. falciparum* accounted for the majority of infections. The hospitals' charges for the care of these 306 children totaled $5.3 million ($17,519 per patient).

■ COMMENTARY

Imported malaria continues to be diagnosed among children in the United States, as well as in Europe.[1,2] In the United States during 2009, there were 1,484 reported cases of malaria, and 16% of these cases were among those younger than 18 years of age.[3] Of these pediatric cases, 89% occurred after travel in Africa, and 73% were in children who had traveled to visit friends and relatives; only 4% reported adherence to an accepted anti-malarial chemoprophylaxis regimen.[3]

While important, malaria is not the most common problem occurring in returned travelers. Of 1,591 children presenting for health care in 19 countries following travel to 218 destinations, 28% had diarrhea, 25% had skin conditions, 23% had fever (8% of the total with malaria), and 11% had respiratory illnesses.[4] When compared to adults presenting for post-travel care, children presented sooner following travel, required more hospitalizations, more often lacked pre-travel care, and more often had traveled to visit friends and relatives.[4]

So, what are the practical implications of these new data? First, realizing that the majority of sick returned pediatric travelers and the majority of patients with imported malaria had traveled to visit friends and relatives, we should expand our pre-travel efforts specifically directed toward these travelers.[5] Second, realizing that most of these travelers did not take appropriate chemoprophylaxis, we should identify ways of both bringing these travelers into contact with pre-travel care and ensuring that they apply appropriate preventive efforts. How might this be accomplished? Strategies should be developed to engage travelers who are not currently presenting for pre-travel care. Current practices could be supplemented with new efforts focused on immigrant populations (those most likely to take children to other countries to visit friends and relatives). A goal would be to reach into communities with good pre-travel interventions. This could be facilitated by including questionnaires about future travel plans in community clinic and primary care practice health maintenance visits.[6]

Malaria still happens among children in the United States. Imported malaria most commonly occurs in those children who traveled to visit friends and relatives, especially in West Africa. Malaria diagnoses are frequently delayed in the United States, and imported malaria is associated with significant morbidity and cost. These are not new messages, but these old findings (reported in *Travel Medicine Advisor* in 2003, 2006, and 2009) are

again confirmed by new data. What will be done to better prevent imported pediatric malaria? A new Pediatric Interest Group of the International Society of Travel Medicine is seeking to work in and beyond the travel medicine community to improve pre-travel care of children.[7] ■

References

1. Garbash M, Round J, Whitty CJ, et al. Intensive care admissions for children with imported malaria in the United Kingdom. *Pediatr Infect Dis J* 2010; 29:1140-1142.
2. Elmansouf L, Dubos F, Dauriac A, et al. Evaluation of imported pediatric malaria management in northern France. *Med Mal Infect* 2011;41:145-151.
3. Mali S, Tan KR, Arguin PM. Malaria surveillance — United States. 2009. *MMWR Surveill Summ* 2011; 60:1-15.
4. Hagmann S, Neugebauer R, Schwartz E, et al. Illness in children after international travel: Analysis from the GeoSentinel Surveillance Network. *Pediatrics* 2010;125:e1072-e1080.
5. Hagmann S, Schlagenhauf P. Prevention of imported pediatric malaria — travel medicine misses the bull's eye. *J Travel Med* 2011;18:151-152.
6. Hagmann S, Reddy N, Neugebauer R, et al. Identifying future VFR travelers among immigrant families in the Bronx, New York. *J Travel Med* 2010;17:193-196.
7. Pediatric Interest Group, International Society of Travel Medicine. Available at: www.istm.org/WebForms/Members/MemberActivities/VolunteerActivities/interest_groups/pediatrics.aspx. Accessed Aug. 27, 2011.

CME Objectives / Instructions

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

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

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

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

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

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Questions

1. **The evaluation of fever in a traveler returning from the tropics:**
   a. should only include blood smears for malaria when the traveler did not take chemoprophylaxis.
   b. may result in more than one diagnosis; hence, it requires a systematic work-up.
   c. nearly always yields a pathogen, leading to specific causality.
   d. is unlikely due to acute human immunodeficiency virus infection.

2. **Which of the following statements about dracunculiasis (Guinea worm) is *true*?**
   a. The black fly serves as the vector of this disease.
   b. Transmission is primarily associated with contaminated seafood.
   c. Globally the disease incidence is on the rise.
   d. Nomadic populations represent an at-risk group.
   e. Disease results in life-long immunity.

3. **Which of the following is *true* regarding *P. knowlesi*?**
   a. *P. knowlesi* usually is resistant to chloroquine, so this drug should not be used to treat this malaria infection.
   b. *P. knowlesi* preferentially infects young red blood cells.
   c. Human cases have been reported in many southeast Asian countries.
   d. *P. knowlesi* causes a milder form of malaria in humans.
   e. *P. knowlesi* morphologically resembles *P. vivax* and *P. ovale*.

4. **Imported pediatric malaria:**
   a. usually occurs after travel to the Indian sub-continent.
   b. frequently is identified in children who were compliant with chemoprophylaxis.
   c. is more frequent among tourists to game parks.
   d. especially occurs in children visiting friends and relatives in Africa.

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 is Heating Up the Anticoagulation Market

In this issue: Apixaban could soon join the anticoagulation market; Chinese herbs for flu; chronic medication and discontinuation after hospitalization; and FDA actions.

Apixaban trial results look promising

There is soon to be a third player in the anticoagulation wars. Apixaban, an oral factor Xa inhibitor, will likely soon join dabigatran and rivaroxaban as alternatives to warfarin for preventing stroke in patients with atrial fibrillation (AF). Dabigatran, a direct thrombin inhibitor, was approved for this indication last year and rivaroxaban, also a factor Xa inhibitor, is likely to be approved in early September. (Rivaroxaban was previously approved for DVT prevention in patients undergoing orthopedic surgery.) Apixaban also looks very promising based on results of the ARISTOTLE trial, which was published online in the *New England Journal of Medicine* on August 28. ARISTOTLE enrolled 18,201 patients with AF and at least one additional risk factor for stroke. Patients were randomly assigned to apixaban 5 mg twice daily or warfarin with a target INR of 2-3. ARISTOTLE was designed as a noninferiority study with a primary outcome of ischemic or hemorrhagic stroke, or systemic embolism. After median follow-up of 1.8 years, the rate of the primary outcome was 1.27% per year in the apixaban group vs 1.60% in the warfarin group (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.66 to 0.95; $P < 0.0014$ noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 30% less with apixaban and the rate of death from any cause was 3.52% with apixaban and 3.94% with warfarin ($P = 0.047$). The rate of hemorrhagic stroke in the apixaban group was about half that in the warfarin group (0.24% per year vs 0.47% per year, $P < 0.001$) and the rate of all other strokes was 0.97% with apixaban vs 1.05% with warfarin ($P = 0.42$). The authors conclude that in patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality (*N Engl J Med* published online August 28, 2011). An excellent accompanying editorial discusses the seminal studies that compared the three new anticoagulants to warfarin for stroke prevention in patients with AF: RE-LY — dabigatran; ROCKET AF — rivaroxaban; and ARISTOTLE — apixaban. All three showed that the new drugs were significantly better than warfarin at reducing hemorrhagic stroke and all were at least as effective as warfarin at preventing ischemic stroke. All three drugs were also associated with a significantly lower rate of serious bleeding compared to warfarin. Apixaban was the only drug that showed a significant reduction in overall mortality, although both dabigatran and rivaroxaban showed trends in that direction. ROCKET AF has been criticized because the warfarin comparator group had a time in therapeutic range of only 55% compared to 64% in the RE-LY trial and 62% in ARISTOTLE; however, patients in the ROCKET AF study were at higher risk for stroke than in the other two studies. The bottom line is that all three drugs are effective in preventing stroke in patients with nonvalvular

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.

AF and seem to be safer than warfarin as well. The new drugs do not require any laboratory monitoring, which is convenient for patients and also lowers the overall cost of care (although all three drugs will be priced significantly higher than generic warfarin). Rivaroxaban has the advantage of a once daily dose vs the other two drugs, which must be dosed twice daily. None of the three drugs can be quickly reversed in the event of major bleeding or need for surgery. Apixaban is not yet approved in this country but when it is, it is likely that the competition between these three agents will be fierce, and for many purchasers of health care it may come down to cost. ■

Chinese herbs for flu treatment

For the flu season this year, you might consider Chinese herbs instead of antivirals based on the results of a study from China published in the *Annals of Internal Medicine*. More than 400 adults age 15-59 years with confirmed H1N1 influenza were randomized to oseltamivir 75 mg twice daily or a combination of 12 Chinese herbal medicines called maxingshigan-yinqiaosan 200 mL four times a day, a combination of oseltamivir plus maxingshigan-yinqiaosan, or placebo for 5 days. The primary outcome was time-to-fever resolution and the secondary outcomes included symptom scores and viral shedding. Both oseltamivir and maxingshigan-yinqiaosan, as well as the combination, resulted in significant reductions in the estimated median time-to-fever resolution compared to the control group (median time-to-fever resolution — no treatment 26 hours; oseltamivir 20 hours; maxingshigan-yinqiaosan 16 hours; combination 15 hours; all statistically significant at $P < 0.001$). Side effects were similar in all groups. The authors conclude that oseltamivir and maxingshigan-yinqiaosan, alone or in combination with each other, reduce time-to-fever resolution in patients with H1N1 influenza. They go so far as to suggest that maxingshigan-yinqiaosan may be used as an alternative treatment for H1N1 infections (*Ann Int Med* published online August 26, 2011). It may be difficult to obtain maxingshigan-yinqiaosan since it contains ephedra (which is not available in this country) and the authors could not determine if the benefits of maxingshigan-yinqiaosan were due to an antiviral effect or merely an antipyretic effect. ■

Chronic medications and hospitalization

Your patients' chronic medications may be inadvertently discontinued after hospitalization according to a population-based cohort study of almost 400,000 patients published recently in the *Journal of the American Medical Association*. Researchers from Canada reviewed the records of residents age 66 or older who were on statins, antiplatelet/anticoagulant agents, levothyroxine, respiratory inhalers, or gastric acid suppressing drugs on a chronic basis. When compared to nonhospitalized patients, patients admitted to the hospital — especially the ICU — were more likely to have their chronic medications discontinued. Discontinuation rates ranged from a low for levothyroxine of 12.3% discontinuation for hospitalizations vs 11% for controls, to antiplatelet/anticoagulant agents which were discontinued at a rate of 19.4% for hospitalizations vs 11.8% for controls. The discontinuation rates were even higher for patients who were admitted to the ICU. The authors conclude that patients admitted to the hospital are at relatively high risk for potential unintentional discontinuation of chronic medications (*JAMA* 2011;306:840-847). This study points out the importance of medication reconciliation at all post-hospital visits and may validate the role of computerized medical records, especially with regard to medication lists. ■

FDA actions

The FDA has approved a new fixed-dose combination pill for HIV-infected patients. Emticitabibine/rilpirivine/tenfovir DF is approved as a once-a-day pill for treatment of HIV-1 infection in treatment-naïve patients. This is the second triple combination anti-HIV agent approved and differs from the previous agent (Atripla) in that it contains the NNRTI rilpirivine rather than efavirenz. The new combination will be marketed as Complera.

The FDA has approved brentuximab vedotin to treat Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma. The drug is approved for HL patients who have progressed after autologous stem cell transplant or after prior chemotherapy regimens and cannot receive a transplant. This represents the first the drug to treat HL since 1977. Brentuximab will be marketed as Adcetris.

The FDA has approved vemurafenib for the treatment of metastatic and unresectable melanoma, specifically in patients whose tumors have the BRAF V600E mutation. The approval was accompanied by a companion diagnostic test that will determine if a patient's melanoma cells have that mutation (about half of the patients with late stage melanomas). Only patients with the BRAF V600E mutation will respond to the drug since it targets the mutated protein that regulates cell growth. Vemurafenib is marketed by Genentech as Zelboraf. ■