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Dengue Surveillance and Dengue in Key West, Florida

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

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

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

Synopsis: *Dengue virus infections in the United States are commonly associated with travel to the Caribbean, but local transmission without travel has occurred in Key West, FL, in 2009-2010. Accurate travel history including domestic travel is critical in the evaluation of patients with fever, headache, myalgia, and rash.*

Sources: Centers for Disease Control. Travel-associated dengue surveillance — United States, 2006-2008. *MMWR* 2010;59(23):715-9.

Centers for Disease Control. Locally acquired dengue — Key West, Florida, 2009-2010. *MMWR* 2010:59(19):577-581.

A NUMBER OF REPORTS ON DENGUE HAVE BEEN PUBLISHED RECENTLY IN THE *Morbidity and Mortality Weekly Report*. The CDC described dengue surveillance in the United States using two sources of data: 1) specimens tested at the CDC Dengue Branch (CDCDB); and 2) the ArboNET surveillance system of the CDC Arboviral Diseases Branch. Probable cases are defined by a positive immunoglobulin M (IgM), and laboratory-confirmed cases are defined by a positive polymerase chain reaction (PCR) or by viral isolation. During 2006-2008, 1,125 reports were submitted to either ArboNET or CDCDB. Among 596 reports to ArboNET, 468 were considered probable (79%) and 128 (21%) were considered confirmed, with the highest number of cases reported from New York (178; 30%), Florida (99; 17%), and Texas (61; 10%).

During the same period, CDCDB tested 529 specimens, of which 136 (26%) were positive for dengue. One hundred six of the 136 (78%) were probable recent dengue infections with positive IgM, and 30 (22%) were confirmed acute dengue infections with positive viral isolation. Serotype data available for 30 cases showed: 14 DENV-1, 7 DENV-2, 6 DENV-3, and 3 DENV-4. A large number (31%) of tests were indeterminate because specimens were not collected within specified time frames. The states with the highest number of dengue-positive specimens were New York (42; 31%), Massachusetts (17; 13%), Arizona (10; 7%), and Georgia (10; 7%).

Among the confirmed and probable cases from ArboNET and CDCDB combined (n = 732) whose travel history included countries visited (n = 613), the

most common region of exposure was the Caribbean (43%), followed by Mexico, Central and South America (34%), Asia and the Pacific (21%), and Africa (2%). The most common specific countries for reported dengue exposure were Dominican Republic (20%), Mexico (9%), and India (7%).

The clinical symptoms, when available, were commonly classified as dengue fever (59-72%), and less commonly as dengue hemorrhagic fever (7-16%). During 2006-2008, an average of 244 confirmed or probable travel-associated dengue cases were reported to CDCDB or ArboNET annually. In comparison, the annual average during 1990-2005 was 33.5 cases. The reporting through ArboNET started in 2003, which likely contributed many additional cases. Previously, only CDCDB had data on dengue infections diagnosed in the United States. Additionally, dengue became a nationally notifiable disease in the United States in 2010, which may lead to improved estimates of dengue infection in the United States.

Another report was on a series of dengue infections acquired in Key West, FL. The first identified case was a 34-year-old resident of New York state diagnosed in August 2009 following a one-week trip to Key West. Her sera and cerebral spinal fluid were confirmed at the CDC by positive dengue IgM and PCR analysis. Subsequent cases in Key West residents without travel were also confirmed in August and September 2009, and most recently in April 2010.

The Florida Department of Public Health (FDOH) collected and tested adult female *Aedes aegypti* mosquitoes throughout Key West, with positive results for DENV-1 in two mosquito pools. A serological survey performed by FDOH and CDC in September 2009 found that 13/240 households (5.4%) had evidence of recent dengue infection. Among 21 patients with symptoms compatible with dengue, 42.9% tested positive for dengue by PCR, by detection of the presence of dengue-specific nonstructural protein 1 (NS-1) in a serum specimen or by an IgM assay.

A total of 27 cases of dengue were identified in Key West in 2009 and one so far in 2010. The patient ages ranged from 15-73 years (median = 47 years). All reported fever. They also frequently reported headache, myalgia, arthralgia, eye pain, and rash, and six reported bleeding (including hematuria, epistaxis, gingival bleeding, and vaginal bleeding).

■ COMMENTARY

Dengue is one of the most important mosquito-borne infections in travelers. An analysis of data from GeoSentinel clinics located on six continents on travel-related illnesses found that dengue was the most common specific infection in travelers returning from southeast Asia, and one of the top three diagnoses in travelers returning from all other regions except sub-Saharan Africa and Central America.[1] Dengue followed malaria as the most common infection diagnosed in travelers seen in these clinics.[2] Furthermore, dengue occurred in 21/1000 ill patients presenting to the GeoSentinel surveillance network, and the rate was even higher for travelers to the Caribbean.[3]

Dengue virus is in the family Flavivirus and is transmitted through the bite of *Aedes* mosquitoes. The infection may be subclinical or symptomatic following 3-14 days of incubation. Clinical presentations typically include fever, headache, myalgia, retro-orbital pain and

rash; typical laboratory findings include leukopenia and thrombocytopenia.[4]

A series of dengue infections among U.S. travelers returning from the Dominican Republic in 2008 illustrates precisely the surveillance findings.[5] The CDC had identified a cluster of specimens with positive dengue IgM antibodies from Iowa subsequently found to be from a group of U.S. missionaries who had returned from the Dominican Republic. Among 33 missionaries from Iowa and Minnesota, 12 were confirmed serologically and at least 14 (42%) met the case definition.

The group traveled to assist with post-hurricane reconstruction for one week and stayed in urban Santiago in a "tropical style" house. The patients' age range was 12-76 years (median = 53 years). All cases reported weakness and fever, and 12 of 13 patients who were interviewed noted chills and pains; several had bleeding. Of note, only 2/13 persons sought pre-travel evaluation; 3 persons used repellent; none used insecticide; none considered mosquitoes to be a health threat. Only 3 persons had ever heard of dengue.

This dengue cluster among short-term missionaries returning from the Dominican Republic illustrates a high attack rate (≥ 42%), that the travelers lacked knowledge regarding dengue virus, that they took little precaution, and that their accommodations and activities were risky. Effective dissemination of information about dengue virus and its prevention should include methods to reach missionary and volunteer organizations.

Local transmission of dengue has occurred in the continental United States primarily along the Texas-Mexico border. As the CDC reports note, the dengue outbreak in Key West is the first such outbreak outside Texas-Mexico in several decades and the first local outbreak in Florida since 1934. Additional concern arises regarding potential nosocomial transmission, which may occur through blood transfusions, needle sticks, and other health care or laboratory accidents.[6,7]

Finally, *Aedes aegypti* is the most efficient and most common mosquito vector for dengue virus. Another vector, *Aedes albopictus*, was introduced into the United States in 1985, and has established itself in more than 30 states, mainly in the southern part of the United States. The presence of *Aedes aegypti* in Florida potentiates the local transmission of dengue virus. *Aedes albopictus* was the vector in the 2001 dengue outbreak in Hawaii that originated from a viremic traveler who returned from the South Pacific. Moreover, Florida mosquitoes, both *Aedes aegypti* and *Aedes albopictus*, have been shown experimentally to transmit chikungunya virus.[8] Therefore, Florida is vulnerable to both dengue and chikungunya virus outbreaks if the viruses are introduced to the region and established in the local mosquitoes. ■

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Updates on Recommendations for Use of Human Papillomavirus Vaccines

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

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

Synopsis: *A new bivalent HPV vaccine is now licensed for use in females aged 10-25 years, and the quadrivalent HPV vaccine is now licensed for use in males aged 9-26 years in the United States.*

Sources: CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59:626-629.

CDC. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2010;59: 630-632.

In October 2009, the Food and Drug administration (FDA) licensed the bivalent human papillomavirus vaccine (HPV2; Cervarix, GlaxoSmithKline) for use in females aged 10 through 25 years. This vaccine joins the quadrivalent HPV4 vaccine (Gardasil, Merck & Co) that was licensed in 2006 for use in females aged 9 through 26 years. Both HPV2 and HPV4 are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of HPV. Neither vaccine is a live vaccine. HPV2 and HPV4 include protection against HPV 16 and HPV 18, the two oncogenic HPV types that together account for 70% of cervical cancers. In addition, HPV4 protection includes HPV 6 and HPV 11, the two nononcogenic types that account for 90% of genital warts and most cases of recurrent respiratory papillomatosis.

The approval of HPV2 came after review of efficacy data in two randomized, double-blind, controlled clinical trials in females aged 15 through 25 years. One study was a phase IIb study, and the other was a phase III trial.[1] The phase III trial included 18,644 females who were followed for a mean of 34.9 months. According to the protocol analysis, the efficacy against HPV 16 or 18 related cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ (CIN2+) was 92%.[2] In both studies, greater than 99% of participants developed an HPV 16 and 18 antibody response 1 month after completing the 3-dose series.

ACIP recommends routine vaccination of females aged 11 or 12 years with 3 doses of either HPV2 or HPV4, but vaccination may be initiated as early as age 9, ideally before potential exposure to HPV through sexual contact. The antibody response after co-administration with Tdap (tetanus toxoid, diphtheria, and acellular pertussis) and meningococcal conjugate vaccine (MCV4) was noninferior for all vaccine antigens. Therefore, these vaccines can be administered at the same time, such as during a routine adolescent visit.

The 3-dose schedule for HPV2 and HPV4 vaccines are the same, namely 0, 1-2 months, and 6 months. The minimum interval between the first and second dose is 4 weeks. If the series is interrupted for any reason, the series does not need to be restarted. For example, if the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks with a minimum interval of 24 weeks between first and third doses. Vaccine doses received after a shorter-than-recommended dosing interval should be repeated.

The FDA also licensed the HPV4 vaccine for use in males aged 9 through 26 years for prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11. A phase III efficacy study enrolled 4,065 males aged 16 through 26 years from North and South America, Europe, Australia, and Asia with a median duration of follow-up of 2.3 years. The efficacy for prevention of genital warts related to HPV types 6, 11, 16, or 18 in the per protocol population (i.e., patients who received all 3 vaccine doses, were seronegative at day 1, and DNA negative day 1 through 7 to the respective HPV type) was 89.4%. The efficacy in the intent to treat population (males who received at least one vaccine dose regardless of baseline DNA or serology) was 67.2%.[3] Seroconversion rates were high for all four HPV types (HPV 6, 11,16, 18) after vaccination with HPV4, but antibody titers were significantly higher in males aged 9 through 15 years compared with males aged 16 through 26 years.

■ COMMENTARY

The approval of HPV4 vaccination for use in males is important in the ongoing effort to reduce the overall health burden of conditions associated with HPV. At this point, the ACIP is not recommending routine use of HPV4 in males, likely in part because mathematical modeling suggests that male HPV vaccination in addition to female-only vaccination is cost effective only when vaccine coverage of females is less than 80 %.[4] However, data do show HPV4 has a high efficacy for prevention of intraepithelial neoplasias in men who have sex with men (MSM).[5] Therefore, this may be an appropriate group in whom to first focus the use of HPV4 vaccine in males.

The vaccine schedules, administration, and potential adverse effects of HPV2 and HPV4 in males and females are similar, which is helpful for health care providers with the increasing complexity of childhood and adolescent vaccine schedules. The post-marketing addition of a warning of possible syncope associated with HPV4 vaccination led to the recommendation of a 15-minute period of observation after vaccine administration. Local injection site reactions were noted in 83.9% of females and 61.5% of males during HPV4 studies, but more than 94% of both groups judged their injection-site adverse reactions to be only mild to moderate in intensity.[3]

The HPV2 and HPV4 vaccines can be co-administered with any live or inactivated vaccine since neither is a live vaccine and both can be administered to immunocompromised patients. They are both category B for use in pregnancy since animal studies showed no evidence of impaired fertility or harm to the fetus. There are very limited data on use of HPV vaccine in lactating women. Since the vaccine consists of viral capsid proteins it is unlikely to have an adverse effect on the infant and therefore is not contraindicated in breastfeeding women.[6]

HPV4 is produced in baker's yeast (*Saccharomyces cerevisiae*) and is therefore contraindicated in persons with an immediate hypersensitivity to yeast. The pre-filled syringes of HPV2 have a latex rubber stopper and therefore should not be used in patients with an anaphylactic latex allergy. These patients can receive HPV2 from single-dose vials, which do not contain any latex. ■

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Tungiasis – Painful Feet in a Tropical Traveler

ABSTRACT & COMMENTARY

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

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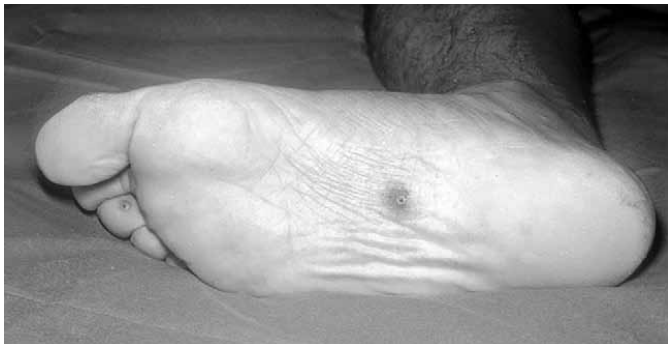
Dr. Barry is a consultant for the Ford Foundation, and her program receives funding from the Johnson & Johnson Corporate Foundation. Dr. Blackburn reports no financial relationships relevant to this field of study.

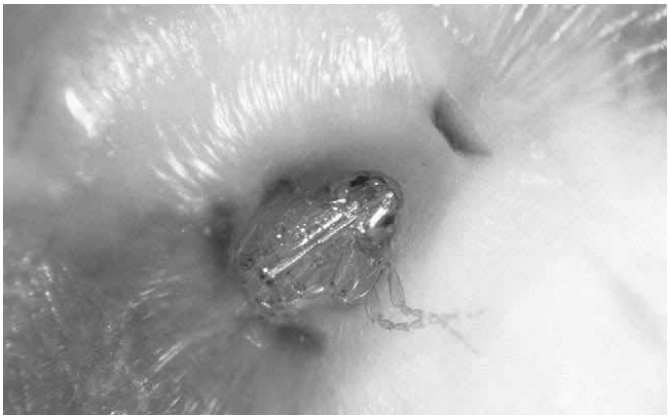
Figure 1.



Typical foot lesions of tungiasis: Papular pale yellow lesions with a central black area.

Reprinted from *Travel Medicine and Infectious Disease*, volume 8. Hakeem MJML, Morris AK, Bhattacharyya DN, et al. Tungiasis — A cause of painful feet in a tropical traveller. p.p. 29-32, Copyright 2010, with permission from Elsevier.

Figure 2.



Female sand flea, *T. penetrans* under the dissecting microscope

Reprinted from *Travel Medicine and Infectious Disease*, volume 8. Hakeem MJML, Morris AK, Bhattacharyya DN, et al. Tungiasis — A cause of painful feet in a tropical traveller. p.p. 29-32, Copyright 2010, with permission from Elsevier.

Synopsis: *Tungiasis is an ectoparasite caused by the impregnated female sand flea* Tunga penetrans*. This is a case report of a traveler who presented with painful foot lesions after spending four weeks in the Pantanal region of Brazil.*

Source: Hakeem MJML, Morris AK, Bhattacharyya DN, et al. Tungiasis — A cause of painful feet in a tropical traveller. *Travel Medicine and Infectious Disease* 2010;8:29-32.

A 39-YEAR-OLD MAN HAD TRAVELED FOR FOUR WEEKS TO the Pantanal region of Brazil, a popular ecotourism area, where he had walked barefoot on several occasions. Ten days before returning to the UK, he noted painful lesions on his feet that were white/pale yellow with a central black punctum. (*See Figure 1.*) He was afebrile and had no associated lymphadenopathy. Microscopy of excised samples confirmed *Tunga penetrans* infestation. (*See Figure 2.*)

■ COMMENTARY

Tungiasis is a parasitic skin infestation caused by the female sand flea *T. penetrans*, or Chigoe flea, which burrows into the epidermis of the host. The flea is endemic in Central and South America as well as the West Indies and sub-Saharan Africa. Its main habitat is warm dry soil and sandy beaches, and the organism is more prevalent during the dry season. To reproduce, the flea requires a warm-blooded host. Domestic animals, rodents, and other wild animals may act as reservoir hosts, as can humans. Once impregnated, the female flea feeds on host blood and releases eggs after a one- to three-week period. Death of the flea follows, and the eggs hatch on the ground, become larvae, and pass through their life cycle.

Severe infestations of more than 100 sand fleas have been described, and secondary superinfection can occur. Surgical extraction of the fleas under sterile conditions is the most appropriate treatment, although oral ivermectin has been reported to be effective.[1] A subsequent randomized study has not confirmed the usefulness of ivermectin therapy for this condition.[2]

A complaint of painful feet with lesions occurring after a tropical trip has a defined differential diagnosis. Cutaneous larval migrans caused by dog and cat hookworm presents as very pruritic lesions, usually on the feet, and they often have a serpentine thread-like subcutaneous lesion that can move slowly through the skin. Botfly or Tumbu fly lesions present a boil-like lesion with a central opening where the larvae head can be seen and even coaxed out with bacon. Other painful foot considerations include verruca vulgaris (plantar warts), various mycoses, pyogenic infections, infected insect bites, dracunculiasis, and melanoma. In short, the best treatment of tungiasis is prevention by wearing shoes and socks as well as by using DEET repellent. The flea is a poor jumper and tends to penetrate the periungual area of the toes, heels, and soles of feet. Thus, flip-flops are not adequate for beach protection, and short socks and shoes should be considered for endemic areas. ■

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Reducing Child Mortality

ABSTRACT & 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 relationships relevant to this field of study.

Synopsis: *The United Nations targets achieving a two-thirds reduction in mortality of children under five years of age by 2015 as compared to 1990. Worldwide, mortality has dropped from 11,900,000 under-five deaths in 1990 to 7,700,000 under-five deaths in 2010. Several African countries have shown increased rates of improvement since 2000.*

Source: Rajaratnam JK, Marcus JR, Flaxman AD, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970-2010: A systematic analysis of progress towards Millennium Development Goal 4. *Lancet* 2010;375:1988-2008.

MURRAY AND COLLEAGUES PROVIDE A RIGOROUS DESCRIPtion of child mortality in 187 nations of the world. The range among countries' mortality rates is vast. Currently, under-five mortality (per 1000) is 2.7 in Sweden, 3.3 in Japan, 4.7 in Australia, 6.7 in the United States, 13 in Libya, 15 in China, 20 in Brazil, 32 in Guatemala, 60 in Cambodia, 82 in Kenya, 111 in Somalia, and 169 in Chad.

Overall, there has been a 52% decrease in under-five mortality since 1970 and a 30% decrease since 1990. Decade-by-decade data reveal that many countries have shown dramatic reductions in under-five mortality. In the Maldives, for instance, under-five mortality has dropped from 247 in 1970, to 89 in 1990, to 34 in 2000, to 14 this year. India's under-five mortality has dropped from 198 in 1970 to 114 in 1990 to 63 now. In other countries, the decline in mortality has been less impressive — Nigeria from 224 in 1970 to 194 in 1990 to 157 this year. However, in several sub-Saharan African countries, rates of decline in mortality have improved during the past decade as compared to previous decades; the relative "success stories" of Angola, Botswana, Liberia, Rwanda, and the Gambia might inform mortality-reduction efforts in

Table. Millennium Development Goals.

Goal	Representative Target
1. Eradicate extreme poverty and hunger	Halve proportion of hungry people
2. Achieve universal primary education	Provide for boys and girls
3. Promote gender equality and empower women	Eliminate gender disparity in schools
4. Reduce child mortality	Reduce under-five mortality by 2/3
5. Improve maternal health	Reduce maternal mortality by 3/4
6. Combat HIV/AIDS, malaria, and other diseases	Provide universal access to HIV treatment
7. Ensure environmental sustainability	Halve proportion without safe water
8. Develop a global partnership for development	Ensure access to essential medications

countries where improvements are currently lagging.

The timing of death leads to classification of mortality as neonatal (during the first month of life), post-neonatal (during the second through twelfth months of life), childhood (between ages one and five years), and under-five (combination of neonatal, post-neonatal, and childhood) mortality. In wealthier countries, the majority of under-five deaths occur during the first month of life. In sub-Saharan African countries, the split is more even among neonatal, post-neonatal, and child mortality.

■ COMMENTARY

All of the 191 member states of the United Nations have agreed to try to achieve eight Millennium Development Goals by 2015. Established in September 2000, these goals provide specific targets and indicators by which tangible improvements in health and welfare can be measured.[1] The eight Millennium Development Goals are summarized in the table.

Tremendous progress is being made toward attainment of the Millennium Development Goals. Nonetheless, as illustrated by the data in this paper from the University of Washington, increased rates of improvement will be required to fully meet the goals within the next five years.

Wide discrepancies in under-five death rates among various countries suggest that significant improvements are attainable within the range of available global resources. For instance, in the resource-rich United States, total under-five mortality (per thousand) is 6.7 in 2010; meanwhile, in resource-challenged Democratic Republic of the Congo, 131 of each 1,000 children die before reaching school age. Discrepant use of global resources leaves millions of children beyond the reach of life-saving health interventions.

The Democratic Republic of the Congo, however, has achieved a greater rate of improvement in under-five mortality than have many other sub-Saharan African countries. Working transnationally, best practices can be adapted across political boundaries so that similarly challenged countries can benefit from the experience of their neighbors.

In seemingly developed countries, remaining reductions in under-five mortality will probably come from improvements in maternal, peri-natal, and neonatal care. In developing countries where children continue to die throughout the pre-school years, multifaceted approaches are needed. Thus, even for young children, it is important that multiple Millennium Development Goals be targeted. Since about half of current under-five deaths are linked to malnutrition, attainment of Goal 1 will directly save lives. Goals 2 and 3 will keep girls in school, delay premature pregnancies, and prepare girls for eventual motherhood and child-care roles. Efforts to meet Goal 5 are already helping increase the safety of deliveries and reduce birth asphyxia. The bednet use and indoor residual insecticide spraying efforts linked to Goal 6 are reducing the toll of childhood malaria. Meeting Goal 7 provides safe water supplies, reduces diarrhea (which still leads to nearly a million under-five deaths each year), and improves child survival. Achieving Goal 8 would help many sick children who currently live beyond the reach of affordable medications. Holistically designed, specifically targeted goal-meeting activities must continue. In meeting the goals, an additional four million children per year will survive childhood and grow to contribute positively to their communities.

In Haiti, more than 10% of children die before reaching school age. As a recent report claimed, "Haiti was home to one of the worst disasters of our time… Then the earthquake hit."[2] We are not oblivious to widespread suffering around us every day, and we must not be complacent. As members of the global community, travel medicine practitioners and their traveling patients care about improving the health of people throughout the world. Awareness of and engagement with the Millennium Development Goals is a worthy means by which we can demonstrate our concern. ■

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CME Questions

1. Dengue virus infections are typically associated with which of the following?
   a. fever, arthritis, pneumonitis, abnormal chest X-rays
   b. fever, myalgia, rash, leucopenia, and thrombocytopenia
   c. fever, joint swelling, elevated renal function tests
   d. fever, headache, nuchal rigidity, cerebrospinal fluid turbidity
   e. fever, rose spots, icterus, abnormal liver function tests
2. Both HPV2 and HPV4 vaccines:
   a. have efficacy for prevention of HPV-related genital warts and HPV-related cervical cancer
   b. are dosed 0, 1-2 months, and 6 months
   c. are live-attenuated virus vaccines
   d. are contraindicated with anaphylactic yeast allergy
3. Which of the following statements regarding the flea that causes tungiasis is correct?
   a. It needs a water cycle to hatch into larvae. Walking near a pond or river in endemic areas puts one at risk.
   b. It can penetrate light cotton socks, which mandates pre-treating clothing with permethrin.
   c. It penetrates under the heel; thus one is protected if one wears shoes or flip-flops.
   d. It has a four-week life cycle in which the flea releases eggs while feeding on blood in a human reservoir.
4. The Millennium Development Goals:
   a. were ratified by most countries, but not by the United States
   b. were developed by the Global Forum for Economic Advancement
   c. were not met by the 2010 deadline
   d. were associated with reductions in child mortality

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.

Answers: 1. b; 2. b; 3. d; 4. d

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.*

Aggressive Modification of Cardiovascular Risk Factors

In this issue: Aggressive approach to CVD reduces MI, folic acid and vitamin B12 for CAD, corticosteroids for acute exacerbations of COPD, prescription drug abuse among young adults, and ARBs and cancer risk.

CVD decreases with aggressive treatment

Aggressive modification of cardiovascular risk factors seems to be paying dividends, at least for a large population of insured patients in Northern California. In an analysis of nearly 18.7 million patient-years between 1999 and 2008, the rate of myocardial infarction (MI) increased in 1999 and 2000 and then decreased significantly every year thereafter (287 cases/100,000 person-years in 2000, decreasing to 208 cases/100,000 person-years in 2008; 24% relative decrease over the study period). The rate of ST-segment elevation MI decreased over the study period (133 cases/100,000 person-years in 1999 to 50 cases/100,000 person-years in 2008; $P < 0.001$) and the 30-day mortality rate decreased from 1999 to 2008 as well (adjusted odds ratio, 0.76; 95% confidence interval, 0.65-0.89). This occurred despite more aggressive diagnosis of MI.

The authors conclude, "The lower incidence of myocardial infarction — particularly ST-segment elevation myocardial infarction — is probably explained, at least in part, by substantial improvements in primary-prevention efforts, …" including statins and aggressive blood pressure reduction, as well as use of cardioprotective medications such as aspirin (*N Engl J Med* 2010;362:2155-2165).

An accompanying editorial points out that while these trends are generally the case in the United States, there are significant geographic differences. "The risk among residents of Oklahoma, the lower Mississippi corridor, and Appalachia, for example, is double that among other Americans, … " suggesting socioeconomic factors play a role. Hypertension and diabetes rates have increased slightly over the last decade, while smoking rates have decreased. Perhaps even more importantly, statin use has increased significantly (among those between age 45 and 64 years, statin use in men increased from 2.5% to 16.8% and from 1.9% to 13.5% in women; among those 65 years of age or older, statin use increased from 1.9% to 38.9% in men and from 3.5% to 32.8% in women). Aspirin, beta-blockers, and ACEIs/ARBs have also contributed to the decline in cardiovascular mortality in the United States (*N Engl J Med* 2010;362:2150-2153). ■

Folic acid and vitamin B12 for CAD

Unfortunately, lowering homocysteine with folic acid and vitamin B12 does not seem to be a benefit to patients with coronary artery disease. In a study from the United Kingdom, more than 12,000 survivors of myocardial infarction were randomized to 2 mg folic acid plus 1 mg vitamin B12 daily vs matching placebo, with the main outcomes being first major vascular event such as coronary event, stroke, or noncoronary revascularization. Folate and vitamin B12 were effective at reducing homocysteine levels by 28%; however, there was no difference in the rate of major vascular events over the 6.7 years of follow-up (25.5% active treatment vs 24.8% placebo; $P = 0.28$). Individually, there was no effect on major coronary events, stroke, or noncoronary

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revascularizations, nor was there a survival benefit from active treatment. Interestingly, the authors also looked at incidence of cancer and found no difference in that outcome either. The authors conclude that long-term reductions in blood homocysteine levels with folic acid and vitamin B12 do not have a beneficial effect on vascular or cancer outcomes (*JAMA* 2010;303:2486-2494). ■

Corticosteroids for exacerbations of COPD

Giving corticosteroids orally in lower doses is as effective as giving the drugs intravenously at higher doses for the treatment of acute exacerbation of COPD (ae-COPD), according to a recent study in the *Journal of the American Medical Association*. The records of nearly 80,000 patients in more than 400 hospital admissions for ae-COPD who received steroids were reviewed. The primary outcomes were treatment failure, defined as the initiation of mechanical ventilation, inpatient mortality, or readmission within 30 days. The vast majority of patients (92%) received IV steroids. After multivariate adjustment, the death rate was similar in the two groups (1.4% IV therapy vs 1.0% oral) and the composite outcome was also similar (10.9% IV vs 10.3% oral). In a propensity-matched analysis, the risk of treatment failure was actually significantly lower among orally treated patients (odds ratio, 0.84; 95% confidence interval, 0.74-0.95), as was the length of stay and cost. Of the orally treated patients, 22% were switched to IV therapy later in the hospitalization.

The authors conclude that for patients admitted for ae-COPD, low-dose steroids administered orally are as effective, and may be safer, than higher-dose IV steroids (*JAMA* 2010;303:2359-2367). An accompanying editorial suggests that rather than doing large non-inferiority studies to confirm these findings, sufficient evidence exists to change practice now with continued comparative effectiveness research via linked registries (*JAMA* 2010;303:2409-2410). ■

Prescription drug abuse in young adults

Prescription drugs are the new drugs of abuse among young adults. While drug use in general seems to be dropping in high schools, prescription drug abuse is skyrocketing. The recently published National Youth Risk Behavior Survey from the Centers for Disease Control and Prevention (CDC) showed that 1 of 5 high school students in the United States reported abusing a prescription drug at some time in their lives. The most commonly mentioned drugs were OxyContin®, Percocet®, Vicodin®, Adderall®, Ritalin®, and Xanax®. Prescription drug abuse was most common among white students (23%), followed by Hispanic students (17%), and then black students (12%). Not surprisingly, high school students were most likely to abuse drugs in their senior year (*MMWR* 2010;59:1-142). While many teens get their prescription drugs from medicine cabinets of family and friends, others order them online, and recently many drug dealers have begun specializing in prescription drugs.

Many young adults, however, seek opioids and benzodiazepines from physicians, especially in emergency departments (ED). A new report from *MMWR* reports that ED visits for nonmedical use of opioid analgesics increased 111% from 2004 to 2008 and increased 29% from 2007 to 2008 alone. The highest number of ED visits was recorded for oxycodone, hydrocodone, and methadone. ED visits for benzodiazepines also increased 89% over the same period. In 2008, the rates of visits for both opioids and benzodiazepines increased sharply after age 17 and peaked in the 21-24 year age group. During the 2004-2008 study period, the largest increase in ED visits to obtain drugs occurred among persons age 21-29 years. Findings were from the CDC and the Substance Abuse and Mental Health Services Administration, reviewing data from the Drug Abuse Warning Network (*MMWR* 2010;59:705-709). ■

ARBs and cancer risk

Do angiotensin receptor blockers (ARBs) increase the risk of cancer? In a widely reported study, researchers from Case Western Reserve performed a meta-analysis of 5 trials for which cancer data were available from more than 61,000 patients. Telmisartan was the ARB used in nearly 86% of the studies. Patients randomly assigned to receive ARBs had a rate of new cancer occurrence of 7.2% vs 6.0% for placebo (relative risk [RR], 1.08; 95% confidence interval [CI], 1.01-1.15; $P = 0.016$). The risk ratio was higher when the analysis was limited to trials where cancer was the prespecified endpoint (RR, 1.11; 95% CI, 1.04-1.18; $P = 0.001$). There was no difference in the rate of cancer deaths between the two groups. The authors conclude that this trial suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis, but it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug and further research is warranted (*Lancet Oncology* 14 June 2010; early online publication). ARBs are involved in the regulation of cell proliferation, angiogenesis, and tumor progression, which are possible mechanisms for these findings. ■