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Congenital Dengue: A Risk For Pregnant Women Who Travel

ABSTRACT & COMMENTARY

Synopsis: *Recent cases from Thailand indicate that children can be born infected by dengue virus. Fever and thrombocytopenia are noted in the first week of life, and death, though unusual, has been reported.*

Source: Sirinavin S, et al. Vertical Dengue Infection: Case Reports and Review. *Pediatr Infect Dis J.* 2004;23:1042-1047.

Dengue fever has been considered primarily a childhood disease in endemic areas. In 2003, however, 40% (3100 of 7760) of Bangkok patients with dengue fever or dengue hemorrhagic fever (DHF) were 15-34 years old.[1] This recognized change in ages that are at risk for dengue infection is important for women of childbearing age.

Sirinavin et al describe a new relationship between dengue fever occurring in pregnant adults, that allows for vertical transmission to infants. In this study, they reviewed hospital records of a Bangkok hospital and found 2 dengue infected mother-neonate pairs. The first pair involved a term female born to a 25-year-old, previously healthy mother via repeat caesarean section. This infant was febrile on days of life (DOL) 5-8. On DOL 6, the infant developed hypovolemia, tachycardia, and thrombocytopenia. The patient ultimately had a spontaneous recovery on DOL 9. As part of this infected pair, the mother had fever on post-partum days 1-3. She then recovered without incident after post-partum day 4. Both mother and infant tested positive for dengue IgM antibody. Subsequently, at 2 and a half years of age, the child had a serum titer positive for DEN-2 antibodies and negative for DEN-1, 3 and 4.

The second mother-neonate pair involved a term boy born to a 31-year old mother via primary caesarean section for cephalopelvic disproportion. The infant had fever on DOL 5-9 and also developed a non-petechial rash with thrombocytopenia. The newborn returned to normal health on DOL 13. This mother was febrile during post-partum days 1-6. She experienced thrombocytopenia, but also had pleural effusion and signs of dengue hemorrhagic fever. Both mother and neonate had an uneventful recovery. The mother and infant tested positive for DEN-4 antibody; further studies suggested DEN-4 acute secondary infection for the mother and primary infection for the neonate.

In addition to reporting these 2 new cases to the literature, Sirinavin and colleagues also reviewed the available literature on dengue fever occurring with vertical transmission. They found an additional 15 cases; the first had been

reported in 1989. The locations for these additional cases included Tahiti (5), Malaysia (2), Thailand (6), and France (2). Neonatal fever began on day 4 (median, range 1-11) and persisted for a median of 3 (range 1-5) days. Thrombocytopenia developed around day 6 (range 1-11) and persisted for about 6 (range 3-18) days, with lowest platelet counts reaching 5,000 to 75,000 per mm^3.

COMMENTARY BY LAUREN M. McGOVERN, MD & PHILIP R. FISCHER, MD, DTM&H

Infection with any of the 4 dengue virus serotypes (DEN-1, DEN-2, DEN-3, DEN-4) can lead to dengue fever or DHF. Dengue, a mosquito-born illness, is primarily a disease of the tropics, with its major distribution being similar to that of malaria. The dengue virus life cycle is dependent both upon infected humans and *Aedes aegypti*, a domestic, day-biting mosquito that prefers feeding on humans. An estimated 2.5 billion people live in areas at risk for epidemic dengue transmission, and approximately 50-100 million cases of dengue fever occur each year; 200,000-500,000 of these represent DHF. Dengue is not uncommon as a cause of fever in returned travelers[2] and seems to be occurring more frequently.[3] In addition, unusual mucocutaneous, nosocomial transmission of dengue in the United States was recently reported.[4]

In planning for an international trip, pregnant women face not only their own health challenges, but also the additional issues of attending to the health and safety of unborn children. All exposures, including illnesses, medications, and trauma will likely impact a fetus to varying degrees. Besides some general contraindications to travel, including threatened miscarriages, severe comorbidities, and coagulopathy disorders, traveling pregnant women must pay particular attention to malaria prevention.

Malaria in pregnancy causes significant morbidity and mortality for both the mother and the fetus.[5] Expectant mothers are advised to take appropriate chemoprophylaxis, if possible, and to protect themselves from potentially infective mosquito bites. Malaria-transmitting Anopheles mosquitoes, unlike Aedes, typically bite at night. The different mosquito behaviors and relationships to infectivity are significant for the pregnant traveler. The complications of malaria during pregnancy are so well known that many pregnant travelers are advised to avoid evening mosquito bites. However, they could potentially ignore daytime protection, the highest time of risk for acquiring infections with dengue virus.

Sirinavin and colleagues discuss several cases of dengue virus infection in expectant mothers with vertical transmission to their fetuses. Since dengue virus infec-

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tion is not an isolated childhood disease, severe perinatal complications (maternal and neonatal) must be considered and avoided. The risk for vertical transmission of dengue virus needs to be reviewed with women who are traveling to dengue endemic areas during pregnancy, and appropriate counsel must be provided.

Interestingly, 6 of 17 newborns with congenital dengue infection in Sirinavin and colleagues' review had been delivered operatively. It is possible that this rate of operative delivery was higher than routine for those areas, but it is not known if dengue was transmitted prior to or during the delivery process.

Currently there is no chemoprophylaxis against dengue fever, and the best protection against dengue infection is avoidance of mosquito bites. Dengue can be prevented by utilizing basic mosquito bite prevention. Pregnant travelers can avoid insect bites by wearing loose-fit clothing that covers the body. Bed nets, use of permethrin on clothing and nets, and application of DEET-containing repellents to exposed skin are also important measures. The recommendations for DEET use in pregnant women do not differ from those for non-pregnant adults. Women choosing lower concentrations of DEET must increase the frequency of application if staying outdoors for long periods.[6]

There is new evidence of risk for another vertically-transmitted infection which could be relevant to women traveling during pregnancy. Researchers in Japan have identified *Helicobacter pylori* in stools of 30% (15 of 50) of tested newborns. While follow-up testing 24 months later on 8 of the positive children did not reveal persistent infection,[7] there have been concerns generated from The Gambia that early *H. pylori* colonization may be associated with a poor growth history later in infancy.[8]

Thus, new information supports even greater attention to prevention of travel-related infections during pregnancy. Beyond risks for pregnant women, children are also at risk of febrile illness due to congenitally acquired dengue, as well as for reduced subsequent growth following acquisition of *H. pylori* infection. Pregnant women who choose to travel internationally should be vigilant about avoidance of insect bites and about food and water hygiene. ■

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References

1. Dengue Hemorrhagic Fever Surveillance Report. Disease Control Division, Health Department. Bangkok, Thailand: Bangkok Metropolitan Administration; 2003, as cited in the source article by Sirinavin et al.
2. Shaw MT, et al. Illness in Returned Travellers Presenting at GeoSentinel Sites in New Zealand. *Aust N Z J Public Health.* 2003;27:82-86.
3. Frank C, et al. Increase in Imported Dengue, Germany, 2001-2002. *Emerg Infect Dis*. 2004;10:903-906.
4. Chen LH, et al. Transmission of Dengue Virus Without a Mosquito Vector: Nosocomial Mucocutaneous Transmission and Other Routes of Transmission. *Clin Infect Dis.* 2004;23:1042-1047.
5. Fischer PR. Malaria and Newborns. *J Trop Pediatr.* 2003;49:132-134.
6. Fradin MS, et al. Comparative Efficacy of Insect Repellents Against Mosquito Bites. *N Engl J Med.* 2002;347:13-18.
7. Fujimura S, et al. Detection of *Helicobacter pylori* in the Stools of Newborn Infants. *Pediatr Infect Dis J.* 2004;23:1055-1056.
8. Thomas JE, et al. Early *Helicobacter pylori* Colonization: The Association With Growth Faltering in The Gambia. *Arch Dis Child.* 2004;89:1149-1154.

2004—American Society of Tropical Medicine and Hygiene Meeting Highlights

Special Feature By Lin Chen, MD

DAVID HEYMAN, EXECUTIVE DIRECTOR OF Communicable Diseases for the World Health Organization and Representative of the Director-General for Polio Eradication, recently spoke on Infectious Disease Challenges: *From Polio to SARS to Avian Influenza in a Plenary Session*. Since WHO established a goal in 1988 to eradicate polio, the incidence of polio has decreased dramatically. There were 350,000 cases in 125 endemic countries in 1988, compared to 784 cases officially reported from 6 endemic countries in 2003. Eradication strategies included: 1) routine childhood immunizations; 2) national immunization campaigns; and 3) surveillance of acute flaccid paralysis. Despite these efforts, vaccine coverage globally is about 73%, and coverage is low in Africa, The Eastern Mediterranean Region, and Southeast Asia Region.[5]

As of November 2004, 10 countries are endemic for polio. Persistent transmission in Nigeria has led to the re-establishment of polio in 4 additional countries:

Sudan, Chad, Burkina Faso, and Côtes d'Ivoire. In Asia, the number of cases has decreased, and may reach zero transmission by early 2005. Some regions that were free of wild poliovirus have identified cases of circulating vaccine-derived poliovirus infection: China (2 cases in 2004), Hispaniola (22 cases in 2000), Madagascar (4 cases in 2002), and Philippines (3 cases in 2001). Additionally, there are 24 cases of individuals with primary immunodeficiency syndromes who are long-term excretors (> 12 months) of vaccine-derived poliovirus (VDPV).

WHO has formulated an Emergency Response Plan. Risks for polio, after eradication, include that from vaccine-associated paralytic polio (VAPP), long-term excretors of vaccine-derived poliovirus in immunodeficient persons (iVDPV), circulating vaccine-derived poliovirus (cVDPV), lab accidents, and deliberate release of poliovirus. Vaccine-associated paralytic polio (VAPP) poses the greatest risk with the first dose, ie 2-4 per million birth cohorts, or 250-500 cases/year. Potential oral polio vaccination (OPV) cessation may occur about 3 years after disappearance of wild polioviruses. Some conditions are required prior to OPV cessation: confirmation of interruption, containment of all polioviruses, global surveillance, stockpile of monovalent OPV, and readiness of post-OPV plans.

Dr. Heyman reviewed the SARS outbreak, which was initially a respiratory illness noted concurrently with influenza activity in Guangdong Province, China, in November 2002. An outbreak of atypical pneumonia was reported in Guangdong in February 2003, followed shortly by the report of a 33-year-old male from Hong Kong and his 9-year-old son diagnosed with H5N1 linked to Fujian Province. When a physician became infected in Vietnam and died, the disease was recognized as a new entity, and the first global alert was issued concerning Vietnam and Hong Kong on March 12, 2003. The disease was soon diagnosed in Ontario and Singapore. On March 15, 2003, an ill physician from Singapore flew to New York and then Europe, which led to another global alert and containment strategies. Additional airline passengers who were subsequently symptomatic for SARS, led to recommendations for travelers on April 2, 2003.

SARS was an example of international amplification; an outbreak driven by health care workers and spread to the community. Airport screening in Hong Kong identified 2 confirmed cases, prevented their travel, and restored some level of confidence. Strategies that contained SARS are case identification, isolation, contact tracing, surveillance, quarantine, travel recommendation, and restriction. Some good luck was apparently around at the time, such that SARS did not spread to weak economies lacking public health infrastructures.

Dr. Heyman also discussed concerns regarding Avian Influenza. Influenza A, H1N1 (Spanish Flu), that caused a pandemic in 1918-1919, infected more than half of the world's population. The pandemics of 1918, 1957 (Asian flu), and 1968 illustrate the concern for reassortment of human influenza genomes with those of avian influenza strains. One example of the risk in developing countries is Madagascar, which experienced an outbreak in 2002 involving 13 of 111 districts. There were 27,519 cases from July to September, and case fatality was < 1%.

In 2003, the circulating avian influenza strains included H5N1, H7N7, H9N2, H5N1, and H7N2. Now, a pandemic of avian influenza is occurring in Asia. Ducks are asymptomatic shedders, and are vectors in the transmission of avian influenza. Non-immunized humans may serve as intermediate hosts in a similar fashion. Strategies to intervene are:

1. Vaccination of chickens with H5N1, although they can still secrete virus.
2. Culling, although migratory birds and animals (ducks, pigs, cats, tigers) can still shed the virus.
3. Vaccination of cullers with human influenza vaccine.

Prevention and control will face many challenges. Vaccine production takes 6-8 months. Vaccine efficacy changes depending on the strains involved. Antivirals are limited in supply and high in cost. ■

ASTMH Abstracts of Interest

Abstracts of the 53rd Annual Meeting of the American Society of Tropical Medicine and Hygiene, Miami Beach, Florida November 7-11, 2004. *J Am Soc Trop Med Hyg.* 2004; 71:Supplement. # refers to abstract number.

Malaria

#331. Duong S, et al. Current Malaria Situation in Cambodia. The number of malaria cases decreased from 170,000 in 1997 to 111,000 in 2002, but increased to 133,000 cases and 492 deaths in 2003. The mortality rate was 3.7/100,000 cases in 2003, and case the fatality rate for severe malaria was 10%. The ratio of *P. falciparum* to *P. vivax* was 7:1. Duong et al commented that the 2003 data may represent a number of factors: improvement of public health facilities in remote areas, movement of people into high-risk areas, decline of control measures, emergence of drug resistance, and incon-

sistencies in diagnostic criteria. The study did not suggest any major change in malaria epidemiology or drug resistance. Travelers to Cambodia should continue to be prepared for malaria transmission, according to existing guidelines that indicate malaria risk throughout the country except for Phnom Penh. Also, parasites may be resistant to mefloquine near the border with Thailand.

#586. Kasili S, et al. Field Trial of 5 Repellents Against Wild Mosquitoes in Ahero, Kenya. Twelve human volunteers tested 4 insect repellents, Avon's SS220 spray, SS220 lotion, Bayrepel lotion, and S.C. Johnson's Autan Bayrepel lotion against a DEET control in western Kenya. All repellents succeeded in protecting through the 12.5-hour nightly test periods conducted in May 2004. If additional studies using more subjects could confirm these findings, alternative repellents might be available as part of personal protection measures against malaria and other vector-borne diseases.

#712. Noedl H, et al. ELISA: Augmenting the Gold Standard in Malaria Diagnosis. Seven hundred blood samples were tested for *P. falciparum* using a commercially available ELISA antigen detection assay, based upon histidine-rich protein 2 (HRP-2). The sensitivity of the test was 98.8% and the specificity was 100%, exceeding those of expert microscopy. Possible use of this test includes complementing microscopy for epidemiological field research, confirming microscopic diagnosis, and screening for blood banking. The test may be useful in travel medicine in assessing the exposure of travelers to *P. falciparum*, and to supplement microscopy in the diagnosis of suspected cases.

#713. Causer LM, et al. Malaria Diagnosis and the Role of Diagnostics: Implications For Malaria Drug Policy. An assessment on the prevalence of malaria parasitemia using exit interviews and malaria smears was conducted on outpatients who visited 3 hospitals, 4 health centers, and 9 dispensaries in rural Tanzania in 2002. Data showed a parasite prevalence of 25%. Among patients with clinical diagnosis of malaria, 66% had no malaria parasites on blood smear. Modeling of the impact of microscopy and rapid diagnostic tests could reduce over-diagnosis of malaria by 91% and 99%, respectively. These results demonstrate its frequent over-diagnosis in developing countries. Travelers should be advised regarding malaria over-diagnosis in order to avoid missing other treatable causes of illness, and minimize the inclination to discontinue malaria chemoprophylaxis.

#747. Pacha L, et al. Reemergence and Persistence of Vivax Malaria in the Republic of Korea. The study identified all reported malaria cases in Korean civilians, military, and US soldiers from 1993-2003. Republic of Korea (South Korea) experienced a reemergence of *P. vivax* since 1993, which peaked in 1997-2000 and subsequently declined. Interviews of 68 military cases indicated that exposure occurred within 25 km of the Demilitarized Zone, but 1 case was attributed to a training site 35 km south of Seoul.

Epidemiology of Infections

#161. Cabada M, et al. Etiology and Impact of Traveler's Diarrhea Among Tourists to Cuzco, Peru. Fifty-three travelers who consulted 3 study physicians in Cuzco, Peru, between August 2003 and April 2004 for TD, were enrolled in a study to assess the causative pathogens. The majority of the travelers were from Europe. Sixty-two percent of subjects had at least 1 pathogen present in the stool, and 27% of these had more than 1 pathogen. Blood in the stool was associated with finding a pathogen. The most common pathogens identified were enterotoxigenic *E. coli* (ETEC, 27.3%), enteroaggregative *E. coli* (EAEC, 21.2%), Cryptosporidium (12.1%), and *Campylobacter jejuni* (9.1%). Sixty percent of the *C. jejuni* were ciprofloxacin-resistant. Findings of the study are consistent with others that have shown ETEC and *C. jejuni* to be common causes of TD. In addition, Cryptosporidium appears to be a frequent cause, and EAEC may be an emerging pathogen.

In addition to the importance in identifying etiologies of fever in the local population, a number of studies demonstrate the epidemiology of infectious diseases that are useful in the evaluation of febrile returning travelers:

#501. Pachas PE, et al. Spotted Fever Group Rickettsial Diseases Associated With Leptospirosis in Pomabamba, Ancash Department, and Peru. Sera from 49 subjects with petechiae or fevers of unknown origin who presented in June 2003 were tested by IFA for antibodies to spotted fever group rickettsia (SFGR), typhus group rickettsia (TGR), and IgM against Leptospira. Fourty-one percent were positive for SFGR, 2% positive for TGR, and 33% were positive for Leptospira; 33% tested positive for both SFGR and Leptospira. Although the species of Rickettsia still needs further identification, SFGR and leptospirosis appear to be emerging diseases from Peru.

#503. Jordan G, et al. Evidence of Murine Typhus Cases in Northern Peru. Sera from 115 patients with suspected dengue fever from Tumbe, in northern Peru, were tested for dengue, yellow fever, Venezuelan equine encephalitis, Oropouche, Mayaro viruses, Leptospira, Brucella, SFGR, *R. typhi*, and *Coxiella burnetti*. Fifteen (13%) were confirmed to have *R. typhi*, and illustrated that murine typhus causes a significant number of cases

clinically, resembling dengue fever in this area.

#556. Zavaleta C, et al. Acute Febrile Illnesses in Yurimaguas, Peru 2000-2004. Three hundred twenty-four subjects with acute febrile illness were tested by serology and/or viral isolation for dengue, yellow fever, Venezuelan equine encephalitis, Mayaro, Oropouche viruses, Brucella, Leptospira, *Coxiella burnetti*, SFGR, and *R. typhi*. Virus isolation confirmed dengue in 25 patients and VEE in 1 patient; serology identified additional cases. Dengue was the leading cause of fever identified in this study (17%), followed by SFGR (7%), leptospirosis (7%), Q fever (5%), VEE (1%), *R. typhi* (0.9%), Oropouche (0.6%), yellow fever (0.6%), and Mayoro virus (0.3%).

#545. Punjabi NH, et al. Cholera As An Important Cause of Diarrheal Outbreaks in Indonesia: A 10 year Observation. Outbreaks of diarrhea in Indonesia were investigated between 1993 to 2002. Eighteen investigations were done, and 17 of them yielded *V. cholerae* 01 biotype El Tor serotype Ogawa in 214 of 1788 specimens tested. Stool specimen from a 1994 outbreak in West Kalimantan identified *V. cholerae* 01 biotype Inaba, which resulted in overall isolation rate of 12.3% for *V. cholerae* 01. The last investigation in 2002 in West Timor identified rotavirus type 1.

#649. Garcia-Rivera EJ, et al. Differential Diagnosis of Dengue-Like Illness in Puerto Rico. Sera from patients with dengue-like illness from 1999 to 2001, who were negative for dengue antibodies, were tested further for leptospirosis, measles, rubella, hepatitis A and B, influenza, rickettsial diseases, and parvovirus B19. Thirty-two percent of the patients were seropositive for another disease. The leading positive studies were influenza (seroconversion), measles, rickettsioses (seroconversion), leptospirosis, and parvovirus B19. Influenza should be considered routinely in febrile returning travelers.

Vaccines

#162. Kirkpatrick BD, et al. A Novel Oral Typhoid Vaccine is Safe and Immunogenic in 2 vaccine presentations. A new single dose of oral typhoid vaccine, called M01ZH09, was prescribed. Thirty-two human volunteers received the vaccine, and demonstrated positive IgA antibody assay (88-93%) at day 7, and IgG seroconversion of 73-81% on day 14 and 28, respectively. The vaccine appears to be well tolerated and immunogenic. The currently available oral typhoid vaccine consists of 4 capsules taken on alternate days, which is associated with lack of adherence. The single dose vaccine would greatly improve the ease of administration and compliance. The duration of protection would need to be elucidated.

#203. Nothdurft HD. Combined Vaccination Against Hepatitis A and Typhoid Fever. Seven hundred fifty subjects studied for antibody levels following a combined hepatitis A and typhoid fever vaccine showed protective levels 14 days after injection, 95.6% against hepatitis A and 86.4% against typhoid. Since the epidemiology of hepatitis A and typhoid fever are similar and associated with food and water hygiene factors, the 2 vaccines are often administered together for travelers. A combined vaccine would reduce the number of injections and would be attractive to travelers. ■

A Malaria Vaccine That Works. . . Somewhat

ABSTRACTS & COMMENTARY

Synopsis: *The RTS,S/AS02A vaccine, a pre-erythrocytic vaccine based upon the* Plasmodium falciparum *circumsporozote surface antigen was recently proven to be safe, well tolerated, and immunogenic in this phase IIb proof-of-concept efficacy study done in Mozambican children.*

Sources: Alonso PL, et al. Efficacy of the RTS,S/AS02A Vaccine Against *Plasmodium falciparum* Infection and Disease in Young African Children: Randomized Controlled Trial. *Lancet.* 2004;364:1411-1420; Van de Perre P, et al. Vaccine Efficacy; Winning a Battle (Not War) Against Malaria. *Lancet.* 2004;363:1380-1383; Vogel G. A Complex New Vaccine Shows Promise. *Science.* 2004;306:587-588; Wilson ME. Malaria Vaccine Trial: Modest Protection, Good Progress. *Current Infect Dis Reports.* 2005;7:31-32.

THERE IS NO DOUBT THAT AN EFFECTIVE MALARIA vaccine is very much needed, and it doesn't have to be perfect. Attempts to develop an efficacious malaria vaccine have been ongoing for about 50 years, but with little promise of success. No wonder. The global figures for malaria morbidity and mortality are truly staggering. Half the world's population is exposed to malaria infections. There are approximately 500 million new acute malaria episodes on an annual basis, with somewhere between 1 and 3 million deaths occurring largely in children under the age of 5 years and mostly in Africa. The risk of death from malaria begins to decrease after age 2-3 years, and one important goal is to produce a vaccine that can be administered to infants who are approximately 2 months of age. In 2000, GlaxoSmithKline Biologicals and the Malaria Vaccine Initiative (MVI)

Programme for Appropriate Technology in Health (PATH) entered into partnership aimed at fostering malaria vaccine development. The Malaria Vaccine Initiative is based in Rockville, MD, having been created in 1999 by the Bill and Melinda Gates Foundation for this purpose.

Of the candidate vaccines under development, RTS,S/AS02A is one of the most complicated and advanced. Previous studies have shown that malaria-naïve adult volunteers exposed to *P. falciparum* infected mosquitoes were protected against infection by *P. falciparum* sporozotes using this recombinant vaccine directed against the pre-erythrocytic stage of the malarial parasite. It had also protected semi-immune individuals from natural infection in The Gambia. In Phase I, during studies of Gambian children age 1-11, the RTS,S vaccine was found to be safe, well tolerated, and immunogenic. A pediatric vaccine studied in Mozambican children age 1- 4 was found to be similar.

This Phase IIb, double-blind, randomized, controlled trial was published in *Lancet* during October 2004. Phase IIb studies are performed to demonstrate efficacy against experimental challenge with organisms in the pre-erythrocytic phase of the malaria cycle and, either prevent or ameliorate natural infections. This study had been performed during the rainy season in the Manhica District of southern Mozambique. The estimated risk of malaria exposure can be illustrated by an entomological inoculation rate of 38 infected bites per person per year. The primary objective was to measure the vaccine's efficacy against clinical episodes of *P. falciparum* malaria in children age 1-4 years, following their first vaccination series over a 6-month period of surveillance that began 14 days after dose 3.

RTS,S/AS02A and control vaccine were administered intramuscularly into the deltoid muscle at 0, 1, and 2 months. Half of the adult dose was used, ie 250-µL volume containing 25µg of RTS,S. RTS,S is a fused hybrid molecule consisting of 2 polypepetides: a circumsporozote protein expressed in *Saccharomyces cerevisiae*, fused to the surface antigen of hepatitis B virus (HbsAg). The AS02A adjuvant is an oil-in-water emulsion containing the immunostimulants, monophosphoryl lipid A and saponin-derived QS21.

In 2001, children aged 12-24 months had already received their hepatitis B immunizations. Control vaccine for children younger than 24 months, therefore, included 2 doses of the pneumococcal conjugate vaccine at first and third vaccinations, and 1 dose of *Haemophilus influenzae* type B vaccine at the second vaccination. For older children, control vaccine was pediatric hepatitis B vaccine. Careful blinded vaccine labeling and administration were necessary, and this was performed by a vaccination team not involved in any other study procedures. Participants were observed after each vaccination, as well as at home visits for the following 3 days. Unsolicited adverse experiences were recorded for 30 days after every dose. Beginning 60 days after the third dose, study children were visited at home once a month.

There were 2 cohorts of children described in this study. The first cohort of 1605 was followed by a system of passive surveillance, in addition to antibody determinations. If febrile illness occurred, they were evaluated for both malaria and other diseases, then appropriately treated. The second cohort of 417 lived in an area where malaria transmission was more intense, and they had to be cleared of their parasitemia between the second and third doses of experimental or control vaccines. These children were followed via active surveillance every 2 weeks for 2.5 months, and then monthly until 6.5 months after the last vaccine dose. Blood smears were evaluated for the presence of malaria parasites and the density of any parastiemia.

COMMENT BY MARIA D. MILENO, MD & FRANK J. BIA, MD, MPH

The malaria vaccine successfully produced anticircumsporozoite antibody titers that were determined both before and after vaccination. Pre-vaccination anticircumsporozoite antibody titers were low in study children (natural infections), however, RTS,S induced specific antibody titers following vaccine dose 3, even resulting in persistent, albeit 75% lower titers, at 6 months. Still, they remained above baseline values. The vaccine was more immunogenic in children than it had previously been shown to be in adults, and particularly for the children who were ages 12-24 months. The vaccine also produced high levels of antibodies against HBsAg. When parasitemia prevalence was determined in a study survey at 6.5 months, it was found to be 37% lower in the vaccine group, although the densities of parasitemia were similar in the vaccine and control groups. What about actual malaria prevention? In the first cohort, the efficacy for prevention of all clinical episodes of malaria was about 27%, and for episodes of severe malaria it was about 58%. Among children between the ages of 1 and 2, the results were even more promising, with a 77% reduction in the chance for severe malaria in this small but important group within the study. There were 123 clinical episodes in the RTS,S vaccine group and 159 in the control group. In terms of severity, 11 of 745 children had at least 1 severe episode of malaria, compared with 21 of 745 children in the control group. The 4 deaths felt to be attributable to malaria, all occurred in the control group. Fewer children with malaria required hospital admission in the RTS,S group, when compared with controls (42 vs 62). In

the second cohort, the vaccine was shown to be 45% effective in extending the time to first infection.

The global burden of disease from malaria continues to grow despite improvements in eradication efforts. Emergence of widespread resistance to available and affordable antimalarial agents also has made it difficult to treat patients in endemic regions. The most vulnerable groups include infants and pregnant women, as well as non-immune individuals traveling into endemic areas.

Although complete protection against malaria infection was not demonstrated, this vaccine promises to decrease the burden of malaria significantly, with its implementation in the most desperately affected regions of the world. These results also offer the hope that protective immunity may now be generated against what has been an immunologically elusive pathogen. Other work presented during sessions of the recent ASTMH meetings in Miami Beach, FL suggests that malaria vaccines, which target the gametocyte, will make an impact on malaria in endemic communities as well. As for travelers, advise them to hang onto their DEET and bed nets for now.

Be aware that the vaccine costs may come in at about $10-20 (US) per dose. Whereas travelers might find that acceptable it could be a significant problem to solve in the parts of Africa where the vaccine is most needed. Also, it is not known how HIV-infected vaccinees will respond, and the interaction between HIV and malaria is of particular significance for pregnant women and their newborns. ■

CME Questions

1. **Dengue fever:**
   a. is only transmitted by the bites of infected Aedes mosquitoes.
   b. has been transmitted mucocutaneously and from mother to child.
   c. may be prevented using a pre-travel vaccination schedule of 3 vaccine doses.
   d. remains exclusively a childhood illness in endemic areas.

2. **Which of the following statements about the new RTS, S/AS02A pre-erythrocytic vaccine *is false*?**
   a. The new malaria vaccine has protective efficacy against both *P. falciparum* and *P. vivax* infections.
   b. The vaccine antigen is a fused hybrid molecule which also causes production of antibodies to hepatitis B surface antigen.
   c. The new malaria vaccine is even more immunogenic in children than it has been in adults.
   d. At an approximately 6-month assessment period, the prevalence of parasitemia was nearly 40% lower in vaccinees than in control subjects.
   e. All deaths attributable to malaria occurred in the control groups.

Answers: 1. (b); 2. (a)

PHARMACOLOGY WATCH

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

Statins and the Incidence of Rhabdomyolysis

The most commonly prescribed statins have a low incidence of rhabdomyolysis, according to the results a new study of more than 250,000 patients. Atorvastatin, pravastatin, and simvastatin were found have very low and virtually indistinguishable rates of rhabdomyolysis of 0.44 per 10,000 person-years (95% CI, 0.20-0.84). The data were obtained from 11 managed care health plans across United States from January 1, 1998, through June 30, 2001. Cerivastatin (Baycol-Bayer), which was withdrawn from the market in 2001, was found have a much of a higher rate of rhabdomyolysis, 5.34 cases per 10,000 person-years (95% CI, 1.46-13.68). The concomitant use of a fibrate with atorvastatin, pravastatin, or simvastatin was found to have increased the rate to 5.98 (95% CI, 0.72-216.0), while use of a fibrate with cerivastatin dramatically increased the rate to 1035 cases per 10,000 person-years of treatment (95% CI, 389-2117), or nearly 1 in 10. Older patients, especially those with diabetes, were found to have higher rates of rhabdomyolysis. The authors conclude that the most commonly prescribed statins have a low incidence of rhabdomyolysis, which is increased with the addition of a fibrate (*JAMA.* 2004;292:2585-2590).

The study confirms the safety of the most commonly used statins, but raises issues regarding the post marketing surveillance of cerivastatin. These concerns were addressed in a review in the same issue of *JAMA* regarding the potential conflict of interest once initial reports of rhabdomyolysis were reported to the company, and the delay in the availability of this information to consumers. The critique is accompanied by Bayer's rebuttal (*JAMA.* 2004;292:2622-2631, 2643-2646, 2655-2657, 2658-2659), which makes fascinating reading given the recent criticisms of the FDA and post marketing surveillance regarding coxibs.

A Crackdown on Importation of Drugs

Officials in both the United States and Canada are taking steps to crack down on the importation of prescription medications across the border. A New York District Court issued an injunction in December against Canada Care Drugs Inc., which gave the FDA authority to inspect the company to assure that they no longer import drugs to American consumers. The FDA had petitioned the court to take this action based on a sting operation run by the agency. FDA investigators purchased Neurontin and Sporanox through Canada

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Care. Instead of Neurontin, investigators received APO-gabapentin and NOVO-gabapentin, formulations of the drug that are not subject to FDA scrutiny in this country. The Sporanox shipment included 84 tablets of the correct drug, but investigators felt that the amount was excessive, determining that patients should not take Sporanox continuously without checking with their physician. The court is scheduling a trial date for Canada Care, an action that is sure to put other Canadian importation companies on alert. Meanwhile, the Canadian government is also cracking down on Internet pharmacies that export drugs to the United States without evaluation by Canadian doctors. The government is considering making it illegal for Canadian doctors to countersign prescriptions from other countries. This move in Canada is prompted by concern over shortages of drugs for Canadian citizens, especially given threats by American drug companies to withhold additional shipments of drugs to Cananda, where they have strict price controls, knowing that many of these drugs may come back to the US market were there are no price controls. These moves are strongly supported by PhRMA, the powerful pharmaceutical advocacy group.

FDA Actions

The FDA has approved a new non-benzodiazepine hypnotic for the treatment of insomnia. Sepracor, a company that specializes in marketing active isomers of currently approved drugs, has received approval to market eszopiclone, the active (S)-isomer of zoplicone, which is available outside the United States. The drug is similar to zopidem (Ambien) and zaleplon (Sonata) in that it has a lower incidence of tolerance, dependence, and withdrawal symptoms than benzodiazepines. Based on a 6-month, double-blind, placebo-controlled safety and efficacy trial, the FDA decided not to limit eszoplicone's indication to short-term use. Eszoplicone will be available in 1mg, 2mg, and 3mg tablets, and will be marketed in United States under the trade name Lunesta. Sepracor is also studying the drug for treatment of insomnia in patients with depression or pain, and in peri-menopausal women.

Novartis has received approval to market darifenacin extended release tablets for the treatment of overactive bladder with symptoms of urging incontinence, urgency, and frequency. The drug is an M3 (muscarinic) receptor blocker that increases urinary capacity and decreases urinary episodes and frequency of incontinence, along with feelings of urgency. Darifenacin, which is already available in Europe, will be marketed in the United States as Enablex.

Drugs approved under the FDAs accelerated approval program are often approved on the basis of surrogate end points, such as tumor markers that would indicate the likelihood of clinical benefit. The FDA, however, requires that cancer drugs in particular, must document clinical benefit in subsequent studies to remain marketable. A recent case-in-point is AstraZeneca's gefitnib (Iressa), which was approved for treatment of non small cell lung cancer in patients who failed other courses of cancer therapy. A recent study of gefitnib involving nearly 1700 patients failed to show a survival benefit better than placebo. The drug, which was initially approved in 2003, now faces a FDA review to determine whether the drug will be removed from the market. In a letter to physicians, AstraZeneca "urges you to consider other treatment options in recurrent non small cell lung cancer patient population." In the meantime, Genentech and Roche's erlotinib (Tarceva), which has shown survival benefit for the same patient population, remains a viable option.

The FDA has issued a Public Health Advisory regarding the use of anti-inflammatories including COX-2 inhibitors because of recent indications that the drugs may increase the risk of cardiovascular disease and stroke. The agency is requiring evaluation of all prevention studies that involve the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) to ensure that adequate precautions are in place. Several prevention studies regarding potential benefit of these drugs on colon polyps and Alzheimer's disease are either in progress or planned in the near future. Meanwhile, the agency is recommending that physicians should prescribed Celebrex or Bextra with caution, particularly in patients at risk for cardiovascular disease, and should weigh the risk vs benefits.

The FDA is also recommending that consumers should use over-the-counter anti-inflammatories in strict accordance with the label directions, taking them for no longer than 10 days without consulting a physician. ■