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Dengue Vaccination

ABSTRACT & COMMENTARY

Synopsis: *A clinical trial involving school-aged children in Thailand shows that a tetravalent dengue vaccine is safe and immunogenic, despite frequently bothersome side effects.*

Source: Sabchareon A, et al. Safety and immunogenicity of a three-dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. *Pediatr Infect Dis J.*2004;23:99-109.

HEALTHY FLAVIVIRUS-SERONEGATIVE CHILDREN AGED 5-12 YEARS received 3 sequential doses of 1 of 2 candidate dengue vaccines or, as a control, rabies vaccine. Moderate reactions including fever, rash, headache, and myalgia were common with the first dose (seen in more than 80% of recipients) but decreased with subsequent vaccine doses. Serious adverse events did not occur, but one child had a weeklong dengue-like illness. Seroconversion rates were high (89% with one vaccine formulation; 100% with the other).

COMMENT BY PHILIP R. FISCHER, MD, DTM&H

Dengue fever is an important disease. It is estimated that 2.5 billion people in more than 100 countries live at risk of acquiring dengue.[1] Cases and outbreaks occur in warm regions of Africa, Asia, Australia, the Pacific Islands, the Caribbean, and the Americas. In Southeast Asia alone, there are more than a million clinical cases of dengue reported each year.[2] Already this year, there have been reports of increased dengue activity in Venezuela, El Salvador, the Seychelles, and Indonesia.[3] Dengue poses a significant concern to international travelers, who currently must limit their protective efforts to mosquito avoidance measures.

Along with yellow fever virus and Japanese encephalitis virus, the dengue virus is a member of the *Flavivirus* genus. There are 4 different virus serotypes, and it is possible for humans to be infected concurrently or sequentially by multiple serotypes. The virus is transmitted by mosquitoes, primarily by *Aedes aegypti*.[4] In endemic areas, school-aged children are at greatest risk of becoming sick with dengue fever.

About three-fourths of dengue infections are asymptomatic.[2] About 94% of clinical cases present with just dengue fever.[2] This is characterized by fever, headache, vomiting, and severe skeletal pain ("break bone fever"). A maculopapular rash spreads from the trunk to the limbs and face. Fevers can recur, along with lymphadenopathy, as the entire illness fades during its 1 - 1.5 week duration.[4]

Approximately 6% of clinically symptomatic cases of dengue manifest as severe illness — either hemorrhagic fever or shock — with potentially high rates of mortality. The diagnosis is usually made clinically, but antibody tests and antigen detection tests are done in some centers. No specific treatment is available, and supportive care is essential.

In a 2-year review of hospitalized Cambodian children, 80% of nearly 600 children with hemorrhagic fever had dengue. In fact, up to 10% of admissions to the hospital were related to dengue at some time.[5] With no specific treatment available, preventive efforts are vital in combating the toll of dengue fever. Still awaiting a useful vaccine, mosquito control measures are critical.[6]

Dengue is widely recognized as a major problem in endemic areas, especially southeast Asia. Professionals and policymakers are interested in preventing dengue fever, and there is evidence of public perception that a vaccine is needed.[7] Could a vaccine be cost effective? A careful, cost-effectiveness study was recently reported.[2] Focusing on the needs in 10 Southeast Asian nations (population 529 million, with 1.2 million cases of dengue reported annually), and expecting that 2 vaccine doses would be needed (whereas 3 doses were used in the study summarized above to achieve protectively high antibody levels against each of the 4 dengue serotypes), vaccine was found to be extremely cost-effective (only $50 per disability-associated life year saved, similar or better than the cost-effectiveness for preventing polio, measles, and tetanus).

One of the concerns about dengue fever is that the life-threatening hemorrhagic and shock forms of the illness seem to be most likely with subsequent, rather than primary, dengue infections. An initial infection seems to "prime" the host defenses to make severe illness more likely in the future. A concern with vaccination is that vaccine might similarly pre-dispose recipients to more severe disease if/when they are subsequently exposed to another dengue serotype. The experience reported in the Thai study is encouraging in this regard. The side effects of vaccine were less bothersome after subsequent doses, suggesting that "priming" is not occurring. And, the 5 children who developed wild-type dengue after the initial vaccination, but before achieving full protection did not show any evidence of more severe, enhanced disease. Additional, larger studies will be needed, but current evidence suggests that disease enhancement is not a major problem with the current candidate dengue vaccines.

Thus, dengue fever is widespread in the world, devastating to millions, and rampaging without effective, specific treatment or implementable prevention strategies. The public desires vaccination in endemic areas, and current projections suggest that a vaccine could indeed be

cost-effective. Thus, the study by Sabchareon and colleagues is timely and important. Dengue vaccine seems to be within reach. To be practically useful for travelers, however, briefer vaccination courses would be helpful, and vaccines with much lower rates of bothersome side effects would be desirable. Nonetheless, the current paper reminds us that progress continues, and a useful dengue vaccine for travelers might one day be in sight. ■

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Cat-Transmitted Sporotrichosis: Epidemic in Brazil

ABSTRACT & COMMENTARY

Synopsis: *Zoonotic transmission resulting from exposure to infected cats was responsible for an epidemic of 178 human cases of sporotrichosis in Rio de Janeiro, Brazil, from 1998 to 2001. Cats infected with sporotrichosis pose a significant risk of disease transmission to humans because of their extensive skin lesions and high burden of organisms. Patients seen during this epidemic received itraconazole as first-line treatment with more than a 90% cure rate.*

Source: Barros MD, et al. Cat-transmitted sporotrichosis epidemic in Rio de Janeiro, Brazil: Description of a series of cases. *Clin Infect Dis.*2004; 38:529-535.

From 1998 to 2001, 178 cases of culture-proven sporotrichosis were diagnosed in the city of Rio de Janeiro and the surrounding municipalities. Most patients were female (68%), adults (70.8%), and involved in a domestic occupation. The majority of patients had either the fixed cutaneous or a lymphocutaneous form of the disease. None of the patients in the outbreak had pulmonary, osteoarticular, or disseminated sporotrichosis.

The diagnosis was made by culturing the fungus from secretions, biopsies, or aspirates of these lesions. As is often the case, the results of direct microscopic wet mount preparations were negative for almost all of the samples. However, fungal elements were detectable in 28.8% of the histopathological samples. The yeast forms are usually 4-6 mm in diameter and often described as oval to cigar-shaped.

A feline sporotrichosis epidemic coincided with the human epidemic. More than 90% of the patients reported either domestic or professional contact (ie, veterinarians) with infected cats. Many patients recalled a traumatic injury, such as a bite or scratch from a cat with sporotrichosis. Those patients who could not recall a traumatic injury often reported close contact with infected cats.

The majority of infected patients were treated with itraconazole 100 mg/d, with 8 patients requiring a dosage increase to 400 mg/d. Seven patients received other agents, such as potassium iodide and/or amphotericin B, in addition to itraconazole. One pregnant patient was treated only with heat therapy. In this epidemic, spontaneous remission, which is unusual, was noted in 13 patients.

■ COMMENT BY MARY-LOUISE SCULLY, MD

Sporotrichosis is caused by *Sporothrix schenckii*, a dimorphic fungus that has a worldwide distribution. The organism grows well in the environment, particularly in sphagnum moss, decaying vegetation, soil, and hay. Persons exposed to these environmental foci are at risk for acquiring infection. Activities frequently associated with acquisition of sporotrichosis are rose gardening, topiary work (ornamental tree or shrub trimming), Christmas tree farming, hay baling, and masonry work.[1]

One of the largest human outbreaks of sporotrichosis occurred in Witwaterstrand, South Africa, from 1941-1944, when almost 3000 gold miners developed sporotrichosis after inoculation from splinters of contaminated timbers in the mines.[2] The largest outbreak in the United States affected 84 patients in over 15 states, when conifer seedlings were packed in *S schenckii* infected sphagnum moss that originated in Wisconsin.[3]

However, an alternative mode of transmission for S schenckii is from the bites or scratches of animals.

Animals most often associated with zoonotic transmission of sporotrichosis have been armadillos and cats. Armadillos do not seem to be infected with the organism but transmit infection to humans through nail scratches, especially while attempting to evade capture. Cats, however, can develop serious and sometimes fatal sporotrichosis. Infected cats are thought to pose a considerable risk of transmission to humans because the cats often have extensive, ulcerative skin lesions with a heavy burden of organisms. In one study, *S schenckii* was isolated from 100% of skin lesions, 66% of nasal cavities, and 39% of the nails of infected cats.[4] Normal cat behavior often involves rubbing against their owners and handlers, with unintentional scratching and biting. In 15 of these Brazilian cases, molecular typing confirmed the relationship between the patient strains of *S schenckii* and that of their cat.

The most common manifestation of infection with *S schenckii* is a primary cutaneous lesion that usually begins as a papule, enlarges to become nodular, and often ulcerates. This initial lesion can persist alone (fixed or localized cutaneous), or progress further to nodular lesions appearing along the proximal lymphatics (lymphocutaneous form). Disseminated visceral, osteoarticular, meningeal, or pulmonary sporotrichosis can occur, but typically are associated with host risk factors such as alcoholism, diabetes mellitus, chronic obstructive pulmonary disease, and HIV infection.

Most would agree that all forms of sporotrichosis warrant treatment, most often with antifungals. The spontaneous remission of infection noted in 13 patients in this study is unusual and very rarely reported in the literature. Saturated solution of potassium iodide (SSKI), which does not kill this organism, was the traditional therapy for cutaneous sporotrichosis since the beginning of the 20th century. However, side effects such as nausea, metallic taste, fever, rash, and salivary swelling have led to the use of itraconazole as the drug of choice for cutaneous and lymphocutaneous sporotrichosis. The success rate is 90-100% when itraconazole is used at 100-200 mg daily for 3 to 6 months. Fluconazole is not as effective as itraconazole, and if used at all, the dose should be at least 400 mg/d.[5]

Local measures, such as heat, for treatment of cutaneous sporotrichosis have been used. The basis for this treatment regimen originates from the observation that some strains of *S schenckii* exhibit growth inhibition at temperatures greater than 35°C. Local heat therapy, as used by the pregnant patient in this study, may be an option for patients with a single cutaneous lesion, but it requires faithful application of heat for at least an hour daily for several months. Azoles and SSKI are both contraindicated in pregnancy. It is quite acceptable to delay treatment of cutaneous sporotrichosis until after the pregnancy, since there is no risk of the infection disseminating to the fetus, and no evidence that the disease is worsened by pregnancy. ■

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Rabies Vaccine Recall and "Lots" of Strain

ABSTRACT & COMMENTARY

Synopsis: *On April 5, 2004, Aventis Pasteur contacted all recipients of IMOVAX Rabies Vaccine to inform them of an urgent recall of their manufactured lots: X0067-2, X0067-3, W1419-2, and W1419-3.*

Source: Decker MD. Urgent vaccine recall, letter; instructions for complying with recall; medical opinion from Aventis Pasteur regarding management of patients. Aventis Pasteur Inc. Discovery Drive, Swiftwater Pennsylvania.

QUALITY-CARE MEASUREMENT INDICATORS ARE taking increasing priority in the current US health care environment. An Institute of Medicine report in 1998 revealed that numerous medical errors occur each year among hospitalized patients. A surge in documentation of quality care has taken place, and the public both demands and deserves safe care with assurance of good quality. Quality preventive care is also of great importance to the traveling public, who seek such services under the assumption that the prevention can be provided with little or no risks.

Recently quality assurance testing of IMOVAX®

Rabies Vaccine revealed one product lot that contained non-inactivated live vaccine virus, albeit the attenuated Pitman-Moore virus. Although this rabies vaccine lot was not ever distributed for use, Aventis Pasteur chose to recall those other vaccine lots that had been produced during the same time period as the affected lot, for "further testing." Thus, the 4 vaccine lots listed above, which were distributed between 9/23/03 and 4/2/04, were called back for confirmatory testing even though they had each "passed all release testing prior to distribution" including tests to confirm the absence of any live virus. No unusual adverse events were noted in any vaccine recipients. Persons who had vaccine from any of the above named lots were advised to undergo additional post-exposure prophylaxis. In some instances, the word of this recommendation caused as much fury and concern in some persons and their family members as though they had actually been bitten by a rabid animal!

COMMENT BY MARIA D. MILENO, MD

While Aventis graciously offered to provide the additional safe vaccine doses free of charge, this was not always practical. We had direct experience with such issues in our own clinic. Some individuals received this information while they were still overseas. In Mongolia, some of our patients felt obliged to seek vaccination immediately, placing themselves at possible risk for blood-borne pathogens via needle exposure. For others extensive reassurance was first required to even begin to implement the suggestions. For persons who received the recalled vaccine within 7 days, rabies immune globulin was obtained and administered, not without significant time and expense, to a number of travel medicine practitioners and their patients. Those who had completed the full 3 dose pre-exposure rabies series required only 2 additional vaccine doses. A number of individuals requested a refund for their original vaccine series administered, given the angst they experienced due to this ordeal. Needless to say, quality assurance should be implemented in a more peaceful manner.

On the other hand, some excellent questions arose from this exercise. "What is the real benefit of this incredibly expensive pre-exposure rabies vaccine?" Most practitioners point out that worldwide there is limited availability of rabies immune globulin, the life-saving component of treatment; thus, the pre-exposure series essentially buys time and requires only 2 additional rabies vaccine doses to complete treatment. "Won't I still have the possibility of acquiring yet another disease via the needles used to give the rabies treatment?" We answer, "yes, but remotely so." "How long does one have after a rabies-infected dog bite to complete the 2 additional vaccine doses, if one has already had the 3 dose pre-exposure series?" I have yet to receive a clear and definitive answer to this question, yet the reality is that it probably takes between 1 day and 1 week at the least to find and access health care that provides post-exposure rabies treatment. No rabies deaths have been reported in persons who have taken the pre-exposure series and then completed the vaccine course as indicated. I guess this information should assure us and allow everybody to sleep at night, right? For patient management or to report adverse events call 1-800-835 3587. ■

Visceral Leishmaniasis Relapses: Don't Lose HAART

ABSTRACT & COMMENTARY

Synopsis: *Despite some initial controversy, it appears that HIV-infected patients with relapses of visceral leishmaniasis have higher levels of HIV-RNA viral loads and lower CD4+ counts than those without relapses. Non-compliance with HAART regimens and intravenous drug use possibly contribute to this greater risk of relapse.*

Source: Mira JA, et al. Frequency of visceral leishmaniasis relapses in Human Immunodeficiency Virus-infected patients receiving Highly Active Antiretroviral Therapy. *Am J Trop Med Hyg*. 2004;70:298-301.

THIRTY-ONE HIV-INFECTED PATIENTS IN SOUTHERN Spain who received HAART after developing visceral leishmaniasis (VL) were included in this retrospective cohort study. Ten patients received secondary prophylaxis for VL, whereas 21 patients did not receive any prophylaxis. Four patients were lost to follow-up, and 10 died. Two deaths were due to symptomatic VL relapse.

Of the 21 HIV patients receiving HAART who were not treated with VL prophylaxis, 8 patients (38%) had a VL relapse. Five of these 8 patients were active intravenous drug users at the time their VL relapse was diagnosed. All patients who relapsed had a CD4+ cell count less than 200 cells/mm^3, with a median CD4+ cell count of 33 cells/mm^3 at the end of follow-up. None of the patients with relapses showed an increase of more than 100 CD4+ cells/mm^3 over their baseline. In contrast, patients who did not receive VL prophylaxis, but did not relapse either, had a median CD4+ count of 188 cells/mm^3 at the end of follow-up, and significantly lower HIV-RNA viral loads.

In the group of 10 patients that received secondary VL prophylaxis, only 1 patient relapsed after beginning HAART. This intravenous drug user had 4 relapses of symptomatic VL before starting HAART and 3 subsequent relapses after HAART began, despite directly observed therapy of his antiretroviral medications.

COMMENT BY MARY-LOUISE SCULLY, MD

Visceral leishmaniasis is the fourth most frequent opportunistic infection associated with acquired immuno-deficiency syndrome in Southern Spain. A recent study documented a 64.8% decrease in incidence of VL since the standard use of HAART in 1997.[1] In addition, it has been shown that HAART prevents the development of overt kala-azar in patients with subclinical VL.[2] Therefore, the use of HAART has had a clear impact on the incidence and progression of symptomatic VL.

This study set out to clarify the effect of HAART on relapses of VL in HIV patients. An earlier report, albeit on a small number of patients, showed VL relapses occurred despite patients having an undetectable HIV viral load.[3] These findings were in contrast to others in which VL relapse was more common in HIV patients who had a poor recovery of CD4+ counts.[4]

The present study examined relapse rates both in patients that had secondary prophylaxis for VL and those who did not. Only 1 patient among the 10 patients who had prophylaxis relapsed. This patient was unusual in having 4VL relapses before, and 3 relapses after, HAART was initiated, despite directly observed therapy and undetectable HIV viral load. The fact that this patient was an active drug user raises the possibility of reinfection rather than relapse, as it is known that *Leishmania infantum* infection can be spread among intravenous drug users.[5] This 1 patient also demonstrates that relapses or reinfections of VL can occur despite secondary VL prophylaxis.

Of the patients with VL relapse not receiving prophylaxis, relapse was seen in those patients with less than a 100 CD4+ cell increase over baseline and higher levels of HIV viral RNA at their last visit. These results confirm that relapses of VL are more likely to occur in patients showing poor control of viral replication and poor immunologic responses. Although not statistically significant, there was evidence that failure of immune reconstitution was in part due to low adherence to HAART in this drug user cohort. None of the patients who had CD4+ cell counts over 200 cells/mm^3 relapsed, indicating that this may be a safe level at which prophylaxis for VL can be discontinued. Presently, most physicians wait until the CD4+ count is greater than 350 cells/mm^3 before discontinuation of prophylaxis. Prophylaxis regimens vary, but some options include pentavalent antimony or pentamidine given monthly, liposomal amphotericin B every 2 weeks, allopurinol, or itraconazole. Comparative studies are few, but 1 study showed pentavalent antimony, given monthly, prevented relapse in 93% of patients during the first year, as opposed to only 23% relapse prevention in those given allopurinol alone.[6]

As the incidence of symptomatic VL decreases in the era of HAART, it will be increasingly difficult to find enough patients to further study risk factors for VL relapses. Although conflicting data have appeared in previous literature, the take-home message is this: relapses of VL in HIV patients receiving HAART are primarily seen in patients with poor immune reconstitution and uncontrolled viral replication. In such patients, the best approach to prevention of VL relapse would be encouraging patient compliance to HAART and continuation of secondary prophylaxis until appropriate CD4+ counts are achieved. ■

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Monkey Malaria Infects a Large Cluster of Humans in Borneo

ABSTRACT & COMMENTARY

Synopsis: *This is a fascinating report of a cluster of human Plasmodium knowlesi cases misdiagnosed as Plasmodium malariae in a rural rainforest area of Sarawak.*

Sources: Singh B, et al. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet.*2004;363:1017-1024; White N. Sharing malarias. *Lancet.*2004; 363:1006

Between 1998 and 2002, the yearly incidence of malaria in Sarawak, Malaysian Borneo was between 2496 and 3155 cases. *Plasmodium vivax* represented 69.1% of all cases followed by *Plasmodium falciparum* (19.7%) with *Plasmodium malaria* accounting for 9.4%. Singh and colleagues noted that *P malariae* cases were mainly reported in the central divisions of Kapit and Miri; indeed, one-fifth of all malaria cases in Kapit were identified as *P malariae*. However, these clinical cases were noted to be atypical for *P malariae* infection, and nested PCR assay failed to identify *P malariae* DNA. Singh et al studied and sequenced the small subunit ribosomal RNA and circumsporozoite gene and characterized *Plasmodium knowlesi* in 58% (120/208) of cases initially identified by smear as *P malariae*. *P knowlesi* infection has a natural host in the Kapit area—long-tailed and pig-tailed macaque monkeys, which live in close proximity to humans.

Clinical cases were reviewed in 94 patients who sought care. Almost all (91%) of these patients had fever and rigors. Other major symptoms were headache, cough, and vomiting. One-third had parasitemia of over 5000 parasites per µL. All stages of the erythrocytic cycle were identified by Giemsa-stained thick and thin blood smears. Early trophozoites appeared as ring forms indistinguishable from those of *P falciparum*. Occasionally, more than 1 ring form was noted in each erythrocyte, and double chromatin dots were also seen. Late trophozoite band forms that are typical of *P malariae* were observed, but without the characteristic stippling of the erythrocytes as sometimes associated with *P malariae* infections. Patients responded to chloroquine and primaquine. Ten patients were given single-dose Fansidar® and 2 patients were given quinine. There was no evidence of early treatment failure as microscopy showed parasites cleared rapidly from peripheral blood after treatment.

COMMENT BY MICHELE BARRY, MD, FACP

Patients belonged to the Iban ethnic group and lived in river-side housing while working in the logging industry within the surrounding jungle. There was no clustering of cases within 1 housing community, and only 12.5% of diagnosed cases were in children, indicating working in the jungle was a risk factor for the mostly adult men diagnosed with this infection.

P knowlesi has an interesting history for humans, as it was used prior to the penicillin era as pyretic treatment for neurosyphilis. It was first identified in 1931 in a long-tailed macaque, and although there have been isolated single reports of natural human infection, this is the first large focus of natural infection astutely noted by the epidemiologic observation of an unusual clustering of *P malariae*. The course of infection with *P knowlesi*, the only primate infection with a 24-hr asexual blood-stage cycle, is dependent on the host. In its natural host, the macaque monkey, low-level parasitemia is observed, while in rhesus monkeys, parasitemia evolves rapidly and is lethal. In humans, when it was used as a pyretic agent, symptoms ranged from mild infection that resolved spontaneously to those that required antimalarial intervention. In this study of patients ill enough to seek clinic treatment, all responded to chloroquine and other conventional antimalarials, and no deaths were reported. Whether the parasite has switched hosts and transmission is between humans, or whether all infections were zoonotic remains to be established. Thus, a general rule for travel physicians is that malaria must be excluded in any patient with fever traveling to a tropical area—even if that travel took place in an uninhabited forest. ■

CME Questions

5. Current dengue vaccines under investigation:

a. promote increased risk of severe illness, if the recipient is exposed subsequently to wild virus.
b. are effective against all 4 dengue serotypes with a single vaccine dose.
c. hold promise for use in endemic dengue regions.
d. provoke rare side effects after the first dose.
e. offer cross-protection against yellow fever.

6. Which of the following statements about sporotrichosis is incorrect?

a. Itraconazole for 3-6 months is considered the treatment of choice for cutaneous sporotrichosis.
b. Activities and hobbies associated with soil contact can put patients at risk for cutaneous sporotrichosis.
c. Pregnancy is a risk factor for disseminated sporotrichosis.
d. Cats can be heavily infected with *S schenckii*.
e. Azoles and SSKI are both contraindicated in pregnancy.

7. **Which of the following statements is *not true* about visceral leishmaniasis?**
   a. Leishmania infantum has been spread among intravenous drug users in Southern Spain.
   b. Visceral leishmaniasis is the fourth most frequent opportunistic infection in AIDS patients in southern Spain.
   c. Low CD4+ counts and higher HIV viral loads are risk factors for development of VL relapses in HIV patients on HAART.
   d. Monthly pentavalent antimony appears superior to allopurinol as a secondary prophylaxis regimen for VL.
   e. Cases of VL have not occurred in patients taking secondary prophylaxis for VL.

8. **Malaria infection caused by *P knowlesi* is :**
   a. rapidly fatal for humans and primates, usually within days of clinical illness.
   b. most likely to be confused upon examination of peripheral blood smears with either *P falciparum* or *P malariae*.
   c. resistant to both quinine and tetracycline.
   d. endemic in those temperate climates where primates roam freely and are in close association with humans.
   e. usually the cause of asymptomatic human infections.

Answers: 1(c); 2(c); 3(e); 4(b)