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A Nutty Idea for Controlling the Spread of Malaria

ABSTRACT & COMMENTARY

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MALARIA RANKS AMONG THE WORLD'S MOST IMPORTANT INFECTIOUS diseases. The last year for which good statistics have been amassed, 2006, saw 250 million cases and at least one million deaths.¹ The number of new malaria cases in the world each year dwarfs the same statistic for other well-known scourges.² AIDS newly infected 2.7 million people and killed approximately 2 million in 2006.² Tuberculosis also killed more people than did malaria (~ 2 million), but new infections were in the range of 4-5 million.² Progression in malaria reduction can be attributed to several factors. The expanding use of insecticide-treated bed-nets has greatly reduced transmissions, particularly in sub-Saharan Africa.³ In the past five years, use of such insecticide-treated bed-nets has increased more than five times. Prevention of malaria reduces the need for antimicrobial treatment and, thus, conserves limited healthcare dollars. Widespread treatment of malaria with combination therapy, particularly utilizing the Chinese herbal medicine artemisinin, also has reduced both morbidity and mortality more than 50% over the last five years.^{4,5} Although the parasite has developed resistance to many Western antimicrobials in response to the widespread use, these drugs seem to regain efficacy when combined with artemisinin, a compound derived from a plant known as Sweet Wormwood (*Artemisia annua*).^{3,6} Used in ancient times by Chinese herbalists to treat fevers, the herb had fallen out of favor until a Chinese herbal pharmacopeia originally written in 340 A.D. was rediscovered in 1970.⁶

One important point often overlooked when malaria statistics are quoted is epitomized by the results of a study conducted several years ago in Ghana.⁷ Most diagnoses (from which prevalence statistics are derived) are clinical only. In carefully conducted trials using highly trained laboratory scientists, at best only 15% of cases diagnosed as malaria by physicians

(and treated as such) were substantiated by laboratory test results.⁷ Other infections, such as bacterial meningitis and sepsis, were the primary true causes of the patients' symptoms. So although it is possible that malaria is not so prevalent as has been thought, it still affects an immense proportion of the populations in tropical countries of both hemispheres.^{1,2}

Rapid diagnostic tests are being suggested for resource-poor areas to aid physicians' diagnoses. Unfortunately, a new study from Mali evaluating the efficacy of one rapid test (Paracheck-Pf) compared with laboratory microscopy for *Plasmodium falciparum* diagnosis found that although the test was 83% sensitive and 79% specific, the "treat all" strategy was more cost-effective than the "test and treat" strategy.⁸ This is one of several sandwich immunoassays used throughout the world. Recently a similar test was FDA-cleared for use in the United States. The Binax (Binax, Inc., Portland, Maine) is an immunochromatographic test in the same format as the Binax tests for respiratory syncytial virus and *Streptococcus pneumoniae* antigen in urine. A comparison of the malaria test to microscopy and the gold standard polymerase chain reaction showed the Binax to be 94% sensitive for the detection of *P. falciparum* malaria but only 84% for non-*P. falciparum* infections.⁹ Another evaluation of the Binax performed at the patient's bedside revealed a slightly less desirable 88% sensitivity for *P. falciparum* diagnosis.¹⁰ U.S. laboratories are advised to use the rapid test as an adjunct to current tests and not as a replacement. Better diagnostic tests are needed along with better prevention strategies. One cre-

ative approach to prevention deserves better publicity.

Malaria is spread by the bite of the female *Anopheles* mosquito. Mosquito abatement has been the basis of preventive efforts throughout much of the world.¹¹ Removing standing water and treating ponds and other sites of larvae development with insecticides has been successful, but mosquitoes seem to develop resistance to the insecticides quickly.¹² Global climate change also seems to have extended the range of *Anopheles* and other mosquitoes.^{13,14} A simple community-based but more sustainable mosquito larvae-killing method is needed. Recently, I worked side-by-side for a week in Mozambique with a Peruvian scientist who clearly was thinking outside of the box. Her story was so extraordinary that I wanted to write about it for this newsletter.

Dr. Palmira Ventosilla had a stroke of genius back in the mid-1990s. She was working with a strain of *Bacillus thuringiensis* (subspecies *israelii*), the very effective insect-larvae-destroying bacterium. Strains of this same species are used to kill pests throughout the American agricultural industry because of their virtual lack of toxicity to humans or any other organism and their single-minded attack on the larvae of insect pests. The bacterium is voracious in its destruction of mosquito larvae, but how could one provide sufficient cultures of BT1 to rural, economically challenged communities in the malaria-prone parts of the developing world? The organism itself is expensive when purchased directly from microbial suppliers. Microbiological skills, even incubators, were non-existent. The villagers had coconuts, though, so Dr.

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Ventosilla created a mini-incubator in a coconut! The method is deceptively simple. You provide swabs laced with the organism's spores to the villagers, and you teach the locals (mainly schoolchildren) to recognize mosquito larvae in water. One drills a hole in the top of a coconut, swishes the swab in the coconut milk, and seals the hole with candle wax. The coconuts are allowed to sit out in the sun for several days while the organisms multiply logarithmically in the warm coconut milk. The wax seal is then popped open and the Bacillus-laden coconut liquid is poured onto the offending water source. The bacteria remain active for at least 45 days. Nearly complete mosquito abatement ensued, and follow-up studies in a demonstration project in a Peruvian village have shown not only major reduction in malaria, but in dengue as well.^{12,15}

■ COMMENTARY

Using low-tech methods to deliver high-tech solutions to global problems will be the path to the future we hope to realize. Understanding the local culture and working with it, rather than above it or against it, is reaping rewards in places from Peru to India. Dr. Palmira Ventosilla is showing us the way. ■

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CDC Preparing Fact Sheet on ART, Risk of Transmission

Assessing the science as clinical trials continue

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THE CENTERS FOR DISEASE CONTROL AND PREVENTION is planning to issue a fact sheet on what is currently known about Antiretroviral Therapy (ART) and sexual transmission in the first quarter of this year, the agency announced. The CDC will also submit a scientific statement for publication in a peer-reviewed scientific journal. In the interim, CDC has reiterated its recommendation that people living with HIV who are sexually active use

condoms consistently and correctly with all sex partners.

Observational studies to date have shown that ART is associated with a decreased risk of transmission to sex partners. A clinical trial to directly address this question is ongoing. The CDC sponsored a meeting in Atlanta on October 23-24, 2008, entitled, "CDC Expert Consultation on the Effect of ART on Risk of Sexual Transmission of HIV Infection and Superinfection." Approximately 50 HIV experts attended, including laboratory scientists, clinicians, social and behavioral scientists, and public health personnel from CDC and other federal agencies, state and local health departments, universities, advocacy groups, and international organizations. Participants reviewed available data and discussed implications for treatment and prevention programs and for future research.

"The consultation highlighted the contribution of ART to prevention of HIV transmission, and the potential to increase the prevention benefit by expanding HIV testing, ensuring linkage to and availability of treatment services, and, possibly, making treatment available to infected individuals with CD4 counts $> 350/\text{mm}^3$," the CDC reported. "However, additional laboratory, clinical, epidemiologic, mathematical modeling, and behavioral research, along with health care financing and policy discussions, are needed to inform specific guidance on these issues."

The presentations and discussions indicated that there is evidence that the infectiousness of HIV-infected persons is related to their blood viral load, which is correlated with genital viral shedding. ART can be expected to reduce HIV concentrations in the blood and seminal plasma, female genital tract secretions, and rectal secretions. While some studies have shown successful long-term suppression of genital HIV shedding with ART, in other studies episodes of genital HIV shedding have been observed despite ongoing ART. There is also significant variation in the penetration of antiretroviral drugs from the blood into the genital tract. ■

And, Around the World. . .

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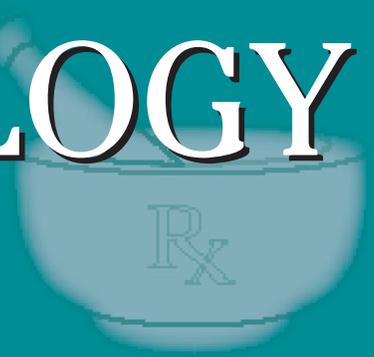
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IN KENYA, WHERE THE PREVALENCE OF HIV INFECTION runs anywhere from 10%-30% in most communities, funerals are common. But in an interesting twist, reminiscent of the macabre nights of the Day of the Dead or Mardi Gras, funerals are becoming big business, with up to 100 family and friends gathering to celebrate the life of their family member or friend, and to party. Families of the deceased host large gatherings as a way to raise funds for funeral expenses, complete with party favors and disc jockeys. People party, dance, and drink for days, sometimes up to two weeks. Sex is apparently commonplace, much of it unprotected and some of it coerced. It's considered a way to meet the neighbors, especially for young people, who are often left unattended.

These authors interviewed 44 young female and male participants, and observed six "disco matanga" or disco funerals. During their trip to this part of Kenya, about three disco funerals were held per week. Casual sex, even group sex, is common, and apparently condoned by older members of the family as a way to experiment. Many forego condoms in the interest of convenience. After conducting numerous interviews, the authors believe that alcohol plays a significant role in forced sex, especially with underage or teenage girls. Other studies have shown that young women who accept gifts, such as a drink or a ride home, have lost their bargaining power and cannot refuse sex or insist on condoms.

The authors caution that these events must be viewed in light of the cultural customs of this part of Kenya, where polygamy is common and premarital sex is condoned as a way to experiment and to get to know a future partner. The funerals are generally seen as a form of celebration. But these types of venues, similar to barebacking parties in San Francisco, or large club gatherings, carry the same risk of rapid spread of HIV infection within a group in a very short time. ■

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.*

FDA Warning: Pharmaceuticals in “Natural” Products

In this issue: Aspirin dose and cardioprotection; uncovering modafinil’s abuse potential; proton-pump inhibitors and clopidogrel; FDA actions.

Finding pharmaceuticals in natural products

Some natural products are not so “natural” after all. The FDA has warned consumers for several months that a number of weight-loss products contain undeclared pharmaceutical ingredients. The newest products to join the list are Herbal Xenicol which contains cetilistat (a drug similar to orlistat that is not approved in this country), as well as Slimbionic and Xsvelten, both of which contain sibutramine (the prescription medication also known as Meridia®). The FDA’s list of over-the-counter weight-loss agents that contain undeclared active pharmaceutical ingredients now includes 72 products. Some of the other undeclared pharmaceutical ingredients found in these products include fenproporex (an amphetamine derivative no longer available in this country), fluoxetine (Prozac®, an SSRI), furosemide (Lasix®, a loop diuretic), and even phenytoin (Dilantin®, an antiseizure medication). The FDA is seeking recalls on many of these products; however, some are available only online and previous recall efforts have proved inadequate.

In a related story, the FDA has announced a voluntary recall of Zencore Plus, the heavily marketed product for “natural male enhancement,” which has been found to contain benzamidenafil, a new PDE5 inhibitor not yet available in this country. Benzamidenafil is similar in action to sildenafil (Viagra®) and tadalafil (Cialis®). PDE5 inhibitors are noted to have a drug interaction

with nitrates, leading to potential life-threatening risk of sudden and profound drop in blood pressure. Zencore Plus is distributed by Hi-Tech Pharmaceuticals in Norcross, GA, and is widely sold in health food stores, by mail order, and by Internet sales.

Aspirin dose and cardioprotection

What is the best dose of aspirin for patients taking dual therapy with clopidogrel to prevent cardiovascular events? Investigators looked at 15,595 patients with cardiovascular disease or multiple risk factors in an observational analysis from a double-blind, placebo-controlled randomized trial. Patients were randomized to doses of aspirin less than 100 mg (75 mg or 81 mg), 100 mg, or greater than 100 mg (150 mg or 162 mg) with or without clopidogrel. The primary efficacy outcome was the composite of myocardial infarction, stroke, or cardiovascular death and the primary safety endpoint was severe life-threatening bleeding. In patients given aspirin alone, the hazard ratio for the efficacy and safety endpoints were the same regardless of aspirin dose. In patients given aspirin with clopidogrel, there was a statistically nonsignificant associated reduction in efficacy with aspirin doses over 100 mg, and a

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significantly higher increase in harm (hazard ratio, 1.30 with clopidogrel plus aspirin greater than 100 mg). The authors conclude that daily doses of aspirin greater than 100 mg were not associated with benefit and may be associated with harm in patients also taking clopidogrel. Therefore, daily doses of aspirin 75-81 mg optimize efficacy and safety in patients requiring long-term aspirin therapy, especially in patients receiving dual antiplatelet therapy (*Ann Intern Med* 2009;150:379-386). This is especially important given the recent U.S. Preventive Services Task Force recommendation that encourages men ages 45-79 years to take aspirin preventively when the potential benefit of a reduction of myocardial infarction outweighs the potential harm of an increase in gastrointestinal hemorrhage. Women ages 55-79 years are also encouraged to use aspirin when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of increased gastrointestinal hemorrhage (*Ann Intern Med* 2009;150:396-404).

PPIs and clopidogrel

Increasing evidence suggests that proton pump inhibitors (PPIs) may attenuate the effect of clopidogrel on platelet aggregation. PPIs are often used prophylactically in patients with acute coronary syndrome (ACS), as patients on clopidogrel and aspirin may be at higher risk for GI bleeding. A new study from VA researchers was set up to determine if there are clinical implications from the interaction between PPIs and clopidogrel.

In a retrospective cohort study of 8205 patients with ACS taking clopidogrel, 63.9% were also prescribed a PPI at discharge, during follow-up, or both. Death or rehospitalization for ACS occurred in 20.8% of patients taking clopidogrel without a PPI and 29.8% patients taking clopidogrel with a PPI. Use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without a PPI (adjusted odds ratio, 1.25; 95% confidence interval, 1.11-1.41). Patients taking a combination of the two drugs were at higher risk for hospitalizations for ACS and revascularization procedures, but not for all-cause mortality. Patients taking a PPI without clopidogrel were not at higher risk for rehospitalization. The authors conclude that concomitant use of clopidogrel and a PPI after hospital discharge for ACS is associated with an increase risk of adverse outcomes, suggesting that PPIs may attenuate the benefits of clopidogrel, and that

PPIs should only be used with clopidogrel if there is a clear indication, and not for routine prophylaxis (*JAMA* 2009;301:937-944).

Modafinil's abuse potential

Modafinil (Provigil®) is a wake-promoting medication used to treat narcolepsy and other sleep disorders. Recently, the drug has been used off-label to enhance cognition in psychiatric patients and even in healthy patients seeking a memory boost. Modafinil has been touted as having a low abuse potential; however, a new study questions that assumption. Most stimulant medications, such as methylphenidate and amphetamine, increase brain dopamine levels. Modafinil was thought to exert its effect in the brain on pathways other than dopamine, but now there is evidence that dopamine is involved. Researchers from the National Institute on Drug Abuse looked at 10 healthy male volunteers to measure the effects of modafinil at therapeutic dosing of 200 mg and 400 mg given orally. PET scans were used to measure the effect of modafinil on extracellular dopamine and dopamine transporters. Modafinil increased extracellular dopamine and showed evidence of occupancy of dopamine transporters, effects similar to drugs with the potential for abuse. The authors conclude that, considering the increasing use of modafinil, there needs to be heightened awareness for potential abuse of and dependence on modafinil in vulnerable populations (*JAMA* 2009;301:1148-1154).

FDA Actions

The FDA is requiring the manufacturers of metoclopramide (Reglan®) include a boxed warning on their labeling regarding the risk of long-term or high-dose use and tardive dyskinesia. Manufacturers will also be required to implement a risk evaluation and medication strategy (REMS) to ensure patients are provided with a medication guide that discusses the risk. Metoclopramide is approved for the treatment of gastric motility problems associated with GERD, diabetic gastroparesis, and nausea and vomiting.

A new proton pump inhibitor has been approved by the FDA, bringing the number of PPIs on the market to six. Dexlansoprazole is the purified active isomer of lansoprazole (Pepcid®). The drug has a delayed-release formulation designed to provide two separate releases of the medication. It is approved for the treatment of GERD and erosive esophagitis. Takeda Pharmaceuticals will market dexlansoprazole as Kapidex™. ■