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Resistance to Atovaquone-Proguanil?

ABSTRACT & COMMENTARY

Synopsis: *These cases of post-travel malaria in multiple members of the same family provide important "teaching points" about malaria prevention in travelers, yet they raise a significant concern that resistance to atovaquone-proguanil might already be appearing.*

Source: Farnert A, et al. Evidence of *Plasmodium falciparum* malaria resistant to atovaquone and proguanil hydrochloride: Case reports. *BMJ*. 2003;326:628-629.

In September 2000, 2 febrile brothers were diagnosed with *Falciparum malaria* in Sweden following a 2-month visit to the Ivory Coast, where they used chloroquine and proguanil as prophylaxis. Their asymptomatic and possibly semi-immune mother was also parasitemic. Each of them was treated with the combination agent atovaquone-proguanil (AP). One boy became sicker and recovered following mefloquine treatment. The other boy's illness resolved but then recurred 4 weeks later when it was also successfully treated with mefloquine. The mother recovered following her initial treatment.

Each of these individuals had adequate serum levels of both atovaquone and proguanil metabolites. Parasite analysis revealed that 1 boy and the mother were infected with single parasite clones, while the other child was infected with 5 genetically diverse parasite populations. A cytochrome b mutation that had been previously linked to atovaquone resistance was found in the mother and only 1 of the boys. Only the other boy, and not the mother, had mutations in a dihydrofolate reductase gene previously related to proguanil resistance.

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

It was clear during the recent International Society of Travel Medicine meeting in New York that AP is one of the preferred prophylactic agents for travelers visiting malaria-endemic areas. Nonetheless, enthusiasm for the long-term future of AP was tempered a bit because of growing awareness of the cases just noted above. It seems that already, just a few years after the introduction of AP, parasite resistance has been identified.

Atovaquone is an antiprotozoal agent that interferes with mitochondrial electron transport and pyrimidine biosynthesis.[1] When used orally, it is rapidly effective but is associated with a high, approximately 30%, recrudescence rate.[2] Parasites initially isolated from patients with recrudescent illness had a mutation in the parasites' cytochrome b gene.[1] Proguanil potentiates the effect of ato-

vaquone, and the combination product is usually not associated with recrudescence of infection.

Together, atovaquone and proguanil have proven efficacy in the prevention[3,4] and treatment[1] of malaria. The combination product has been licensed for prophylaxis and curative treatment of malaria in the United States since July 2000. Due to a lack of data, this product is not widely recommended for use in children weighing less than 11 kg or during pregnancy and lactation of small children.[5] Recommended dosing is shown in the Table.[5]

These reports of persistent and recurrent malaria due to AP-resistant *P falciparum* just a few years after AP's introduction raise important concerns. What can we learn from these cases? First, travelers should use personal protective measures appropriately along with chemoprophylaxis. More apparent now than when the reported family visited West Africa, the combination of chloroquine and proguanil is not an adequate prophylactic agent for travelers to West Africa. Second, no antimalarial treatment is perfect. Physicians treating malaria must vigilantly follow their patients during and after treatment so that good outcomes result, as in the reported cases, even in the face of rare and unexpected resistance. Third, it is certainly too early to "give up" on AP. Extensive, recent experience from around the world[1] has documented that AP is either better than, or similarly effective to, other antimalarial agents. Finally, we still have much to learn. The parasites identified in this family were complex, and the mechanisms of resistance are still quite poorly understood.

By what mechanisms are *P falciparum* parasites resistant to the combination of atovaquone and proguanil? Mutations in the cytochrome b gene had been previously identified[1] in atovaquone-resistant parasites and were identified in the boy with recurrent illness in the recent report. Nonetheless, such a mutation was not found in the boy with early treatment failure and yet was found in the mother who did respond well to AP treatment. In addition, the dihydrofolate reductase gene mutation was found in the boy with recrudescent illness but might not relate to AP resistance; the role of proguanil in AP is likely more for a synergistic effect in boosting atovaquone effectiveness than in a primary antiparasitic action by proguanil.[6]

For now, travel medicine practitioners can continue to use AP as a valued component of malaria prevention and therapy. At the same time, however, we must carefully watch our own experiences and the reports of others as AP resistance might become more common. ■

Table

Daily Dosing of Atovaquone-Proguanil

Body Weight, kg	Prophylactic,* mgA/mgP	Curative,** mgA/mgP
11-20	62.5/25	250/100
21-30	125/50	500/200
31-40	187.5/75	750/300
> 40	250/100	1000/400

* daily dose beginning 1-2 days prior to departure and continuing 7 days after leaving malarial area

** daily dose for 3 consecutive days

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Schistosomiasis in Travelers

CONFERENCE COVERAGE

By Mary-Louise Scully, MD

The growing awareness and interest in schistosomiasis among travelers to endemic areas was a topic of discussion at the recent eighth Conference of the International Society of Travel Medicine. In addition, there are several new relevant publications in this area.

Hewison and Jones from Edinburgh, Scotland, presented a study of the clinical aspects of 199 patients with positive *Schistosoma haematobium* serology, of whom 115 had swum in Lake Malawi (*Abstract FC 08.02*). Cough was the most common respiratory complaint occurring in two-thirds and in those with genitourinary (GU) symptoms; hematuria was present in 25% and uri-

nary urgency or frequency in 20%. A subsequent discussion considered Eli Schwartz's article on travelers with hematospermia due to schistosomiasis and the need to consider treatment with higher doses of praziquantel or a longer course of treatment.[1] In Schwartz's report, 3 of the 4 patients treated with praziquantel, at 40 mg/kg given in 2 divided doses, had an initial clinical response, but all 3 patients experienced relapse of *S haematobium* infection after several months. The 1 patient treated initially with a higher dose (60 mg/kg) did not experience a recurrence of infection. Unless a travel and exposure history are taken, the diagnosis of schistosomiasis can be easily missed.

Christoph Hatz of Switzerland gave an excellent overview of schistosomiasis (*Sy 10.01*). It is estimated that 200 million people are infected with schistosomiasis with at least 120 million being symptomatic and 20 million with severe disease. The European Network on Imported Infectious Diseases Surveillance (TropNetEurop) has just published its data of the first 3 years of sentinel surveillance for imported schistosomiasis.[2] Not surprisingly, the majority of imported cases were from Africa, with the largest contributors at a country level being Malawi (14.4%), Ghana (13.5%), Mali (8.1%), Burkina Faso (5.7%), and Egypt (4.5%).

Turning toward prevention, data from N'Goran's recent publication of the randomized, double-blind, placebo-controlled trial of oral artemether for the prevention of *S haematobium* infection were discussed.[3] Artemether, a derivative of the antimalarial artemisinin, has been shown to have antischistosomal properties against the young developmental stages of schistosomal parasites. Praziquantel is not effective during this early period. Studies have previously demonstrated artemether to be safe and effective in preventing acute infection with *Schistosoma japonicum* and *Schistosoma mansoni*.[4]

N'Goran's study was done in a village in the highly endemic area of Lake Taabo in the Ivory Coast. Artemether at a dose of 6 mg/kg, vs placebo, was given once monthly for 6 months to 322 children. These children had been pretreated with 2 systemic doses of praziquantel 4 weeks apart and found to be free of schistosome infection by examination of urine specimens. Previous work in the village had shown that at least 50% of placebo patients would become reinfected with *S haematobium* within 6 months. Surveillance for malaria parasitemia was performed every 4 weeks, and children who developed malaria were treated with a single oral dose of SP (25 mg/kg sulfadoxine and 0.75 mg/kg pyrimethamine). In the final cohort of 306 children, the incidence of *S haematobium* infection was 25% lower in the artemether group (artemether 76/156 vs placebo 97/150). Also, the patients who received artemether, but did become infected with *S haematobium*, had less intense infections than the placebo group (artemether, 3.4 eggs per 10 mL urine; placebo, 7.4 eggs per 10 mL urine). The incidence of reduction of *S haematobium* infection in this study was less than that previously reported for *S japonicum* and *S mansoni*. N'Goran suggests that the results might be improved by decreasing the artemether dosing interval to 3 weeks, which had been used in the *S mansoni* study.[5]

The potential use of artemether for prevention of schistosomiasis is only recommended in areas where schistosomiasis is endemic but malaria is not (certain parts of Brazil, China, Middle East, and North Africa). Artemether or other artemisinin derivatives should not be used for prevention or cure of schistosomiasis in areas where malaria and schistosomiasis are coendemic because of possible evolution of resistance in malaria parasites.

Another study of prevention was presented in a poster by Jackson et al, *Schistosomiasis Prophalaxis Using DEET (PO 13.03)*. Fifteen subjects participated in an expedition to record the fauna of Lake Malawi, including the intermediate snail hosts for schistosomes. Their research would require wading, kayaking, and diving in wet suits into Lake Malawi. Previous *in vitro* studies in mouse tail skin had demonstrated that topical DEET in sufficient amounts will diffuse through skin and destroy cercariae as they migrate during the first 72 hours after exposure.[6] A 50% DEET solution in ethyl alcohol (to achieve adequate dermal concentration) along with Ultrathon for mosquito protection, was applied nightly. Despite 2 patients reporting "swimmer's itch," no new schistosome infections occurred during a 3-month follow-up. Two patients found to have positive serology on blood collected before the study were felt to be infected previously. More studies addressing the safety of such an approach and studies looking at different doses of DEET are clearly needed. However, this study raises some interesting possibilities in terms of potential product development that could combine protections against mosquitoes and schistosomes.

Edward Pearce, from the University of Pennsylvania, reported last month on the current situation in vaccine development for schistosomiasis.[7] Many of the antigens that are still being tested in vaccine research were identified more than 10 years ago. One of these, glutathione S-transferase (GST), is in independent development by the Pasteur Institute. *S haematobium* GST, formulated as Bilhvax, has advanced through Phase I trials and is now in Phase II trials. However, all experimental vaccines for schisto-

somiasis to date have only been able to induce partial resistance to infection (ie, animals vaccinated harbor *fewer* parasites). Some encouraging studies in animals suggest a possible role for the cytokine, IL-12, as an adjuvant to induce complete protection. Pearce concludes by encouraging continued support for research in the basic biology and immune mechanisms of schistosomes, which hopefully will lead to advances in immunotherapy. ■

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Envenomations

CONFERENCE UPDATE

By Lin Chen, MD

At the eighth conference of the International Society of Travel Medicine (CISTM8) held in New York City, May 7-11, 2003, one symposium addressed envenomations, land and sea. Dr. Robert Norris discussed poisonous animals. The American Association of Poison Control Centers reported 93,821 calls for bites and stings in 2001, which comprised 4% of all calls to poison centers. There were only 3 recorded deaths from snake bites, all due to pit viper. Greatest threats for stings were the Hymenoptera (bees, wasps, ants). Anaphylaxis can occur in 0.5-5% of the population, resulting in 40-150 deaths per year. Yellow jackets rank first in the killer bee category.

Envenomation with spiders and scorpions occurs in the United States and includes widow spiders (*Latrodectus* spp.), brown spiders (*Loxosceles* spp.), hobo spiders (*Tegenaria agrestis*), and bark scorpion (*Centruroides exilicanda*). The widow spiders and bark scorpion are neurotoxic, whereas brown spiders and hobo spiders cause necrotic arachnoidism. Children are more severely affected. Tarantulas will bite when handled, but do not cause significant systemic toxicity. The hairs can cause urticarial dermatitis when aerosolized. The management for tarantula bite is primarily ice. Management of widow spider bite includes ice, tetanus-diphtheria booster, analgesics, and only rarely antivenom.

Snakebite rates were last assessed in the 1950-1960s, according to Dr. Norris, with an incidence of 8000 bites and 6 deaths per year. Most common causes in the United States are Mojavi rattlesnake, cottonmouth pit viper, copperhead, which is the least toxic of pit vipers, coral snakes, and Western diamondback rattlesnake. Risks associated with venomous snakebites are young age of the person bitten, male gender, and prior alcohol use. Pressure and immobilization are indicated in acute management. Antivenom, CroFab (sheep or ovine), binds to venom, and has a broad spectrum of activity. CroFab is manufactured by immunizing a host animal, harvesting the IgG, converting IgG to Fab, and purifying the product. It is an improved product when compared to previous antibody preparations. No skin testing is needed, it is safer, requires no pretreatment, and has a shorter duration of action. Acute reactions occur in 17%, but they are considered mild to moderate; serum sickness occurs in 3% of recipients. Each vial of CroFab costs $800, and 4-6 vials are needed to treat mild-to-moderate symptoms of snakebites.

Dr. David Warrell discussed current global issues concerning snakes, scorpions, and spiders. Community based studies on the risk to indigenous populations showed 14/100,000 bites per year in Senegal and 7.7/100,000 per year in Nigeria. Travelers also get bitten, as illustrated by 4 cases that Dr. Warrell presented:

Case 1. A 36-year-old male German tourist in central Bangkok heard some rustling in grass, and was bitten by a Cobra;

Case 2. A 45-year-old male visited Mazamari waterfall in Chanchamayo, Peru, grabbed a "rope," which turned out to be a bushmaster, *Lachesis muta*;

Case 3. A 38-year-old American herpetologist in Rat Baw, Burma, mistook a krait, *Bungarus* spp., as a benign *Dinodon septentrondis*. He succumbed to the neurotoxicity after prolonged resuscitation efforts;

Case 4. A 27-year-old male Dutch tourist was in Malacca, Malaysia, and uncovered a spitting cobra, *Naja sumatrama*, in his hotel bed.

High-risk areas for terrestrial snakebites are West Africa, Southeast Asia, Amazon, and New Guinea. Habitats include rain forest, savanna, and plantations. Rainy season and nighttime pose high risk. Risk is also related to activity, with zoologists, botanists, and explorers experiencing high risk.

First aid should emphasize immobilization, especially the bitten limb. Pressure-immobilization should be used for neurotoxic Elapid bites only and not for viper bites. The victim should be transported to medical care immediately to prevent death from shock or respiratory paralysis. Long bandage and splint are appropriate, but avoid harmful treatment.

Medical treatment should focus on rapid assessment, species diagnosis, and resuscitation. At bedside, a 20-minute whole blood clotting test can be done to determine whether coagulopathy is present. Laboratory evaluation should be obtained. Determine whether antivenom is indicated. Close observation of the patient and support of failing systems should continue. Treat the bitten limb. Provision and use of antivenom (which, unfortunately, can cause angioedema) should be considered by expeditions at remote locations, especially when signs of envenoming appear. If medical care is within 2 hours, the most appropriate approach would be immobilization with or without pressure, and evacuation. If medical care is more than 2 hours away, antivenom should be considered as IV or IM in anterolateral thigh, provided necessary skills and equipment are available. Evacuate on a strecher. Prevention should include learning something about indigenous snakes, protecting feet, and avoiding undergrowth and deep sand. Use a flashlight at night, and avoid sleeping on the ground.

Scorpions have a chitinous exterior, which is illuminated by ultraviolet rays. Between 4000 and 5000 stings occur each year. Risks are highest in North Africa, Middle East, southern Africa, India, southern United States, Mexico, Latin America, and Trinidad. Clinical features include excruciating local pain, autonomic storm (tachycardia, hypertension, myocarditis), vomiting, diarrhea, and fasciculations. First aid following scorpion stings should include local anesthetic by digital or nerve block, analgesia (opiates), antivenom for systemic envenoming, and ancillary drugs such as vasodilators (α-blockers), and anticonvulsants. Avoid harmful measures such as local dehydroemetine, electric shock, and cardiac glycosides.

Hot spots for spider bites are Australia, United States, Latin America, Mediterranean Europe, and South Africa. Clinical features are differentiated into *necrotic* bites vs *neurotoxic* bites. Necrotic bites are associated with increased pain over 12-36 hours, a local skin lesion, the red-white-blue skin sign, eschar formation in 7 days, fever, rash, hemolysis, hemoglobinuria, and renal failure. Case fatality rates are 1.5-3.7%. Neurotoxic bites are associated with severe pain, redness, sweating, headaches, nausea, vomiting, fasciculations, and muscle cramps. Treatment is with antivenom. For necrotic bites, dapsone, which inhibits leukocyte migration, can be considered. Steroids should be avoided. For neurotoxic bites, calcium gluconate can be considered.

Dr. Dietrich Mebs discussed marine envenomation and poisoning. Although the horseshoe crab is benign when touched, it may be poisonous when eaten. The box jellyfish has nematocysts that inject a toxic venom, which causes reactions from local blebs to cardiac failure. The Portugese Man-of-War looks like a plastic bag under water. First aid following jellyfish sting includes application of vinegar (acetic acid), which inactivates undischarged nematocysts.

Hot water treatment is controversial for venomous fish such as the stingray. Pufferfish (Fugu), another venomous fish, contains high concentrations of tetrodotoxin. Another toxin, ciguatera, is associated with diarrhea, vomiting, neurologic symptoms such as hot and cold reversal, paresthesia, and pruritus. Following envenomation, the goal is to treat symptoms using i.v. mannitol in the first 1-2 hours. Prognosis is good.

Shellfish can be associated with paralytic shellfish poisoning, caused by toxins such as saxitoxin. Symptoms are paresthesis, numbness, and progressive paralysis. Amnesia can result with cerebral symptoms, coma, or irreversible short-term memory impairment. Diarrhea can also occur. Scombroid toxicity is another poisoning associated with seafood and produces symptoms resembling allergic reactions. Ingesting the meat of whales and polar bears, which have high vitamin A concentrations in their livers, has lead to vitamin A intoxication. ■

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Monkeypox in Wisconsin!

ABSTRACT & COMMENTARY

Synopsis: *Health officials in Wisconsin have confirmed 4 cases of monkeypox in the Milwaukee area in what is believed to be the first outbreak of the disease in the Western Hemisphere.*

Source:
http://www.cdc.gov/ncidod/monkeypox/report_060903.htm.

Another 18 people in Milwaukee are suspected of having monkeypox which public health authorities suspect was passed to humans by prairie dogs sold by a local pet distributor. This distributor had gotten his prairie dogs from an Illinois distributor who had housed prairie dogs with an ill Gambian rat, another popular rodent pet. A potential 33 contacts are being monitored in Illinois and Indiana. All cases had direct or close contact with a recently purchased prairie dog.

COMMENT BY MICHELE BARRY, MD, FACP

Monkeypox is an orthopoxvirus related to smallpox and has a clinical presentation often indistinguishable from smallpox. Onset of illness in the 4 confirmed US human cases began with prodromal fever, headache, myalgias, and drenching sweats. Roughly one-third had nonproductive cough. This prodrome was followed 1-10 days later by the development of a papular rash that went through typical stages of vesiculation, pustulation, umbilication, and crusting. All patients reported contact with prairie dogs, most of which were sick. Illness in prairie dogs was frequently reported as beginning with blepharo-conjunctivitis progressing to nodular lesions and, in some cases, death.

On the basis of these preliminary cases, CDC recommends:

1. Avoiding contact with ill prairie dogs or Gambian giant rats;
2. Physicians should consider monkeypox in persons with fever, cough, headache, rash, or lymph node enlargement after contact with prairie dogs or Gambian giant rats;
3. Using hand hygiene and infection control (N95 mask, gown, glove, eye goggles, negative pressure room) for any suspected case;
4. Submission of all specimens should follow smallpox laboratory precautions and guidelines. http://www.bt.cdc.gov/agent/smallpox/lab-testing/index.asp.

Monkeypox was first described in 1959 as a primate infection in a Danish laboratory and subsequently was determined to be the cause of 8 additional laboratory monkey outbreaks between 1958 and 1968. In 1970, the first human case was identified in a tropical rain forest village in the Democratic Republic of the Congo (formerly Zaire). Between 1970 and 1995, more than 400 human cases were detected primarily in the Democratic Republic of the Congo. The cases were scattered primarily among people who trapped or consumed ground squirrels, but in a few instances larger outbreaks in villages raised the question of human-to-human transmission. Case fatality has ranged from 2% to 10% in some of the larger outbreaks.

Among the best field studies of human cases was the 1981-1986 outbreak of 338 cases of monkeypox occurring in 17 health zones of 3 regions of then Zaire. Primary infection was mostly related to trapping, eating, or contact with ground squirrels. Secondary attack rate was studied in households. Only 10% of 431 unvaccinated household contacts who lived in poorly ventilated huts came down with disease, and almost all were children who had not received smallpox vaccination due to the discontinuation of the smallpox vaccination program. Having had smallpox vaccination was felt to have conferred an 85% protection rate. By contrast, smallpox can have a 30% mortality rate with a secondary attack rate of 70% in unvaccinated hosts. The epidemic potential of monkeypox to humans in the post-smallpox vaccination era was calculated after these field studies and felt not to be an indication for reintroducing smallpox vaccination; chains of transmission were felt to arrest themselves easily with food, hygiene, and risk reduction practices such avoiding contact with dead or diseased rodents, monkeys or ill patients.

Monkeypox, like smallpox, has an incubation period of 12 days with a range of 7-17 days. A 2-5 day period of high fever, malaise, and headache is followed by a maculopapular rash appearing first on the mucosa of the mouth, pharynx, face, and forearms with eventual spread to trunk and legs. The rash of monkeypox is indistinguishable from smallpox; however patients exhibit prominent lymphadenopathy, which is less common in smallpox. Within 1-2 days, the rash becomes vesicular and then pustular and crusts begin to form on the eighth or ninth day. Palms and soles can be involved. Crops of monkeypox like early lesions of smallpox are synchronous and always found at the same stage of development, unlike varicella lesions, which are often found at different stages of development.

The principal distinguishing characteristic of monkeypox from smallpox is the temporary enlargement of lymph nodes, which are present in 86% of unvaccinated people. This lymphadenopathy is most often generalized, but local-

ized lymphadenopathy can also be seen. Nodes are firm and often tender. They appear shortly after the onset of prodromal fever, rarely 1-2 days after onset of rash. Secondary infection of pox lesions, abscess formation in nodes and broncho-pneumonia may cause morbidity and mortality.

The methodology for laboratory diagnosis of poxvirus often requires PCR to distinguish orthopoxvirus species since the 4 orthopoxviruses that infect humans (variola, vaccinia, cowpox, and monkeypox) cannot be readily differentiated from one another in most cell cultures. Recovered patients exhibit high titers of neutralizing hemagglutination inhibiting and complementing fixing antibodies, but cross-absorption studies are required to identify the species. Scientists in Wisconsin recovered viral isolates from a patient and a prairie dog, then demonstrated a poxvirus by electron microscopy. PCR and immunohistochemical studies done at CDC confirmed the orthopoxvirus to be monkeypox.

There is no specific treatment for monkeypox, but the antiviral drug cidofovir has been promising in laboratory studies. Smallpox vaccine has been reported to reduce the risk of monkeypox among previously vaccinated persons in Africa. CDC is assessing both a potential role for postexposure use of smallpox vaccine, as well as the therapeutic use of the antiviral cidofovir. ■

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Rapid Antigen Testing in Influenza Surveillance

ABSTRACT & COMMENTARY

Synopsis: *Rapid antigen testing may serve as an early warning system in influenza surveillance.*

Source: Wunderli W, et al. Rapid antigen testing for the surveillance of influenza epidemics. *Clin Microbiol Infect*. 2003; 9:295-300.

With the specter of SARS hanging over the world, we have lost sight of the morbidity and mortality caused by influenza epidemics each year. This article from University Hospital in Geneva, the Swiss Federal Office of Public Health, and Roche Pharma in Switzerland addresses the important question of how useful a rapid antigen test would be in surveillance of influenza epidemics. It also raises the question of how useful such a test would be for diagnostic insights during an outbreak of influenza.

The study seasons were the winter of 1999-2000 and 2000-2001. There was an epidemic of influenza in Geneva for each study period, though the first season was about twice the intensity of the second. More than 200 practitioners participated in the project, under the auspices of the Swiss Sentinel Surveillance Network (SSSN). Influenza virus was isolated at the National Center of Influenza. During the study, 55 practitioners actually sent samples for virus detection by isolation on cell culture (throat and nasal swab), and 198 practitioners sent samples for "near patient" testing, which was an influenza virus antigen. The rapid test used was the INFLUENZA A/B-RAPID TEST provided for the study by Roche Diagnostics. Results were published twice weekly at the influenza study web site, www.influenza.ch.

In the first season, the peak of intensity was seen in the first week of 2000, whereas for the second winter the peak was in the sixth week. There were 39 cases of virus isolation in the first winter at the peak and only about 20 in the second winter. The antigen detection, near patient test lagged slightly behind and was not as sensitive picking influenza out of influenza-like illnesses. The average time for a positive cell culture was 11 days, while the near test results were available 6 days earlier. Note that samples from the same patient were not available for comparison. Nevertheless, the cell culture was more sensitive, 33% vs 26% in the first year and 23% vs 12% in the second year. The sensitivity of the near patient assay increased as the epidemic evolved, suggesting the practitioners were more likely to detect influenza when it was the primary virus causing influenza-like illness.

■ COMMENT BY JOSEPH F. JOHN, Jr., MD

The global SARS epidemic has intensified the need for accurate, rapid tests for acute viral illness. Viral antigen detection systems have been around for years, but studies like the present one have not been numerous.

The advantage to the rapid test is that it can be done with minimal laboratory support. Developing countries do not have the restrictions set upon US practitioners, and there is no reason why some of these rapid tests cannot be adapted for office practice. Switzerland is a small but very well-organized country. In such countries, regional laboratories may be able to process rapid testing fast enough to make it useful for public health purposes. It is not hard now to imagine 1 effect of the SARS epidemic being more vigi-

lance of influenza virus outbreaks, perhaps to the extent that person-to-person transmission can be reduced.

Several rapid tests for influenza have been developed but are not widely used globally or in the United States. The Swiss study gives credence to the use of rapid testing for public health purposes and suggests that there may be clinical use, particularly during influenza outbreaks, of using rapid antigen testing. ■

Dr John is Chief, Medical Subspecialty Services, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston, SC.

CME Questions

7. *P falciparum* resistant to atovaquone-proguanil:

a. has never been reported outside the laboratory.
b. is commonly encountered in travelers from Asia.
c. is primarily due to a mutation in the dihydrofolate reductase gene affecting proguanil metabolism.
d. has been clinically overcome by treatment with mefloquine.
e. is only seen in semi-immune adults treated with this agent for prolonged periods (> 3 months).

8. The following statement is correct regarding schistosomiasis:

a. Lower doses of praziquantel have been found to be effective for patients with hematospermia secondary to schistosomiasis.
b. Use of artemether or other derivatives of artemisinin for cure or prevention of schistosomiasis is not recommended in areas where malaria and schistosomiasis are co-endemic.
c. To date, potential vaccines for schistosomiasis are capable of inducing complete immunity.
d. Praziquantel is only effective for the young developing forms of schistosomiasis.

9. Which of the following statements regarding envenomations is true?

a. Skin testing with current preparations of snake antivenom (sheep or ovine CroFab) is mandatory prior to use in the treatment of snakebites.
b. Widow spiders and bark scorpions produce necrotic arachnoidism in those who are bitten.
c. Tarantulas will bite but do not cause significant systemic toxicity
d. Horseshoe crabs may be eaten, but are toxic when touched
e. The physiology of undischarged jellyfish nematocysts is not altered by vinegar (acetic acid)

10. Which statement regarding monkeypox is correct? Monkeypox:

a. shows mainly person to person transmission once present in its epidemic form, with a secondary attack rate of 30% in unvaccinated household contacts.
b. can be distinguished from smallpox by observing its growth within cell cultures.
c. shows a truncal maculopapular rash, which evolves synchronously (all in one stage) and is indistinguishable from smallpox.
d. is caused by the bite of fleas infesting prairie dogs who are silent reservoirs for virus.
e. unlike smallpox, can be effectively aborted with cidofovir when used intravenously.

Answers: 7 (d), 8 (b), 9 (c), 10 (c)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Travel Medicine Advisor*. Send your questions to: Robin Mason, *Travel Medicine Advisor*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. ■