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INSIDE

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Malarone™ for Chemoprophylaxis of Malaria

ABSTRACT & COMMENTARY

Synopsis: *Malarone™, an oral antimalarial containing a fixed combination of atovaquone and proguanil (A/P), was released in August 2000 for the chemoprophylaxis and treatment of malaria. This drug had been studied extensively for prevention and treatment of Plasmodium falciparum malaria in semi-immune hosts (ie, persons who live in malaria-endemic regions and are assumed to be partially immune to malaria), but it had not been evaluated in nonimmune persons such as a traveling population.*

Source: Hogh B, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travelers: A randomised, double-blind study. *Lancet.* 2000; 356:1888-1894.

Publication of the first trial of malarone™ chemoprophylaxis in travelers was highly anticipated. Would the drug be well-tolerated in travelers and provide the same excellent protection that had been seen in semi-immune populations? In this trial, 21 travel clinics in Europe, Canada, and South Africa collaborated in a study of 1022 adolescents and adults traveling to malaria-endemic areas for up to 28 days. GlaxoSmithKline, the manufacturer of Malarone™, funded the trial. Travelers were randomized to take either Malarone™ or chloroquine-proguanil (C/P). Because of different dosing schedules for the 2 regimens (Malarone™ 1 tablet daily, chloroquine 2 capsules weekly, and proguanil 2 capsules daily), travelers took additional placebo pills to allow a double-blind trial. Travelers were surveyed by telephone both 7 and 60 days following travel and seen at a clinic visit at 28 days. They were asked about their health during travel—which included questions about medication side effects and signs/symptoms of malaria. They were provided a diagnostic kit to use if malaria was suspected. The kit contained a card to record details about the diagnosis, slides for blood smears, and filter strips for PCR amplification of parasite DNA in a blood sample. Infection with *Plasmodium falciparum* was assessed using serum samples and testing for antibody to circumsporozoite protein (the repeat region of the *P falciparum* sporozoite) at baseline and 28 days. Some participants had hemograms and chemistries checked at 28 days. The primary study end point was the overall frequency of adverse events 7 days following departure from the malaria-endemic region. Secondary end points were the frequency of treatment-limiting adverse events and efficacy of prophylaxis.

A total of 1008 persons completed the trial—501 in the A/P group and 507

in the C/P group. Sixty-three percent traveled to countries in Africa. At 7 days, 22% of the A/P group reported treatment-related side effects compared with 28% of the C/P group (P = .024). When gastrointestinal side effects were compared, there were significantly more side effects in the C/P group (20% vs 12%; P = .001). This was not the case when neuropsychiatric side effects were examined (10% each group). Severe events, not delineated, were reported in 5 persons taking A/P and 11 persons on C/P. Eleven persons discontinued A/P because of adverse events and 16 discontinued C/P. For the 180 persons who had laboratory testing, there were no differences in the laboratory results between the groups, and no "clinically important" abnormalities were detected.

Clinical malaria was confirmed in 4 travelers; 3 cases of *P falciparum* occurred in persons while they were taking C/P, and 1 case of *Plasmodium ovale* occurred 28 days following completion of A/P. In the cases of *P falciparum*, parasites were resistant to chloroquine and had decreased sensitivity to proguanil by genetic testing. Antibody to the circumsporozoite protein was detected in 7 people taking A/P and 8 people taking C/P. The minimum protective efficacy of A/P for *P falciparum* was 100% (95% CI: 59-100%) and for C/P 70% (35-93%).

COMMENT BY DAVID R. HILL, MD, DTM&H

The fixed combination of A/P is highly effective for both the treatment[1] and prophylaxis[2] of *P falciparum* malaria in persons who live in areas endemic for malaria.[3] In treatment studies, Malarone™ has been shown to be more effective than mefloquine for adults in Thailand,[4] than amodiaquine in adolescents and adults in Gabon,[5] and chloroquine or chloroquine plus sulfadoxine/pyrimethamine (Fansidar) in adolescents and adults in the Philippines.[6] It was equally effective as Fansidar® for adolescents and adults in Zambia,[7] as quinine and tetracycline in adults in Brazil,[8] and as halofantrine in children in Kenya.[9] In each of these trials, the efficacy of Malarone™ ranged from 87% to 100%. It also has activity in treatment of nonfalciparum malaria species[13,14] but does not eradicate the hypnozoite form of *Plasmodium vivax* or *P ovale*. Therefore, primaquine phosphate is required for radical cure of these species.

In prophylaxis studies, it was highly effective (> 95% protection) in protecting against *P falciparum* in adults in Kenya[10] and Zambia,[11] and in children in Gabon.[12]

The trial by Hogh and colleagues of Malarone™'s tolerance in nonimmune travelers is the necessary complement to studies in semi-immune persons. The drug was well-tolerated, and people experienced few side effects or treatment-limiting events. Although efficacy was not a primary end point, the diagnosis of malaria was rigorously examined and Malarone™ was highly effective. Nevertheless, the exposure of this group of travelers to malaria is not definitively known (there were only 15 persons who developed antibody to circumsporozoite protein, suggesting limited exposure). Malarone™ will need to be studied in additional groups with varying levels of exposure to malaria to gain a complete picture of efficacy. A study presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapeutics in Toronto, Canada, last year included travelers on Malarone™ compared to those on mefloquine,[15] and a small study of nonimmune South Africans taking Malarone™ for new exposure to malaria was published in 1999.[16] In both of these groups, Malarone™ was highly effective.

The place of Malarone™ in malaria chemoprophylaxis and treatment will evolve as more experience is gained with the drug. Many travelers who are concerned about potential neuropsychiatric side effects of mefloquine will choose Malarone™ for prophylaxis. It has an advantage of having causal prophylactic efficacy against *P falciparum* (ie, killing developing erythrocytic phase organisms),[17,18] and this permits the early discontinuation of the drug following exposure to *P falciparum* malaria. It is ideal for the traveler who will have short-term exposure to malaria, such as the traveler to South Africa who will be in Kruger National Park for only a few days during a trip. They can start the drug the day before exposure, take it during exposure, and for a week thereafter. It can be used as an alternative to doxycycline for prevention of multi-drug resistant *P falciparum*, which may be encountered by the rare traveler who visits rural, forested, border areas of Thailand with Cambodia and Myanmar,[4] and by travelers who visit the ruins of Ankor Wat in Siam Reap, Cambodia. It is an option for self-treatment of malaria in the event of failure of chemoprophylaxis during travel. Finally, its availability in a pediatric formulation makes it convenient to prescribe malaria medication for children and provides an option for children younger than the age of 8 years who are intolerant of mefloquine, and in whom doxycycline is contraindicated. For long-term travelers with exposure to *P vivax* or *P ovale*, consideration should be given to terminal prophylaxis with primaquine, since Malarone™ will not eradicate the hypnozoite phase of these parasites. It currently is not recommended for use during pregnancy, since atovaquone is in pregnancy category C.

An important consideration is cost, which is now about $10 per pill, making its use problematic for use in long-term travelers.[3] Francois Nosten raised the issue of cost and the place of Malarone™ in a global context in a thoughtful *Lancet* editorial that accompanied the Hogh

paper.[19] He asked if this drug would be available for treatment of malaria in the developing world's population that suffers most from the burden of malaria? Will resistance develop if the drug is used indiscriminately? These are important issues to address by travel and tropical medicine specialists and by the drug's manufacturer, GlaxoSmithKline.

For specific CDC recommendations on the use of Malarone™, the CDC web site can be accessed at www.cdc.gov/travel/diseases/malaria/malarone.htm. ❖

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Water Treatment Systems

ABSTRACT & COMMENTARY

Synopsis: *Portable water treatment systems for travelers vary greatly. The efficacy of a system depends on its mechanism of treatment as well as its specific design. The hand-pump filters tested are in general the most reliable and efficacious in removing bacteria.*

Source: Schlosser O, et al. Bacterial removal from inexpensive portable water treatment systems for travelers. *J Travel Med*. 2001;8:12-18.

Efficacies of portable water treatment systems available on the French market under $140 were studied. These systems included 4 chemical agents, 2 iodine resin purifiers, and 4 filters.

The chemical agents tested included 3 chlorine compounds (Drinkwell chlorine®, Aquatabs®, and Hydro-

clonazone®), and 2% iodine in ethanol. The iodine resin purifiers tested were the PentaPure® straw Outdoor M1-E™ and the PentaPure® Traveler (which is attached to the faucet). The filters tested included Pres2Pure® (a flexible bottle), and 3 hand-pumps (Mini Ceramic®, First Need® Deluxe, and WalkAbout®).

The water in the study came from the river Marne, near Paris. Both raw river water (turbid water) and sand-filtered water from a water treatment plant (clear water) were used. Bacterial contents of the water samples were measured before and after treatment using 3 methods: conventional culturing techniques, Colilert®/Quantitray method, and fluorescent count of viable but not culturable bacteria.

Testing showed that sand-filtered water was clear but contained a significant number of coliforms including *Escherichia coli*. Tests on clear water showed that Hydroclonazone® and Pres2Pure® bottle were ineffective. Thus, these 2 systems were not tested further with turbid water. The Mini Ceramic® performed well, followed by the First Need® Deluxe. The WalkAbout® filter removed bacteria well in the first test, but the system became contaminated. The rest of the systems performed poorly.

Tests on turbid water showed that the hand pump filters were all effective in decreasing the turbidity of the water, with Mini Ceramic® leading in performance followed by the WalkAbout® and then the First Need® Deluxe. Furthermore, the 3 hand pumps effectively removed coliforms including *E coli*, with the exception of the WalkAbout® on 1 sample, when 2 coliforms/100 mL in the effluent were cultured (from a sample that contained 57,000 total coliforms/100 mL). Enterococci was identified in the effluent after treatment with Aquatabs® and the straw Outdoor M1-E™. Similarly, the chemical agents and the PentaPure® straw Outdoor M1-E™ were ineffective in inactivating coliforms.

COMMENT BY LIN H. CHEN, MD

The most reliable method of making water safe for drinking is to boil it. This is not feasible for many travelers. Therefore, some travelers rely on purchasing bottled water. Yet other travelers may be going to areas where the availability and reliability of bottled water are uncertain, and portable water treatment systems become crucial. Travel medicine consultants may be asked to recommend a water treatment system, but there is little scientific literature comparing the numerous systems.

NSF International is a company that tests and certifies water filters for removal of protozoa.[1] A list of filters that have passed NSF tests is available (1-800-673-8010; NSF, 3475 Plymouth Road, P.O. Box 130140, Ann Arbor, MI 48113-0140). However, the filters are not certified for their ability in removing bacteria or viruses.

In a prior study, Ongerth and associates had evaluated water treatment systems at removing *Giardia lamblia* for the backcountry traveler.[3] None of the chemical treatments and none of the contact disinfection devices provided sufficient cyst inactivation. Cysts were inactivated by heating to 70°C for 10 minutes, and cysts were effectively removed by some (but not all) of the filters tested. The First Need® Water Purification Device and the Katadyn Pocket Filter® were shown to be effective.

In evaluating drinking water for public health protection, *E coli* is felt to be the best biological indicator.[2] The Schlosser study investigates the removal of bacteria by portable water treatment systems, and complements the Ongerth study on *G lamblia*. This information is sorely needed to make specific recommendations for travelers. The conclusions are straightforward and comparable to the study on *G lamblia* cysts: the chemical systems and iodine resins are ineffective or unimpressive; the hand-pump filters in general are the most reliable in removing bacteria.

Each water treatment system has inherent problems or inconveniences. The chemical systems may impart an unpleasant taste. The iodine resins may lead to thyroid abnormalities.[4,5] The hand-pump filters may be bulky. Given their performance in removing bacteria, the hand-pump filters are easily the preferred portable water treatment systems. The Mini Ceramic®, manufactured by Katadyn Produkt AG, the First Need® Deluxe, manufactured by General Ecology, Inc., and the WalkAbout®, manufactured by SweetWater, should all be available in the US market. Additional studies that evaluate bacterial removal by the other portable water treatment systems available in the United States would be welcomed. ❖

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Students and Histoplasmosis in Acapulco

ABSTRACTS & COMMENTARY

Synopsis: *You probably never thought about college students returning from their rites of spring with histoplasmosis—but it happened this year. In this context, our associate editor also reviews the recently published guidelines for the treatment of histoplasmosis, a potentially serious infectious disease, with several different clinical manifestations.*

Sources: CDC. Outbreak of acute respiratory febrile illness among college students—Acapulco, Mexico, March 2001. *MMWR Morb Mortal Wkly Rep*. 2001;50(14):261; CDC. Public Health Dispatch. Update: Outbreak of acute febrile respiratory illness among college students—Alcapulco, Mexico, March 2001. *MMWR Morb Mortal Wkly Rep*. 2001;50:359-360; Wheat J, et al. Practice guidelines for the management of patients with Histoplasmosis. *Clin Infect Dis*. 2000;30:688-695.

Cdc recently reported an acute outbreak of febrile respiratory illness compatible with acute pulmonary histoplasmosis, occurring in college students returning from spring break holidays in Acapulco, Mexico. As of May 1, 44 colleges in 22 states reported 229 students who returned from Acapulco with an acute respiratory febrile illness defined as fever for at least 3 days and 1 or more of the following symptoms: cough, shortness of breath, chest pain, or headache. Initially, 21 students presented with fevers, dry cough, chest pain, and headache, and 2 students had patchy pulmonary infiltrates. At least 10 students had been hospitalized. Gomori methenamine silver stain of a transbronchial specimen suggested the presence of *Histoplasma capsulatum* in 1 student. Initially, specimens from 5 students returning with this syndrome in 3 separate states serologically tested positive for histoplasmosis using immunodiffusion and complement fixation tests. CDC first issued a travelers' warning for Acapulco available on the web: http://www.cdc.gov/travel/other/res-mexico-apr2001.htm. Physicians should contact the CDC's Mycotic Diseases Branch at (404) 639-1299. Since the first report in April, a cohort study has been performed among college students who stayed at 3 hotels in the area during the first 2 weeks of March and defined the relative risk of acquiring acute infection at these hotels. Analysis of 109 students indicated the risk ratio (RR) for this illness was 13.8 ($P < .001$) for those students (31) who had stayed at the Calinda Beach Hotel. The outbreak appears to be ongoing since a couple from California who stayed at the same hotel in early April appear to have also acquired documented histoplasmosis. Detailed cohort studies aimed at determining specific activities and exposures are being conducted among college students. The source(s) of the infections is not yet known, and may not be, until soil sample analysis for *H capsulatum* is also completed. Serological studies are also in progress using acute and convalescent phase serum specimens tested by complement fixations and immunodiffusion methods.

COMMENT BY MICHELE BARRY, MD, FACP

Most cases of acute pulmonary histoplasmosis in immunocompetent persons are self-limited and will not require treatment. Prolonged cases, lasting more than 1 month, would require antifungal therapy. Wheat and colleagues review all the indications for antifungal treatment for pulmonary histoplasmosis and its complications in a recent practice guideline paper appearing in *Clinical Infectious Diseases*. Severity of illness

Table 1

Indications for Antifungal Treatment in Patients with Histoplasmosis

Treatment indicated	Treatment not indicated
Acute pulmonary histoplasmosis with hypoxemia	Acute self-limited syndromes
Acute pulmonary histoplasmosis for >1 month	Acute pulmonary histoplasmosis, mildly ill
Chronic pulmonary histoplasmosis	Rheumatologic
Esophageal compression and/or ulceration	Pericarditis
Granulomatous mediastinitis with obstruction and/or invasion of tissue	Histoplasmoma
Disseminated histoplasmosis	Broncholithiasis
	Fibrosing mediastinitis*

* Antifungal therapy has not been proven to be effective for this form of histoplasmosis but should be considered, especially in patients with elevated erythrocyte sedimentation rates or complement fixation titers ≥ 1:32.

Adapted from: Wheat J, et al. Practice guidelines for the management of patients with histoplasmosis. Clin Infect Dis. 2000;30:688-695.

depends on intensity of exposure acquired from the usual source of soil inhalation and the immunity of the host. Hematogenous dissemination from the lungs occurs in all infected individuals during the first 2 weeks of infection but is usually nonprogressive and leads to asymptomatic calcified granulomas in the liver and/or spleen.

Progressive dissemination occurs primarily in patients with immunosuppressive disorders or in patients at the extremes of age. Progressive pulmonary infection is also common in patients with underlying centrilobular emphysema. Chronic manifestations of histoplasmosis appear to result from unusual inflammatory or fibrotic responses to infection. Rheumatologic syndromes and pericarditis can occur within the first year of infection, and chronic granulomatous, fibrosing mediastinitis, or broncholithiasis occur later. A variety of treatment options exist, but the most important decision for the physician caring for a patient with histoplasmosis is whether to observe or treat. (*See Table 1.*)

Acute Pulmonary Histoplasmosis: Treatment of Moderate Disease

Fever, chills, headache, myalgias, and pleuritic chest pain are seen in 85-100% of cases. Rales and pleural friction rubs may occur. Treatment is not indicated in the typical immunocompetent patient unless one shows lack of improvement at 1 month. Itraconazole, 200 mg daily, by mouth for 6-12 weeks would then be administered.

Severe Disease

If a patient becomes severely hypoxemic or requires ventilatory support, then amphotericin B 0.7 mg/kg/d, or an appropriately dosed lipid preparation of amphotericin for a patient with renal impairment should be administered initially. Corticosteroids might be considered as adjunctive therapy (60 mg/d) for 2 weeks because an inflammatory response is often a contributor to respiratory compromise. Itraconazole 200 mg twice daily is used to complete a 12-week course once the patient stabilizes clinically on amphotericin B. If amphotericin is used exclusively, a total course of up to 35 mg/kg over 2-4 months is recommended. (*See Table 2.*)

Length of Therapy

For disseminated histoplasmosis occurring in non-AIDS patients therapy should continue until histoplasma antigen concentrations are < 4 units in urine and serum. AIDS patients will require chronic maintenance with itraconazole after the initial 12-week induction therapy period. Antigen concentrations should be monitored for life in both serum and urine, every 3-6 months in AIDS patients with a history of histoplasmosis.

Prophylaxis

Travel medicine providers should consider advising prophylaxis (itraconazole 200 mg once daily) for immunocompromised travelers with CD4 lymphocyte counts less than 150 who are going to regions experienc-

Table 2

Summary of Treatment Recommendations for Patients with Histoplasmosis

	Severe manifestation	*Moderately severe or mild manifestation*
Type of histoplasmosis	**Treatment**	**Treatment**
Acute pulmonary	AmB with corticosteroids[a] then Itr for 12 w	Symptoms < 4 w; none; persistent symptoms for > 4 w; Itr for 6-12 w
Chronic pulmonary	AmB[b] then Itr for 12-24 mo	Itr for 12-24 mo
Disseminated in non-AIDS	AmB[b] then Itr for 6-18 mo[c]	Itr for 6-18 mo
Disseminated in AIDS	AmB[b] then Itr for life	Itr for life
Meningitis	AmB for 3 mo then Flu for 12 mo	Same as for severe because of poor outcome
Granulomatous mediastinitis	AmB then Itr for 6-12 mo	Itr for 6-12 mo
Fibrosing mediastinitis	Itr for 3 mo[d]	Same as for severe
Pericarditis	Corticosteroids or pericardial drainage	Nonsteroidal anti-inflammatory agents for 2-12 w
Rheumatologic	Nonsteroidal anti-inflammatory agents for 2-12 w	Same as for severe

[a] Effectiveness of corticosteroids is controversial

[b] If amphotericin B is used for the entire course of treatment, 35 mg/kg should be given over 3-4 months

[c] Therapy should continue until Histoplasma antigen concentrations are < 4 U in urine and serum

[d] Therapy is controversial and probably ineffective except in cases of granulomatous mediastinitis that are misdiagnosed as fibrosing mediastinitis

[e] If corticosteroids are administered, concurrent antifungal therapy is recommended.

Adapted from: Wheat J, et al. Practice guidelines for the management of patients with histoplasmosis. Clin Infect Dis. 2000;30:688-695.

ing high rates of histoplasmosis (> 5 cases 100 patient-years). Fluconazole is not an acceptable alternative to itraconazole for prophylaxis against histoplasmosis. ❖

Conjugate Typhoid Vaccine Arrives!

ABSTRACTS & COMMENTARY

Synopsis: *Each year, there are at least 16 million cases of typhoid fever worldwide, resulting in approximately 600,000 deaths. The majority of cases occur in southeast Asia, where resistance to multiple antibiotics is increasingly prevalent. A new typhoid vaccine appears ready to break the hold that typhoid fever has on children both living within and traveling to the developing world.*

Sources: Guerrant RL, Kosek M. Polysaccharide conjugate typhoid vaccine. *N Engl J Med*. 2001;344:1322-1323. Editorial; Lin FYC, et al. The efficacy of a *Salmonella typhi* Vi conjugate vaccine in two- to-five-year-old children. *N Engl J Med*. 2001;344:1263-1269.

TMA update has recently reviewed the issue of increasing resistance of *Salmonella typhi* to multiple antibiotics. We now address recently published data from the *New England Journal of Medicine* to show evidence of a promising, well-tolerated typhoid vaccine[1] that may not only help travelers but may potentially assist in the control of both endemic and epidemic disease due to *S typhi*.

Currently existing typhoid vaccines include a parenteral inactivated whole-cell vaccine, an oral-attenuated *S typhi* Ty21A vaccine and a Vi polysaccharide vaccine. At best, each may confer about 70% protection against typhoid fever in older children and adults, but these vaccines do not protect young children to the same extent. There are other limitations to current typhoid vaccines. Frequent local and systemic side effects occur upon administration of the heat- and phenol-inactivated vaccine, and it has recently been discontinued from the US market. The oral vaccine has been essentially unavailable recently; its multiple dosing regimen and refrigeration requirement makes it cumbersome to administer.

Conjugate vaccines have been developed for other organisms, such as *Hemophilus influenzae* and *Neisseria meningitidis*, to produce T-cell priming glycoconjugates that induce far better immune responses than do unconjugated polysaccharide vaccines, even in young children. The new conjugated typhoid vaccine achieves enhanced immunogenicity by binding Vi, the virulence factor and capsular polysaccharide of *S typhi*, to a nontoxic recombinant protein that is antigenically identical to *Pseudomonas aeruginosa* exotoxin-A (r-EPA). In initial trials, Vi-rEPA elicited a booster response in 2- to 4-year-old children producing antibody titers approximately 3 times higher than those elicited by Vi polysaccharide vaccine in 5- to 14-year-olds.

A double-blind, randomized, placebo-controlled vaccine trial was conducted in Vietnamese children from ages 2 to 5. In this 1998 study, 11,091 children received either the vaccine or placebo. The participating children were given 2 vaccine doses 6 weeks apart and were observed at 20 minutes, 6, 24, and 48 hours after inoculation for fever and inflammatory changes at the injection site. Children whose axillary temperatures exceeded 37.5°C were excluded. Subsequently, all received weekly visits. Axillary temperatures were measured, and, if elevated, evidence for typhoid fever was sought with blood cultures. Paired sera were obtained prior to the first, and 4 weeks after the second vaccination. No serious adverse experiences were identified in either group.

Following the first inoculation, 81 of 5525 children in the vaccine group had axillary temperatures measuring higher than 37.5°C, with 17 of these having a temperature higher than 39°C. This compares to 32 out of 5566 in the placebo group who had temperature readings higher than 37.5°C, 5 of whom had temperatures higher than 39°C. After the second injection, 109 vaccine recipients had temperatures higher than 37.5°C vs. 25 placebo recipients. Swelling at the injection site, greater than 5 cm in circumference, occurred in 20 vaccinated individuals vs. 1 in the placebo group. Erythema, greater than 5 cm, without swelling occurred in 2 vaccinated children vs. none in the placebo group. All changes occurring at the injection site resolved within 48 hours.

The efficacy of the vaccine was found to be greater than that of any existing typhoid vaccine. Four cases of typhoid fever were diagnosed by blood culture in vaccine recipients, compared with 47 cases diagnosed in those who were given placebo (possibly 48, if counting 1 subject who received a placebo injection that was deemed not properly labeled). Counting all improperly labeled recipients, there were 5 typhoid cases diagnosed in the vaccine group compared with 56 diagnosed cases in the placebo group. Twenty-one of these 61 typhoid fever patients were hospitalized; all were from the placebo group.

Antibody titers (serum IgGViAb) increased by a factor of more than 575 when measured 4 weeks after the second injection. Persistence of antibodies was documented 2 years after the 2-dose series. Titers remained

approximately 19 times higher in those who were vaccinated compared with those children who received placebo injections.

COMMENT BY MARIA D. MILENO, MD

Typhoid fever is all too common and increasingly difficult to treat in developing countries with emergence of *S typhi* resistance to multiple antibiotics. Lin and colleagues describe a safe and highly immunogenic conjugate typhoid vaccine that provides outstanding protection to children who are between 2 and 5 years old. This vaccine should prove to be at least as protective, if not more so, in older individuals. Travelers, missionaries, and volunteers working abroad face enormous challenges finding safe food and drinking water, especially while venturing into rural areas of the developing world. A sufficient number of reports indicate that even travelers who are vaccinated with the currently available typhoid vaccines risk contracting typhoid fever. Now that the whole-cell preparation of typhoid vaccine is off the market, individuals younger than 2 years old have no alternative vaccine protection. The high antibody titers induced by the conjugate vaccine are promising in potentially conferring some protection on this age group, although further investigation is needed to show this. There is no doubt in my mind that this new vaccine will have a strong role in the protection of travelers against typhoid fever. The greatest promise it holds is for the control of typhoid fever among the youngest of those living in impoverished areas of the developing world. ❖

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CME Questions

7. The distinguishing feature of the newly published typhoid vaccine includes:

a. minimal pain, swelling, or redness at the injection site.
b. single-dose schedule.
c. antibody titers that persist more than 5 years.
d. efficacy greater than 90%.
e. enhanced immunity for immunocompromised individuals.

8. In which of the following situations is the use of Malarone™ (atovaquone/proguanil) not indicated?

a. Prophylaxis of *P falciparum* malaria
b. Treatment of *P falciparum* malaria
c. Radical cure of *P vivax* malaria
d. Self-treatment of malaria during travel in persons not taking Malarone™
e. Treatment of pediatric malaria caused by *P falciparum*

9. Which one of the following statements regarding histoplasmosis is *false*?

a. All cases of acute pulmonary histoplasmosis with infiltrates should be treated with a course of oral itraconazole.
b. Fluconazole is not considered an acceptable antifungal agent for the prevention of histoplasmosis.
c. Corticosteroids may be indicated during the initial treatment of histoplasmosis to decrease the complications of inflammation.
d. Most cases of pulmonary histoplasmosis are self-limited.
e. There is a clearly defined role for parenteral amphotericin B in the treatment of pulmonary histoplasmosis.

10. Acute pulmonary histoplasmosis is a:

a. febrile respiratory illness with infiltrates that should always be treated with antifungal therapy.
b. febrile respiratory illness with infiltrates that is sometimes self-limited but should always be treated with itraconazole to mitigate symptoms.
c. febrile respiratory illness that has hematogenous dissemination from the lungs to other organs in all infected patients whether immunocompetent or immunocompromised.
d. febrile respiratory illness that has hematogenous dissemination from the lungs to other organs in immunocompromised patients only.