DEPARTMENT OF HEALTH AND HUMAN SERVICES

and

CENTERS FOR DISEASE CONTROL AND PREVENTION

convene the

EXPERT MEETING ON MALARIA CHEMOPROPHYLAXIS

Atlanta, Georgia
January 29-30, 2003

RECORD OF THE PROCEEDINGS

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Summary of the Meeting

The Centers for Disease Control and Prevention (CDC) of the Department of Health and Human Services (DHHS) convened an Expert Meeting on Malaria Chemoprophylaxis. The proceedings were held at the DoubleTree Hotel in Atlanta, Georgia on January 29-30, 2003.

***Opening Session*.** Dr. Ali Khan, the Acting Associate Director for Global Health in the CDC National Center for Infectious Diseases (NCID), called the meeting to order at 8:30 a.m. on January 29, 2003. He welcomed the participants to the proceedings and thanked the attendees for sharing their valuable expertise with CDC. He yielded the floor to Dr. James Hughes, Director, NCID.

Dr. Hughes pointed out that the global burden of disease associated with malaria continues to be an ongoing health issue. As a result, the expert panel was convened to assist NCID in updating guidelines for malaria prevention in travelers who go to endemic areas. He was pleased to note that the attendees represented the Department of Defense (DoD); Department of State (DOS); Food and Drug Administration (FDA); National Institutes of Health; Peace Corps; World Health Organization (WHO); and international organizations in Canada, Mexico and the United Kingdom.

Dr. Hughes acknowledged Dr. Monica Parise, of the NCID Division of Parasitic Diseases (DPD), for overseeing the enormous effort involved in reviewing, critiquing, abstracting and consolidating more than 2,000 references cited in the background meeting materials. He underscored the importance of the attendees providing NCID with evidence-based recommendations to update CDC's malaria prevention guidelines. Dr. Hughes reiterated CDC's gratitude for the expert panel's valuable contributions in this effort.

***Review of Meeting Agenda*.** Dr. Khan announced that the expert meeting to discuss malaria chemoprophylaxis issues was a novel event for CDC. The proceedings were designed to be objective and transparent, but NCID would not seek consensus from the expert panel. Instead, individual opinions would be used to formulate the next set of malaria prevention recommendations in the United States for travelers. To more broadly disseminate expert guidance, CDC hopes to eventually publish the

recommendations in a variety of venues, including *Health Information for International Travel* (Yellow Book) and the *Morbidity and Mortality Weekly Report* (*MMWR*).

Currently, approximately 500,000 travelers require chemoprophylaxis in some form per year. Despite global malaria control activities, 300-500 million cases of malaria occur worldwide each year. The majority of the 1 million deaths that occur in Africa each year are among children <5 years of age. The expert panel was convened to specifically address the population of worldwide travelers to these countries who require chemoprophylaxis; approximately 1,000 cases of malaria are reported each year in the United States.

To focus the discussion, Day 1 of the meeting would be entirely devoted to reviewing and discussing malaria drugs. On Day 2, the expert panel's recommendations for malaria chemoprophylaxis would be reviewed; health communication strategies would be outlined; and data on standby treatment (SBT) would be presented. The proceedings would conclude with a summary of next steps in this process.

***Meeting Purpose and Expected Outcomes*.** Dr. Parise acknowledged the diligent efforts of NCID staff and others in formulating the meeting, convening the expert panel and gathering background materials. These persons include Dr. Martin Cetron, Deputy Director of the Division of Global Migration and Quarantine (DGMQ) and Acting Branch Chief, Surveillance and Epidemiology; Dr. Phillip Coyne of the Walter Reed Army Institute of Research; Ms. Meghna Desai of DPD; Dr. Phyllis Kozarsky of DGMQ; Dr. Linda Lewis, a CDC consultant; Dr. Robert Newman of DPD; and Dr. Richard Steketee, Chief, Malaria Branch. Dr. Parise also thanked the experts who agreed to serve as session leaders.

She reported that the Malaria Branch makes CDC's malaria prophylaxis recommendations in consultation with DGMQ, but external advice has also been informally solicited from the American Society of Tropical Medicine and Hygiene (ASTMH) and other providers. The expert panel would serve as a more formal mechanism for NCID to obtain external input on whether the current guidelines need revision or if existing policies should simply be reaffirmed.

Because the options for malaria chemoprophylaxis are fairly limited, CDC has made relatively few changes in its recommendations over the last several decades. Chloroquine (CQ) was the standard of care until resistance to the drug worsened in the 1980s. During the 1980s, CDC recommended weekly CQ and sulfadoxine-pyrimethamine (SP) for a period of time, but this regimen resulted in an unacceptably high number of adverse skin reactions. In 1985, CDC recommended a stratified approach: short-term travelers were advised to take CQ and carry presumptive SP. Longer term travelers were advised to still consider using both weekly CQ and SP approach (with amodiaquine or doxycycline as alternatives). After MQ was approved in 1990, it became the drug of choice with doxycycline (DC) as an alternative. Although

data were more limited for DC, an alternative was needed and this drug was recommended from 1985 to the present.

After the approval of atovaquone/proguanil (AP) in 2000, CDC changed its recommendations from having one drug of choice to providing individuals with three options for drugs in areas with *P. falciparum* rather than listing one drug of choice. Decisions on which of these drugs is best for an individual traveler depend on age, whether a person is pregnant, and the presence of other medical conditions. Because 3 more efficacious options were then available, at that point, CDC dropped CQ/proguanil as an option. In preparation for the expert meeting, NCID conducted an exhaustive review of the evidence-based literature to compile background materials. The key points for each drug are highlighted in a shorter recommendation document that outlines potentially controversial or unclear discussion points to be raised during the meeting.

The expert panel will be asked to provide CDC with input on its overall recommendations for both CQ-sensitive and CQ-resistant areas. Guidance will also be solicited on health communication strategies CDC has developed to refine message delivery. In addition, a discussion will be held on whether recommendations for prophylaxis should apply to all malarious areas or whether a more stratified approach should be considered – i.e. use SBT in very low risk areas. Input from the proceedings will be captured in a verbatim transcript and executive summary. The meeting report will be available on CDC's website.

NCID will consider all opinions from the experts during the decision-making process to revise policies and recommendations. Changes to CDC's current guidelines that result from the meeting will be broadly disseminated and incorporated into existing print and web-based health communication materials. For issues that are outstanding at the conclusion of the meeting, the experts will be asked to send additional comments to Dr. Parise or Ms. Desai via e-mail.

Dr. Cetron described the relationship between the expert meeting and the publication cycle for the Yellow Book. New editions are typically printed in the spring, but NCID will delay submitting new materials to the publishers in an effort to incorporate key recommendations from the expert panel. However, the new edition of the Yellow Book is still expected to be produced, launched and distributed in May 2003.

***Chloroquine (CQ) and Hydroxychloroquine (HCQ)*.** Dr. Coyne reported that CQ was first synthesized in the 1930s and was the most widely used anti-malarial drug in the world for many years. CQ is indicated for both treatment and prophylaxis with a labeled prophylaxis dose of 500 mg salt (300 mg base) taken weekly, starting two weeks prior to travel to an endemic area if circumstances permit. Of note, the labeling: (a) Has a

loading dose provision of 300 mg base x 2, six hours apart; and (b) Recommends continuing suppressive therapy for eight weeks after leaving an endemic area.

According to the CDC recommendation, CQ is the drug of choice for travel to areas without CQ-resistant *P. falciparum* (CRPF). Additional recommendations that are specific for prophylaxis of CQ-resistant *P. vivax* (CRPV) are not needed at this time because no areas with CRPV exist that do not also have CRPF. However, it was suggested that a statement should be made about where CRPV exists, since that could impact treatment of ill travelers. In terms of adverse drug reactions (ADRs), it was suggested that the rate of serious neuropsychiatric events (estimated at 1 in 13,600, which is similar to some estimates of severe ADRs to MQ) should be mentioned to make people aware that these can also occur with CQ.

With respect to HCQ, the drug was first synthesized in the late 1940s. CDC recommends HCQ as an alternative drug for travel to areas without CRPF. As per the drug label, continuation of suppressive therapy is recommended for eight weeks after leaving an endemic area. The HCQ label dose for connective tissue disease is 400 mg once or twice daily, but malaria prophylaxis is recommended at 400 mg once weekly. One of the most significant differences between the two drugs is that HCQ is now a rheumatologic product, while the CQ label focuses solely on malaria with no rheumatology language. An additional point that was made was that consideration should be given to mentioning neuromyotoxicity as a rare ADR seen with HCQ.

In terms of comparative costs for a 14-day stay, in some research Dr. Coyne did at an Atlanta pharmacy last evening, he found a fair difference in price between CQ and HCQ: CQ costs $41 for the generic brand and $59.19 for the trade name; HCQ costs $18 for the generic brand and $32 for the trade name.

> Discussion Point: Do selected circumstances exist where CQ/proguanil should be explicitly recommended since the drug is no longer listed as an option for travel to areas with CRPF?

Various opinions were expressed:
The combination of CQ/proguanil is substantially inferior to other more efficacious antimalarial drug options that may be used by persons traveling to areas with CRPF. However, issues related to women in the first trimester of pregnancy and children weighing <5 kg must be taken into account when considering use of CQ/proguanil. The usefulness of CQ/proguanil or CQ in pregnant women should be mentioned. Due to strong contraindications of MQ in some persons, CQ/proguanil or CQ would be preferable to no drug.

- Proguanil was approved in the United States but the drug company withdrew their new drug application (NDA) because there was no market

(not because of safety issues). Because proguanil is not available anyway in the United States as a single entity (i.e. only in combination with atovaquone, as Malarone™), it should not be recommended by a U.S. government health agency—such a recommendation will be extremely confusing to family practitioners with limited knowledge of travel medicine and should not be considered by the expert panel. Others' opinions differed – expressing that since Americans can purchase proguanil through the internet or in foreign countries, the drug should be mentioned in the CDC guidelines with a general blanket statement directing the traveler to contact CDC, DOS, Peace Corps or a travel medicine physician if none of the other more preferable antimalarial prophylactic options are appropriate to their individual situation.

- The benefit of proguanil is minimal in areas with pyrimethamine or SP resistance due to the cross-resistance. The value of proguanil will also be limited in areas with a lot of *P. falciparum* as well as in locations with resistance to CQ and SP.

- CDC should not endorse CQ/proguanil due to deaths that have resulted because of prophylactic failures associated with use of this drug combination in the last few years. The areas where WHO still recommends CQ/proguanil as an option are shrinking and currently include parts of Colombia, parts of India, Mauritania, Nepal, the Solomon Islands, Sri Lanka, Tajikistan, and Vanuatu.

Discussion Point: Should the statement be removed that HCQ is better tolerated than CQ, since the only evidence found for this statement was that it may be true for long-term users and will be addressed in a special considerations section?

The hydroxyl group in HCQ supposedly impairs the molecule's ability to cross the retinal barrier and results in less retinal toxicity than CQ on both molecular and conceptual bases. Thus HCQ may be better tolerated than CQ for long-term users, and this issue could be explored in a special considerations section. HCQ results in less corneal deposits than CQ in rheumatology patients receiving high doses of HCQ and may also cause less retinal toxicity than CQ. Ophthalmologists treating patients with systemic lupus erythematous (SLE) patients who develop corneal lesions but otherwise tolerate HCQ well do not change the patient's treatment but instead regularly monitor retinal toxicity.

Although comparative animal data suggest HCQ is better tolerated, head-to-head clinical trials of the two drugs used as antimalarial drugs are lacking.

Discussion Point: Although long-term use of HCQ is listed as a contraindication in the US drug label, no medical evidence was found that indicated the drug cannot be used long-term in children (and there were numerous studies where it was used)—do the experts agree that this will not be listed as a precaution or contraindication?

- The presenter (Dr. Coyne) commented on the fact that no medical evidence has been generated to suggest that the drug cannot be used long term in children. Most notably, HCQ has been used long term in this population in numerous studies. There was little discussion of this point at the meeting, mainly due to time limitations.

Discussion Point: Should CDC remove the recommendation to divide the CQ dose into a twice-weekly regimen since no data are available to support the efficacy of this regimen?

- There is no well-documented evidence of failures that occur after splitting the CQ dose. Although recent studies have shown that the CQ/proguanil combination is not well tolerated, splitting the CQ dose may make the drug tolerable for certain subgroups.
- A C-level recommendation of "limited expert opinion" should be incorporated instead of removing the language altogether. The guidance should state that some individuals may be able to better tolerate CQ if it is given twice weekly. Pharmacokinetic data (if it exists) would be useful to demonstrate that drug levels are acceptable with split dosing.

Discussion Point: Should CDC avoid recommending a CQ daily dose of 100 mg base due to limited information on this dosing scheme?

- The point was made that no 100 mg formulation even exists in the United States, limiting the usefulness of a recommendation were it to be made.

- CQ 100 mg daily (with proguanil as Savarine^{TM}) was the dose used in a recent paper by Schlagenhauf and colleagues and was one of the regimens with highest rates of ADRs. This study examined tolerability and not antimalarial efficacy.

Discussion Point: Should persons who have taken a weekly CQ regimen of 300 mg base for over four years obtain eye examinations twice per year? (This is based on 60 Gm cumulative dose potentially being harmful).

- The official product labeling for CQ and HCQ should be considered. The malaria portion of the HCQ label does not mention that eyes needs to be

monitored at all. The rheumatologic portion of the HCQ label states that when prolonged therapy with any anti-malarial compound is considered, a baseline ophthalmologic exam should be done as well as subsequent periodic exams every three months. The CQ label states that when prolonged therapy with any anti-malarial compound is contemplated, a baseline ophthalmologic examination, and then follow-up exams, should be performed.

Of note, the labels differ with respect to ophthalmologic contraindications/precautions as well. The label for HCQ mentions that the drug is contraindicated in the presence of retinal or visual field changes attributable to 4-aminoquinoline compounds (but, in contrast to the CQ label, does not mention the drug is contraindicated if these occur due to other etiologies). Specifically, the CQ label states that the use of CQ is contraindicated in the presence of retinal or visual field changes attributable to either 4-aminoquinoline compounds or any other etiology.

The opinion was expressed that CDC should harmonize its U.S.-based recommendations on this issue to the extent possible with those of the Committee to Advise on Tropical Medicine and Travel (CATMAT), the United Kingdom and WHO. This approach will eliminate frustration among practitioners and other users in reviewing different guidance from various groups. For example, some researchers suggest that CQ is safe until a cumulative dose of 100 grams is reached while others define safety up to a dose of 60 gram base. Although harmonizing recommendations from various groups will be extremely challenging, this effort will be much easier if the guidance is evidence-based.

The overall general opinion of the experts was that eye exams were not needed when CQ and HCQ were used for malaria prophylaxis, even if long-term, given that adverse retinal effects were extremely rare at prophylactic doses. The UK experience was that recommendations for periodic eye exams for long-term users were causing many concerns and decreasing adherence to the drugs among long-term users.

Discussion Point: In view of a dearth of evidence that CQ induces hemolysis in persons with G6PD deficiency, do experts agree that screening for G6PD enzyme levels is not needed prior to use of CQ?

- This issue was discussed very briefly. The general opinion was screening for G6PD is not required prior to using CQ or HCQ.

Additional issues raised related to CQ or HCQ:

- Whether a practitioner chooses to use CQ or HCQ may at times depend on what drug is available. For example, since HCQ is used more for

rheumatologic conditions than CQ, at times it is easier to obtain in pharmacies.

- Because there are no head-to head comparisons, at this point, HCQ is primarily a niche drug for persons who are already on it for rheumatologic indications (or other special circumstances – see below). If such patients were traveling to areas with CSPF, HCQ would be the obvious choice. Antimalarial efficacy data for HCQ are fairly limited. CDC's recommendation for HCQ as an alternative to CQ in areas with CRPF should be clarified or footnoted. The guidance is based on C-level expert opinion rather than on AI evidence from randomized controlled trials.

- HCQ is available in a smaller tablet than CQ and may be easier to prescribe for children.

- The generic brands of the two drugs are much easier for a pharmacist to score or compound than the trade names.

- HCQ may be cheaper than CQ, which may be a consideration some providers consider in choosing which drug to prescribe.

- Scandinavians are extremely cautious in using CQ due to the drug's toxicity. The amount that can be dispensed at any one time is limited. Consideration should be given to including language on the appropriate management of CQ poisoning in the Yellow Book.

- Since some data are not consistent between the 2 drugs, one must be careful about interchanging contraindications, precautions and drug interactions for CQ and HCQ. Of note, the HCQ ADR part of the drug label is totally oriented towards rheumatologic use and this likely cannot be directly extrapolated to antimalarial use (since antimalarial doses are much lower).

<u>General comments</u>:

There were some more general comments raised in this session, which included:

- The best options for DOS staff, Peace Corps volunteers and other populations living long term overseas should be outlined on an informational expatriate sheet. The notice should contain a disclaimer listing drugs that are not available or recommended in the United States. These groups should be directed to contact a health care provider in the headquarters facility for that organization for additional advice.

- The Yellow Book recommendations should be designed to be clear and succinct; the guidance should also be targeted to the majority of the intended audience.

- Pregnant women should be informed that malaria presents a more significant risk for losing a baby than taking an anti-malarial drug.

- Some persons going to areas with CSPF cannot tolerate CQ or HCQ. The CDC YB should specifically state that one can use one of the drugs recommended for areas with CRPF if one cannot tolerate the drugs recommended for areas with CSPF.

Before yielding the floor to the next session leader, Dr. Khan asked Dr. Rigoberto Roca of the FDA to clarify the drug approval process. Dr. Roca explained that he as the FDA representative does not have at his fingertips all the information that was included in the NDA that influenced what is put into a particular drug's label, but a medical officer review is attached to each product approval. For any approved product that was discussed during this meeting, he offered to facilitate a search for data that supports information included on labels. The expert panel would then be in a better position to evaluate the evidence base.

Dr. Roca acknowledged that logistical difficulties may delay locating the data. Some of the older approvals are filed in crates in warehouses, while some medical officer reviews may lack detail. Dr. Douglas Proops conveyed that this effort would be extremely helpful, particularly for HCQ. The label should have valuable data that could be used to support efficacy of the drug.

***Doxycycline (DC)*.** Dr. Alan Magill, of the Walter Reed Army Institute of Research, explained that DC, tetracycline (TC) and minocycline (MC) are not the same. Dr. Magill presented a table comparing TC, MC, and DC characteristics, including % protein binding, % absorption when fasting and how affected by food, how lipophilic, serum half-life, dosing in renal failure, and extent of hepatic metabolism to illustrate this point. One must keep this in mind since a considerable amount of DC data for a particular indication has been extrapolated from TC and MC data for other indications. For example, much of the long-term safety data on DC are from MC and TC experiences in the dermatology field. DC evidence on ADRs for pregnancy, breast-feeding and children comes directly from the TC literature. Overall, the data on DC alone is minimal.

> Discussion Point: Are additional data available or needed to support the statement that persons receiving 100 mg of MC per day for the treatment of skin conditions are probably protected against malaria and would not need additional anti-malarial chemoprophylaxis? However in persons not already on MC, would

not recommend MC as a replacement for DC since efficacy data are much more limited.

In a 1970 field trial (Colwell et al) of uncomplicated CRPF among semi-immune males in Thailand, quinine/TC and quinine/MC were compared. In this setting, MC and TC appeared to be basically equivalent when used as adjuncts to an effective treatment (quinine) in semi-immune males. In a 1970 experimental challenge (Willerson et al) among eight partial immune and three non-immune adults in a prison setting, MC was used for treatment for seven days. The paper does not specify how soon treatment was started after symptom onset. Most subjects were cured with the drug regimen, but two non-immune persons failed treatment and were given higher doses.

In another part of this same 1970 study by Willerson, 24 adult males were subjected to experimental mosquito challenge using two different strains of CRPF. Sixteen of 18 individuals were protected while two who received 100 mg of MC on Day 0 broke through and became patent on days 10 and 12. Based on these results, MC most likely has causal prophylactic efficacy similar to DC.

In terms of ADRs, DC is slightly more photosensitive than MC. In addition, there have been case reports of severe hepatotoxicity in persons on MC 100 mg/day.

The group had the following opinions:

- Dermatologists seem to prefer minocycline. The majority of persons being treated with MC for acne are taking 50 mg/day.

- Because there is so much more data on the antimalarial efficacy of DC compared to MC, the best option is that travelers who are already on MC be switched to 100 mg of DC for the duration of the trip and then switched back to MC after DC prophylaxis is completed. If this is not acceptable to the clinician (dermatologist) or patient for some reason, next best option is to increase the MC dose to 100 mg/day during and for 1 month after travel—however some members of the group were concerned about possible ADRs with this regimen. The least desirable option would be for them to remain on 50 mg MC/day.

- The statement should be categorized as a CIII recommendation due to a paucity of data.

Discussion Point: Are additional data available or needed to support current evidence that suggests DC can be concurrently used with OCs without leading to a higher rate of contraceptive failure than would be expected among OC users not currently taking antibiotics? A possible interaction with OCs has been a concern cited in the literature.

Dr. Magill noted that anecdotal reports show that DC had a 1%-3% background failure rate with oral contraceptives (OCs). The DC/ penicillin hypothesis is associated with altering intestinal flora. Antibiotics suppress bacterial flora by interfering with the enterohepatic circulation of steroids and thus decrease levels of the parent steroid molecule. Plasma concentrations of estrogen would thus be lowered, which could result in ovulation or breakthrough bleeding.

In examining the effect of DC on serum estrogen levels, 24 adults 18-35 years of age who were all receiving a low OC dose received 100 mg of DC twice a day for seven days starting on day 14 of the cycle. Blood samples for estrogen were drawn during the control phase and the subjects served as their own controls. The study found no significant difference in estrogen blood levels between the control and treatment phases. However, extensive intra- and inter-subject variability in estrogen levels was noted. In a review of OC failure reports, some authors concluded that the data were retrospective, contained multiple biases and were not supported by pharmacokinetic data with any antibiotic.

In 2000, the American College of Obstetricians and Gynecologists (ACOG Practice Bulletin) stated that TC, DC, ampicillin and metronidazaole do not affect OC steroid levels. Of note, in U.S. District Court for the Northern District of California, a woman became pregnant and filed suit alleging that her health care practitioner had failed to warn her of this potential interaction. The court found that scientific evidence regarding the alleged interaction between antibiotics and OCs did not to satisfy the *Daubert* standard of causality and the court found no evidence of causation between the use of antibiotics and decreased effectiveness of OCs.

Other points raised:

- Dr. Magill felt that this statement could be strengthened slightly and suggested:

  Although a possible interaction with oral contraceptives (OCs) has been cited in the older literature, current evidence suggests that DC can be used concurrently with OCs without leading to a higher rate of contraceptive failure than would be expected among OC users not currently taking antibiotics.

  He suggested that this could be graded as a B+III recommendation.

- Anecdotal reports indicate that many women elect not to use DC due to the inconvenience-- thinking they would then need to use a second method of birth control if they use DC.

Discussion Point: Are additional data available or needed to support the statement that DC should not be recommended for prophylaxis in women who are breast-feeding? The guideline is based on the theoretical risk of ADRs on infant teeth, as well as the fact that there are other antimalarial drug options available to these women.

Only one study (Morganti) was found that looked at DC in breast milk. Fifteen nursing mothers were given 200 mg of DC followed by 100 mg of DC. Milk/plasma ratios at three and 24 hours following the second dose were 0.3 and 0.4, respectively. Mean milk concentrations were low at 0.77 and 0.38 Φg/ml. There is much more data on TC. TC penetrates well in breast milk, but chelation with calcium in milk results in low bioavailability. Newer data on TC and breast-feeding will continue to be extremely limited after the finding in the 1960s that the drug causes abnormalities in infant teeth.

Recommendations from CDC and other groups have not always been consistent with regard to DC and breast-feeding women. In the November 16, 2001 edition of the *MMWR*, CDC recommended the use of DC for post-exposure anti-microbial prophylaxis for anthrax in its updated guidance for children and breast-feeding mothers. However, the CDC Traveler's Health website states that DC is contraindicated for malaria prophylaxis during breast-feeding. The American Academy of Pediatrics (AAP) also considers ciprofloxacin and the tetracyclines (which includes DC) to be usually compatible with breast-feeding. AAP further noted that the amount of the drug absorbed by infants is small, but little is known about the safety of long-term use. Of note, if one looks at the AAP statement, it only references TC and does not mention DC.

Discussion included the following points:

- Consideration should be given to adopting similar language to that CDC has used in prophylaxis recommendations for children and breast feeding women after exposure to anthrax that were published in the *MMWR*. Suggested wording proposed by Dr. Magill:

  "Although data are extremely limited on the use of DC in breast-feeding women, most experts feel the theoretical possibility of adverse events such as dental staining and inhibition of bone growth would be remote. Concerned mothers or doctors may consider alternative drugs." MQ and other examples of "alternative drugs" approved for breast-feeding should be listed to provide practitioners with additional guidance.

- Breast-feeding women are a niche population; changing the guidance to a CIII recommendation to support DC use will not affect large numbers of travelers.

- One would choose MQ over DC for breastfeeding women. But if a woman cannot take MQ, DC would be an acceptable alternative.

Discussion Point: Are additional data available or needed to support the statement that DC can be used for long-term malaria chemoprophylaxis? The guidance is based on a history of TC use at equivalent doses for a few months to years in the treatment of dermatological conditions.

With respect to long-term use, a study (Shanks et al) was conducted in which DC was used for four months in 900 men deployed to Somalia and twelve months in 600 men deployed to Cambodia. The study concluded that DC was well tolerated and did not result in increased ADRs, but the author readily admits the difficulty in collecting data in an operational military setting. For example, ADRs that occurred in a very small portion of the cohort were not outlined. These persons were switched to MQ. Anonymous post-deployment questionnaires were used and no data was provided on the details of what was asked in the questionnaire, how many persons it was administered to, and what the response rate was. Daily compliance was only followed in Cambodia and the rate was extremely poor. Thus, these data were not sufficiently reassuring to support the tolerability of long-term malaria prophylaxis with DC.

- Caution should be taken in extrapolating safety data from MC and TC to DC. Due to the extremely limited data available, Dr. Magill proposed the following language as a CIII recommendation:

  "Although long-term safety and tolerability studies have not been performed with DC as malaria chemoprophylaxis, similar drugs in the same class, TC and MC, have been used in equivalent doses for a few months to several years in the treatment of various dermatological conditions and thus, DC can be used for long-term malaria chemoprophylaxis."

- The proposed language should be refined to address several issues: In some of the studies, the MC dose was not 100 mg daily (which would be equivalent to 100 mg DC, the dose used for antimalarial prophylaxis), though in some studies the dose was equivalent. Also, concerns have been raised in the dermatology literature about long-term safety of MC, and there are some case reports that link benign intracranial hypertension and TC.

- Global recommendations on long-term use of DC should be harmonized, *i.e.*, the cut-off is four months in the antimalarial prophylaxis section of the U.S. product insert, while other recommendations differ from this.

- "Long-term" use should be defined for expatriate settings, such as Peace Corps volunteers, DOS staff and deployed military personnel. In these settings, one opinion was that DC could be recommended for six to 12 months at a maximum of two years.

Additional issues raised:

- CDC's current guidelines contain no clear statement to screen for pregnancy to ensure providers select the appropriate drug for women of reproductive age. A strong and clear recommendation should be included since 55% of pregnancies are unintended in women 18-35 years of age. Because a large number of individuals present to travel medicine providers each year, "screening" in this instance would be limited to asking the patient about the possibility of pregnancy rather than administering a urine test.

- DC has added benefits since it is also an effective chemoprophylactic agent for some other diseases that may be a problem for travelers, particularly leptospirosis and rickettsiosis. From a travel medicine perspective, the efficacy of DC is tremendous.

- Another issue that not infrequently comes up is how to best dose DC if one wants to use it for malaria prophylaxis in persons with seizure disorders. Drugs such as phenytoin and carbemazepine are potent inducers of the hepatic enzymes involved in doxycycline metabolism so they shorten the half life of doxycycline. A specific statement might be made (based on the limited pharmacokinetic data that is available) -- to double the patient's DC dose to 100 mg BID (or alternatively could one use 50 mg BID?). Agreement was not reached on this issue.

- Language should be incorporated into the guidelines to address the co-administration of the oral typhoid vaccine and antimalarial drugs, including DC.

- Specific guidelines to women should be added to address the issue of vaginal yeast infections and DC use. Anecdotally, many female patients have rejected CDC's current guidance to take a cream on their trip. This rationale is based on the fact that the yeast infection will continue to return so long as the traveler is taking DC. In addition, many women prefer oral antifungal medication and might require several doses be given to be taken empirically if they are going on a long trip.

- CDC communication material should provide as much information as possible on interactions between antimalarial drugs and vaccines, possibly

in a different section on biological agents and antimalarial drugs as opposed to putting such information in the drug interactions section.

***Primaquine (PQ)*.** Dr. Edward Ryan, of Massachusetts General Hospital, acknowledged that data on PQ are limited. The three major uses for PQ are primary prophylaxis, terminal prophylaxis and radical cure. The best evidence-based data available for PQ is for the indication for primary prophylaxis since most trials have been done recently; the prophylactic efficacy is in the 85%-95% range. Of 10-11 studies conducted to evaluate the efficacy of PQ for primary prophylaxis, one was among non-immune travelers and the remainder was in semi-immune or immune persons. Based on these data, the prophylactic efficacy for *P. falciparum* was 90%-95%, while it was 85%-90% for *P. vivax*.

To achieve an 85% rate of protection for primary prophylaxis, 0.5-0.6 mg/kg base is needed, which is 30 mg daily for a typical adult dose. (Note the salt equivalent is 15 mg base = 26.3 mg salt). Studies have indicated a lower prophylactic efficacy when the drug is given less frequently than daily. The drug should be started one to two days before entering an endemic area. Data from challenge trials performed in the 1960s showed that PQ on Day 1 to Day 3 after challenge with an infective bite provides solid protection. PQ should be given for one week after leaving an endemic area.

Of note, data for terminal prophylaxis are more limited and need to be extrapolated from radical cure data. Determining dosages for radical cure is difficult because the strain and location of malaria is an important factor. Strains from the South Pacific and other tropical locations tend to be more PQ-tolerant, while strains examined during the Korean and Vietnam wars, for example, were more PQ-sensitive. Based on the malaria strain, the failure rate of radical cure can range from 5% to 40%. The data on what is the best does for radical cure are quite limited. In terms of duration, five-day studies showed much higher relapse rates compared with the 14-day studies.

> Discussion Point: Can the group suggest any guidelines on when terminal prophylaxis with PQ should be given, such as the length of the trip or geographical location? Does a level of risk of relapse exist above which terminal prophylaxis would be recommended, *i.e.*, that could be calculated from existing data on denominators of travelers and reported malaria cases by duration of stay?

- PQ terminal prophylaxis should be considered for individuals who are considered to be at high risk for *P. vivax* and *P. ovale* infection, *i.e.*, soldiers in a military unit, long-term travelers, Peace Corps volunteers, missionaries, and persons who will reside long term in an area with significant *P. vivax* transmission. Several clinicians made the point that they prescribed very little terminal prophylaxis.

- A point that should be made in the introduction to the guidelines is to acknowledge that the most important goal of malaria chemoprophylaxis over the last ten years has been to prevent *P. falciparum*-related deaths. But given that a substantial proportion of cases are due to *P. vivax*, and that there many areas with significant transmission of both *P. vivax* and *P. falciparum*, more emphasis should be given to the goal of trying to prevent infections from all species—which makes a causally prophylactic drug (including PQ) attractive. Exclusively focusing on *P. falciparum* and blood-stage prophylaxis may undermine patients' confidence in their health providers – for example, it can be perceived that a provider failed a patient who followed instructions and yet developed malaria after return from a trip.

- The guidelines should be improved to map locations where *P. falciparum* and *P. vivax* transmission occurs.

- One of the main problems with terminal prophylaxis is that travelers are frequently poorly adherent to the full 14-day course.

- An important practical point is that most insurance companies will not cover the cost of a G6PD test that is done before you use PQ for prophylaxis because they consider it preventive care. The cost can run $150-200.

Discussion Point: When should terminal prophylaxis be given, *i.e.*, during or after the last two weeks of blood schizonticides, such as MQ or DC; or during or after the week of AP post-travel prophylaxis?

- The main factors in decision-making include: (1) Whether there is a pharmacological reason such as drug interactions or effect on pharmacokinetics not to co-administer the drugs (Dr. Ryan did not find any evidence for this); (2) Will there be poorer tolerance if persons need to take 2 drugs at the same time; and (3) Adherence – giving them sequentially may make adherence harder since they may need to be taking drugs for 6 weeks after travel.

- There were no strong opinions expressed as to what was the best timing of the PQ terminal prophylaxis. The group indicated that a general statement should be included in the guidelines to reflect that terminal prophylaxis can be administered during the last two weeks of the blood schizonticide (if using MQ or DC) post-travel. When used with AP, PQ

can either be given during the 1 week of AP and for 1 additional week or sequentially after the week of AP.

Note: After the meeting, some of the experts noted older data (Alving 1955) that indicates the efficacy of PQ for radical cure is improved when it is co-administered with a 4-aminoquinolone.

Discussion Point: Do geographical locations or circumstances exist in which higher doses of PQ, such as 30 mg/day, should be used for terminal prophylaxis?

- The prevailing opinion was that one should use 30 mg/day in all geographic areas and this is what many experts are doing. The rationale were: (1) There have been a multitude of case reports and series in varied geographic areas where 15 mg/day for 14 days has failed; (2) Patients are often non-compliant with the entire course and given that it is total dose that is most important, if you give 30 mg/day they will have taken more PQ if they stop early; and (3) Recent primary prophylaxis trials have indicated that 30 mg/day is safe (as long as a patient is not G6PD-deficient). The evidence-cased rating was felt to be BII.

- We have known for a long time that 6 mg/kg total dose is required to eliminate the Chesson strain and 30 mg/day for 14 days delivers that dose.

- Several participants indicated they used 0.5 mg/kg/day for children's dosing.

Discussion Point: Should persons who miss one or two days of the 14-day regimen resume treatment and continue until all pills are completed?

- The guidelines should reflect that total dose is more important than duration. Persons who miss a daily dose should be advised to resume treatment until all pills are completed. However, one must adjust this to the particular patient situation – for example, if a patient tells you they lost the 2nd week, it may be that they did not take the 1st week and so they need the full 2 weeks.

Discussion Point: Should terminal or primary prophylaxis be used in persons with any level of G6PD deficiency in view of risk and benefit considerations?

- The opinion of the experts was that PQ should not be used for prophylaxis (i.e. where you are giving it to someone without documented *P. vivax* or *P. ovale* infection) in persons with any degree of G6PD deficiency. Physicians should be advised to follow the patient and if *P. vivax* or *P. ovale* develops, could consider a modified PQ regimen at that time.

Discussion Point: Can PQ be considered for radical cure at a dose of 45 mg/kg per week for eight weeks in persons with mild G6PD deficiency and residual enzyme activity greater than 10%?

- A-variant persons with 10%-15% residual enzyme activity for G6PD can either: (a) Be followed to see if they relapse; (b) Be given a once-weekly PQ regimen of 45 mg/kg for eight weeks; or (c) Be placed on CQ prophylaxis for 1-2 years.

Discussion Point: Should PQ be given to persons receiving treatment with drugs that depress the bone marrow? The literature contains very little evidence for this contraindication.

- On the one hand, the guidelines should not continue to list a contraindication for which there appears to be no data. On the other hand, given that the contraindication is already listed makes it a bit more difficult to just remove—it was felt that an attempt should be made to find data that disproves the contraindication. The expert panel requested that original FDA data (the new drug application, NDA) be examined to further address and clarify this issue.

Discussion Point: Can PQ be given to acutely ill persons suffering from systemic diseases manifested by a tendency to granulocytopenia, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis? The literature contains very little evidence for this contraindication.

- Again, the expert panel requested original FDA data (the NDA) to further address and clarify this issue.

Discussion Point: Should the recommendation to use PQ in children of any age be changed?

- There was no published data found that reported PQ use in children <6 months of age and who weigh <9 kg. Thus, some participants felt that recommendations should indicate the paucity of data in young children.

The risk:benefit ratio would change when the drug is used for radical cure as there is no other option to eliminate *P. vivax* or *P. ovale* hypnozoites.

- Pediatric recommendations must qualify pediatric dosages with "(up to maximum dose)."

- The question was raised if there was any pharmacokinetic data in children as knowledge of that could be helpful in this decision-making process.

Discussion Point: Should PQ be recommended as an option for primary prophylaxis?

- PQ can be recommended as an alternative -- second line --drug for primary prophylaxis, but the recommendations should clearly state that one must first do a G6PD test. In addition, protective efficacy may be slightly less than some of the other options.

- It may especially be appropriate for those persons who one is considering for terminal prophylaxis – who are the ones most heavily exposed to P. vivax or P. ovale. One is doing a G6PD test in these persons anyway and so one may consider PQ primary prophylaxis.

Additional points:

- Pregnancy needs to be added as a contraindication.

Atovaquone/Proguanil (AP). Dr. Bradley Connor, of the Weill Medical College of Cornell University, explained that AP is 250 mg atovaquone plus 100 mg proguanil. AP is a causal liver stage and suppressive blood-stage prophylactic agent that can be discontinued one week after leaving a malarious area. The causal prophylactic activity of proguanil, atovaquone and AP have been demonstrated in human challenge studies. While the proguanil literature dates back to the 1940s, atovaquone and AP have much more recent data from human challenge studies.

AP is indicated for prophylaxis of *P. falciparum* malaria and treatment of acute and uncomplicated *P. falciparum* malaria, including areas with reported CRPF. For prophylaxis, the daily dose is started one to two days before entering an endemic area, is taken daily during the stay and then continued for seven days after leaving a malarious area. The adult dosage is one daily AP tablet of 250 mg atovaquone and 100 mg proguanil. The pediatric dosage is given by weight, but the formulation is 62.5 mg atovaquone and 25 mg proguanil. For acute treatment, the adult dosage is four AP

tablets once daily for three days; the pediatric dosage is a once-daily dose for three days based on body weight.

According to the package insert, multiple studies have shown AP to be highly efficacious in preventing malaria in both semi-immune and non-immune persons. In three randomized double-blind placebo controlled studies in 369 semi-immune adults and children, AP efficacy rates were shown to be 98%-100%. In four studies that examined efficacy in non-immune adults, three were randomized double-blind studies and one was an open label study with no comparator. Data in semi-immune persons showed 96%-100% efficacy for *P. falciparum* and 86% efficacy for *P. vivax*. One limitation of the South African study was that the risk in the population was unknown since no comparator arm was used.

To achieve sufficient power to estimate drug efficacy, a large study population of 16,000 non-immune travelers would be needed in active controlled prophylaxis studies to compare two highly efficacious drugs. The logistics of this effort would be extremely difficult. The wide confidence intervals in the existing studies to date among non-immune travelers suggest they did not have sufficient power to evaluate drug efficacy. In summarizing clinical trial data, the drug manufacturer estimated a prophylactic failure rate of 0.039 failures per 100 person weeks. However, post-marketing surveillance data found 15 failures per 250,000 travelers with a calculation of 7.52 million tablets sold and an average of three weeks of travel. According to this calculation, the prophylactic failure rate was 0.002 failures per 100 person weeks of exposure.

The rationale for differences in the clinical trial and post-marketing surveillance data (with a lower rate in post-marketing surveillance) is three-fold: (1) the traveler may also use personal protective measures (which lowers risk); (2) travelers often spend limited time in endemic areas; and (3) There may be an under-reporting of clinical failures.

AP has demonstrated treatment effectiveness with cure rates of 94%-100% in *P. falciparum*. The drug was also shown to be effective at clearing *P. vivax* blood stage, but the recurrence rate (between 19-29 days) was 68%.

AP interferes with two different pathways involved in the biosynthesis of pyrimidines that are required for nucleic acid replication. Atovaquone inhibits parasite mitochondrial electron transport and collapses mitochondrial membrane potential, while proguanil inhibits the plasmodial dihydrofolate reductase through its active metabolite cycloguanil.

The combined drugs have shown a synergistic effect in both *in vitro* and *in vivo* studies. In terms of absorption and dosing, AP's poor absorption in the GI tract increases with food and fat intake. Although the package insert recommends that AP be taken with a milky drink, travelers are advised against drinking milk in many areas due to problems with enteric diseases.

At least one travelers study has indicated that adherence rates to prophylaxis were higher with weekly rather than daily doses. However, needing to take AP for only 1 week after travel is beneficial because adherence rates for four weeks post-exposure are generally low. AP is contraindicated in patients with severe impairment (creatinine clearances <30 mL/minute). AP has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including hyperparasitemia, pulmonary edema, or renal failure. Patients with severe malaria are not candidates for oral AP therapy. Clinical trial data showed that the most commonly reported ADRs from AP were headache and abdominal pain. The package insert states that therapy was prematurely discontinued in three of 381 adults and none of the 125 pediatric patients. For treatment, ADRs that occurred in ≥10% in adult patients included abdominal pain, nausea, vomiting and headache. Elevated liver function tests (LFTs) were seen in treatment but not prophylaxis trials, and appeared to normalize after treatment was completed.

In a study comparing AP and MQ for prophylaxis, neuropsychiatric ADRs, moderate to severe intensity ADRs and treatment-limiting ADRs were all lower with AP than with MQ. Data are limited on long-term use of AP, but prophylaxis efficacy studies have shown dosing up to 20 weeks. Other studies have documented proguanil use for two to three years in Peace Corps volunteers and atovaquone use as PCP prophylaxis for two years.

With respect to drug interactions, rifampin, rifabutin, TC and DC decrease atovaquone absorption, while metoclopramide reduces both bioavailability and absorption. Metoclopramide should be used only if no other antiemetics are available. Interestingly, however, a combination of atovaquone and DC for malaria treatment was found to be extremely efficacious. For special populations, several studies in children ≥3 years of age reported ADRs similar to those in adults. AP is not indicated for prophylaxis in children weighing <11 kg because no safety or efficacy data is available for this population.

Treatment studies in Nigerian and Gabonese children weighing 5-11 kg showed safety and efficacy in these populations. In PCP prophylaxis, atovaquone has been tolerated by infants and children ages one month to 13 years. Proguanil has been used for 40 years with no evidence of fetal toxicity. AP is classified as pregnancy category C; continuation of folate supplementation during pregnancy does not appear to be an issue. Animal studies of atovaquone showed no teratogenicity; adverse fetal outcomes were only associated with maternal toxicity. Excretion of atovaquone in breast milk is unknown, but proguanil is excreted in human milk. Women breast-feeding infants weighing <11 kg should not take AP unless the benefit outweighs the potential risk.

AP is extremely safe as far as overdosing and therapeutic indexing. Anecdotal reports show that persons have taken high doses of 31,500 mg atovaquone or 15,000 mg proguanil with no ADRs. In terms of cost comparisons, a 14-day stay with pre- and

post-exposure dosing is $103.48 for AP, $63.38 for MQ and $3.66 for generic DC. For very short (1-2 days trips) AP is less expensive but AP is more expensive at the 2-week mark and significantly more expensive for a 3-week trip.

Discussion Point: Should the following statement remain in the Yellow Book? A traveler who starts prophylaxis with a blood schizonticide, such as MQ or DC, and then changes to AP during or after travel may not have been covered with the causal prophylactic agent at the time of an infective mosquito bite. No evidence has been generated that AP will eradicate exo-erythrocytic stages already established at this point. The drug is being relied upon for its blood activity alone and should be continued for one month after travel.

- The statement should be modified to reflect the theoretical concern that AP may not be active on developing liver-stage. One must also take into account that the compliance rate with prophylaxis after travel is poor. Revisions to the statement are proposed as follows: "AP should be continued for one month after the change, or for one week after travel, whichever is longer."

Discussion Point: Should the following statement remain in the Yellow Book? AP may not be effective at preventing the establishment of *P. vivax* hypnozoites. Thus, travelers to areas with moderate to high *P. vivax* transmission who would otherwise be candidates for terminal prophylaxis should receive PQ terminal prophylaxis.

- It should be made clear that terminal prophylaxis is not being recommended for everyone but if exposure were such that a given traveler was considered a candidate for terminal prophylaxis, they should receive it (since there are not data as yet that indicate that AP prevents the establishment of *P. vivax* hypnozoites).

Discussion Point: Is post-marketing data and one controlled study that were powered to assess efficacy in non-immune persons sufficient to recommend AP as a first-line drug for prevention of *P. falciparum* in non-immune travelers?

- The Irian Jaya study demonstrating efficacy was a properly randomized trial that was designed and conducted well. This evidence is sufficient to support the recommendation.

- Additional post-marketing surveillance data related to safety should be collected. More data is needed on its long-term safety.

- AP is being used as a front-line drug regardless of the expert panel's opinion. Based on current practice, 70% of malaria prescriptions are for

AP. Newer drugs like AP are actually probably being scrutinized more closely than the older drugs that were approved years ago.

Discussion Point: Have adequate efficacy data of prophylaxis or treatment of *P. vivax* been collected to recommend AP in areas with substantial *P. vivax* transmission?

- There is data to indicate it can prevent *P. vivax* but protective efficacy rates are not as high as with *P. falciparum*.

- In one treatment study in southeast Asia, there were high recrudescence rates in the month after treatment (higher than would be expected if they were all relapses).

Discussion Point: Do safety and efficacy data of treatment in children 5-11 kg support extending the chemoprophylaxis recommendation to children who weigh 5 kg and women breast-feeding these infants?

- Optimally, the sponsor of the product should conduct appropriate studies, submit the data to FDA for review and seek a formal label change for these populations. The expert panel would then be in a better position to offer more concrete guidance because the age indication for the product would be noted on the label. However, this undertaking most likely will not occur since studies in young infants are difficult to conduct.

- There was mixed opinion on this issue, with some participants stating it would be difficult to recommend without data, while others pointed out that CDC had extrapolated MQ dosing in very young children and should do the same for AP.

- GSK is in the process of doing pharmacokinetics in young children. If this indicates not much difference from older children, that may allow us to extrapolate dosages more.

- The guidance should be targeted toward the parental responsibility of malaria prevention in children $\leq$1 year of age rather than just chemoprophylaxis, to also include personal protective measures and sleeping arrangements.

Discussion Point: Should AP continue to be contraindicated during pregnancy and for women breast-feeding infants weighing <11 kg?

- The contraindication should be deleted and the recommendation should be rephrased to indicate that no data have been published to support the use of AP during pregnancy and for women breast-feeding infants weighing <11 kg.

Discussion Point: Can AP be used for long-term chemoprophylaxis?

- The expert panel debated on what constituted long term travel and noted that there were different varying definitions of this

- The group generally indicated that CDC did not need to place an upper limit on its use

***Mefloquine (MQ)*.** Dr. Anne McCarthy, of the Ottawa Hospital in Canada, reported that MQ's efficacy rate of ≥90% is extremely good. MQ is effective in most locations with the exception of limited areas in Southeast Asia. Reported cases of MQ failures are small. Most ADRs with MQ appear to be in the mild to moderate range. Severe ADRs appear to be rare, but neuropsychiatric side effects have been cited at 1/6,000-1/13,000. It is interesting that ADRs reported in trials may be impressively high, but not only for MQ.

Discussion Point: Should MQ be started three to four weeks before travel to better determine if the drug will be tolerated?

- Most side effects occur by the 3rd dose (but travelers also need to be told they can occur at any time) so starting it early provides practitioners with an opportunity to identify ADRs and switch drugs before the individual travels to an endemic area. The group generally felt that following the product label was best (start 1-2 weeks ahead) but giving people the option of starting MQ early (2.5-3 weeks prior to travel) would be helpful in some cases and would help identify 70%-80% of ADRs

- MQ is started 2.5 weeks before travel in Canada to give the individual three doses before entering an endemic area.

- The expert panel agreed with the suggestion of starting early may not be realistic in many cases, but people should be given the option. Most patients, particularly short-term travelers, present to travel health providers only one to two weeks prior to travel. . Longer term travelers often tend to come in earlier.

- There was debate as to whether CDC should consider adopting WHO language that recommends starting MQ "at least one week, but preferably

two to three weeks before departure to provide optimal protective blood levels and allow any side effects to be detected before travel." One point made was that this may give the a false sense of security that "optimal protective blood levels" will be achieved prior to entering an endemic area, which will not be the case with starting only 3 weeks before. It was generally felt that instead, the guideline should be carefully phrased to focus on an individual's ability to tolerate MQ.

- One suggestion was made that a blanket recommendation should be made for all anti-malarial drugs in which patients are advised to present to a travel health provider prior to entering an endemic area to ensure ADRs are evaluated. CDC strongly opposed this suggestion because the language would create public fear. The guideline would represent a major change in the Yellow Book and would require CDC to undertake a considerable health education campaign. The expert panel added that such a recommendation would not be based on data.

- The recommendation should be structured as a tool for health care providers to reassure patients. For example, patients who do not experience any ADRs with MQ after three doses will have a much higher level of comfort about the drug during travel.

- Travelers also need to be advised that ADRs can last weeks due to the long half life of MQ. They should also be told that they may need to fill a 2nd prescription if they have ADRs.

- The group discussed whether there was less risk for ADRs in persons who had taken MQ in the past but there have still been anecdotes of persons having an ADR on the 2nd course when they had no problems the first time.

Discussion Point: Should an MQ loading dose be listed as an option for all or certain groups of travelers, such as troops that are rapidly deployed to highly endemic areas or persons changing from DC to MQ in high transmission areas?

- AI evidence has been generated to support an MQ loading dose as an option where one achieves therapeutic levels in four days rather than eight or nine weeks. Studies did not show much difference in tolerance between a MQ loading dose versus a regular dose.

- An MQ loading dose should not be recommended for routine or short-term travelers. The vast majority of persons in this group do not need to achieve good blood levels rapidly since they do not have much malaria

exposure Evidence to support using an MQ loading dose strategy for routine travelers is limited.

- Rather than incorporate a recommendation, permissive language should be included for niche populations.

- A MQ loading dose for troops that are rapidly deployed to high-transmission areas is a policy issue for military agencies. In addition, a loading dose of MQ may have other applications, such as for Peace Corps volunteers who are changing from DC to MQ while they remain in high-transmission areas.

Discussion Point: Should we state that a split dose of 125 mg twice weekly is not recommended until more data are available on pharmacokinetics and efficacy?

- There are no data available on the efficacy of split dosing, but the practice has been anecdotally reported by long-term expatriate missionaries, Peace Corps volunteers and missionaries. Once travelers are at steady state levels, the group felt is was acceptable to be permissive for travelers to use split dosing.

Discussion Point: Should CDC be communicating risks of ADRs differently? Is it fair to say that rates of overall ADRs seen with MQ are generally the same as those seen with comparator drugs but that rates of neuropsychiatric ADRs are higher with MQ? Should CDC say more about studies showing tolerance among drug comparators?

- There needs to be more standardization of the terms to grade ADRs, for example, the standard case definition for “severe ADRs.” The vaccine model should be adopted for malaria chemoprophylaxis in which a standard case definition is developed and endorsed by countries. This is especially relevant when one is considering very low risk areas, where at times the risk associated with the intervention (be it vaccine or drug) may be higher than the risk of getting disease. The International Conference of Harmonization (ICH) would be an appropriate forum to undertake this effort. ICH is a drug development consensus framework that has produced guidelines endorsed by Canada, Europe, Japan and the United States.

- The Yellow Book and web sites should be more consistent in terms of communicating potential risk factors for an adverse event – for example, mentioning the fact that children can have depression in the pediatric pages, which should be taken into account before prescribing MQ.

Another example would be mentioning on the pregnancy pages that women may have more risk for ADRs due to MQ than men.

- Issues related to informed consent of the traveler and how much information they should be given was discussed. One model might be vaccine safety sheets, which are not necessarily exhaustive in the information they provide but are designed to be readable and understandable to the lay public.

- The risk of malaria must be emphasized more. For example, the 1/100 chance of dying from *P. falciparum* has been poorly communicated.

- The overall communication process should be restructured to be an ongoing relationship between provider and patient with the initial information sheet, as well as continuing dialogue prior to entering an endemic area and in follow-up after the traveler returns.

Discussion Point: What are the groups' perceptions about reports of long-term ADRs that persist long after MQ is eliminated from the blood stream?

- One problem with this issue is that there are no solid data and so the default becomes anecdotes. It is difficult to explain a mechanism whereby a drug will have such long-lasting effects after it has long been eliminated from the system. However, one attendant noted that there are some other potential analogies such as electroconvulsive therapy – one gives it for a short term (2-3 weeks) but it often cures depression for years after the acute therapy – as if there is a "reset" mechanism.

- One problem is that all these anecdotes are written by patients rather than by clinicians, which limits the ability of the medical community to interpret the reports.

- Another problem is that patient's may have predisposing factors that contribute to the bad outcome—for example, significant pre-existing psychiatric history and the drug then serves as the trigger perhaps. After this triggering event, they can go on to have long term problems that we just don't understand. In addition, depression and anxiety are extremely common and at times it is advantageous to the patient to have something to blame those problems on. It can be hard to separate out if the travel is a coincidence or is the cause of the problem – and is it the travel or something taken concomitantly with the travel.

- MQ can be the cause of neuropsychiatric problems but while there may also be other etiological factors involved; there may be a tendency to attribute all the problems to MQ. More work is needed to sort out what is due to MQ. In addition, we need to communicate these issues better.

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Discussion Point: Should CDC guidelines mention gender differences with MQ?

- Randomized comparative trial data, support the statement that women do not tolerate MQ as well as men. Citing this evidence in the Yellow Book may be helpful to travel health providers.

Discussion Point: Should a precautionary statement be included for MQ and alcohol?

- A precautionary statement about MQ and alcohol should not be included in the guidelines due to the lack of data that the two taken together contribute to increased adverse effects due to MQ.

Discussion Point: Should periodic LFTs or ophthalmologic examinations be recommended for persons using MQ long-term?

- The product label mentions monitoring LFTs for persons on MQ for six months or longer, but neither DOS nor the Peace Corps undertakes this practice and the group was not aware of problems in liver dysfunction in those on long term MQ prophylaxis. Due to time limitations, the expert panel did not reach a clear opinion on this issue.

- The group indicated that ophthalmologic exams should not be recommended given that we are not recommending for CQ based on existing data and there are no/less data that MQ causes problems.

Discussion Point: Can MQ be used in persons with a history of febrile seizures?

- MQ can be recommended in persons with a history of febrile seizures. The specific details of the seizures and the travel should be addressed by individual travel health providers.

- CDC's guidelines should be consistent with AAP's efforts to avoid stigmatizing febrile seizures—in particular we don't want these kids to get fevers due to malaria which will only aggravate their problem. CDC needs to look at AAP's specific wording. MQ would be ok in those children who have had typical febrile seizures.

Discussion Point: Can MQ be used in persons with cardiovascular problems or those on cardiovascular drugs?

- The group did not come to conclusion on this point. There was some discussion regarding whether the precaution could be more limited – for example, to those with ventricular dysrhythmias only. It was pointed out that some of the problems that occurred in persons on MQ have also been atrial arrhythmias, but that overall this is a rare problem and the statement is largely precautionary. In addition, most of patients who were reported to have dysrhythmias have been asymptomatic.

Discussion Point: Is a special precautionary statement needed for pilots, divers and other persons performing tasks requiring alertness and fine motor coordination?

- Neither the Canadian nor U.S. military recommends MQ for pilots.

- There have been deaths reported among pilots who did not take MQ nor alternative chemoprophylactic drugs.

- The data do not support the need for a precautionary statement for pilots and others performing tasks requiring alertness and fine motor coordination. However, the group acknowledged that if an ADR did occur in a pilot it would be of much greater consequence. If MQ were to be used by this group, it would be advantageous to start it early to evaluate tolerance.

- There is no evidence that MQ causes more problems in divers than others but potentially ADRs due to MQ could be confused with the bends.

Discussion Point: Does the group have concerns about reports of high rates of spontaneous abortions in women on prophylaxis or high rates of stillbirth after MQ treatment that should cause CDC health communications messages to be modified?

- One problem with the Somalia study (Smoak) was that some of what was reported as spontaneous abortions may actually have been therapeutic abortions.

- Concerns were raised about methodological flaws in the study on MQ and stillbirths. The drug was distributed by two non-governmental

organizations with different treatment. A definitive conclusion was not reached on whether the MQ or other factors in the study population caused the stillbirths.

- Consideration should be given to adopting language such as Canada uses: "Randomized controlled trials have shown MQ prophylaxis to be safe and efficacious after 20 weeks. More limited data suggest MQ is safe during the first trimester, but increased spontaneous abortions have been reported."

- Recent data that provide more conclusive evidence on MQ use in pregnancy should be collected before the current recommendation is modified. One must balance the potential/unknown risks from MQ versus the risks of getting malaria during pregnancy since there is not another good chemoprophylactic option for women traveling to areas with CRPF.

Dr. Khan recessed the meeting at 5:18 p.m. on January 29, 2003.

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***Meeting Review*.** Dr. Khan reconvened the meeting at 8:32 a.m. on January 30, 2002 and highlighted a few major themes from the deliberations on the previous day. First, it is apparent that in many areas we do not have adequate data but we are trying to be as evidence-based as possible. Thus, decisions may of necessity be based on art more than science in many instances. Because contraindications, indications and other specific issues for each drug were reviewed on the previous day, the current session would be devoted to synthesizing opinions of the experts into clear guidance for CDC.

Dr. Khan re-emphasized that this is not a consensus meeting but that we are seeking individual opinions that we will consider as we review CDC chemoprophylactic guidelines.

Dr. Khan advised the expert panel to be mindful of the fact that CDC's guidelines are disseminated to a broad audience of physicians, nurses and persons with limited knowledge of malaria, endemic areas and underlying medical conditions. Although issues related to special circumstances and patients or travelers with special needs will arise during the discussion, he asked the expert panel to structure language to be relevant to the majority of travelers and practitioners who provide prophylaxis.

***Overall Malaria Chemoprophylaxis Recommendations*.** Dr. Mary Wilson, of the Harvard School of Public Health, explained that the decision-making process for the guidelines will be based on a variety of factors, including: risk in the geographic area, drug efficacy, safety of the drug in a particular traveler, and drug preference in terms of ease of administration, cost, efficacy and ADRs. The choice of agent assumes accurate

information about the malaria risk situation in the travel destination, a decision to give chemoprophylaxis, and a focus on *P. falciparum* resistance.

CQ is the drug of choice and HCQ is the alternative for areas without CQ resistance. MQ, DC or AP are the drugs of choice for areas with CQ resistance. DC or AP are the drugs of choice for areas with CQ and MQ resistance. Dr. Wilson remarked that the deliberations on the previous day focused on the actual drugs, but the current session would be focused on the travel destination. The expert panel would then attempt to integrate guidance on drugs and travel locations in varying endemic areas.

> Discussion Point: Is the scheme of recommended drugs appropriate or should another ranking system be developed? For example, should a prominent indication be made that a few recent studies showed AP was better tolerated than MQ in some aspects? Should any comment be added with respect to AP use in areas where most of malaria is *P. vivax*? Should PQ be mentioned as an alternative for primary prophylaxis or CQ-resistant areas? Should cost be considered as recommendations are made?

- Traditionally we have focused more on preventing death due to *P. falciparum* but there has been focus more recently to also preventing illness due to *P. vivax.*

- It is appropriate to point out the some recent studies have indicated that AP is better tolerated than MQ.

- CDC should not implement a “drug of choice” strategy because this approach does not allow for individualization for what is best for travelers on an individual basis, for example, considering their duration of stay, cost, ADRs, convenience and medical history. For example, AP is often preferred for tourists and other short-term travelers due to an individual’s ability to better tolerate the drug. For Peace Corps volunteers, military personnel and other long-term travelers, cost and adherence issues become more important.

- It should be clearly stated in health communications materials that options for areas with CRPF (AP, DC, MQ) can be used on areas with CSPF if a traveler cannot take CQ or HC.

- Each drug’s protective efficacy against *P. falciparum*, advantages and disadvantages should be clearly outlined in a table to allow providers to make informed decisions that are appropriate for a particular traveler. CDC noted that cost comparisons of products have never been included its materials. This issue would need to be thoroughly and cautiously considered before the information can be included in the guidelines.

The expert panel amended the recommendation by stating that a head-to-head cost comparison or cost table should not be developed for the Yellow Book. The cost of drugs constantly change and would be outdated before the Yellow Book is again updated. Instead, cost should be generically mentioned without quoting prices to alert the traveler. If a traveler first learns about cost from a pharmacist, an expensive prescription may not get filled and the individual will take no drug.

- CDC should alphabetically list drugs by generic name in the Yellow Book and on the web site to eliminate perceptions of a ranking system. A disclaimer should be added that the drugs are all options and are not listed in any particular order.

- Some members of the panel felt that the guidelines should not recommend that practitioners prescribe medications based on gender. However, it was noted that data from well-designed studies on DC and MQ that suggest differences in an individual's ability to tolerate drugs based on gender be cited. DC is associated with vaginal infections and is contraindicated in pregnancy. More neuropsychiatric reactions from MQ have been reported for women than men. No data have been produced on gender-specific tolerance differences for AP.

- The first two messages targeted to general practitioners in the Yellow Book should be "The main role of malaria prophylaxis is to prevent serious *P. falciparum* malaria" and "CQ or CQ combinations should not be prescribed for travel to Africa." The guidelines should then clearly define what *P. vivax* is (since many practitioners may not even know the difference between species) and describe at-risk persons. Specific discussions about efficacy of AP against *P. vivax* should be avoided to minimize confusion among providers. Education of providers and travelers that *P. vivax* can present up to a year after exposure should be strongly emphasized. The public and providers need to understand that current drug options do not prevent relapses of *P. vivax*.

- Efforts should be made to improve the current knowledge and information base by mapping each area in the world with CRPF and CRPV. These data would be extremely helpful for malaria experts to make evidence-based recommendations. CDC noted that it is currently undertaking a huge project to map risk areas, but the data will not at least initially provide much information on species-specific risk. However, efforts can be made to obtain more information, with one possible source being the US military.

- The expert panel should serve as mechanism to advance PQ as an appropriate product to consider for primary prophylaxis. It was noted that the efficacy is a little lower than that of the other agents but the main barrier is safety due to the need to ensure a patient's G6PD level is normal prior to prescribing PQ. Several members of the expert panel were extremely uncomfortable recommending PQ as a first-line agent due to the G6PD issue. A fatality may occur due to a general practitioner's negligence to administer a G6PD test. For example, Canada is uncomfortable with the average physician dispensing travel advice, particularly for complicated, risky or long-term issues. Canada's strategy is to collect the most solid evidence, make the data available, and encourage physicians with less expertise in travel medicine to refer patients to academic clinics, travel medicine practitioners and other appropriate sources.

- Given currently available drugs, the only way we will make inroads into preventing late onset P vivax, which makes up a significant proportion of cases, is to use PQ for prophylaxis – but we must balance that potential benefit with risk if it is not done safely.

- Despite its disadvantages, however, solid evidence has been produced that PQ is well tolerated, efficacious and can be used. Members of the group felt that CDC should include PQ for prophylaxis in their recommendations, though it should be a 2nd line agent. Any language on PQ should be prefaced with "NEVER prescribe PQ without knowing the patient's G6PD status." The recommendation should also reflect the Canadian model by referring physicians who want to consider use it to a travel health expert – either call CDC or have patient go to a travel health clinic or other appropriate source. An added benefit of a group like this expert panel making this recommendation for PQ use is that it may help advance DoD agenda on pushing for a point of care (POC) G6PD test.

- There was further discussion on the specifics of G6PD testing. The currently available test is semi-quantitative and tells you if the person has approximately 70% enzyme activity. Basically a person who has at least 10% enzyme activity can take PQ. But worry with a POC test would be if a practitioner performs it incorrectly and gives PQ to someone who is actually severely G6PD deficient. Thus, it is not likely FDA will not allow this test to be CLIA-waivable – that is, it will not be used by clinicians in their offices but instead would need to be performed in a laboratory. An additional problem with the currently available test is that it is not cost-effective to run just one test, which is why laboratories batch them --- which causes delays for practitioners who want quick results. Having to come back for the result may add on an extra visit, which will increase

cost. However, some of the persons PQ would be used in include the person who travels multiple times – once they are G6PD-tested once, you have the result in their record and they can use PQ each time.

- CDC should consider implementing a two-tiered model to disseminate information on malaria chemoprophylaxis. A simple message should be delivered for clinicians and travelers, based on the evidence. More detailed information should also be made available, perhaps in the form of appendices, tables and summary of research for travel medicine experts who have a desire to obtain more detailed information. Links to other resources can be posted on the CDC web site as well.

Discussion Point: Should statements about efficacy versus effectiveness be prominently included in messages, such as adherence may be better in drugs taken weekly versus daily or adherence may be better with shorter post-travel regimens?

- The key is that individual preferences need to be taken into account; time needs to be taken with the individual traveler to figure that out.

- There was a number of different opinions on this issue. Some indicated that the evidence is not that strong that adherence to a weekly regimen is necessarily better than to a daily regimen. For example, some of the older literature especially indicated that weekly/daily mixes like CQ/proguanil particularly fared badly on the adherence front. On the other hand, weekly is much better from the military and Peace Corps standpoints. For example, the Peace Corps prefers MQ over DC since the adherence rate is higher with MQ among volunteers in the field.

- Communication between the traveler advisor and patient plays a key role in adherence.

- The distinction between efficacy and effectiveness should be clearly outlined, particularly for providers with no expertise in travel medicine.

Discussion Point: Is information that CDC provides on potential ADRs sufficient? What are the implications for providing the public with a wealth of information on potential ADRs? Could such information reduce use of needed chemoprophylaxis? What is the best mechanism to balance risks of ADRs vs benefit (prevention of malaria)? What approaches should be taken to categorize and list mild, moderate and severe ADRs?

- More information on ADRs should be disseminated, but the need for chemoprophylaxis should be strongly emphasized as well. Information on

ADRs to the public should be balanced with the risk and consequences of malaria to travelers and thus, the benefits of chemoprophylaxis. A personal preference that some travelers seem to have for getting a "treatable" disease such as malaria rather than taking a drug with potential severe ADRs should be countered with solid data and compelling messages as outlined below.

First, U.S. surveillance data for 2001 showed that >800 *P. falciparum* cases in travelers and two of 11 malaria deaths in the United States among U.S. travelers occurred. Second, *P. falciparum* malaria is not always treatable if it reaches the severe stage and has resulted in death in some cases. The likelihood of dying after getting *P. falciparum* is 1/100. If severe complicated malaria develops, the percentage of dying dramatically increases to 1/5. Third, malaria prevention with chemoprophylaxis is successful. Of 1,200 malaria cases among Peace Corps volunteers and staff over the past 12 years, no deaths have occurred. The hard data can also be strengthened with personal experiences about the disease from former malaria patients.

- The Yellow Book does not contain sufficient information on ADRs. For example, actual discontinuation rates should be listed since we have hard data on those. This approach will allow practitioners and patients to collectively make informed decisions about malaria chemoprophylaxis. CDC noted the difficulty in summarizing randomized trials, observations, comparators, placebos, background rates and other issues for different populations in a forum that would be helpful to providers and travelers.

  One suggestion was that CDC limits this summary on ADRs to only high-quality AI trials with the best medical evidence. However, it was also pointed out that these trials will mainly report mild/moderate ADRs – but what people really want to know about is the rate of severe ADRs and all we have are estimates of those. Severe outcomes reported in the media and case reports could be addressed through the following, for example, "the background rate of suicides and depression in X population is X. The causal relationship between MQ and these ADRs is unknown."

  For non-severe ADRs, CDC could generally list reported side effects and the frequency in which these occur. Evidence for both severe and common ADRs should be cited. Emphasis should be placed on public concern and recent media attention to MQ. CDC will place some information in the Yellow Book but more detail will go into the evidence-based documents—for example, case reports.

- Travelers are also concerned about side effects like insomnia that can affect the quality of their trip

- CDC should collaborate with experts in the risk communication field to craft messages on malaria chemoprophylaxis and ADRs.

- The Yellow Book should contain more clear guidance on certain seasons, for example, where chemoprophylaxis is not needed. CDC noted that it must take a conservative approach on this issue since seasonal variations frequently change. CDC would be extremely challenged in updating and effectively communicating this information. In addition, practitioners only have a few minutes to spend with a patient and, for example, when they look at the map and see all of Thailand shaded in, they will give prophylaxis for any area of Thailand rather than read the fine print that only certain areas in the country have malaria risk.

- Mild, moderate and severe ADRs can be better categorized with uniform published definitions and not just vague semi-quantitative statements such as: CQ and HCQ have "rare side effects," a statement that is not accurate.

Discussion Point: Should explicit recommendations be made in the guidelines about interrupted prophylaxis?

- The Yellow Book should contain a statement about this issue because CDC, the Peace Corps and other organizations receive many calls from long-term travelers about missed dosages.

- Interrupted prophylaxis is an issue that is too complex to address in the Yellow Book, particularly for long-term travelers. A general statement should be made advising the traveler to contact an expert about appropriate actions to take for missed doses. More importantly, the importance of completing treatment should be emphasized to the traveler up-front.

Discussion Point: Should halofantrine be mentioned in the guidelines?

- A strong statement should be made warning against the use of halofantrine in persons taking MQ. The drug is not available in North America, but is used in some countries. CDC released a strong statement in the *MMWR* following the death of a U.S. traveler to West Africa who was on MQ prophylaxis, developed *P. ovale* in the first week of travel, was diagnosed with malaria and died. At the expert panel's recommendation, CDC will incorporate this statement into the Yellow Book.

- CDC guidelines should more strongly emphasize to travelers that many malaria drugs are available overseas, but are not approved in the United States. These drugs can be dangerous or ineffective and are not referenced in U.S. recommendations.

- CDC should consider adopting the Canadian model of a two-page question/ answer "Malaria Myths and Facts" sheet. The document lists common questions from travelers and fact-based answers from experts, such as "malaria does not apply to me;" "malaria drugs will make me crazy;" and "malaria drugs in Africa are better." The fact sheet also lists drugs that are available in Africa by both generic and trade names. Canadian travel health experts distribute the fact sheet to each individual who is prescribed an anti-malarial.

- WHO recommends that Halofantrine only be used in a hospital setting or under strictly controlled medical supervision. The drug is not recommended for persons presenting to a travel medicine clinic.

***Health Communications for Malaria Chemoprophylaxis*.** Ms. Ann Barber, of the CDC Malaria Branch, reported that the number of calls to CDC for malaria advice, as well as health communications formats, have increased in recent years. The Department of Commerce's Office of Travel and Tourism Industry estimates that 27.7 million U.S. travelers went to countries with malaria risk in 2000. CDC provides prevention information to the traveling public, health care providers, the travel industry, as well as to blood collection agencies that depend on CDC to define risk areas for potential blood donors. CDC's current sources of information are outlined below.

First, malaria risk and prevention information was added to the Traveler's Health Web Site (THWS) in 1995. Target audiences are health care providers and international travelers. In 2001, THWS received 3.5 million hits; the malaria general information page receives ~25,000 hits per month. Each region described on THWS contains a general document on vaccination information, food and water precautions and tips to remain healthy while abroad. A malaria-specific document lists individual country risks, recommends chemoprophylaxis regimens, and provides information on personal protection measures against mosquito bites.

THWS also contains a series of documents written for both health care providers and the general public, including materials with additional information about anti-malarial drugs, dosing regimens, potential ADRs, SBT use, and malaria prevention in pregnant women, infants and children. A document was added to familiarize physicians with AP.

Second, the voice and fax information systems (accessed through the number FYI-TRIP) provide travel health information to health care providers and travelers without Internet access. Users of the system may listen to prerecorded tapes or request documents via facsimile. The FYI-TRIP system provides the same information as THWS.[1]

Third, the malaria hotline was established in 1992 to answer routine malaria calls during the day and ensure Malaria Branch staff is available to respond to malaria cases 24-hours/day. Users of the hotline include travel health providers with questions about malaria risk areas and appropriate chemoprophylaxis regimens as well as blood collection agencies with questions about malaria risk areas where potential blood donors will be referred. Health care providers with management questions can reach Malaria Branch staff or the CDC on-call physician through the hotline 24-hours/day at (770) 488-7788.

Fourth, the Yellow Book provides comprehensive information on travel precautions and immunization requirements, including malaria. The document was first published in the 1970s, is updated every two years and is primarily targeted to health care providers; 20,000-25,000 hard copies are printed and 360,000 electronic versions have been downloaded from the CDC web site. The malaria chapter provides background information on the disease, symptoms, protection against mosquito bites, chemoprophylaxis, potential ADRs and presumptive self-treatment regimens. Additional malaria prevention information is provided for pregnant women, infants and children.

Fifth, the CDC *Preventing Malaria* traveler's brochure is one of the agency's most popular publications. The document is disseminated to travel clinics, travel agencies and health care providers for further distribution to travelers. Travelers can take the small brochure on trips as a convenient reference for risk areas, symptoms, prevention and self-treatment. The updated brochure will be released this year and will contain information on AP, a more extensive section on presumptive self-treatment, and a wallet card for travelers to record dates and countries of travel, physician contact information and their current anti-malarial drug. The wallet card will list dosing schedules for presumptive self-treatment and CDC contact information.

Despite these resources, however, many travelers, health care providers and blood collection agencies report problems with accessing malaria information and applying the data to individual travelers or potential blood donors. NCID staff is currently involved with a mapping project to update and improve the accuracy of malaria risk information and increase user-friendliness of this resource. WHO, the Pan-American Health Organization (PAHO), ministries of health, and country-based epidemiologists and scientists are assisting CDC in this effort.

[1] Since the date of these proceedings, the voice and fax system accessed through FYI-TRIP has been discontinued as of August 2005.

A database of malaria risk has been developed and will be linked to mapping software to create searchable maps. The project is scheduled to be piloted with blood banks and travel clinics in March 2003; searchable maps should be posted on THWS by the summer of 2003.

A survey administered to U.S. travelers to East Africa in 1997; showed that ~95% were taking an effective chemoprophylaxis regimen. However, among returned US travelers diagnosed with malaria in 2000, 60% had not taken any chemoprophylaxis, 12% had taken an inappropriate drug for the area of travel and 25% were known to be non-compliant.

Malaria is a reportable disease in the United States with slide-confirmed cases being reported to local or state health departments and the CDC National Malaria Surveillance System with a standardized case report form. The surveillance form that was revised in 2002 now collects more detailed information on adherence to chemoprophylaxis, such as whether all pills were taken as prescribed and the reason doses were missed, if any. NCID hopes the new adherence questions will help tailor prevention messages, increase compliance and reduce the number of malaria cases in U.S. travelers in the future.

Many travelers are not receiving or complying with CDC's recommendations for various reasons; ~1,400 U.S. cases of malaria were diagnosed annually in the past five years. Travelers may be unaware of malaria risk and the need for prevention; may receive incorrect information about chemoprophylaxis, malaria risk or an appropriate drug regimen; may fail to fill the prescription; may ignore recommendations; or may refuse to adhere to the dosing schedule. To better educate health care providers and inform travelers about potential health risks associated with international travel, Ms. Barber asked the expert panel to suggest strategies to reach these groups.

Ms. Arlene Perlmutter announced that CDC developed a communication strategy to obtain input about MQ. Although MQ is a commonly used anti-malarial, the drug can be associated with neuropsychiatric side effects. ADRs from MQ have recently received a considerable amount of publicity. CDC was concerned that media reports would decrease effectiveness of its malaria prevention messages. Individual interviews were conducted and focus groups were held with travelers to malarious countries. Participants were asked about malaria, prevention, MQ and other anti-malarial drugs, personal experiences with side effects and compliance issues.

Results from three interviews with frequent travelers to malarious countries are outlined as followed. The respondents had extensive knowledge of malaria; knew individuals who had ADRs from MQ; and were convinced not to take MQ from personal experience, recollections from others or negative publicity. The respondents suggested that communication messages accurately describe side effects, outcomes if the drug is not

taken and alternatives to MQ. CDC used this input to develop a fact sheet and pre-test messages with four focus groups. The responses would then be used to guide program messages.

Focus group participants were a general audience of travelers, including Emory University students, travel clinic patients, CDC employees and returned Peace Corps volunteers. The major questions focused on the dangers of MQ, malaria symptoms and options to MQ. CDC employees had more knowledge about malaria risks and prevention, while returned Peace Corps volunteers had more personal experience with sleep disturbance, vivid dreams and other MQ side effects. Feedback from the focus group participants is outlined below.

Information should be provided on all drug choices; CDC appears to be recommending MQ. Long-term travelers are more likely to discontinue medication, particularly if local residents are not taking the drug. Malarious areas and appropriate drugs to take should be listed. The fact that malaria symptoms can be associated with many other conditions should be acknowledged. Making a recommendation to prevent mosquito bites by staying indoors at dusk and dawn is unrealistic. A strong statement should be made to emphasize the importance for travelers to continue medication after travel. Guidance should be added about pregnant women and malaria prevention.

Language should be included to clarify CQ use and restrictions in certain areas. Statistics should be removed from materials targeted to a general audience since they do not understand them. The importance of travelers taking prophylactic antimalarial drugs should be repeatedly emphasized. The seriousness of and possible death from malaria should be underscored. Messages from former malaria patients should be developed. CDC used input from the four focus groups to dramatically change the pre-test fact sheet into a traveler's alert brochure.

This brochure was written in plain language at a fifth- to eighth-grade reading level. A chart was included listing the country and appropriate drug. The text was reformatted in short distinct paragraphs. A question/answer section was developed. The writing style was modified with action statements, such as "take a medicine that fights malaria" and "know the side effects." Medical jargon and statistics were removed. Sections were added about continuing medication after travel, pregnancy, CQ and MQ, malaria making persons sick, local practices, discontinuation of drugs, and groups that should not take malaria drugs.

CDC obtained expertise from persons at a plain language writing conference and from a risk communicator in revising the post-test brochure. Ms. Perlmutter noted that the traveler's alert brochure is still in draft form. She encouraged the expert panel to edit their copy of the document and submit revisions to her in writing. The floor was opened for the expert panel to deliberate on CDC's health communication strategies for malaria chemoprophylaxis.

- Efforts should be made in the future to design the searchable maps on malaria risk to distinguish between *P. falciparum* and *P. vivax* areas. CDC noted that the searchable maps will be piloted with secure links to transmit data. CDC realizes that transmission areas frequently change; therefore, disclaimers will be posted to inform users that the maps contain the best information available at the present time.

- Templates of the health communication materials should be developed in multiple languages. CDC noted that a portion of THWS has been translated into Spanish; the final version of the traveler's alert brochure will also be available in Spanish. CDC hopes to translate materials into other languages in the future.

- CDC must also consider that there is a spectrum of travelers – both highly educated travelers as well as persons with limited English speaking skills returning to their home country who may read below a fifth-grade level. CDC noted that health communication messages cannot be delivered to each cultural group in a brochure. One suggestion was that CDC should partner with local efforts, such as are occurring in New York, to outreach to specific cultural groups where high rates of *P. falciparum* have been identified in distinct geographical areas. NYC plans to partner with physicians who serve these high-risk travelers. However, it was also noted that many local health departments do not have adequate resources to do this. In both the UK and Canada, they are also focusing on some of the high-risk VFR[2] groups such as West Africans and South Asians. One suggestion was that in the United States, the Indian Physicians' Network should be approached in this effort.

- A statement should be added to the list of countries with malaria risk in the traveler's alert brochure to clarify that "not all areas of the country have risk of malaria." For example, the brochure recommends that MQ, DC or AP be taken in Peru, but malaria drugs are not needed in some parts of the country.

- Two recommendations in the brochure directed to children should be rephrased to parents: "Do not take DC if <u>your child</u> is less than eight years of age." "Do not take Malarone if <u>your child</u> weighs less than 24 pounds."

[2] An immigrant, ethnically and racially distinct from the majority population of the country of residence, who returns to his/her homeland to visit friends and/or relatives.

- The language of the brochure should be stronger to emphasize the seriousness of malaria: "How NOT to get malaria; come back alive and healthy." "Malaria can kill you" rather than "malaria makes people sick." CDC noted that the use of fear messages to influence an individual to take action is a controversial issue. However, the expert panel's comments will be taken into consideration before the traveler's alert brochure is finalized and again pre-tested with various audiences.

- The brochure's subtitle, "How NOT to get malaria," should be rephrased. Persons who are not primary English speakers have a great deal of difficulty comprehending negative statements.

- A date should be placed on brochures.

- The list of malaria symptoms should be revised to illustrate a sequence of events. This approach will inform readers about health problems from malaria from "beginning" to "end" – i.e. it can start with a headache but end in death.

- A clarifying statement should be added to the list of countries in the brochure where MQ, DC and AP are recommended for use: "Do not take CQ if you are traveling in these countries. These are the drugs you can take: MQ, DC or AP."

- Recommendations in the brochure for the traveler to contact a "doctor" if symptoms develop should be replaced with an "expert in malaria prevention."

- The brochure should more strongly emphasize primary prophylaxis, such as DEET and a bed net.

- Efforts should be made to collaborate with the press and increase public visibility of the health communication materials on malaria.

***Standby Treatment (SBT) in Low-Risk Areas*.** Dr. Paul Arguin of DGMQ reported that different populations may have different goals for malaria chemoprophylaxis, which include prevention of: illness among all travelers; death and other severe complications from malaria; the translocation of infectious organisms to non-endemic areas; or the contamination of blood supplies and subsequent transmission by transfusion. Malaria prevention can be categorized into several levels: no preventive measures; preventive measures against illness due to *P. falciparum;* preventing all species of malaria; or preventive measures against clinical and sub-clinical malaria infections to avoid the possibility of late manifestations of the disease.

SBT is self-treatment taken after a self-diagnosis of malaria has been made. In the United States, it is recommended for persons traveling to remote areas where they cannot readily access medical care and so is essentially a failure of prophylaxis. SBT is recommended as an emergency response only ad so must be followed by a medical consultation as soon as possible. Persons who will take SBT should be advised to consider the diagnosis after six days in a malarious area and if symptoms develop that are consistent with malaria, such as fever, chills and malaise. Drugs recommended for SBT are based on background drug resistance patterns in the area of travel, chemoprophylactic regimens used by travelers with malaria breakthroughs, and SBT side effects and contraindications for individual travelers. AP and SP are two medications currently recommended for SBT.

The expert panel is asked to specifically focus on two issues for SBT. First, whether the United States should define low-risk areas or low-risk categories of travel for which no prophylaxis is recommended, such as flight crews or trips less than seven days, but instead have travelers rely on SBT to rapidly treat cases of malaria and prevent severe outcomes. Second, whether SBT use should be expanded to rapidly treat patients who will not take prophylaxis despite existing recommendations. The following studies are summarized to frame the expert panel's deliberations on these issues. In one study, self-reported chemoprophylaxis use had a sensitivity rate of 82% compared with plasma levels as a gold standard. Second, 23% of travelers took no chemoprophylaxis and 18% of users were non-adherent. Third, 12% of persons stopped chemoprophylaxis early.

In another study, 83% of travelers used chemoprophylaxis, but only 63% used appropriate drugs. In yet another study, 92% of travelers took appropriate drugs, but only 60% were fully compliant; adherence ranged from 45%-78% by far region visited. In the next study, 13% of general practitioners were prescribing according to guidelines outdated by four years. And according to the most recent US malaria surveillance data, 12.4% of malaria cases had been prescribed non-recommended drugs.

Looking specifically at SBT, in a 1990 study, Swiss air flight crews switched from chemoprophylaxis to SBT with no increase in the number of malaria cases. In a 1995 study, 67% of 123 persons with reported fever sought no medical care. Of six persons who took SBT, only one had malaria.

In a 1995 study, 40 of 167 persons with febrile episodes took SBT, but only four had malaria; 87% incorrectly used the SBT regimen. In a 1994 case report, SBT was used, but the illness was eventually diagnosed as appendicitis. In a 1989 case report, ADRs were reported with SP use. In another 1989 case report, SBT failed in Kenya due to drug resistance. In a 1989 survey, 23% of respondents would have selected inappropriate responses to malaria symptoms. In an effort to improve the ability of persons to self-diagnose malaria and decrease reliance on clinical symptoms, rapid

diagnostic tests (RDTs) were developed. In a 1999 study, 18% of persons were unable to perform the test. False-negative rates were as high as 72%.

In a 1999 study, 10%-25% of persons were unable to perform the test; 20.6% incorrectly interpreted results. The false-negative rate was 14.1%. In a 1999 study, 32% of persons were unable to perform the test, including 10 of 11 individuals with malaria. In a 2000 study, 11% of persons were unable to perform the test resulting in one false-negative and three false-positive results. Performance from studies with sick persons in the field was generally worse than those among individuals with no symptoms in a trial setting.

In 2002, DPD and DGMQ initiated a study to calculate risks by country and by various characteristics of travelers using 2000 U.S. malaria surveillance data. The data set included all cases by country of acquisition, type of malaria and associated data on chemoprophylactic drug use.

Tourists, business travelers, VFRs, Peace Corps volunteers, missionaries, students and flight crews were included in the study; military personnel, immigrants, refugees and those with an unknown category were excluded. World Tourism Organization (WTO) annual summary data of non-military arrivals to a country by nationality of the visitor were used to obtain a denominator of actual numbers of at-risk persons. The data are limited by the fact that no specific country of acquisition was listed for some cases in the numerator so they could not be included. In addition, we recognize the inherent under-reporting in the surveillance system. The denominator did not account for duration of stay or individual factors that can reduce risk. Individuals with multiple visits to a country were included and all arrivals were assumed to have equal risk. The quality of WTO data varies by country. For example, countries may report data to the central repository based on overnight stays in hotels, actual border information or numbers of persons who transit through the country.

Initial calculations assume no use of chemoprophylaxis. Later data will be shown that takes estimates of prophylaxis use into account. In calculating basic rates of infection by country, risk was found to be quite high in some areas and relatively low in others. Note that this is retrospective surveillance data and not true risk data. Based on representative data, one in 90 travelers to Nigeria will get malaria, while one in 1.8 million travelers to Mexico will get the disease.

Risk drops when examining for *P. falciparum* only: one in 100 travelers to Nigeria and one in 19 million travelers to Mexico. The risk can be calculated at one in 26 travelers to Nigeria and one in 4.8 million travelers to Mexico when adjusting for 75% chemoprophylaxis use.

The data were also calculated to determine the number of persons who would need chemoprophylaxis to prevent a single case of malaria. Inputs included the number of persons with malaria from countries who did and did not take appropriate prophylaxis. An unknown variable is the percentage of persons who did not take prophylaxis of those who did not get malaria. Several assumptions were made in the calculation. The number of malaria cases imported from a country, the ratio of chemoprophylaxis use among cases and the number of U.S. travelers to a country are all relatively constant. In two representative countries, Mexico had a low risk of infection, a low proportion of *P. falciparum* and a high volume of U.S. travelers. Nigeria had a high risk of infection, a high proportion of *P. falciparum* and a low volume of U.S. travelers. The number of persons who would need chemoprophylaxis to prevent a single case of malaria in Nigeria ranged from 11 to 422 depending on chemoprophylaxis use. The numbers ranged from ~200,000 to 2 million in Mexico. The Mexico data were adjusted to assume only 10% of persons traveled to risk areas.

Risk-based advice is not uniform since some areas in endemic countries have different levels of risk. Duration of stay, type of activity and lodging in an endemic area also affect risk, such as backpacking versus limiting the stay to an air conditioned hotel. To address this issue, CDC incorporated specific risk-based advice into the Yellow Book using data from geopolitical boundaries, latitudinal and longitudinal measures, altitudes and elevation levels. However, CDC realizes that these data are confusing and is considering adopting the PAHO model of graphically illustrating risk areas on maps.

In its deliberations on SBT, Dr. Arguin asked the expert panel to be mindful of the following key points. The rate of ADRs from chemoprophylaxis can be higher than the rate of malaria infection in some low-risk countries. The likelihood of infection can be lower than the possibility of some rare causes of death. The number of persons who would need chemoprophylaxis to prevent a single case of malaria can be very high in low-risk areas. SBT use among individuals with no malaria will result in excess exposure and risk of ADRs. SBT may delay treatment or cause of fever. Some persons with symptoms that are suggestive of malaria will not use SBT. These strategies will require improved surveillance to truly identify risk areas and will also need a mechanism to rapidly update risk areas if local transmission patterns change.

After an appropriate strategy is developed, clinicians will need to be educated to fully understand the complexities associated with proper use of SBT. The implications of an SBT strategy on blood bank deferrals would need to be considered as well. Dr. Newman clarified that the Yellow Book is an inappropriate forum to publish these types of data.

Next, Dr. Ron Behrens, of the Hospital for Tropical Diseases in London, discussed the use of SBT in Europe. He acknowledged that there are supporters of changing from chemoprophylaxis to SBT at very low levels of risk. He noted that the predominant species of malaria in an area should probably be considered in such decisions.

For example, WTO data show that the proportion of at-risk persons is so low in large parts of Southeast Asia, SBT may be more appropriate than chemoprophylaxis. In Britain, a study was conducted using a numerator of reported cases and a denominator of International Passenger Survey (IPS) data. The system randomly collects data on persons traveling abroad and asks questions about the reason for travel, destination and duration of stay. IPS showed that the risk of *P. falciparum* malaria among travelers was very low; four cases were reported over a three-year period. The likelihood of developing *P. vivax* was shown to be much higher.

The increase in the number of malaria cases among travelers to Switzerland was not dramatic after chemoprophylaxis was switched to SBT using MQ. However, Dr. Behrens reiterated that travelers frequently do not follow instructions for the correct use of SBT – many take it but do not seek medical care as soon as possible afterwards.

Drug combinations used for SBT include quinine/SP, AP, artemether/lumefantrine, and artesunate. However, many of these drugs are not available in the United States or Europe. The British drug recommendations for SBT in order of preference are AP followed by artemether/lumefantrine. For multi-drug resistance in pregnancy, quinine is used though SP is an option.

SBT is recommended in the United Kingdom if a sub-optimal regimen will be used in a high-risk situation or if appropriate prophylaxis has been refused. In addition, there may be a place for it if short-term or frequent trips will be made by air crews, businesspeople or other travelers. In addition, it may be appropriate for an individual who visits a malarious area and then travels to an area where they will not have ready access to medical treatment—for example, this can happen with air crews.

The advantages of SBT are that the medications are perceived as user-friendly; travelers avoid concerns about prophylaxis ADRs; may not be overused; are less expensive than prophylaxis; and can be used as an option in areas where prophylaxis cannot be prescribed. The disadvantages of SBT are that the medications pose a risk of mismanaging a fever – and thus may cause an individual to suffer from other morbidity due to mistreated disease. In addition, they are typically not used under supervised conditions; they require clear and safe instructions for each regimen used; they require time-consuming advice; and there is no evidence of their efficacy in field studies.

Untrained or sick travelers cannot self-diagnose malaria using RDTs. SBT is specific, sensitive, portable and stable and most importantly, we must do not harm as we consider its use among travelers. Three types of RDTs for malaria have been developed: LDH detects all species, while aldoase and HRP 2 detect *P. falciparum* only. Some RDTs also distinguish between viable and non-viable parasites. RDTs provide rapid results and are sensitive if >200 parasites/Φl are detectable. OptiMal is

an LDH system that is available in Britain. The test is practical and easy to use, but a study needs to be conducted to gather hard data. False-negative results can occur with dipsticks for malaria if parasites are below the detection level for strips (100-200 Φl/blood).

Humidity, poor technique and false-positives all have a significant impact on dipstick performance. False-positives can be caused by heterophile antibody, rheumatoid factor and elevated levels of IgM. In a study to test RDT performance among 160 asymptomatic travelers who were given written instructions, the success rate was 75%. It rose to 90% when both written and oral instructions were given. These results demonstrate the importance of training in achieving a favorable outcome. In another study to test RDT performance among symptomatic British patients, the failure rate was 10% with high sensitivity and specificity rates. Problems include travelers not following instructions, refusing to do the test, and not making the correct diagnosis once they do the test. Despite these problems, users reported finding RDTs to be acceptable and reported that they would use the kit again. All of these studies reinforce the importance of appropriate instructions and education to achieve successful use.

When Britain changed its written instructions for self-administered tests, performance and correct diagnoses significantly improved. The types of lancets persons used were also found to play a significant role, but the entire system must be evaluated to try to improve performance. Although current data are conflicting on the usability of RDTs, kits are now widely used in many parts of Europe. In addition, additional data must be gathered on the stability of RDTs when kits are carried by travelers.

Dr. Newman was pleased Dr. Behrens presented the interesting data on RDTs, but he reminded the expert panel that RDTs are not currently licensed for use in the United States and cannot be recommended in the Yellow Book at this time. He asked the expert panel to limit the discussion to SBT. The floor was opened for deliberations.

- Canada is not a strong advocate for SBT because solid evidence-based medicine suggests that SBT causes harm and is misused by a majority of persons. Travelers develop fevers that are due to other causes, but are treated as malaria. For example, Dr. Kevin Kain pointed out that one study by Schlagenhauf showed that 3 of the 6 patients who did use SBT used it once they returned back home in Switzerland. In addition, he indicated that they have also evaluated blood smears and PCR on patients who reportedly were diagnosed with malaria overseas while on AP prophylaxis – none of the smears/PCR have been positive.

- WHO does not recommend SBT (alone) for non-immune travelers to Africa.

- CDC should strongly consider removing SP as an SBT, particularly since AP is now available. Studies clearly indicate that SP resistance is rising. The most efficacious and tolerable regimens should be recommended as SBT. The majority of travelers in the field will most likely take MQ, while long-term travelers will take DC because of cost issues. CDC reiterated that a federal government agency cannot recommend drugs not approved for use in the United States or those with no good manufacturing practice.

- Several members of the panel indicated that they rarely use SBT for travelers on prophylaxis and would not over-emphasize it. However, some groups like the Peace Corps do use it more and it should not be deleted from the Yellow Book.

- There was considerable discussion on whether it was acceptable for CDC to clearly define "very low-risk" areas, list these locations, and recommend that persons take only SBT instead of use chemoprophylaxis. Several members of the panel favored this approach for those going to very low risk areas. Issues that were not resolved on this topic related to what is the definition of very low risk as well as use of this practice in the short term versus long term traveler.

- Consideration should be given to adopting the CATMAT model in which information is collected on long-term travelers, missionaries and other special populations. With this approach, more targeted recommendations on SBT or prophylaxis can be made for individual travelers.

- CDC is also trying to obtain more accurate information on risk areas so as to potentially narrow the list of places where chemoprophylaxis is recommended.

- CDC should adopt Britain's model of listing scenarios where SBT should be considered and then providing expert advice on malaria. Due to the complexities of SBT, CDC raised the possibility of convening another conference in the future specifically for this issue.

***Review of Outstanding Issues and Next Steps*.** Dr. Steketee summarized key points from the discussion and described next steps in the process to update CDC's malaria chemoprophylaxis guidelines. The expert panel made significant accomplishments in reviewing drug recommendations, addressing each discussion point, examining the overall guidelines and commenting on communication strategies. CDC is pleased that the expert panel's deliberations were evidence-based to the extent possible. The expert panel joined Dr. Steketee in applauding the tremendous undertaking by the session

leaders in reviewing materials, raising new issues and highlighting other important topics. Drs. Parise and Lewis were again recognized for their tremendous contributions.

Dr. Steketee confirmed that the meeting was extremely helpful to CDC. A number of possibilities for organization will need to be considered in updating CDC's malaria chemoprophylaxis guidelines: a drug-by-drug discussion; the role of each drug; appropriate time and location for drug use; efficacy and effectiveness issues; malaria risk; species of parasite; and children, pregnant women and other special populations. In terms of next steps, CDC will produce a meeting summary and will update and revise the background documents based on the expert panel's deliberations and additional information.

The Malaria Branch must be mindful of DGMQ's publication deadline for the new edition of the Yellow Book. With respect to dissemination, detailed information can be placed on the CDC web site. Brochures and other useful materials can be distributed to consumers and providers. The expert panel is now being asked to assist CDC in synthesizing drug-by-drug reviews, SBT guidelines and overall recommendations. The materials will then be published, posted on the web site and used as a benchmark for future research.

For example, CDC could request that ASTMH produce a series of articles in a journal supplement. Features could include a drug-by-drug review, overall recommendations, an SBT article, and a communications article with samples of materials targeted at various populations. Members of the expert panel who volunteer to participate in this effort would be organized as a workgroup. Published materials would list authors according to their contribution. Dr. Steketee clarified that this model is merely an example; the expert panel was asked to suggest other mechanisms to facilitate its role in short- and long-term efforts.

He emphasized the need for each expert to remain committed to protecting U.S. and global travelers against malaria but our ultimate goal is to ensure the disease continues to be controlled and is eventually eliminated. CDC will sustain its commitment with colleagues in Canada, Europe and Mexico. In the near future, CDC plans to address the unmet need of care of malaria-infected persons in the United States. Better guidance on this issue will be provided to clinicians who deliver care to malaria patients throughout the country. Dr. Steketee opened the floor for the expert panel to deliberate on next steps in updating CDC's malaria chemoprophylaxis guidelines.

- CDC should consider *JAMA* and other venues in addition to the ASTMH journal to reach a wider audience, particularly physicians with part-time travel clinics who are not ASTMH members. A drug manufacturer could sponsor the CDC publication; reprints of the materials could then be made available in multiple settings. The publication could also be designed as another level to the Yellow Book, *i.e.*, "Guidelines for Malaria Prophylaxis."

CDC noted that *JAMA* is more restrictive on the length of articles. The ASTMH journal was suggested due to its existing relationship with CDC. Overall, CDC confirmed that this activity is feasible since a small amount of funding is currently available to publish clinical articles.

- Some experts should serve as peer reviewers to the CDC publication because the ASTMH journal will not publish articles that have not been peer reviewed.

- A strategy should be developed to address copyright restrictions. Articles published in the ASTMH journal cannot be posted on the CDC web site. CDC noted its previous experience in publishing articles in peer-reviewed journals that were available in the *MMWR* and on its web site as a downloadable .pdf file. If negotiations are successful with ASTMH, CDC plans to link the publication to the web sites of CATMAT, DoD, MedLine, U.K. travel organizations and WHO. Some aspect of the articles could potentially be published in CDC's publications: *Emerging Infectious Diseases* and the *MMWR*. CDC will have the ability to reprint and distribute materials that are published as a supplement to the ASTMH journal.

- Consideration should be given to launching a press release of this activity. A media campaign to raise public awareness about mortality and morbidity associated with malaria would be timely in light of recent publicity. Other opportunities to publicize malaria include announcements on travel channels that promote exotic vacation locations and publication of the review of U.S. malaria deaths. This document will soon be distributed for review and will present an opportunity to highlight the often fatal nature of *P. falciparum* malaria in the United States.

- Another publication from the expert panel's deliberations should be developed to highlight the critical need for additional data. The document should summarize key issues the experts raised to advance the field of evidence-based prophylaxis. These unanswered questions could then be investigated in the future by other researchers. Potential topics to place on a research agenda include mapping diseases and improving preventive malarial measures. To leverage funding for this research effort, however, the topics should be prioritized.

- Stronger attention should be paid to existing evidence from well-designed studies than to observational studies.

- Several experts at the meeting volunteered to take the lead to assist CDC in getting the evidence-based drafts to publication.

***Closing Session*.** Dr. Steketee confirmed that CDC would communicate with the experts via e-mail to identify volunteers for the publication. He conveyed that the meeting was a first step in an ongoing process. CDC will continue to obtain input from and share information with colleagues from CATMAT, WHO, the United Kingdom and other groups as these opportunities arise.

The expert panel thanked and applauded CDC for hosting the important malaria chemoprophylaxis conference. Dr. Steketee adjourned the meeting at 4:04 p.m. on January 30, 2003.