THE EFFICACY OF MALARIA CHEMOPROPHYLAXIS

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Abstract

Introduction:
Malaria is a highly contagious disease. According to W.H.O., its cases are expected to increase due to climate changes. Despite eradication efforts, malaria still remains one of the most significant causes of morbidity and mortality in tropical and subtropical regions. Many different antimalarial regimens are used; however resistance is emerging to many of them.
Purpose:
This critical review was conducted, in order to respond to the following questions. A) Which antimalarial regimen is the most effective? B) Which regimen is the safest for travelers in endemic regions? C) Which regimen is best tolerated?
Methodology:
The literature research was conducted through the Internet. The Medline and Cinahl databases were used, as well as the search engines google, altavista and lycos. The research included clinical trial articles. The studies were selected based on the aforementioned research questions and the chronological time limits.
Results:
Atovaquone/proguanil, tafenoquine, primaquine were the most effective regimens. Tafenoquine, as well as, primaquine were related to hemolytic incidents in individuals with G6PD deficiency, gastrointestinal disorders, backache and flu-like syndrome. Doxycycline and mefloquine were related to gastrointestinal and neurological disorders. Those were the less tolerated regimens.
Conclusions:
Atovaquone/proguanil, tafenoquine, primaquine were the most effective regimens. As far as safety is concerned, tafenoquine and primaquine should not be prescribed to individuals with G6PD deficiency. All the regimens were considered well tolerated, while most withdrawals due to adverse effects, took place in the doxycycline and mefloquine trials.

Keywords: malaria prophylaxis, malaria chemoprophylaxis, atovaquone - proguanil, tafenoquine, primaquine, doxycycline, mefloquinehe

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Introduction

Malaria is a highly contagious disease[1]. Humans contract malaria through the bite of an infected female anopheline mosquito. The responsible organism, is the Plasmodium

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spp. There are 4 different plasmodium species, able to cause disease in humans. P. falciparum malaria is the most serious, as its mortality may reach as high as 10%. Other more benign plasmodium species are P. vivax, P. malariae and P. ovale. (Table 1). P. f

Table 1

TABLE 2. Number of malaria cases, by *Plasmodium* species — United States, 2001, 2002, and 2003

Plasmodium species	2001		2002		2003	
	No.	(%)	No.	(%)	No.	(%)
P. falciparum	693	(50.1)	699	(52.3)	682	(53.4)
P. vivax	385	(27.8)	339	(25.4)	293	(22.9)
P. malariae	62	(4.5)	38	(2.8)	46	(3.6)
P. ovale	50	(3.6)	37	(2.8)	33	(2.6)
Mixed	14	(1.0)	11	(0.8)	12	(0.9)
Undetermined	179	(12.9)	213	(15.9)	212	(16.6)
Total	1,383	(100.0)	1,337	(100.0)	1,278	(100.0)

alciparum prevails in the sub-Saharan area, Africa, East Asia, Oceania and the Amazon. It poses a serious threat to the residents and the travelers of these areas as well.

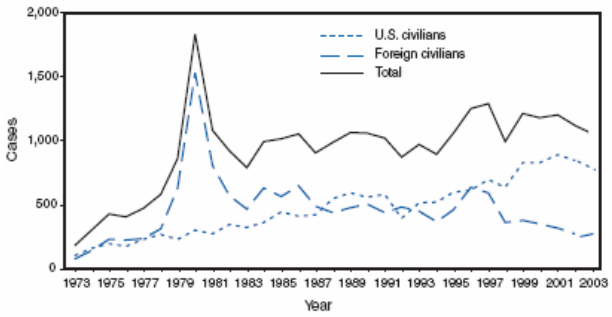
In the last decades, war, natural disasters, unemployment and tourism have brought many population changes in malaria endemic countries. Moreover, the emerging resistance of plasmodium species to antimalarial drugs, dictate constant vigilance, in order to avoid new cases or epidemic outbreaks in malaria free countries. Despite all efforts, malaria still remains one of the most important causes of morbidity and mortality in tropical and sub-tropical areas. According to W.H.O., there are 300 – 500 million cases of malaria annually and every year, approximately 1.5 - 2.7 million people die from the disease[2,3]. What's more, malaria incidence is expected to increase due to climatological changes.

In the United States, the mean of imported malaria cases is 1300 patients annually (Table 2, appendix). The risk for travelers, who do not receive chemoprophylaxis varies according to the destination, but lies among 24 / 1000 travelers per month in West Africa, 2.5 / 1000 travelers per month in India and 0.5 / 1000 travelers per month in South America[4].

Unfortunately, the emerging resistance against the malaria chemoprophylactic drugs

Table 2

FIGURE 1. Number of malaria cases among U.S. and foreign civilains, by year — United States,* 1973–2003†



* Includes Puerto Rico, Guam, and the U.S. Virgin Islands.
† The substantial increase in the number of cases reported for 1980 primarily reflects cases diagnosed among immigrants from Southeast Asia.

renders many of them, inefficient. While, some of the new drugs can cause serious adverse effects and may be more expensive than former therapies.

In order to tackle malaria, many regimens are being employed.[5,6] (Table 3, Appendix). Drugs or drug combinations that are currently suggested for malaria prophylaxis are chloroquine, atovaquone/proguanil, mefloquine, doxycycline and primaquine.[7,8,9]

Resistance has been developed against most of these drugs, especially in South East Asia, where doxycycline and perhaps primaquine are the only efficient drugs. Unfortunately, they have been correlated with frequent adverse effects. Thus, new, efficient and safe chemoprophylactic antimalarial regimens are necessary.[10,11,12]

The purpose of this critical review is to conclude which regimen is best suited for recommendation to travelers of malaria endemic areas.

Purpose:

This critical review has been conducted in order to address the following questions:

1. Which antimalarial regimens are more efficient?
2. Which regimens are safer for travelers in endemic regions?
3. Which regimen is best tolerated by the travelers?

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Table 3

Drug	Usage	Adult dose	Pediatric dose	Comments
Atovaquone/proguanil (Malarone™)	Prophylaxis in areas with chloroquine-resistant or mefloquine-resistant Plasmodium falciparum	Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride. 1 adult tablet orally, daily	Paediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride. 11-20 kg: 1 tablet 21-30 kg: 2 tablets 31-40 kg: 3 tablets 41 kg or more: 1 adult tablet daily	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area, and for 7 days after leaving such areas. Contraindicated in persons with severe renal impairment (creatinine clearance < 30mL/min). Atovaquone/proguanil should be taken with food or a milky drink. Not recommended for children < 11 kg, pregnant women, and women breastfeeding infants weighing <11 kg.
Chloroquine phosphate (Aralen™ and generic)	Prophylaxis only in areas with chloroquine-sensitive *P. falciparum*	300 mg base (500 mg salt) orally, once/week	5 mg/kg base (8.3 mg/kg salt) orally, once/week, up to maximum adult dose of 300mg base	Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. May exacerbate psoriasis

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Drug	Usage	Adult dose	Pediatric dose	Comments
Doxycycline (Many brand names and generic)	Prophylaxis in areas with chloroquine-resistant or mefloquine-resistant P. falciparum	100 mg orally, daily	8 years of age or more: 2 mg/kg up to adult dose of 100mg/day	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in children < 8 years of age and pregnant women.
Hydroxychloroquine sulfate (Plaquenil™)	An alternative to chloroquine for primary prophylaxis* only in areas with chloroquine-sensitive *P. falciparum*	310 mg base (400 mg salt) orally, once/week	5 mg/kg base (6.5 mg/kg salt) orally, once/week, up to maximum adult dose of 310 mg base.	Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. May exacerbate psoriasis

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Drug	Usage	Adult dose	Pediatric dose	Comments
Mefloquine (Lariam™ and generic)	Prophylaxis in areas with chloroquine-resistant P. falciparum	228 mg base (250 mg salt) orally, once/week	≤9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once/week 10-19 kg: ¼ tablet once/week 20-30 kg: ½ tablet, once/week 31-45 kg: ¾ tablet once/week ≥46 kg: 1 tablet, once/week	Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Contraindicated in persons allergic to mefloquine or related compounds (e.g. quinine and quinidine) and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a previous history of depression. Not recommended for persons with cardiac conduction abnormalities.
Primaquine	An option for prophylaxis in	30 mg base (52.6 mg salt)	0.5 mg/kg base (0.8 mg/kg salt)	Begin 1-2 days before travel to malarious areas. Take

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Drug	Usage	Adult dose	Pediatric dose	Comments
	special circumstances. Call Malaria Hotline (770-488-7788) for additional information.	orally, daily	up to adult dose, orally, daily	daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in persons with G6PD1 deficiency. Also contraindicated during pregnancy and lactation unless the infant being breast-fed has a documented normal G6PD level. Use in consultation with malaria experts.
Primaquine	Used for presumptive anti-relapse therapy (terminal prophylaxis) to decrease the risk of relapses of *P. vivax* and *P. ovale*.	30 mg base (52.6 mg salt) orally, once/day for 14 days after departure from the malarious area.	0.5 mg/kg base (0.8) mg/kg salt) up to adult dose orally, once/day for 14 days after departure from the malarious area.	Indicated for persons who have had prolonged exposure to P. vivax and P. ovale or both. Contraindicated in persons with G6PD (1) deficiency. Also contraindicated during pregnancy and lactation unless the infant being breast-fed has a documented normal G6PD level.

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Methodology:
The literature research for this critical review included the Internet and the library of the Department of Health Sciences of the National and Capodistrean University of Athens. The Medline and Cinahl databases have been used, as well as the search engines google, altavista and lycos. Data were also found in the sites of W.H.O. and C.D.C.
The articles researched, were clinical trials studies.
Keywords were: malaria prophylaxis, malaria chemoprophylaxis, atovaquone/proguanil, tafenoquine, primaquine, doxycycline, mefloquine
The time frame involved articles, which were published between the years 1999 and 2006. The chosen articles were clinical trials, which were not conducted on pregnant women or children. Articles written prior to 1999, in languages other than English and abstracts only, were excluded.
In the end, 8 articles remained.

Results:
The study of Dennis Shanks, et.al, with the title, "A New Primaquine Analogue, Tafenoquine (WR 238605), for Prophylaxis against Plasmodium falciparum Malaria (2001)".
This study assessed the ability of tafenoquine (WR 238605) to prevent malaria in a P. falciparum holoendemic area. It is a double–blind,placebo–controlled,
randomized clinical trial in West Kenya.
The study population included healthy male and female volunteers, aged between 18 and 55. They were all residents of a highly malarious area, in West Kenya. In the statistical analysis, failure of prophylaxis rates were compared by calculating point estimates ant 95% Confidence Intervals for the protective efficacy of each tafenoquine dose relative to placebo.
However, despite the 95% Confidence Intervals, the researchers do not explain whether the sample size has been selected based on statistical power or significance level. Thus, it is uncertain, whether the results are statistically significant. Furthermore, as the authors point out, the participants were all residents of a highly endemic region and they might have developed stronger immunity against malaria compared to the general population, therefore they might not be a representative sample.
The study of Alper Sonmez, et.al, with the title, "The Efficacy and Tolerability of Doxycycline and Mefloquine in Malaria Prophylaxis of the ISAF Troops in Afghanistan".
This study took place in Afghanistan, one of the endemic regions for chloroquine resistant P. falciparum. Mefloquine and doxycycline are recommended for chemoprophylaxis. The purpose of the study was to compare the efficacy and tolerability of the regimens in Turkish soldiers in Kabul, Afghanistan.
The duration of the chemoprophylaxis was approximately 12 weeks for each soldier. The side effects and the compliance were evaluated with questionnaires in the 2^{nd} and 8^{th} week of the chemoprophylaxis.
The SPSS 10 for windows was used for the statistical analysis. The comparisons between groups used the x^2 test and the Fischer exact x^2 test. Only alpha values <0.05 were considered statistically significant.
However, it is undetermined whether the results should be considered statistically significant. The sample is purposive and the authors do not clarify whether the size has been selected based on the statistical power, although there is a significance level. Moreover, there was a large subject withdrawal and there was no control group. Additionally, we are not certain if the questionnaires used in order to evaluate the compliance and the adverse effects, have been estimated for their reliability. Finally, as the authors indicated, the region was malarious hypoendemic and therefore, the prophylactic efficacy may not be as high as estimated.
The study of Bertrand Lell, et. al., with the title, "Malaria chemoprophylaxis with tafenoquine: a randomised study".
The authors conducted a randomized, double blind study, where they evaluated

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the prophylactic efficacy and the safety of tafenoquine in different doses. The study took place between February and July, 1999, in Gabon, a region highly endemic for P. falciparum malaria. Individuals, aged between 12 – 20 years old, were invited, from 3 different secondary schools.
The 95% C.I. for protective efficacy were calculated as the ratio of two Poisson variables. The reported data were obtained by per protocol analysis. The pair Student's t test for continuous laboratory data was used for the statistical analysis. The x^2 test was used in order to calculate differences in the number of individuals reporting adverse effects.
This study had a good external, as well as internal validity. However, there was a large subject withdrawal. Furthermore, the participants had increased immunity due to the highly endemic region, they resided.

The study of J. Dirk van der Berg, et.al, with the title, "Safety and Efficacy of Atovaquone and Proguanil Hydrochloride for the Prophylaxis of Plasmodium falciparum Malaria in South Africa".

The aim of this study was to determine the safety and efficacy of the atovaquone and proguanil hydrochloride combination therapy for the prophylaxis of P. falciparum malaria. The trial took place in South Africa during the main season of malaria transmission, February through July. The participants were 175 healthy, non immune volunteers. They were all South African National Defense Force personnel, male and female, aged between 16 and 65 years old and they had a risk for malaria infection. A written informed consent was provided. The mean duration of exposure to the drug was 8.9 weeks. The proportion of prophylactic success was summarized using a 95% Confidence Interval.
The study was not randomized, thus the results can not be applied to the general population. Furthermore, it is not clear, whether the sample size was selected based on statistical power or significance level. Nevertheless, there was a 95% Confidence Interval. Therefore, the results should not be considered statistically significant. Moreover, there was no control group and the subject withdrawal was large. These factors have a negative effect in the internal validity of the trial.

The study of J. Kevin Baird, et.al., with the title, "Randomized, Parallel Placebo-Controlled Trial of Primaquine for Malaria Prophylaxis in Papua, Indonesia".

This study is a randomized, parallel placebo-controlled trial. The efficacy of primaquine for malaria protection was compared to the placebo. The participants were residents of three villages in the northeastern Papua. Their age was between 12 and 65 years old, their weight was >40 kg and they lived in Papua for a period between 3 and 26 months. All the participants had lived in malaria free areas for more than 2 years. They provided written informed consent. The researchers used a randomization code assigning sequential numbers to either inclusion or exclusion for the trial in a 3:1 ratio.
The statistical analysis was carried out using the statistical package SPSS 9.0 and Epi Info (version 6.04 Center for Disease Control and Prevention). The differences in means were assesed using the paired or unpaired Student's t test or Mantel Haenszel test. P values $\leq$ 0.05 were considered significant.The integral validity of the study was adequate. It is not clear whether the sample size was chosen size based on statistical power, although there was a significance level. Thus the results should not be considered statistically significant. Moreover, the sample may not be representative, because all the participants were residents of the area.

The study of Judith Ling, et.al., with the title, "Randomized, Placebo-Controlled Trial of Atovaquone/ Proguanil for the Prevention of Plasmodium falciparum or Plasmodium vivax Malaria among Migrants to Papua, Indonesia".

This is a randomized double- blind study on 297 individuals from a non endemic area in Indonesia, who migrated to Papua, where malaria is endemic. Atovaquone/ proguanil is compared to the placebo in order to determine the prophylactic efficacy of the regimen for P. falciparum and P. vivax infection. The age of the volunteers was between 12 and 65 years old and their weight was over 40 kg. They had migrated

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from a non endemic area during a period of 3 to 26 months. Every participant signed a written informed consent. Subjects were randomized in a 3:1 ratio to continue or discontinue the study. The 95% Confidence Interval was calculated from the binomial distribution. The Yates's corrected x^2 test was used in the statistical analysis.
Apart from the participant withdrawal in the control group, mainly due to infection, the trial had adequate internal and external validity.

The study of Eli Schwartz and Gili Regev-Yochay, with the title "Primaquine as Prophylaxis for Malaria for Non immune Travelers: A Comparison with Mefloquine and Doxycycline".

This is a comparative study among primaquine, mefloquine and doxycycline for their ability to prevent malaria. It is a retrospective study during 1995 -1998. The travelers joined rafting trips to Ethiopia. The study population consisted of 158 Israelis who joined rafting trips to the river Omo in Ethiopia, for a duration of 12 to 20 days. The trips took place during 1995 – 1998. All travelers were followed up in different clinics for malaria symptoms and their compliance was assessed. In addition, 50 participants who took primaquine filled out questionnaires on side effects.
The binomial distribution with correction for continuity was used for the comparison of efficacy of primaquine with that of the other drugs. The x^2 test and the Fisher exact test were used for the statistical analysis.
The sample of the study was not randomized and we do not know if the size was estimated based on statistical power or significance level. Therefore the results should not be considered statistically significant Furthermore, it is not clarified whether the reliability of the questionnaires was estimated. Finally, the internal validity of the study is threatened because there was no control group.

The study of T. Y. Sukwa, et.al., with the title "A Randomized, Double-Blind, Placebo-Controlled Field Trial to Determine the Efficacy and Safety of Malarone, (Atovaquone/ Proguanil) for the Prophylaxis of Malaria in Zambia".

The authors conducted a randomized, double–blind, placebo-controlled study, in order to determine the efficacy and safety of Malarone (250 mg atovaquone/ 100 mg proguanil hydrochloride per tablet) for malaria chemoprophylaxis and especially P. falciparum malaria in Zambia.
The study population included healthy male and female volunteers, aged between 18–65 years old, who resided in a highly malarious endemic region in Zambia All the participants provided written informed consent forms and the research protocol was approved by the Zambia's Institute of Tropical Diseases.
The prophylactic efficacy for the two groups were compared by considering the 2 * 2 frequency table and performing a Fisher's exact test. The mean difference was estimated with Hodges-Lehmann and there was 95% C.I. for the biochemical and hematological factors.
The study had good internal and external validity.

Research Results:

The prophylactic efficacy of atovaquone/ proguanil was 97% against P. falciparum. Two more studies showed that the prophylactic efficacy of the regimen against all Plasmodium spp. is 95% and 93% with 95% C.I.
The prophylactic efficacy of tafenoquine against P. falciparum was 68% with a 400mg/ day for 3 days, 86% with 200mg / day for 3 days and consequently 200 mg weekly and 89% with 400 mg/ day for 3 days and consequently 400mg weekly. In another study, none of the participants who received 250 mg tafenoquine daily for 3 days contracted malaria.
The prophylactic efficacy of primaquine against malaria was 93% for all Plasmodium spp.. One study simply refers to the regimen as more efficient compared to mefloquine and doxycycline. Finally, in one trial none of the participants who received mefloquine or doxycycline contracted malaria.
As far as the safety of the regimens is concerned, tafenoquine has been related to hemolytic incidences in patients with G6PD deficiency and mild gastrointestinal disorders. Primaquine was related to

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hemolytic incidences, toxinemia, gastrointestinal disorders, headache, cough, sore throat, malaise, dizziness and back pains. The complains for the atovaquone/ proguanil regimen regarded stomatitis, headache, gastrointestinal disorders, back pain, flue like syndrome and exfoliative skin rash. Doxycycline was related to gastrointestinal disorders, rash, malaise, headache, insomnia, and neurological disorders. Finally, mefloquine was associated with gastrointestinal and neurological disorders.

As far as the tolerance of the regimen is concerned, in one trial 2 out of 223 participants discontinued tafenoquine use, due to toxinemia and hemolysis. In a study of 158 travelers one had to discontinue primaquine prophylaxis due to gastrointestinal disorders and another one doxycycline prophylaxis due to a rash. In another trial, 12.5 % and 4.6% of the participants withdrew from doxycycline and mefloquine use, respectively, due to adverse effects. Furthermore, in a study on 175 participants, 3 discontinued atovaquone/ proguanil treatment due to headache and dizziness, while in another one, 4 out of 150 participants had to withdraw due to abdominal pain and exfoliative skin rash.

Conclusions

The most efficient regimens were atovaquone/ proguanil, tafenoquine and primaquine, while mefloquine and doxycycline were less efficient. As for the safety, tafenoquine and primaquine should not be prescribed to patients with G6DP deficiency, due to the risk of hemolysis. All the regimens were well tolerated and most withdrawals were, due to adverse effects in patients on doxycycline and mefloquine. However, we should be cautious with these results. Apart from the trials on atovaquone/ proguanil, by Judith Ling et.al. and T. Y. Sukwa et al., and that on tafenoquine, by Bertrand Lell et.al, all the other studies faced methodological inconsistencies. Thus, more reliable studies have to be conducted, in order to provide valid results for the protection and the safety of the travellers.

Directions

This review leads to the following directions for future research:

- More trials should be conducted, on non-immune individuals.
- Safer regimens have to be employed for high risk groups such as children and pregnant women.

An appropriate antimalarial drug should be demonstrated, in order to reduce the risk of emerging resistant Plasmodium spp

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Appendix

STUDY	RESEARCHERS- DATE
A New Primaquine Analogue, Tafenoquine (WR 238605), for Prophylaxis against Plasmodium falciparum Malaria	G. Dennis Shanks,, Aggrey J. Oloo,, Gladys M. et.al, 2001
The efficacy and tolerability of doxycycline and mefloquine in malaria prophylaxis of the ISAF troops in Afghanistan	Alper Sonmeza,*, Ali Harlakb, Selim Kilicc et.al, **2000?**
Malaria chemoprophylaxis with tafenoquine: a randomised study)	Bertrand Lell, Jean-Franŋois Faucher, Michel Anoumou Missinou, et.al., 2000
Safety and Efficacy of Atovaquone and Proguanil Hydrochloride for the Prophylaxis of Plasmodium falciparum Malaria in South Africa	J. Dirk van der Berg, MBChB,l Cornelia S. J. Duvenage, et.al, **2000?**
Randomized, Parallel Placebo-Controlled Trial of Primaquine for Malaria Prophylaxis in Papua, Indonesia	J. Kevin Baird,1 Mark D. Lacy,1 Hasan Basri , et.al, 2001
Randomized, Placebo-Controlled Trial of Atovaquone/Proguanil for the Prevention of *Plasmodium falciparum* or *Plasmodium vivax* Malaria among Migrants to Papua, Indonesia	Judith Ling,1,5,a J. Kevin Baird,1 David J. Fryauff, et.al, 2002
Primaquine as Prophylaxis for Malaria for Nonimmune Travelers: A Comparison with Mefloquine and Doxycycline	Eli Schwartz and Gili Regev-Yochay, 1999
A Randomized, Double-Blind, Placebo-Controlled Field Trial to Determine the Efficacy and Safety of Malarone, (Atovaquone/ Proguanil) for the Prophylaxis of Malaria in Zambia	T. Y. SUKWA, M. MULENGA, N. CHISDAKA, N. S. ROSKELL, AND T. R. SCOTT, 1999

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