EVIDENCE SYNOPSIS

Title: Benefits and Harms of Drugs for Prevention of Chloroquine-Resistant Malaria in Travelers

Date completed: April 20, 2015

Authors: Steven Lascher, DVM, PhD, MPH and David R. Goldmann, MD

Clinical question: What are the benefits and harms of drugs for prevention of chloroquine-resistant malaria in travelers?

Author recommendations:

For travelers to areas with known or potential chloroquine-resistent malaria with a predominance of *Plasmodium falciparum* or *Plasmodium vivax*, clinicians should prescribe any of the following malaria preventive drugs: mefloquin, doxycycline, chloroquine-proguanil, or atovaquone-proguanil.

The choice of compound and regimen should be based on patient presentation and preferences, probability of adherence, destination and length of stay, and product adverse event profiles.

Note special groups with potential contraindications to specific agents. These include children, pregnant women, and those who are immunocompromised or have co-morbid conditions.

Evidence and recommendations:

Quality of Evidence[a]	Strength of Recommendations[b]	Conclusion
High	Strong	Evidence favors chemoprophylaxis in malaria-endemic areas

[a]Quality of evidence scale (GRADE): high, moderate, low, and very low.
[b]Strength of recommendations scale (GRADE): strong, weak, or no recommendation. For more information on the GRADE rating system, see http://www.gradeworkinggroup.org/index.htm.

PICO:

Population	Healthy adults 18 years of age or older traveling to areas where chloroquine-resistant malaria is endemic (specific areas in South America, Asia, and sub-Saharan Africa)
Intervention	Mefloquine, doxycycline, atovaquone-proguanil, or chloroquine-proguanil with or without avoidance or protective measures (clothing, bed nets, repellents)
	Dose, frequency, duration
Comparator	No prophylaxis or placebo; other avoidance and protective measures only; active comparators
Primary outcome(s)	Incident malaria with positive smear microscopy or rapid antigen serology

What are the parameters of our evidence search?

Patients or population: Healthy adults 18 years of age or older traveling to areas where chloroquine-resistant malaria is endemic (specific areas in South America, Asia, and sub-Saharan Africa)

Intervention: Mefloquine, doxycycline, or atovaquone-proguanil, with or without avoidance or protective measures (clothing, bed nets, repellents); dose, frequency, duration

Comparison: No prophylaxis or placebo; other avoidance and protective measures only; active comparators

Outcome: Incident malaria with positive smear microscopy or rapid antigen serology

Settings: Various destination countries including the African continent, Southeast Asia, and Central and South America

TABLE 1 Risk Difference for Malaria Prevention Regimens

OUTCOME: INCIDENT MALARIA DISEASE; INTERVENTION: DOXYCYCLINE						
Study (Year) Design Dosage Location	**Comparator (Regime)**	**Intervention Probability of Incident Malaria Estimate (95% CI) n**	**Comparator Probability of Incident Malaria Estimate (95% CI) n**	**Risk Difference Estimate (95% CI) NNT (95% CI)**	**Quality of Evidence (GRADE)**	**Comment**
Ohrt C (1997)[1] RCT 100 mg once a day Indonesia	Mefloquine (250 mg once daily)	0.015 (0, 0.0004) (67)	0	0.015 (–0.03,0.06)	Low risk of bias	No difference Prevalent species: *Plasmodium falciparum* (primary); *Plasmodium* *vivax* (secondary)
Ohrt C (1997)[1] RCT 100 mg once a day Indonesia	**Placebo**	**0.015 (0, 0.0004) (67)**	**.77 (0.65, 0.86)**	**–0.75 (–0.86, –0.65) –1.33 (–1.17, –1.54)**	**Low risk of bias**	**Favors doxycycline Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)**
Arthur JD (1990)[2] RCT 100 mg once a day Thailand	Mefloquine	0 (0, 0.3) 119	0 (0, 0.03) 134	0 (0.15, 0.15)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)

OUTCOME: INCIDENT MALARIA DISEASE; INTERVENTION: CHLOROQUINE-PROGUANIL						
Study (Year) Design Dosage Location	**Comparato (Regime)**	**Intervention Probability of Incident Malaria Estimate (95% CI) N**	**Comparator Probability of Incident Malaria Estimate (95% CI) N**	**Risk Difference Estimate (95% CI) NNT (95% CI)**	**Quality of Evidence (GRADE)**	**Comment**
Croft AM (1997)[3] RCT 300 mg/weekly; 200 mg daily East Africa	Mefloquine (250 mg weekly)	0 (0, 0.02) 176	0 0, 0.020 183	0 (–0.1, 0.1)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
Schlagenhauf P (2003)[4] RCT 100 mg daily/ 200 mg daily African (Sub-Saharan)	Mefloquine (250 mg weekly)	0 (0, 0.03) 142	0 (0, 0.3) 135	0 (–0.01, 0.01)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
Schlagenhauf P (2003)[4] RCT 100 mg daily/ 200 mg daily African (Sub-Saharan)	Doxycycline (100 mg daily)	0 (0, 0.03) 142	0 0, 0.03 135	0 (–0.01, 0.01)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)

Continued

TABLE 1 Risk Difference for Malaria Prevention Regimens—cont'd

OUTCOME: INCIDENT MALARIA DISEASE; INTERVENTION: MEFLOQUINE						
Study (Year) Design Dosage Location	Comparator (Regime)	Intervention Probability of Incident Malaria Estimate (95% CI) N	Comparator Probability of Incident Malaria Estimate (95% CI) N	Risk Difference Estimate (95% CI) NNT (95% CI)	Quality of Evidence (GRADE)	Comment
Nasveld PE (2010)[5] RCT 250 mg weekly Timor-Leste	Tafenoquine (200 mg weekly)	0.001 (0.00, 0.02) 654	0.008 (0.00, 0.1) 654	–0.01 (–0.01, 0.00) –218 (–88.7, 477.0)	Low risk of bias	Favors mefloquine Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
Ohrt C (2010)[1] RCT 250 mg weekly Indonesia	Placebo	0.015 (0.00, 0.1)	0.77 (0.65, 0.86	–0.78 (–0.87, –0.67) –1.3 (–1.15, –1.5)	Low risk of bias	Favors mefloquine Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
OUTCOME: INCIDENT MALARIA DISEASE; INTERVENTION: ATOVAQUONE-PROGUANIL						
Study (Year) Design Dosage Location	Comparator (Regime)	Intervention Probability of Incident Malaria Estimate (95% CI) N	Comparator Probability of Incident Malaria Estimate (95% CI) N	Risk Difference Estimate (95% CI) NNT (95% CI)	Quality of Evidence (GRADE)	Comment
Deye GA (2012)[6] RCT 1000 mg/400 mg single dose 7 days prior to challenge Lab challenge	Placebo	0.17 (0.00, 0.64) 6	1 (0.54, 1.00) 6	–0.83 (–1.19, –0.47 –1.2 (–0.8, –2.1)	Low risk of bias	*P. falciparum* challenge model

Deye GA (2012)[6] RCT 500 mg/200 mg single dose 7 days prior to challenge Lab challenge	Placebo	0 (0, 0.46) 6	1 (0.54, 1.0)	–1.00 (–1.27, –0.73) –1.0 (–0.8, –1.4)	Low risk of bias	*P. falciparum* challenge model
Deye GA (2012)[6] RCT 250 mg/100 mg single dose 7 days prior to challenge Lab challenge	Placebo	0.33 (0.04, 0.78) 6	1 (0.54, 1.0) 6	–.67 (–1.07, –0.26) –1.5 (–0.93, –3.8)	Low risk of bias	*P. falciparum* challenge model
Deye GA (2012)[6] RCT 250 mg/100 mg single dose 1 day prior to challenge Lab challenge	Placebo	0 (0, 0.46) 6	1 (0.54, 1.0) 6	–1.00 (–1.28, –0.73) –1.0 (–0.8, –1.4)	Low risk of bias	*P. falciparum* challenge model
Deye GA (2012)[6] RCT 250 mg/100 mg single dose 4 days after challenge Lab challenge	Placebo	0 (0, 0.52) 5	1 (0.54, 1.0) 6	–1.00 (–1.29, –0.71) –1 (–0.8, –1.4)	Low risk of bias	*P. falciparum* challenge model Post-exposure prophylaxis
Schagenjhauf P (2003)[4] 250 mg/100 mg once a day Africa (sub-Saharan)	Chloroquine/ proguanil (100 mg/200 mg once a day)	0 (0, 0.24) 154	0 (0, 0.03) 135	0 (–0.01, 0,01)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)

Continued

TABLE 1 Risk Difference for Malaria Prevention Regimens—cont'd

OUTCOME: INCIDENT MALARIA DISEASE; INTERVENTION: ATOVAQUONE-PROGUANIL

Study (Year) Design Dosage Location	Comparator (Regime)	Intervention Probability of Incident Malaria Estimate (95% CI) n	Comparator Probability of Incident Malaria Estimate (95% CI) n	Risk Difference Estimate (95% CI) NNT (95% CI)	Quality of Evidence (GRADE)	Comment
Schagenjhauf P (2003)[4] 250 mg/100 mg once a day Africa (Sub-Saharan)	Mefloquine (250 mg once a week)	0 (0, 0.02) 154	0 (0, 027) 135	0 (–0.01, 0,01)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
Schagenjhauf P (2003)[4] 250 mg/100 mg once a day Africa (Sub-Saharan)	Doxycycline (100 mg once a day)	0 (0, 027) 138	0 (0, 027) 135	0 (–0.01, 0,01)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
Hogh B (2000)[7] 250 mg/100 mg once daily Africa (unspecified)	Chloroquine/ proguanil (250 mg/100 mg once daily)	0.002 (0.0005, 0.1) 501	0.006 (0.001, 0.02)	–0.004 (–.01, 0.004)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
Overbosch D (2001)[8] 250 mg/100 mg once daily Africa (unspecified)	Mefloquine (250 mg once a week)	0 (0, 0.01) 476	0 (0, 0.01) 477	0 (–0.004, 0.004)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)
Camus D (2004)[9] 250 mg/100 mg once daily Africa (unspecified)	Chloroquine/ proguanil (250 mg/100 mg once daily)	0 (0, 0.03) 110	0 (0, 0.03) 111	0 (0, –0.02, 0.02)	Low risk of bias	No difference Prevalent species: *P. falciparum* (primary); *P. vivax* (secondary)

Notes: All comparative risks are reported as risk differences, with 97.5% one-sided confidence intervals. Studies in bold font have statistically significant differences in probability of prevention. The NNTs may be positive or negative. The positives favor the intervention, while the negative NNTs indicate comparator superiority. The simplest method for the negative NNTs would be to use the absolute values (removing the negative signs) and consider the NNT as specific to the comparator.
Because of rounding, the intervention and comparator numbers may not add up to the actual reported risk difference.
CI, Confidence interval; *NNT*, number needed to treat; *RCT*, randomized controlled trial.

Guidelines: The 2014 Yellow Book; Chapter 3: Infectious Diseases Related to Travel: Malaria. Arguin PM, et al.[10] (AGREE II Score: unavailable) There is no evidence, strength of recommendations ratings, or methods described.

- The goal of malaria chemoprophylaxis is to prevent malaria caused by all species of *Plasmodium* in both short- and long-term travelers. Malaria prevention strategies are not 100% effective, and preventing prophylaxis-related adverse events is also a priority.
- Depending on the traveler's level of risk, interventions may include mosquito avoidance alone or in combination with chemoprophylaxis.
- All recommended primary chemotherapy regimens require taking medicine before, during, and after travel to areas with malaria. Presumptive antirelapse therapy (also known as terminal prophylaxis) may be considered after long exposure to malaria in endemic areas to prevent relapses or delayed-onset clinical presentations of malaria caused by hypnozoites of *P. vivax* or *Plasmodium ovale*.
- Recommended drugs include atovaquone-proguanil, chloroquine and hydroxychloroquine, doxycycline, mefloquine, and primaquine (for *P. vivax*).
- The Centers for Disease Control and Prevention (CDC) offers information about *Plasmodium* species distribution worldwide: http://www.cdc.gov/malaria/travelers/country_table/a.html.

International Travel and Health: Malaria. Chapter 7. World Health Organization 2012.[11] (AGREE II Score: unavailable) There is no evidence, strength of recommendations ratings, or methods described.

- Young children, pregnant women, people who are immunosuppressed, and elderly travelers are particularly at risk of severe disease. Malaria, particularly *P. falciparum*, in nonimmune pregnant travelers increases the risk of maternal death, miscarriage, stillbirth, and neonatal death.
- Antimalarial drugs (chemoprophylaxis), when appropriate, prevent infection from developing into clinical disease. No antimalarial prophylactic regimen gives complete protection, but good chemoprophylaxis (adherence to the recommended drug regimen) significantly reduces the risk of fatal disease.
  - The following should also be taken into account:
    - Dosing schedules for children should be based on body weight.
    - Weekly chloroquine should be started 1 week before arrival.
    - Weekly mefloquine should preferably be started 2-3 weeks before departure, to achieve adequate drug blood levels and to detect possible side effects before travel so that possible alternatives can be considered.
    - Daily prophylaxis with doxycycline or atovaquone-proguanil should be started 1-2 days before arrival (or earlier if drug tolerability needs to be checked before departure).
    - All prophylactic drugs should be taken with unfailing regularity for the duration of the stay in the malaria-risk area and should be continued for 4 weeks after the last possible exposure to infection.
- There are specific contraindications and side effects for all antimalarial drugs. The latter are frequent and mild and generally do not affect the activities of the traveler. Serious adverse events are rare.
  - Severe neuropsychiatric disturbances (seizures, psychosis, encephalopathy) occur in approximately 1 in 10,000 who receive mefloquine or chloroquine prophylaxis.
  - The contraindications are drug specific and must be considered prior to prescribing.
- For long-term prophylaxis, consider adherence and tolerability. Also consider certain restrictions on duration of use. For example, atovaquone-proguanil is registered in European countries with restrictions varying from 5 weeks to 1 year (these do not apply in the United States).

Author commentary: This synopsis is based on nine high-quality randomized controlled trials.[1–9] Eight studies are field studies of travelers or military personnel stationed in

malaria-endemic areas of Africa, Indonesia, Thailand, and Timor-Leste.[1–5,7–9] The remaining study (Deye et al.) reports on a laboratory-based *P. falciparum* challenge comparing various chemoprophylactic regimens against placebo.[6] Because of the high degree of heterogeneity among the studies, meta-analytic methods could not be used to pool the results. Nevertheless, the results are consistent. Chemoprophylaxis using the drugs covered in this synopsis is effective in preventing malaria, as evidenced by the placebo-controlled studies by Ohrt and Deye.[1,6]

Based on the remaining head-to-head comparisons, there are no statistically significant differences among the agents other than the slight but statistically significant superiority of mefloquine over tafenoquine.[5] Because of the diverse geographic settings and the consistency in primary and secondary *Plasmodium* species, the evidence supports the use of any of these compounds in areas where these species are endemic and chloroquine resistant. These conclusions do not address destinations where other *Plasmodium* species (e.g., *P. ovale*) predominate.

Given the consistent effectiveness across chemotherapeutic compounds, the decision to use a specific agent will depend on the predominant *Plasmodium* species, the frequency of administration, and the probable degree of adherence. Tantamount are special groups with potential contraindications (children, pregnant women, immunocompromised people, those with co-morbid conditions) and product adverse event profiles.

The clinical practice guidelines from the CDC and World Health Organization are consistent with these recommendations.

Update Alerts: Important new citations relevant to this topic are added here as they become available.

Glossary: AGREE II, Appraisal of Guidelines for Research and Evaluation; CDC, Centers for Disease Control and Prevention; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; RCT, randomized controlled trial.

REFERENCES

1. Ohrt, C., Richie, T.L., Widjaja, H., et al., 1997. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. 126 (12), 963–972.
2. Arthur, J.D., Echeverria, P., Shanks, G.D., et al., 1990. A comparative study of gastrointestinal infections in United States soldiers receiving doxycycline or mefloquine for malaria prophylaxis. Am. J. Trop. Med. Hyg. 43 (6), 608–613.
3. Croft, A.M., Clayton, T.C., World, M.J., 1997. Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. Trans. R. Soc. Trop. Med. Hyg. 91 (2), 199–203.
4. Schlagenhauf, P., Tschopp, A., Johnson, R., et al., 2003. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ 327 (7423), 1078.
5. Nasveld, P.E., Edstein, M.D., Reid, M., et al., 2010. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob. Agents Chemother. 54 (2), 792–798.
6. Deye, G.A., Miller, R.S., Miller, L., et al., 2012. Prolonged protection provided by a single dose of atovaquone-proguanil for the chemoprophylaxis of *Plasmodium falciparum* malaria in a human challenge model. Clin. Infect. Dis. 54 (2), 232–239.
7. Hogh, B., Clarke, P.D., Camus, D., et al., 2000. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Malarone International Study Team. Lancet 356 (9245), 1888–1894.
8. Overbosch, D., Schilthuis, H., Bienzle, U., et al., 2001. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin. Infect. Dis. 33 (7), 1015–1021.

9. Camus, D., Djossou, F., Schilthuis, H.J., et al., 2004. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune pediatric travelers: results of an international, randomized, open-label study. Clin. Infect. Dis. 38 (12), 1716–1723.
10. Arguin, P.M., Tan, K.R. Infectious Diseases Related to Travel: Malaria. Centers for Disease Control and Prevention. <http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria>. Updated August 9, 2013 (accessed April 27, 2015).
11. World Health Organization. International Travel and Health, Chapter 7: Malaria. <http://www.who.int/ith/ITH_chapter_7.pdf>. Updated 2014 (accessed April 27, 2015).

Recommended citation: Lascher S, Goldmann DR; Elsevier Evidence-Based Medicine Center: Evidence Review: Benefits and Harms of Drugs for Prevention of Chloroquine-Resistant Malaria in Travelers. Publication date: April 20, 2015. Access date: May 1, 2015.