The 3-Day Malarone Schedule: Acceptability and Tolerability for Malaria Prophylaxis

Background

Poor compliance with malaria chemoprophylaxis is known to be a common problem and a major contributing factor to the risk of malaria in travellers. Most cases of travel-related malaria are associated with poor compliance, inappropriate drug choice, or complete failure to take anti-malarial medications. Studies around the world have found poor compliance amongst the full spectrum of travellers including tourists, backpackers, expatriate workers, military personnel, and those returning to home countries to visit families and friends (1-7). A study of cases of imported malaria in Australia found that of 246 cases, only 56% took chemoprophylaxis and only 29% fully complied with recommendations regarding dosage and duration of medications (8). Improving compliance with malaria chemoprophylaxis could therefore significantly reduce the risk of travel-related malaria.

Malarone ™ (combination of Atovaquone and Proguanil) is one of the three commonly prescribed medications for malaria chemoprophylaxis. The standard dosage for the prevention of malaria is one tablet per day, starting 2 days before arriving in a malaria endemic area, and continuing daily until 7 days after leaving the malaria endemic area. Malarone given in this dosage is well tolerated, with a low incidence of reported side effects and requires a shorter course of tablets compared to other commonly used anti-malarials. Doxycycline and Mefloquine need to be continued for 4 weeks after leaving a malarious area. However, Malarone is relatively expensive compared to the other anti-malarial medications and this increased cost can be prohibitive for travellers spending extended time at-risk locations. We propose the use of a modified prophylactic dosing schedule for Malarone aimed at improving compliance and thereby reducing the risk of acquiring malaria in at-risk travellers. The dosage schedule, (referred to henceforth as the 3-day schedule) consists of 4 tablets of Malarone per day for 3 consecutive days. Previous studies have shown that this dosage provides protection against malaria for up to 4 weeks even in highly endemic areas (9-12). For travellers spending more than three days in a malaria endemic area, the 3-day schedule will also be cheaper than the current daily dosing schedule for Malarone. For short trips of less than 4 weeks, travellers could complete the 3-day schedule prior to travel, and be protected for the entire trip, without the need to take medications while away. For longer trips, the 3-day schedule could be repeated every 4 weeks. The 3-day schedule is the same as the standard Malarone treatment dose, which has been shown to be safe, well tolerated and highly effective.

Objectives
To assess the acceptability, tolerability and compliance of a pre-travel 3-day schedule of Malarone for malarial chemoprophylaxis in travellers aged 18 years and above.

Study Aims
The proposed research project aims to reduce the risk of malaria in travellers by improving compliance with chemoprophylaxis. In the proposed study, we will assess the acceptability, tolerability, and compliance of the 3-day schedule of Malarone for malaria chemoprophylaxis. The proposed study will be conducted in travellers to malaria endemic areas with low to medium risk of infection in Asia, Pacific Islands and South/Central America. Any future studies on the effectiveness of the 3-day schedule will need to be conducted in high-risk areas such as sub-Saharan Africa.

Study Participants

Participants will be recruited from two specialist travel medicine clinics: Dr Deb – The Travel Doctor clinic in Brisbane, and Travel-Bug Vaccination Clinic in Adelaide. Adult Australians travelling to malaria endemic countries in Asia, Pacific Islands, or South/Central America for ≤ 4 weeks will be invited to participate.

Australians travelling to malaria endemic areas for ≤ 4 weeks will be invited to participate if they meet the enrolment criteria.

Pre-travel preparation

In addition to the services provided during a standard pre-travel consultation (vaccinations, pre-travel health counselling and first aid items), all travellers will be given the option of taking daily Malarone (as per the standard schedule), the 3-day schedule of Malarone being assessed by this study, or another anti-malarial medication. Travellers will be advised about the rationale for the Malarone 3-day schedule and the off-label use for malaria chemoprophylaxis in this study. Travellers will be advised that the 3-day schedule is the same as the dosage used for treating malaria, and has been shown to be safe and very effective after many years of use worldwide.

Timing of 3- day Malarone™ schedule

Travellers will be advised to take 4 tablets per day for 3 consecutive days, with the last 4 tablets taken at least one day before departure from Australia. Malarone tablets will be supplied by the travel clinics at the participant's or their company's expense.

Study procedures

For travellers who choose to take the 3-day schedule and agree to participate in the study, the following procedures will be followed. Participants will be

- Provided with written and verbal information explaining the rationale for the 3-day schedule. The written information will be in the form of a Participant Information Sheet.
- Assessed for eligibility during pre-study screening when a travel medical history will be taken.
- Advised they can withdraw from the study at any time, and alternative malaria prevention medication will be discussed and organised.
- If they do not tolerate the doses of the 3-day schedule eg vomiting their first dose, they will be offered the option of taking the dose again with food. If they decline to take another dose due to nausea/vomiting or some other reason, their primary doctor or nurse practitioner will discuss changing their regimen to daily Malarone or daily doxycycline depending on their intolerances or choice.
- Advised that no anti-malarial medication is 100% effective and therefore mosquito avoidance measures should also be used.
- Advised to see a doctor as soon as possible (and within 24 hours) if they develop any fever. If participant is located in Australia at the time of fever, they will be asked to contact their travel clinic for assessment and management of their illness. If unwell while overseas, travellers will need to see a doctor as soon as possible, obtain a medical record of their diagnosis and treatment and attend their travel clinic on return to Australia for a post-travel medical consultation.

- Asked to sign an Informed Consent Form, confirming they agree to participate in the study, complete the three questionnaires involved and report any adverse symptoms or events that occurred during the study period. The Informed Consent Form will be provided prior to any study-related procedures.
- Asked to complete a baseline questionnaire (Q1) at the clinic (duration approximately 10 minutes) with a specialist travel medicine nurse. The questions will include information on the current trip, any previous history of malaria, travel to malaria endemic areas in the previous 12 months, previous experience with taking anti-malarial medications, past medical history, current medications and allergies.
- Issued with
    - Malarone at their own expense or their company's expense,
    - A Memory Aid and Symptom Diary, and
- Asked to take the 3-day schedule at home on the days of the week as outlined in Table 1, and record symptoms in the Memory Aid and Symptom Diary for the 10 days after starting the 3-day schedule. (The dose schedule in Table 1 has been prepared to allow nurses to ring patients on weekdays).
- Telephoned by a clinic nurse to complete a questionnaire (Q2) shortly before departure (duration approximately 5 minutes). The clinic nurse will confirm that the Malarone tablets have been taken correctly, and document any immediate adverse reactions.
- Telephoned by a clinic nurse to complete a post-trip questionnaire (Q3) (duration approximately 5 minutes). This call will be made approximately 1 week after return to Australia to ask about any adverse reactions that occurred during the study period and any illness during or after the travel.
- Participants will be asked to send their Memory Aid and Symptom Diary to their travel clinic.

Table 1. Timing of Malarone tablets and Q2 Telephone Schedule

Day of Departure	Day 1 tabs	Day 2 tabs	Day 3 tabs	Nurse Ring Q2
Monday	Tues	Wed	Thurs	Fri
Tuesday	Fri	Sat	Sun	Mon
Wednesday	Sat	Sun	Mon	Tues
Thursday	Sun	Mon	Tues	Wed
Friday	Mon	Tues	Wed	Thurs
Saturday	Tues	Wed	Thurs	Fri
Sunday	Tues	Wed	Thurs	Fri

Sample size

The proposed project will aim to collect a case series of 222 participants, and it is anticipated that data collection will take 6 to 12 months. Our sample size is based on current data, which report the prevalence of side effects of Malarone™ to range between negligible (e.g. depression) to 38% (e.g.

diarrhoea). A target enrolment of 222 participants will provide 185 evaluable subjects assuming 20% withdrawal and lost to follow-up. This sample size yields an overall power of 80% and an alpha of 5% to detect a 10% difference between the reported prevalence of side effects and those reported from our study.

Inclusion criteria

- Over 18 years of age
- Travelling to a malaria-endemic area in Asia, Pacific Islands, and South/Central America for ≤ 4 weeks
- Able to give written Informed Consent and sign consent after all aspects of the protocol explained
- Subject must agree to participate in all planned follow-up telephone reviews, and to return their Memory Aid and Diary to their travel clinic.

Exclusion criteria

- Previous adverse reactions to Malarone
- Taking other medications that adversely interact with Malarone (metoclopramide, rifampicin and tetracyclines may decrease the efficacy of Atovaquone; fluvoxamine may decrease the efficacy of Proguanil).
- Pregnancy or planning pregnancy.
- Significant medical conditions including diabetes, heart problems, asthma, epilepsy, depression, renal impairment, gastrointestinal disorders, and those taking long-term antibiotics.
- Travelling to highly endemic countries with a high risk of malaria, e.g Sub-Saharan Africa.

Study Outcomes

- The study will provide information on the tolerability, acceptability, and compliance of the 3-day Malarone™ schedule for malaria chemoprophylaxis.

Ethics considerations:

- Ethics approval will be obtained from the Human Research Ethics Committee of The University of Queensland.

Researchers	Roles
Dr Colleen Lau (Principal Investigator) MBBS, MPH&TM, CTH, PhD, FRACGP, FACTM NHMRC Fellow, Research School of Population Health, ANU Travel Medicine Doctor Dr. Deb – The Travel Doctor, Brisbane	• Coordinate and manage the research project • Answer questions from co-investigators, clinic doctors and nurses, and participants. • Develop research protocols and documents • Obtain necessary ethics approvals • Collate and manage research data • Conduct statistical analysis of results • Produce a report of study outcomes and peer-reviewed publication in a medical journal
Dr Deborah Mills MBBS, MPH&TM, CTH Medical Director Dr Deb – The Travel Doctor, Brisbane	• Coordinate project logistics at Dr Deb - The Travel Doctor clinic in Brisbane and ensure that clinic doctors, nurses, and participants follow study protocols • Answer questions and assess participants as needed, including those who experience adverse reactions to Malarone, require further assessment • Report any significant adverse events to the Principal Investigator • Arrange post-travel clinical assessment of participants if they have been unwell during their trip
Lani Ramsey, RN, NP, CTH, DTM, MNP Travel Medicine Nurse Practitioner Travel-Bug Vaccination Clinic- Adelaide	• Coordinate project logistics at The Travel-Bug Vaccination clinic in Adelaide and ensure that clinic doctors, nurses, and participants follow study protocols • Answer questions and assess participants as needed, including those who experience adverse reactions to Malarone, require further assessment • Report any significant adverse events to the Principal Investigator • Arrange post-travel clinical assessment of participants if they have been unwell during their trip
Dr Andrew Ebringer MBBS, CTH, MPH&TM, FRACGP Senior Medical Director, International SOS, Brisbane	• Assist with study design, development of research protocols, questionnaires and documents • Assist with interpretation of results and producing a report of study outcomes

Prof. Dennis Shanks (Director of the Australian Army Malaria Institute) has agreed to be an expert external reviewer for the study.

References

1.   Behrens RH, Taylor RB, Pryce DI, Low AS. Chemoprophylaxis compliance in travelers with malaria. J Travel Med 1998;5(2):92-4.

2.   Jute S, Toovey S. Knowledge, attitudes and practices of expatriates towards malaria chemoprophylaxis and personal protection measures on a mine in Mali. Travel Med Infect Dis 2007;5(1):40-3.

3.   Laver SM, Wetzels J, Behrens RH. Knowledge of malaria, risk perception, and compliance with prophylaxis and personal and environmental preventive measures in travelers exiting Zimbabwe from Harare and Victoria Falls International airport. J Travel Med 2001;8(6):298-303.

4.   Pistone T, Guibert P, Gay F, Malvy D, Ezzedine K, Receveur MC, et al. Malaria risk perception, knowledge and prophylaxis practices among travellers of African ethnicity living in Paris and visiting their country of origin in sub-Saharan Africa. Trans R Soc Trop Med Hyg 2007;101(10):990-5.

5.   Piyaphanee W, Wattanagoon Y, Silachamroon U, Mansanguan C, Wichianprasat P, Walker E. Knowledge, attitudes, and practices among foreign backpackers toward malaria risk in southeast Asia. J Travel Med 2009;16(2):101-6.

6.   Resseguier N, Machault V, Ollivier L, Orlandi-Pradines E, Texier G, Pradines B, et al. Determinants of compliance with malaria chemoprophylaxis among French soldiers during missions in inter-tropical Africa. Malaria J 2010;9:41.

7.   Ropers G, Du Ry van Beest Holle M, Wichmann O, Kappelmayer L, Stuben U, Schonfeld C, et al. Determinants of malaria prophylaxis among German travelers to Kenya, Senegal, and Thailand. J Travel Med 2008;15(3):162-71.

8.   Robinson P, Jenney AW, Tachado M, Yung A, Manitta J, Taylor K, et al. Imported malaria treated in Melbourne, Australia: epidemiology and clinical features in 246 patients. J Travel Med 2001;8(2):76-81.

9.   Shanks GD, Ragama BO, Oloo AJ. Time to reappearance of malaria parasites following various drug treatment regimens in a holoendemic area of western Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene 1999;93(3):304-5.

10.   Polhemus ME, Remich S, Ogutu B, Waitumbi J, Lievens M, Ballou WR, et al. Malaria treatment with atovaquone-proguanil in malaria-immune adults: implications for malaria intervention trials and for pre-exposure prophylaxis of malaria. Antimicrobial agents and chemotherapy 2008;52(4):1493-5.

11.   Edstein MD, Kotecka BM, Anderson KL, Pombo DJ, Kyle DE, Rieckmann KH, et al. Lengthy antimalarial activity of atovaquone in human plasma following atovaquone-proguanil administration. Antimicrobial agents and chemotherapy 2005;49(10):4421-2.

12.   Butcher GA, Sinden RE. Persistence of atovaquone in human sera following treatment: inhibition of Plasmodium falciparum development in vivo and in vitro. The American journal of tropical medicine and hygiene 2003;68(1):111-4.