JBI EVIDENCE SUMMARY

Malaria Prevention in Travelers: Drugs

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Question

What is the best available evidence regarding the safety and efficacy of drugs to prevent malaria in travelers?

Clinical Bottom Line

Malaria is a common acute parasitic disease in the tropics and sub-tropics. It is characterized by the invasion and destruction of red blood cells caused by one or more of the 4 species of *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.[1]Genetics, immune status, age of the infected person and the type of species influence the clinical presentation of malaria.[1] P *falciparum* species causes the severest form of malaria, which is characterized by spiking fevers, chills, headache, muscular aching and weakness, vomiting, cough, diarrhea and abdominal pain.[1] Serious complications from malaria caused by *P. falciparum* may cause organ failure such as acute renal failure, generalized convulsions and circulatory collapse followed by coma and death.[1] The prevalence of malaria caused by *P. falciparum* is greater than 90% in sub-Saharan Africa, greater than 50% in most East Asian countries and almost 100% in Haiti and Dominican Republic.[1] Travelers are defined as visitors from a malaria-free area to a malaria-endemic area.[1] It has been reported that more than 125 million international travelers each year visit around 100 countries where malaria is endemic and these result in around 25,000 cases annually.[1,2]

- A systematic review and meta-analysis summarized the safety and effectiveness of mefloquine for prophylaxis for malaria in travellers. Comparisons were made between mefloquine, doxycycline, atovaquone-proguanil, and no prophylactic medication.[1] (Level 1)
  - Mefloquine compared to no medication showed that mefloquine was associated with lower rates of malaria; however, the range of malarial episodes without prophylactic medication was 1% to 82% and from 0% to 13% in the mefloquine group.
  - Direct comparison of mefloquine to atovaquone-proguanil, and doxycycline revealed that all 3 medications are equally effective in preventing malaria in non-immune, short-term international travellers.
  - Mefloquine was more likely to be associated with abnormal dreams, insomnia, anxiety and depressed mood compared to atovaquone-proguanil and doxycycline.
  - Doxycycline was more likely to be associated with dyspepsia, photosensitivity, vomiting and vaginal thrush.
  - Discontinuation of the drug was more likely with mefloquine, or doxycycline compared to atovaquone-proguanil.
  - Malaria-endemic areas and antimalarial resistance patterns in the country of travel should guide

malarial prophylaxis choice as well as the individual traveller's importance to specific adverse events, pill burden dosing (daily compared to weekly or monthly), and cost.

- A systematic review appraised reports of death or parasuicide associated with mefloquine prophylaxis. The authors stated that the number of deaths that could be reliably attributed to the prophylactic use of mefloquine was much lower than previously reported; however, due to poor reporting a single summary estimate could not be made.[2] (Level 1)
- A systematic review was conducted to examine the safety, tolerability, and efficacy of repeated doses of dihydroartemisinin-piperaquine (DP) for prevention and treatment of malaria. The review found that monthly DP appears well tolerated and effective for intermittent preventive treatment. The review further suggested that additional data are required in pregnancy and to further explore the cardiac safety with monthly dosing.[3] (Level 1)
- A systematic review with meta-analysis was conducted to characterize prevalence, chemoprophylaxis and causes of deaths for severe imported malaria. The authors reported the pooled prevalence rates for the following outcomes: 1) severe malaria among patients with imported cases, 2) mortality among patients with severe imported malaria, 3) the use of antimalarial chemoprophylaxis in patients with severe imported malaria, and 4) the underlying causes of death in patients with severe imported malaria. The authors found that severe imported malaria occurs in approximately 12.5% of all imported malaria cases, reflecting a significant health concern for travelers to malaria-endemic regions. Despite the availability of preventive measures, only 9.7% of individuals with severe malaria had adequately used antimalarial prophylaxis, indicating low adherence to preventive practices. The mortality rate among those with severe imported malaria was 5.1%, with multi-organ failure identified as the leading cause of death. These findings showed the critical need for education on the proper use of antimalarial chemoprophylaxis and the importance of preventive strategies to reduce severe disease and mortality risks among travelers.[4] (Level 2)
- A systematic review and meta-analysis examined the effectiveness of 3-day pre-travel loading dose of tafenoquine alone in preventing malaria in short-term travellers (trips lasting ≤28 days). It was revealed that the loading dose of tafenoquine alone is equally effective as traditional schedules requiring weekly maintenance doses of tafenoquine or mefloquine. Furthermore, the loading dose of tafenoquine showed a favourable safety profile, with fewer adverse events compared to the maintenance-dose regimens, although the differences were not statistically significant. This pre-travel-only approach is especially advantageous for improving compliance, as it eliminates the need for travelers to continue taking medication during their trip. However, the study emphasizes the need for longer follow-up studies to confirm its effectiveness in preventing delayed malaria attacks post-travel.[5] (Level 1)
- A guideline from the Centers for Disease Control and Prevention (CDC) emphasize the importance of preventing malaria for travelers visiting areas where the disease is present. Key measures include taking antimalarial medications as prescribed before, during and after travel, tailored to the destination, type of travel and individual health conditions. Travelers should avoid mosquito bites by using EPA-registered repellents, wearing protective clothing, using permethrin-treated gear and ensuring accommodations are well-screened or air-conditioned. The guidelines highlight that acquired immunity to malaria can wane, making preventive measures critical for all travelers, including those returning to endemic regions. Awareness of counterfeit medications is stressed, and (as this recommendation is from the CDC) travelers are advised to source antimalarials in the U.S. If symptoms such as fever or flu-like illness occur during or after travel, immediate medical attention is recommended.[6](Level 5)
- A guideline from the World Health Organization (WHO) broadly addresses malaria prevention, including vector control and chemoprophylaxis. Recommendations on chemoprevention emphasize the use of drugs tailored to regional resistance patterns, which is a critical consideration for selecting prophylaxis for

international travelers. Non-immune travelers, categorized as individuals without prior exposure to malaria, are highlighted for their heightened susceptibility, with artemisinin-based combination therapies like artemether-lumefantrine recommended for treating uncomplicated malaria upon return from endemic regions.[7] (Level 5)

Characteristics Of The Evidence

This evidence summary is based on a structured search of the literature and selected evidence-based health care databases. The evidence in this summary comes from:

- A systematic review of 20 RCTs (11,470 participants); 35 cohort studies (198,493 participants); and 4 large retrospective analyses of health records (800,652 participants).[1]
- A systematic review of 17 publications which referred to death or parasuicide in users of mefloquine prophylaxis: 9 reports from spontaneous drug reporting databases, 4 case reports, 2 retrospective cohort studies, 1 review article, 1 RCT involving pregnant women.[2]
- A systematic review of 11 studies including 2 repeat treatment studies (o1ne in children younger than 5 years and 1 in pregnant women), and 9 intermittent preventive treatment trials (5 in children younger than 5 years, 1 in schoolchildren, 1 in adults, 2 in pregnant women).[3]
- A systematic review and meta-analysis of 52 studies (38 retrospective observational studies, 9 prospective observational studies, 4 cohort studies, and 1 cross-sectional study) involving 118,325 cases of imported malaria.[4]
- A systematic review and meta-analysis of 9 RCTs involving 1,714 participants.[5]
- Clinical practice guideline.[6,7]

Best Practice Recommendations

1. The decision to prescribe prophylactic antimalarial medication and which prophylactic medication to prescribe should be based on current malarial-endemic areas and the antimalarial resistance patterns. (Grade A)
2. It is recommended that clinicians when prescribing prophylactic antimalarial drugs in travelers consider the pill burden dosing, adverse effects and cost. (Grade A)

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6. CDC. Preventing Malaria While Traveling . Centers for Disease Control and Prevention; 2024.
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Archived Publications

1. JBI-ES-3539-2 (Published at 15 November 2021)
2. JBI-ES-3539-1 (Published at 14 April 2021)

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For details on the method for development see Munn Z, Lockwood C, Moola S. The development and use of evidence summaries for point of care information systems: A streamlined rapid review approach. Worldviews Evid Based Nurs. 2015;12(3):131-8.