Tammubua et al. JIMKI 2025; 12(1):60-78 - http://doi.org/10.53366/jimki.v12i1.849

Tinjauan Pustaka

Adverse Events of Atovaquone-Proguanil Compared with Mefloquine as Malaria Chemoprophylaxis Used by Visitors of Malaria Endemic Country : A Systematic Review and Meta Analysis

Jerroll Septian Tammubua[1], Made Kurnia Widiastuti Giri[1*], Made Ayu Rahayu Agastyane Rahmadewi[1], I Made Lingga Tresnadinata[1], Ni Putu Cempaka Pradnyadewi[1], Made Devina Febryanti[1]

[1]Faculty of Medicine, Ganesha University of Education, Buleleng
*Korespondensi: kurnia.widiastuti@undiksha.ac.id

Abstrak

Pendahuluan: *Kemoprofilaksis memegang peranan penting dalam mencegah malaria bagi pengunjung yang bepergian. Atovaquone-proguanil dan mefloquine merupakan dua kemoprofilaksis utama yang direkomendasikan oleh WHO dan CDC untuk pencegahan malaria. Keduanya efektif mencegah malaria, namun memiliki efek samping yang berbeda dan dapat memengaruhi penggunaannya.*
Metode: *Pencarian literatur komprehensif dilakukan di basis data ScienceDirect dan PubMed hingga 2025 tanpa batasan bahasa. Kriteria inklusi difokuskan pada studi yang menilai penggunaan atovaquone-proguanil dan mefloquine sebagai profilaksis malaria pada pengunjung ke negara endemik malaria. Risiko bias dievaluasi menggunakan The Newcastle-Ottawa Scale serta Cochrane "RoB".*
Pembahasan: *Sebanyak 10 studi diikutsertakan dan menghasilkan 15 kategori efek samping. Efek samping yang dilaporkan meliputi diare (RR 1,07; 95% CI; p = 0,72), sariawan (RR 2,88; 95% CI; p = 0,32), dispepsia/masalah lambung (RR 1,17; 95% CI; p = 0,80), nyeri abdomen (RR 1,41; 95% CI; p = 0,10), muntah & mual (RR 0,64; 95% CI; p = 0,16), insomnia (RR 0,25; 95% CI; p = 0,007), pusing/vertigo (RR 0,41; 95% CI; p = 0,02), tinitus (RR 0,70; 95% CI; p < 0,00001), kecemasan (RR 0,13; 95% CI; p < 0,00001), depresi (RR 0,20; 95% CI; p < 0,00001), mimpi buruk (RR 0,18; 95% CI; p = 0,001), sakit kepala (RR 0,47; 95% CI; p = 0,003), efek dermatologis (RR 0,89; 95% CI; p = 0,74), gangguan mata (RR 0,42; 95% CI; p = 0,02), serta analisis gabungan termasuk efek samping yang tidak disebutkan secara spesifik (RR 0,38; 95% CI; p = 0,33). Heterogenitas antar studi tergolong rendah hingga sedang.*
Simpulan: *Secara praktis, mefloquine sesuai digunakan untuk profilaksis jangka panjang dengan pemberian mingguan kecuali pada individu dengan gangguan psikiatri, sedangkan atovaquone-proguanil lebih disarankan untuk perjalanan jangka pendek dengan rekomendasi dikonsumsi bersama makanan.*

Kata Kunci: Atovakuon-Proguanil, Kejadian Merugikan, Malaria, Meflokuin, Wisatawan

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*Korespondensi: kurnia.widiastuti@undiksha.ac.id

Abstract

Introduction: Chemoprophylaxis plays a crucial role in preventing malaria among travellers to endemic regions. Atovaquone-proguanil and mefloquine are two of the main chemoprophylactic agents recommended by the WHO and CDC to prevent malaria. Both are effective in malaria prophylaxis but are associated with distinct adverse events that can influence their use in travellers.
Method: Literature search was conducted in ScienceDirect, and PubMed databases until 2025 without language constraints. Inclusion criteria focused on studies assessed the use of both atovaquone-proguanil and mefloquine as malaria prophylaxis in visitors to malaria-endemic countries. The risk of bias was evaluated using TheNewcastle-Ottawa Scale and Cochrane "RoB" tool.
Discussion: A total of 10 studies were included and resulting in 15 categories of adverse events. Reported events were diarrhea (RR 1.07; 95% CI; p = 0.72) mouth ulcers (RR 2.88; 95% CI; p = 0,32), indigestion (RR 1.17; 95% CI; p = 0.80), abdominal pain (RR 1.41; 95% CI; p = 0.10), vomiting & Nausea (RR 0.64; 95% CI; p = 0.16), insomnia (RR 0.25; 95% CI; p = 0.007), dizziness/vertigo (RR 0.41; 95% CI; p = 0.02), tinnitus (RR 0.70, 95% CI; p < 0.00001), anxiety (RR 0.13; 95% CI; p < 0.00001), depression (RR 0.20; 95% CI; p < 0.00001), nightmares (RR 0.18; 95% CI; p = 0.001), headaches (RR 0.47; 95% CI; p = 0.003), dermatological effects (RR 0.89; 95% CI; p = 0.74), eye disorders (RR 0.42; 95% CI; p = 0.02), and a pooled analysis along with events not specifically mentioned (RR 0.38; 95% CI; p = 0.33). Heterogeneity among included studies was generally low to moderate.
Conclusion: Practically, mefloquine is suitable for long-term weekly prophylaxis except for those with psychiatric disorders, whereas atovaquone-proguanil is preferred for short-term travel with the recommendation to administer it with food.
Keywords: Adverse Event, Atovaquone-Proguanil, Malaria, Mefloquine, Travelers

Tammubua et al. JIMKI 2025; 12(1):60-78 - http://doi.org/10.53366/jimki.v12i1.849

1. INTRODUCTION

Over the last few decades, rapid advancements in transportation infrastructure and increased global connectivity have significantly boosted international travel and tourism.[1] As global mobility increases, so does the risk of travellers being exposed to various infectious diseases, environmental hazards, and region-specific health threats.[2] Consequently, medical professionals, particularly those specializing in travel medicine, play a critical role in providing travellers with evidence-based guidance to ensure safe journeys. Travel medicine is a multidisciplinary field that focuses on the prevention, diagnosis, and management of health problems associated with international and domestic travel, including the prevention of transregional transmission of infectious diseases such as malaria.[3]

Malaria remains a major global health challenge, especially in tropical and subtropical regions. It is an acute and sometimes life-threatening infectious disease caused by protozoan parasites of the *Plasmodium* genus, which are transmitted to humans through the bite of infected female *Anopheles* mosquitoes.[4] There are five species known to infect humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. Knowlesi* with *P. falciparum* and *P. vivax* being the most clinically significant.[5,6]

The disease typically presents with non-specific symptoms such as fever, chills, headache, myalgia, and fatigue, but can progress to severe complications including cerebral malaria, acute respiratory distress, multi-organ failure, and death, particularly if not treated promptly.[7]

According to the World Health Organization (WHO), more than 249 million cases and hundreds of thousands of deaths from malaria will occur in 85 malaria-endemic countries in 2022, mostly in sub-Saharan Africa and Southeast Asia.[8] Visitors who visit malaria-endemic areas, especially those without prior exposure or immunity, are at significant risk. Furthermore, approximately 2,000 imported malaria cases are reported annually among international travellers, highlighting the risk for non-immune individuals visiting endemic regions.[9]

Chemoprophylaxis plays a crucial role for preventing malaria among travellers to endemic regions, particularly in non-immune individuals.[10] Atovaquone-proguanil and mefloquine are two of the main chemoprophylactic agents recommended by the WHO and CDC to prevent malaria.[9,11]

Both agents are effective in malaria prophylaxis but are associated with distinct adverse events that can influence tolerability and compliance [10]. Considering the adverse event is crucial in drug selection for malaria chemoprophylaxis, as it directly impacts tolerability, compliance, and the overall effectiveness of the medication[12]. The objective of this systematic review and meta-analysis is to compare the adverse events of atovaquone-proguanil and mefloquine in malaria prophylaxis, addressing the current gap in comparative evidence and providing clinicians with critical insights to guide decision-making for travellers to malaria-endemic regions.

2. METHOD

a) Study Design and Inclusion Criteria

This meta-analysis was reported according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[13] The literature search concentrating on randomized controlled trial (RCT), cross sectional studies, and both retrospective and prospective cohort studies that specifically analyse the use and associated adverse events of malaria prophylactic agents among visitors to malaria-endemic regions. All procedures including literature search, data extraction, and bias assessment were performed independently by two reviewers. Any disagreement or uncertainty regarding the eligibility of the study was carefully addressed through discussion and resolved by consulting a third reviewer.

The PICO (Patients, Intervention, Comparator and Outcomes) questions were used to develop inclusion criteria in this study (see Table 1). Inclusion criteria comprised several factors: studies assessed the use of both atovaquone-proguanil and mefloquine malaria prophylaxis in visitors to malaria-endemic areas. Visitors take atovaquone-proguanil or mefloquine for the purpose of preventing malaria, not for any other condition. Only studies with reported adverse events of each type of prophylaxis were included. Reported adverse events were required to be specific symptoms or diseases (such as diarrhea, nausea, dizziness) rather than grouped by body system, and studies reporting only aggregated or system-level adverse events were excluded.

Table 1. PICOS Question.

Question	Application of the criteria
P	Visitors to malaria-endemic countries with
I	Atovaquone-Proguanil as malaria chemoprophylaxis
C	Mefloquine as malaria chemoprophylaxis
O	Adverse event
S	Randomized Controlled Trial, Cohort Study, Cross Sectional

b) Literature Search and Selection

A systematic literature search was performed using the ScienceDirect, and PubMed databases, covering publications up to May 2025. Language restrictions were not applied during the search process. The search strategy utilized specific keywords, such as (((((Malaria) AND (Travel)) AND ((Prophylaxis) OR (Drugs))) AND (Atovaquone-Proguanil)) AND (Mefloquine)) AND ((Adverse Events) OR (Symptoms)). In addition, a meticulous manual review of the references in the selected studies was conducted to confirm the comprehensiveness of the search and to identify any supplementary data. From the initial set of 1,573 retrieved articles, ultimately, 10 studies were suitable for inclusion in the quantitative analysis, as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Fig. 1). In line with PRISMA guidelines, grey literature and unpublished studies were not included in this review.[13]

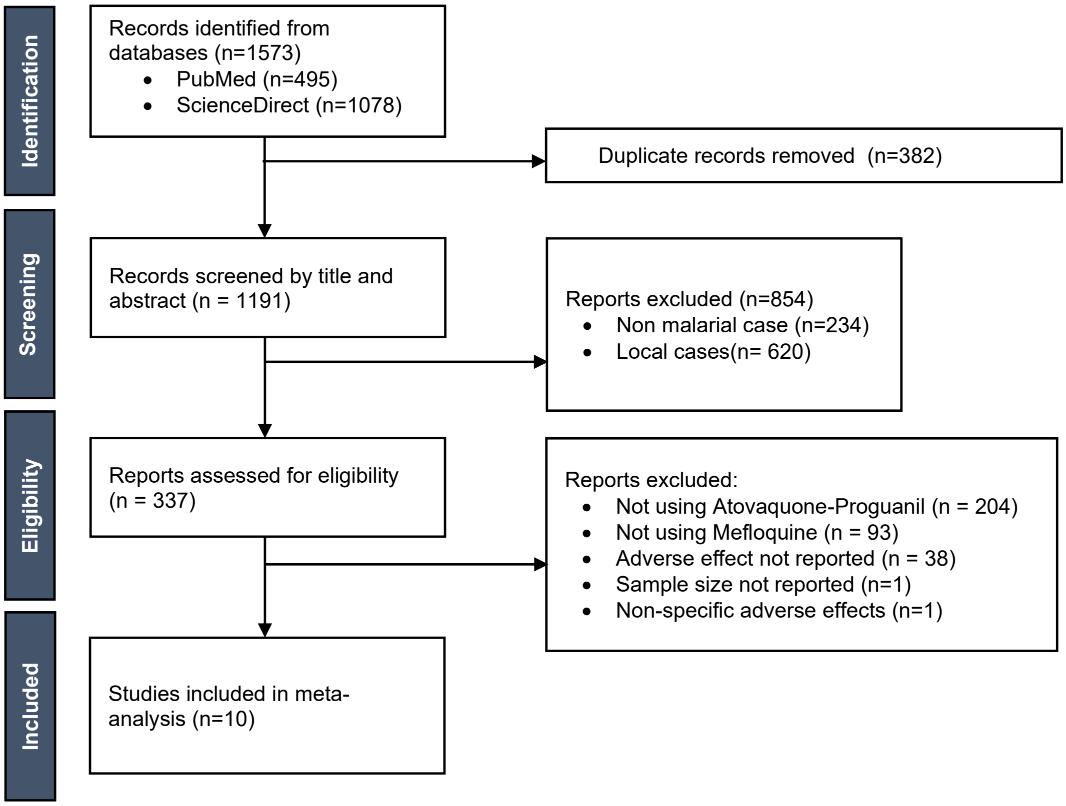

Figure 1. PRISMA Flowchart.[13]

c) Quality Assessment of Included Studies

The risk of bias in the included studies was independently evaluated by two authors. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess cohort and cross-sectional studies. The scale includes three sections, “Selection”, “Comparability”, and “Outcome”, each consisting of three to four concise questions.

For the RCT, the authors used Cochrane Collaboration’s "Risk of Bias" tool. The RCT study was categorized as having a “low,” “high,” or “unclear” risk of various types of bias including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The quality assessment for each study is presented in figure 2.

NOS for Cohort & Cross-Sectional Studies

Study	Selection	Comparability	Outcome	Score
Reinsberg et al, 2023[26]	★★★★	★	★★	7
Eick-Cost et al. 2017[27]	★★★★	★★	★★★	9
Cunningham et al. 2014[25]	★★	★	★★	5
Schneider et al. 2014[24]	★★★	★★	★★	7
Tuck et al. 2016[23]	★★★	★	★★	6
Landman et al. 2015[22]	★★★	★	★★	6
Andersson et al. 2008[21]	★★★	★	★★	6
Laverone et al. 2006[19]	★★	★	★★	5
Stoney et al. 2016[18]	★★★	★	★★	6

Cochrane Collaboration's "Risk of Bias" tool for RCT Studies

Figure 2. Risk of bias summary. Red, high risk of bias; blank space unclear risk of bias; green, low risk of bias.

d) Data Extraction

Data extraction was conducted using a standardized data extraction form to ensure consistency across studies. Extracted variables comprised the destination region, total study population, percentage of female participants, age range, duration of prophylaxis use or travel period, type of malaria prophylaxis administered, and specific adverse events reported. Missing or unclear data were addressed by contacting study authors whenever possible, if data remained unobtainable, the information will be excluded from the analysis. This approach was implemented to maintain the accuracy and reliability of the extracted dataset.

e) Data Synthesis and Analysis

The findings of the included studies were systematically organized and summarized for the qualitative synthesis. Outcomes were pooled, separately by symptom category, and were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) using the DerSimonian and Laird random-effects model to account for inter-study variability. OR was chosen instead of RR because odds ratios are more statistically stable, especially when event rates are low or when studies report zero events. This approach is consistent with recommendations from the Cochrane Handbook for meta-analyses of dichotomous outcomes.[14]

Using the I^2 statistic, we assessed the included studies for heterogeneity, with an I^2 of 0–25%, 25–50%, 50–75%, and 75–100% respectively indicating low, moderate, substantial, and considerable heterogeneity. [15] Publication bias was evaluated through visual inspection of funnel plots (Fig. 3). Forest plots were used to display the results. A significance level was set at $p < 0.05$. All analyses were conducted in Review Manager version 5.4.1.

Tammubua et al. JIMKI 2025; 12(1):60-78 - http://doi.org/10.53366/jimki.v12i1.849

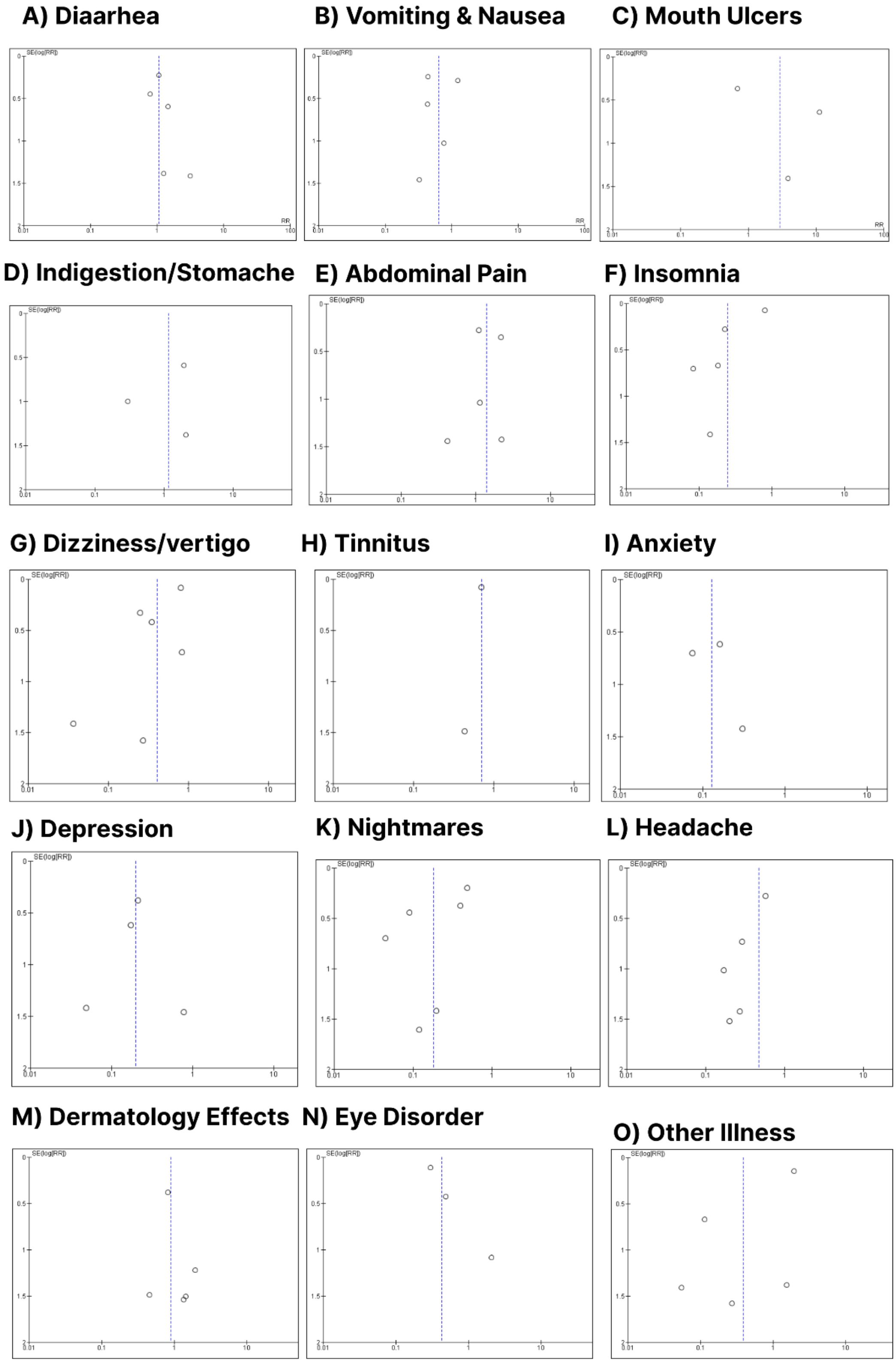

Figure 3. Funell plot from the adverse event of atovaquone-proguanil versus mefloquine usage.

Tammubua et al. JIMKI 2025; 12(1):60-78 - http://doi.org/10.53366/jimki.v12i1.849

3. RESULT

a) Study Selection

The literature search process from selected databases yielded 1,573 studies. A total of 382 duplicate studies were removed. Based on the abstract and title screening, 234 studies were not based on malaria treatment, and 620 studies were located on the patient local region and were not in travel context. The rest of studies underwent the full text screening and resulted in 10 studies were eligible to be quantitatively analysed in this review. The details of the study selection process were displayed in figure 1.

b) Baseline Characteristics

The characteristics of the 10 studies[16–25] included in this review are presented in Table 2. The studies were conducted between 1999 and 2018. Regarding study designs, this meta-analysis consist of one cross-sectional study[24], one randomized controlled trial[18], and eight cohort studies[16,17,19–23,25]. Geographically, most of the studies (50%) were conducted in Africa, and (20%) were conducted in South America. Additionally, studies also conducted in India (10%) and Haiti (10%). A Total of 4 studies[17,22,23,25] did not report the specific region of the study as it only mentioned the region as "malaria endemic region". The number of individuals involved across studies varied, from 115 participants to over 367,000 per study, showing the scale differences between studies. The population consisted of civilian travelers, office employees, Peace Corps volunteers, and military personnel from various countries such as the USA, UK, and Sweden. The majority of studies (80%) disaggregated the age of the individual data by age groups, although one study explicitly included individuals aged 4 to 80 years. The duration of travel ranged from 4 to 65 days where reported, with several studies not specifying visit duration. In addition to mefloquine, and atovaquone-proguanil, these studies also examined groups with other prophylactic consumption, such as doxycycline, and chloroquine, although this study will only focus on the use of mefloquine and atovaquone-proguanil.

c) Adverse Events Reported

A total of 15 categories of adverse events were included in a meta-analysis comparing atovaquone-proguanil (AP) and mefloquine (MQ) as malaria prophylaxis for visitors to malaria endemic areas. The results showed that in several categories of adverse events there were significant differences between the side effects of the two drugs (Fig. 4). Reported gastrointestinal adverse events showed variable results. There was no significant difference in the risk of diarrhea between the two drugs (RR 1.07; 95% CI 0.74–1.55), while mouth ulcers (RR 2.88; 95% CI 0.34–24.40), indigestion (RR 1.17; 95% CI 0.36–3.94), and abdominal pain (RR 1.41; 95% CI 0.93–2.12)

Tammubua et al. JIMKI 2025; 12(1):60-78 - http://doi.org/10.53366/jimki.v12i1.849

Table 2. Baseline Characteristics.

Author	Study Design	Study Period	Sample included in the study	Type of individuals	L	P	Age Range	Visiting Time Range (Day)	Destination Region	Types of Prophylaxis
Reinsberg et al, 2023[24]	Cross-sectional	June 2017 to December 2018	448	Travelers	228	220	Any age[a]	14-30	Africa, South American	1. Mefloquine 2. Atovaquone-proguanil 3. Doxycycline
Eick-Cost et al. 2017[25]	Cohort	1 January 2008 to 30 June 2013	367840	USA Military Service Members	323363	44477	Any age[a]	NA	Unspecified endemic region[b]	1. Mefloquine 2. Atovaquone-proguanil 3. Doxycycline
Cunningham et al. 2014[23]	Cross-sectional	July 2012	327	Office employees	0	327	Any age[a]	NA	Unspecified endemic region[b]	1. Mefloquine 2. Atovaquone-proguanil 3. Doxycycline 4. Chloroquine
Schneider et al. 2014[22]	Cohort	January 1, 2001 to October 1, 2009	652	Travelers	285	367	Any age[a]	NA	Unspecified endemic region[b]	1. Mefloquine 2. Doxycycline 3. Atovaquone-proguanil 4. Chloroquine
Tuck et al. 2016[21]	Cohort	15 to 22 February 2015	115	UK Military	NA	NA	Any age[a]	NA	Sierra Leone	1. Mefloquine 2. Atovaquone-proguanil 3. Doxycycline
Landman et al. 2015[20]	Cohort	19 August to 30 September 2013	781	Peace Corps Volunteers	255	526 (68%)	Any age[a]	NA	African region except Ethiopia, Kenya, Tanzania, Namibia, Botswana, South Africa	1. Mefloquine 2. Atovaquone-proguanil 3. Doxycycline
Andersson et al. 2008[19]	Cohort	March 2004 to November 2006	609	Swedish Military	580	29	Any age[a]	NA	Liberia	1. Mefloquine 2. Atovaquone-proguanil
Overbosch et al, 2001[18]	Randomized controlled trial	April to October 1999	976	Travelers	542	434	4-80	NA	Africa and South American	1. Mefloquine 2. Atovaquone-proguanil
Laverone et al. 2006[17]	Cohort	1 January 2003 to 31 December 2004	1176	Travelers	573	603	Any age[a]	NA	Unspecified endemic region[b]	1. Mefloquine 2. Atovaquone-proguanil 3. Chloroquine
Stoney et al. 2016[16]	Cohort	2009 to 2011	370	Travelers	104	266	20-82	4-65	India, Tanzania, Kenya, South Africa, and Haiti	1. Mefloquine 2. Doxycycline 3. Atovaquone-proguanil 4. Chloroquine

USA, United States of America; UK, United Kingdom; NA, Not Available.

[a] Data were reported by age groups, without exact range

[b] The article only mentions countries where malaria is endemic without specifically mentioning which region.

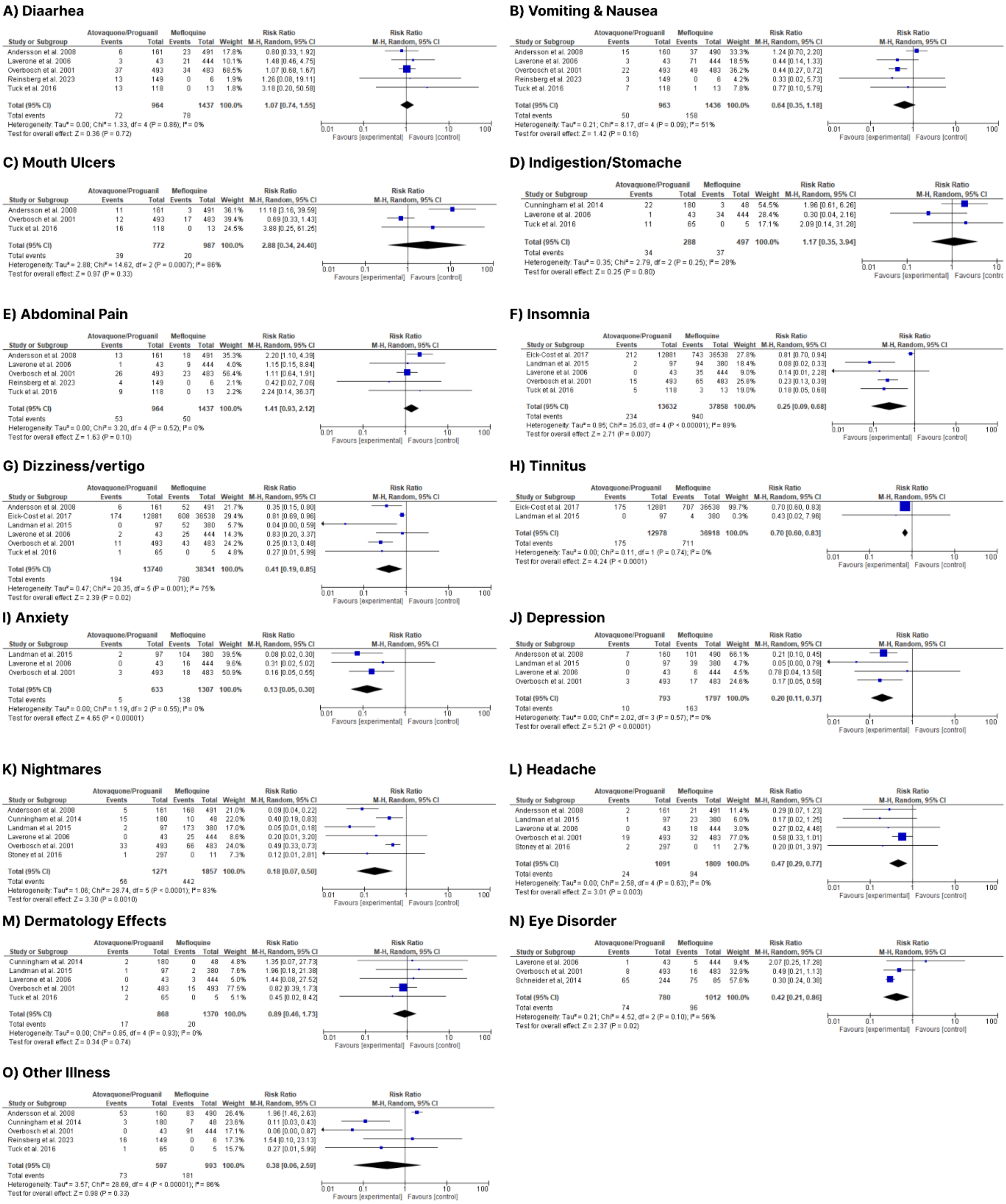

Figure 4. Forest plot showing the adverse event of atovaquone-proguanil versus mefloquine usage. Abbreviations: CI, confidence interval. Symbols: blue square, effect estimate; black diamond, pooled effect estimate.

were more frequently reported with atovaquone-proguanil, although these differences did not reach statistical significance. In contrast, vomiting and nausea were more often reported among mefloquine users, but again without statistical significance (RR 0.64; 95% CI 0.35–1.18).

Atovaquone-proguanil has been reported to have fewer neuropsychiatric adverse events than mefloquine. The agent was associated with a significantly lower risk of insomnia (RR 0.25; 95% CI 0.09–0.68), dizziness or vertigo (RR 0.41; 95% CI 0.19–0.85), tinnitus (RR 0.70; 95% CI 0.60–0.83), anxiety (RR 0.13; 95% CI 0.05–0.30), depression (RR 0.20; 95% CI 0.11–0.37), nightmares (RR 0.18; 95% CI 0.07–0.50), and headaches (RR 0.47; 95% CI 0.29–0.77).

For dermatological and sensory adverse effects, no significant differences were found in the incidence of dermatological reactions (RR 0.89; 95% CI 0.46–1.73) or eye disorders (RR 0.42; 95% CI 0.21–0.86). Other events such as malaise, fever, and muscle pain, which were each reported in only one study [17,19,21], were pooled into an "other illnesses" category along with adverse effects that were not specifically reported. This grouping was necessary to enable quantitative synthesis of infrequently observed outcomes. The pooled analysis showed a non-significant trend toward lower risk in the atovaquone-proguanil group (RR 0.38; 95% CI: 0.06–2.59; p = 0.33; Z = 0.98)

Heterogeneity among included studies was generally low to moderate for most outcomes, except for few adverse effects (dizziness/vertigo, anxiety, and other illness) where heterogeneity exceeded 50%. A random-effects model was applied throughout the analysis.

4. DISCUSSION

This systematic review and meta-analysis synthesized data from 10 eligible studies involving 373,294 participants across different countries. The findings showed that atovaquone-proguanil was more frequently associated with gastrointestinal adverse events, whereas mefloquine was more often linked to neuropsychiatric and visual adverse events. These differences can be explained by their distinct pharmacological mechanisms. Atovaquone-proguanil acts synergistically to prevent malaria by targeting both the liver and blood stages of the *Plasmodium* life cycle by inhibiting bc1 complex, which is a key component of the mitochondrial electron transport chain.[26] Atovaquone-proguanil (250 mg/100 mg) is recommended once daily, starting one day before travel until seven days after leaving the endemic area.[9] Atovaquone-proguanil mainly used in short traveling duration of three weeks or less.[27,28] On the other hand, mefloquine acts by inhibiting heme detoxification in the

Tammubua et al. JIMKI 2025; 12(1):60-78 - http://doi.org/10.53366/jimki.v12i1.849

blood stage of the *Plasmodium* life cycle.[29] The 250 mg regimen once a week was recommended for prophylaxis use from two weeks prior to departure until four week after leaving the endemic area.[9] Heme detoxification mechanism by mefloquine has been linked to neuropsychiatric side effects due to its interactions with the central nervous system.

A) Neuropsychiatric Adverse Events

Neuropsychiatric adverse events (Fig. 4F,4H,4I,4J,4K,4L), such as sleep disturbances, intense nightmares, anxiety, and even mild to moderate depressive symptoms, were reported by respondents with the majority being mefloquine users. A review study in 2017, reported the mechanism of mefloquine involves several critical biochemical pathways that contribute to central nervous system.[30] Mefloquine acts as a non-competitive inhibitor of acetylcholinesterase (AChE), the enzyme responsible for hydrolyzing acetylcholine (ACh) in the synaptic cleft.[31] Inhibition of AChE leads to the accumulation of ACh, resulting in overstimulation of both muscarinic (mAChR) and nicotinic (nAChR) receptors.[32,33]

The overstimulation of cholinergic receptors triggers intracellular signaling cascades, including activation of phospholipase C and subsequent inositol trisphosphate (IP3)-mediated calcium (Ca^{2+}) release from the endoplasmic reticulum. The elevated intracellular Ca^{2+} levels contribute to excitotoxicity, dendritic damage, and potentially neuronal apoptosis.[34,35]

Additionally, mefloquine has been shown to inhibit the dopamine transporter (DAT), a key protein involved in dopamine reuptake from the synaptic cleft.[30] This inhibition may lead to increased synaptic dopamine levels, potentially altering neuropsychiatric symptoms such as psychosis.[30,36] Clinically, such adverse events are particularly concerning for travelers, as they may impair adherence to prophylaxis and compromise safety in remote or resource-limited settings.

In contrast, atovaquone-proguanil appears to cause only mild neuropsychiatric effects related to limited CNS penetration and subtle mitochondrial or folate metabolism disturbances which explains its overall better tolerability.[37] This finding aligns with CDC caution against mefloquine use in individuals with a history of psychiatric illness.[9]

B) Gastrointestinal Adverse Events

Gastrointestinal adverse events were reported by respondents with various result between the two groups of prophylaxis. Adverse event such as diarrhea, mouth ulcer, indigestion and abdominal pain were reported to occur more frequently in the atovaquone-proguanil groups (Fig. 4A,4C,4D,4E). Atovaquone-proguanil are more difficult to absorb in the digestive tract than mefloquine because their bioavailability is affected by fatty foods, so if consumed without food they can irritate the stomach and intestines and resulting in various adverse event.[38,39] However, most gastrointestinal adverse events associated with atovaquone-proguanil are clinically mild and self-limiting, rarely leading to discontinuation

Both prophylaxis, mefloquine and atovaquone-proguanil (specifically the proguanil) were reported to have antagonize homomeric 5-HT_3 receptor responses, which plays a role in regulating nausea and vomiting.[40,41] Based on a meta-analysis, it was found that the two prophylaxis group of user were experienced nausea and vomiting, but the mefloquine group experience it more often (Fig. 4B). This suggests that the nausea and vomiting events of mefloquine are not solely due to interactions with 5-HT_3, but are more related to mefloquine's activity in the central nervous system, including its affinity for 5-HT_2A, 5-HT_2C, dopaminergic, and $GABA_A$ receptors that can trigger perception of nausea through the gut-brain axis.[41,42]

C) Dermatology Adverse Event

Pruritus was reported as the main dermatology symptoms of the two prophylaxis users. A similar review of antimalarial medications have been reported to cause non-aquagenic pruritus in over 75% of patients.[43] n the present meta-analysis, however, there was no statistically significant difference in the incidence of pruritus between the two prophylaxis groups, indicating that this adverse event is likely a general class effect rather than drug-specific. There is no definite reason why pruritus occurs with the use of malaria prophylaxis or the difference between the two groups of prophylaxis, but it is thought to be due to inflammatory effects. Prophylaxis that enters the body acts as a hapten, namely a small molecule that binds to body proteins and is recognized as "foreign" by the immune system and produces a local inflammatory response that can occur on the skin, causing pruritus.[43,44]

D) Eye Disorder Event

The results of a meta-analysis reported that most of the visual disorder such as glaucoma and cataract were experienced by mefloquine users (Fig. 4N). Mefloquine has a high lipophilic property that allows it to penetrate the blood-brain barrier and accumulate in brain tissue, including the visual center in the brain.[45,46] This neurotoxicity can affect optic nerve function and cause visual impairment including decreased visual acuity and disrupt intraocular pressure (IOP) regulation, thereby increasing the risk of glaucoma.[46,47] It has also been reported that mefloquine can increase oxidative stress in the eye lens which triggers changes in the structure of the lens protein, thereby accelerating the formation of cataracts.[46] Clinically, these visual symptoms are important because they may resemble or be misinterpreted as malaria-related complications, such as cerebral malaria, thereby complicating accurate diagnosis and appropriate management in endemic settings.

E) Other Adverse Events

Malaise, fever, and muscle pain along with other nonspecific symptoms have been reported in small numbers. These symptoms appear to be related to the body's ability to tolerate malaria prophylaxis.[9,48] These adverse events are generally mild and harmless, but they should still be monitored to distinguish them from symptoms of malaria infection itself or other conditions. Clinically, this distinction is critical in real-world settings, as misattributing early malaria symptoms to drug-related effects could delay timely diagnosis and appropriate treatment.

F) Clinical Implication

The findings of this review have direct implications for malaria prophylaxis selection in travelers. Atovaquone-proguanil, while more often associated with mild gastrointestinal effects, is generally well tolerated and may be preferable for short-term travelers, particularly those without prior immunity. Mefloquine, given its higher risk of neuropsychiatric and visual adverse effects, should be avoided in individuals with a history of psychiatric illness, seizure disorders, or other neurological conditions.

Based on the result, this review also has limitations, including heterogeneity in study designs, populations, and adverse event reporting, often without standardized diagnostic criteria. Most data also come from short-term travelers, with limited evidence in long-term travelers and vulnerable groups.

The heterogeneity (I^2) across studies in this review also had variability between each other, with some pooled analyses showing low values and others high. Populations, study designs, and adverse event reporting methods varied, leading to inconsistent estimates. Rare events (such as visual or dermatological symptoms) contributed to higher heterogeneity, while more common outcomes such as gastrointestinal symptoms showed lower variability. This highlights the need for standardized definitions and reporting to improve comparability across studies.

Future studies should employ standardized adverse event definitions, larger cohorts, and longer follow-up, while also comparing other prophylactic agents to support safer, more tailored malaria prevention strategies.

.

5. CONCLUSION

This meta-analysis compared adverse events of atovaquone-proguanil and mefloquine used as malaria prophylaxis for visitors to malaria-endemic countries. Overall,

mefloquine was more frequently associated with neuropsychiatric and visual adverse effects, consistent with its strong central nervous system activity. In contrast, atovaquone-proguanil is more commonly linked to gastrointestinal issues, especially when taken without food, but generally causes fewer severe neuropsychiatric symptoms. Both drugs can cause mild dermatological reactions like pruritus and other nonspecific symptoms such as malaise and muscle pain.
Clinically, these findings suggest that mefloquine should be avoided in individuals with a history of psychiatric or neurological disorders, while atovaquone-proguanil may be a better-tolerated option for short-term non-immune travelers. Future research should include high-quality randomized controlled trials, standardized definitions of adverse events, and comparisons with other prophylactic agents such as primaquine and chloroquine to strengthen the evidence base and guide safer malaria prevention strategies.

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