

Mefloquine Prophylaxis Results and Evaluation of adVerse Effects iN Peacekeepers Travelling to South Sudan: Mefloquine PREVENT–SS Study

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Abstract

Background

Malaria is endemic to South Sudan, and UN peacekeepers deployed in the country from member nations are at significant risk. Most of the member nations prescribe chemoprophylaxis to their troops. The present study focuses on the effects of Mefloquine prophylaxis on Indian peacekeepers deployed in South Sudan.

Methods

In this retrospective cohort study, we collected data on Indian peacekeepers using a self-reported questionnaire during the time of their de-induction. The study analysed the efficacy of Mefloquine, the incidence of breakthrough infections, adverse effects, and common reasons for discontinuation of the drug.

Results

A total of 534 Indian Peacekeepers participated in the study. Out of 534, 85.6% (n = 457) were compliant with the chemoprophylaxis, while 14.4% (n = 77) reported non-compliance. The relative risk of developing malaria in non-compliant individuals was approximately 5-fold (RR 5.28, 95% CI 2.81–9.90, $p < 0.0001$). The protective efficacy of mefloquine chemoprophylaxis was 81.2% (95% CI: 64.5–89.9%). A total of 11.1% (n = 55) of participants reported adverse effects. The most reported adverse effects were sleep disturbances and neuropsychiatric manifestations, which were reported by 9.4% (n = 47) and 6.2% (n = 31) of the participants, respectively. The most reported reason for non-compliance was fear of experienced or anticipated adverse effects, reported by 29.6% (n = 37).

Conclusion

In the present study, a strong association was demonstrated between adherence to weekly Mefloquine chemoprophylaxis and a significant reduction in malaria incidence. Drug-related adverse effects (experienced as well as anticipated) were the most important reported barriers to compliance. These findings reinforce the effectiveness of Mefloquine when taken consistently and highlight that adverse effects are the most important determinant of non-compliance. It underscores the need for pre-induction counselling, preventive behavioural modifications in addition to chemoprophylaxis, and promoting use of alternative regimens among individuals who have experienced troubling adverse effects to Mefloquine.

Background

Malaria is endemic in South Sudan, with perennial transmission and seasonal peaks during the wet season. In 2024, the WHO (World Health Organization) reported a malaria incidence of 403 per 1,000 in South Sudan. [1] There is a high case burden on already limited medical facilities in the country, which leads to high malaria-related mortality and morbidity. Travellers, especially from non-endemic regions, to South Sudan are at increased risk of contracting complicated malaria. South Sudan, being the youngest country in the world, struggles with regional political instability. The United Nations employs military personnel from member nations for peacekeeping operations in various parts of the country. These individuals spend around six months to a year in areas with high transmission of malaria. These peacekeepers follow country-specific chemoprophylaxis guidelines and personal protective measures, as antimalarial prophylaxis is known to reduce malaria incidence among travellers. [2, 3]

Mefloquine is the WHO-recommended drug for long-term chemoprophylaxis. [4] Most member nations follow WHO guidelines and recommend weekly Mefloquine for chemoprophylaxis to their soldiers. Mefloquine, a quinine derivative, has high reported efficacy in preventing malaria infection. It acts during the erythrocytic phase of the infection and blocks parasite replication. It

can be safely prescribed in G6PD-deficient individuals. The weekly dosage is less cumbersome compared to the daily dosage of alternative chemoprophylaxis drugs like Doxycycline and Atovaquone/Proguanil. The drug, however, is associated with multiple adverse effects, including neuropsychiatric manifestations, owing to its effect on serotonin receptors. The notorious adverse effects lead to frequent drug discontinuations. The peacekeepers function in high-stress environments, and the neuropsychiatric adverse effects can further compound the psychological stress.

Studies on the efficacy and adverse effects of Mefloquine prophylaxis in military cohorts have not been reported frequently from South Sudan. An extensive literature review revealed a few studies on the efficacy of Mefloquine from Southeast Asia and Eastern Africa. The earliest papers include a study by Ohrt et al. on Indonesian soldiers in 1997 and a study by Wyler et al. on European travellers in 1993. [2, 3]. Both of these studies established the high efficacy of Mefloquine in preventing Malaria among travellers. Similarly, a Cochrane review conducted by Tickell-Painter et al. in 2017 confirmed the high efficacy of Mefloquine prophylaxis and found no significant differences in efficacy between Mefloquine and other drugs such as Doxycycline and Atovaquone/Proguanil. [5]. However, these studies did not explore the reasons for non-compliance or the rates of various adverse effects, including the psychological effects of Mefloquine, especially among peacekeepers operating in high-stress environments. The present study aims to address this lacuna. The study cohort consists of Indian peacekeepers affiliated with various United Nations agencies who had travelled to South Sudan. These peacekeepers were prescribed Mefloquine in accordance with their national policy on malaria chemoprophylaxis. The study focuses on compliance rates, reasons for drug discontinuation, and adverse effects, while evaluating the overall efficacy of chemoprophylaxis. Thus, the study strives to help formulate practical preventive guidelines for future deployments of peacekeepers in malaria-affected regions.

Methods

We conducted a retrospective cohort study using a self-reported questionnaire to collect data from Indian military personnel deployed in South Sudan between 1 March 2025 and 31 August 2026. The data were collected at the time of de-induction, and all these soldiers had spent at least six months in the mission area. All these soldiers had undergone rigorous medical screening before their deployment and were free of any comorbidities. A total of 534 participants took part in this study. Their responses regarding compliance with Mefloquine and adverse effects were recorded. An individual who had never missed a dose or had intermittently missed only one dose at a time and had subsequently restarted the weekly dose was considered compliant with the prophylaxis. A person who had missed two or more consecutive doses was considered non-compliant.

When a participant reported malaria infection during the period of deployment in the questionnaire, the diagnosis was confirmed using the patient database. Only individuals with a record of confirmed infection based on a rapid diagnostic test and a peripheral smear were considered positive. The rates of breakthrough infection in compliant individuals were compared with those in non-compliant individuals. Attack rates and proportions were calculated with Wilson 95% confidence intervals. The associations between the dichotomised groups and categorical outcomes were tested using the chi-square test of independence (Fisher's exact test was used when expected cell counts were small). Protective efficacy was calculated as $1 - \text{relative risk}$ (compliant vs non-compliant reference group), with the 95% CI derived from the standard error of the log of the relative risk.

For any individual who had developed malaria and was admitted to the hospital, their records were retrospectively analysed. Their hospital stay duration and incidence of malaria-related complications were noted. The incidence of complicated malaria infection between the compliant and non-compliant individuals was also compared.

Results

Cohort overview:

The cohort consisted of 534 Indian Peacekeepers deployed in South Sudan for a minimum of 6 months to a maximum of 18 months. Of the 534 individuals, 97.3% (n = 520) were males, and 2.7% (n = 14) were females. The mean age of the cohort was

35.6 ± 7.2 years. All the individuals underwent rigorous pre-induction medical screening and were free of any comorbidities/chronic illness/psychiatric illness. These individuals were not on any long-term medications. Mefloquine was the sole chemoprophylactic agent prescribed to the cohort.

Compliance rates and outcomes:

The cohort had a compliance rate of 85.6% (n = 457), of whom 76.4% (n = 408) of peacekeepers reported never missing a weekly dose, and an additional 9.2% (n = 49) reported occasionally missing a single dose. A total of 14.4% (n = 77) reported non-compliance with chemoprophylaxis. A total of 3.9% (n = 18) of individuals developed malaria infection in the compliant group, compared with 20.8% (n = 16) in the non-compliant group. The relative risk of developing malaria infection in non-compliant individuals was approximately 5-fold (RR 5.28, 95% CI 2.81–9.90, p < 0.0001). The protective efficacy of mefloquine chemoprophylaxis was 81.2% (95% CI: 64.5–89.9%). Mefloquine, when taken as prescribed, prevented roughly 4 in 5 malaria cases that would otherwise have occurred in the cohort. Out of 34 cases of confirmed Malaria infection, 32.4% (n = 11) required hospital admission. A total of 6 individuals remained admitted for more than 7 days, and 8 of the total 11 hospitalised had a complicated malaria infection. The hospitalisation rates in non-compliant vs compliant individuals were 43.8% (95% CI: 23.1–66.8%) and 22.2% (95% CI: 9–45.2%), respectively. The differences in admission rates between the two groups were not significant (p = 0.27). The rate of complicated malaria infections in the non-compliant group was 31.2% (n = 5) compared with 16.7% (n = 3) in the compliant group. The differences between the groups were not statistically significant (p = 0.43).

Adverse effects of Chemoprophylaxis:

A total of 11.1% (n = 55) of 495 respondents who had taken the chemoprophylaxis at least once (Excluding 39 individuals who had never taken a dose) reported adverse effects. Figure 1 summarises the reported adverse effects. Sleep disturbances were the most reported adverse effect. A total of 9.4% (n = 47) of individuals reported sleep-related adverse effects, of which 5.0% (n = 25) had difficulty with sleep induction and maintenance, while 4.4% (n = 22) had vivid nightmares leading to frequent awakenings. The most concerning adverse effects were neuropsychiatric manifestations, which were reported by 6.4% (n = 32) of the respondents. These symptoms included headache, anxiety, restlessness, depression, suicidal ideation, tremors, loss of balance and memory loss. One worrisome neurological symptom was transient visual disturbance, which was reported by 1.8% (n = 9) of individuals. These symptoms included blurring of vision and visual field defects. Gastrointestinal symptoms were reported by 0.8% (n = 4) of individuals. Adverse effects were reported much more frequently in the non-compliant group compared to the compliant group (55.2% vs 7.4%, respectively). The difference was statistically significant (p < 0.0001).

Reasons for non-compliance:

A total of 126 respondents reported reasons for missing doses. These included individuals in the non-compliant group and those in the compliant group who occasionally missed weekly doses. The most reported reason for non-compliance among these individuals was drug-related adverse effects, which was mentioned by 29.6% (n = 37). The other common reasons reported were forgetfulness (15.0%) and reliance on non-pharmacological measures (15.0%). Reasons for non-compliance have been listed in Table 1. As evident, adverse-effect-related concerns – both experienced (n = 37) and anticipated (n = 14) – together account for roughly 40% of all reasons given, making them the single largest driver of non-adherence, ahead of logistical factors (forgetfulness, non-availability) and risk-perception factors (belief that non-pharmacological measures suffice, low-season discontinuation, etc).

Table 1
Reasons for non-compliance to chemoprophylaxis

Stated reason	Respondents
Drug-related side effect	37
Spray/ointments/nets deemed sufficient	19
Forgetfulness	19
Lack of trust in medicine	15
Fear of medication or side effects	14
Discontinued in low malaria season	12
Non-availability of drug	8

Discussion

The present study cohort achieved high efficacy with Mefloquine chemoprophylaxis in preventing malaria infection. Given the participants' military backgrounds, the compliance rate was high (85.6%). Their commanders ensured high compliance, as the entire contingent would consume the drug as a routine on the same day of the week (Tuesday). The records of all individuals were religiously maintained. High compliance with chemoprophylaxis led to a much lower malaria incidence in the cohort than the national average in South Sudan. Evidence from previously conducted studies among military and peacekeeping cohorts provides context for these findings. Most studies on malaria chemoprophylaxis in military personnel report high rates of compliance and efficacy. One such study by Hopperus Buma et al. studied 2,289 Dutch marines deployed to Cambodia during 1992–1993 and demonstrated substantial protection in a region with very high malaria transmission. [6] The study demonstrated high Mefloquine compliance (86.3%) in its military cohort and reported only 31 malaria cases during the deployment period. Similarly, Peragallo et al. reported a high compliance with mefloquine (95.7%) in a 1999 study among Italian soldiers deployed to Mozambique.[7] A study conducted among Australian Defence Force personnel deployed to East Timor for peacekeeping operations demonstrated good Mefloquine tolerance (93.5%). However, Mefloquine-related adverse effects were reported at a much higher rate (57%) in their study than in the present study (11.1%). [8] The operational environments of these cohorts were similar to those in our study, and the findings were consistent, as evidenced by high compliance and significant risk reduction among compliant individuals.

The largest study on civilian travellers assessing the efficacy of chemoprophylaxis was conducted by Stefan et al. in 1993, who reported 91% efficacy for Mefloquine in a study of 145003 European travellers returning from Africa. [9]. The most important factor for favourable outcomes was strong adherence to the prophylaxis.

Most studies concluded that adherence to Mefloquine prophylaxis was significantly affected due to its adverse effects. This finding was further highlighted in a survey of 781 Peace Corps Volunteers serving in Africa. The study reported lower adherence to Mefloquine compared to other prescribed regimens, such as atovaquone-proguanil or doxycycline. [10]. Although other regimens are based on daily dosing compared to weekly dosing of Mefloquine, the lower adherence to Mefloquine stems from its higher rates of serious side effects, especially neuropsychiatric manifestations. A systematic review by Ahluwalia et al. examined factors affecting malaria chemoprophylaxis, with a focus on reasons for adherence breaks. The study identified medication-related concerns, perceived malaria risk, forgetfulness, and characteristics of the travel or deployment period as important determinants, similar to those in the present study. [11] A strong association was noted between adverse-effect reporting and drug compliance in the present study. Adverse effects were reported by 55.2% (n=21) of non-compliant individuals compared with 7.4% (n=34) of compliant individuals ($p < 0.0001$). As the data collection was cross-sectional in nature in the present study, establishing causality between non-compliance and adverse effects is not feasible. However, the magnitude of this association suggests that experience or anticipation of possible adverse effects may

be an important determinant of respondents' prophylaxis behaviour. Refer to Table 2 for the summary of relevant research on Mefloquine prophylaxis.

Table 2
A comparison of the present study with previous studies on Mefloquine Chemoprophylaxis

Study	Study population and setting	Study design	Sample size	Principal findings on compliance	Malaria outcomes / effectiveness
Hopperus Buma et al., 1996	Dutch marines deployed to Cambodia as UN Peacekeepers	Retrospective cohort	2,289	Full compliance with weekly mefloquine was reported by 86.3%	During deployment, 31 <i>P. falciparum</i> infections occurred. Mefloquine provided substantial protection but was not completely effective in eliminating infections
Peragallo et al., 1999	Italian soldiers deployed to Mozambique using Mefloquine; compared with another military cohort using chloroquine-proguanil in Somalia	Prospective study	1,386 mefloquine users; 5,120 soldiers overall	Compliance with mefloquine was 95.7%, significantly higher than the comparator regimen	Primarily evaluated compliance and tolerability; detailed comparative malaria effectiveness was not the principal outcome
Kitchener et al., 2005	Australian soldiers deployed on peacekeeping duties in East Timor	Prospective study with cross-sectional questionnaire and interview	1,157	83.7% completed deployment on mefloquine; 16.3% did not complete deployment on the drug	The principal focus was tolerability rather than comparative malaria risk
Landman et al., 2015	Peace Corps Volunteers serving in malaria-endemic areas of Africa	Cross-sectional KAP survey	781	Overall adherence was 73%; among mefloquine users, adherence was 84%	Malaria outcomes were not the principal comparative endpoint
Present Study, 2026	Indian peacekeepers deployed to South Sudan	Retrospective cohort study using questionnaire data and retrospective verification of malaria outcomes	534	85.6% were classified as compliant (mostly adherent or never missed a dose); 14.4% were non-compliant	RR for malaria in non-compliant personnel was 5.28 (95% CI 2.81–9.89). Estimated protective efficacy associated with compliance was 81.0% (95% CI 64.5–89.9%)

The present study suggests that Mefloquine prophylaxis may have led to lower rates of hospitalisation and complications. However, the sample size of individuals with breakthrough infections was not large enough to establish statistical significance. A study conducted by D. He et al. in South Sudan reported a significant reduction in complication rates in the compliant group (1.2%) compared with the non-compliant group (44.8%). [12] A larger study to investigate this finding may establish Mefloquine as a drug which can reduce hospitalisation and complication rates associated with malaria in this region. An interesting finding in the present study was a lower attack rate of 15.4% among individuals who never took prophylaxis, compared with 26.3% among those who intermittently missed doses. This finding likely suggests greater behavioural adaptations in the former group, as they were aware of the increased risk of malaria without chemoprophylaxis. The latter group may have a perceived sense of security leading to poorer adherence to personal protective measures.

The KAP (Knowledge, Attitude and Practice) findings of the present study carry direct programmatic implications. Adverse-effect concerns (rather than logistics or availability) were found to be the leading driver of non-adherence. Interventions such as pre-deployment counselling on expected, usually self-limiting symptoms (sleep disturbance, vivid dreams) may improve compliance. Interventions targeting troops' sleep habits, such as addressing sleep disorders caused by time zone changes during the initial stages of deployment and maintaining good sleep hygiene, may help mitigate sleep-related concerns among peacekeepers. Early identification of neuropsychiatric symptoms has to be stressed, as prompt discontinuation of the drug becomes mandatory, especially in a high-stress environment in which the peacekeepers are deployed. Although the prophylaxis significantly reduced the attack rates, there were incidences of breakthrough infections in even fully compliant individuals. Thus, chemoprophylaxis cannot replace personal protective measures such as using insecticidal-treated nets, wearing covered clothing after dusk, using mosquito repellents, and addressing mosquito breeding sites, wherever possible. Lastly, providing alternative options to Mefloquine to the individuals who have reported adverse effects to the drug can be explored.

Limitations of the study:

- Self-reported compliance and adverse-effect data are subject to recall and social desirability biases, particularly in a hierarchical military setting.
- Establishing causality with adverse effects was not feasible in the present cross-sectional study.
- A smaller number of breakthrough infections in the cohort prevented statistical significance for certain parameters, such as hospitalisation and complication rates.

Conclusion

In conclusion, the present study demonstrated a strong association between adherence to weekly Mefloquine chemoprophylaxis and reduced malaria attack rates among Indian peacekeepers deployed to South Sudan. Compliance with prophylaxis resulted in a fivefold reduction in the risk of malaria infection. Drug-related adverse effects (Experienced as well as anticipated) were the most important reported barriers to adherence. These findings reinforce the effectiveness of Mefloquine when taken consistently while highlighting the importance of adherence, risk perception and drug tolerability in determining real-world protection. The study also highlights the importance of personal protective measures, in addition to chemoprophylaxis, as key measures to prevent malaria infection.

Declarations

- Ethics Declaration: The authors presented the study proposal to the Institutional Ethics Committee and obtained the necessary permission.

Consent for Publication:

- Informed consent was obtained from each participant using a standard consent form included in the self-reported questionnaire.

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Author Contribution

AK, DU and AP conceptualised the study and wrote the manuscript. DS, AS and BP contributed to data collection and statistical analysis.

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Availability of data and materials:

Available with the corresponding author upon requisition

- Conflict of interest: The authors disclose no competing interests.

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Figures

Reported Adverse Effect Symptoms (n=55, multi-select)

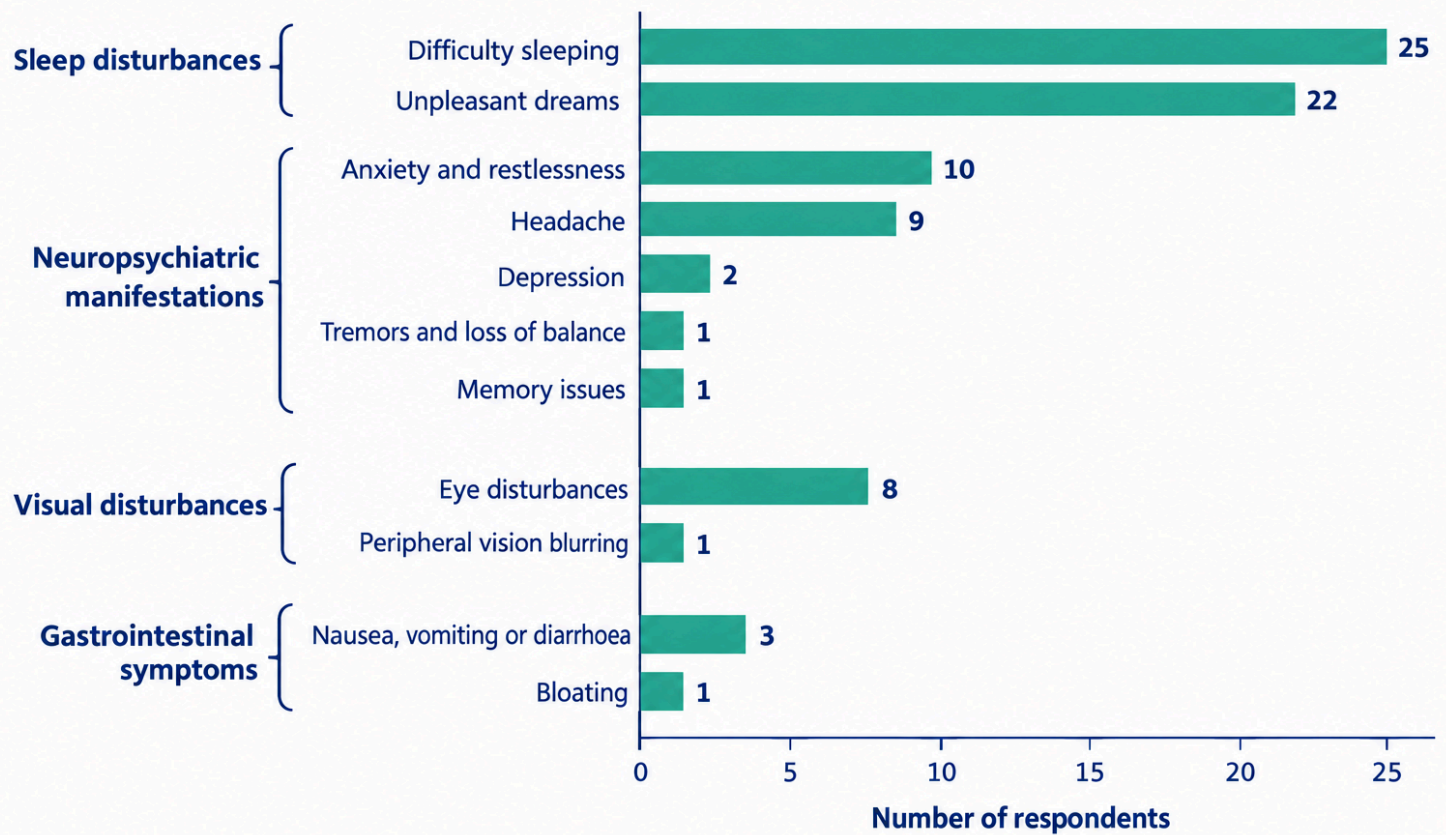


Figure 1

Legend not included with this version