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Abstract

Background: Malaria remains a significant health threat to military and civilian personnel deployed to endemic regions. Despite recommended chemoprophylaxis, compliance varies substantially, potentially impacting clinical outcomes when infections occur. This study investigated the relationship between antimalarial prophylaxis compliance and disease severity among United Nations peacekeepers and associated personnel in South Sudan. Methods: A prospective observational study was conducted at the Vietnam Level 2 Field Hospital in Bentiu, South Sudan from 2018-2024, analyzing 258 confirmed malaria cases. Patients were stratified based on prophylactic medication adherence: a prophylaxis group (n=140, including both regular and irregular users) and a non-prophylaxis group (n=118). Clinical manifestations, laboratory parameters, parasite density, and disease severity were compared between groups. Results: Despite similar rates of atypical fever presentations between groups (65.0% vs. 55.9%, p=0.14), significant differences emerged in disease severity and laboratory parameters. Non-adherence to prophylaxis was associated with increased risk of anemia (OR=2.81, 95%CI 1.27-6.25, p<0.01), severe thrombocytopenia (OR=3.76, 95%CI 2.24-6.31, p<0.01), and elevated liver enzymes (AST: OR=2.26, 95%CI 1.36-3.75, p<0.001; ALT: OR=1.86, 95%CI 1.13-3.05, p<0.01). Most importantly, prophylactic abstention significantly increased risk for malaria with warning signs (OR=2.33, 95%CI 1.25-4.34, p<0.01) and high parasite density (OR=3.07, 95%CI 1.81-5.20, p<0.001). All patients achieved parasitological clearance by day three post-treatment. Conclusions: While antimalarial prophylaxis did not prevent infection in our cohort, it significantly reduced disease severity, parasitemia, and laboratory abnormalities when breakthrough infections occurred. These findings emphasize the importance of prophylactic compliance among non-immune individuals in high-transmission settings, even when perfect adherence cannot be achieved.

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1. Introduction

Malaria remains one of the most significant infectious disease threats to military and civilian personnel deployed to endemic regions, with particular impact on peacekeeping missions in sub-Saharan Africa [1]. The disease not only compromises individual health but also affects operational readiness and mission effectiveness [2]. Despite substantial progress in malaria control globally, South Sudan continues to experience high transmission intensity, with an estimated 2.8 million cases annually in a population of approximately 11 million [3].

Chemoprophylaxis represents a cornerstone of malaria prevention for non-immune individuals entering endemic areas [4]. Standard prophylactic regimens, including mefloquine, doxycycline, and atovaquone-proguanil, have demonstrated efficacy in reducing the risk of clinical disease [5]. However, the real-world effectiveness of these interventions is frequently compromised by suboptimal adherence, emerging drug resistance, and medication side effects [6,7]. A systematic review by Tickell-Painter et al. reported that adherence to chemoprophylaxis among travelers to high-risk areas varied widely from 10% to 90%, depending on destination, duration, and medication type [8].

Military personnel and peacekeepers represent a unique population regarding malaria risk assessment. Unlike short-term travelers, they typically experience prolonged exposure in high-transmission settings, often under challenging environmental conditions that favor vector contact [9]. While peacekeeping mission medical protocols typically mandate prophylactic medication usage, compliance monitoring remains challenging, and adherence diminishes over time [10,11].

Previous studies have documented substantial malaria incidence among peacekeeping forces despite prophylaxis availability. Frickmann et al. reported a 14.4% malaria incidence among German soldiers in Mali despite prescribed doxycycline prophylaxis [12]. Similarly, Tuck et al. observed a 7.8% attack rate among British troops in Sierra Leone, with non-adherence to prophylaxis identified as the primary risk factor [13]. However, limited data exist regarding the impact of prophylactic compliance on clinical outcomes and disease severity when breakthrough infections occur.

The Vietnam Level 2 Field Hospital, deployed in South Sudan since 2018 as part of the United Nations Mission, provides healthcare services to peacekeeping personnel and local populations [14]. This setting offers a unique opportunity to evaluate the relationship between prophylactic adherence and malaria severity in a cohort with varying levels of compliance but similar exposure risk.

This investigation aimed to compare clinical manifestations, laboratory abnormalities, parasitemia levels, and disease severity between patients with different prophylactic adherence patterns. We hypothesized that even imperfect compliance might attenuate disease severity when breakthrough infections occur, potentially providing a rationale for emphasizing partial adherence when perfect compliance cannot be achieved.

2. Materials and Methods

2.1. Study Design and Setting

This prospective observational study was conducted at the Vietnam Level 2 Field Hospital located in Bentiu, Unity State, South Sudan, from November 2018 to October 2024. This healthcare facility provides comprehensive medical services to United Nations personnel and local inhabitants in a region with high perennial malaria transmission with seasonal fluctuations corresponding to rainfall patterns.

2.2. Study Population and Eligibility Criteria

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The study included 258 patients diagnosed with malaria who received medical care at the facility. Inclusion criteria adhered to standardized diagnostic parameters established by the WHO (2015) [15] and United Nations Medical Staff Guidelines (2019) [16]: (i) documented fever within 72 hours of presentation; (ii) epidemiological risk factors, including residence in malaria-endemic regions for at least seven days or previous malaria infection; and (iii) laboratory confirmation through either rapid diagnostic testing or microscopic examination of Giemsa-stained blood films. Exclusion criteria comprised concurrent infections with other pathogens, incomplete follow-up data, and insufficient documentation for comprehensive analysis.

2.3. Data Collection

Patient information was collected using a standardized clinical form. Demographic data included age, gender, occupational status (individual officers, contingent members, or local civilians), and previous malaria episodes. Prophylactic medication usage was recorded, including pharmaceutical agent (doxycycline, mefloquine, atovaquone/proguanil) and adherence patterns, categorized as: regular use (≥80% compliance), irregular use (50-80% compliance), or non-use (<50% compliance or abstention) during the month preceding infection.

Clinical assessments documented fever patterns, associated symptoms, and physical examination findings. Laboratory investigations included complete blood count, biochemical parameters (glucose, creatinine, liver function tests), and parasitological assessments (species identification and parasite density quantification). Disease severity was classified according to established guidelines as uncomplicated malaria or malaria with warning signs. Treatment protocols and outcomes were documented, with clinical resolution and parasitological clearance on day three post-treatment designated as successful treatment.

2.4. Laboratory Methods

Hematological parameters were determined using an automated analyzer (Sysmex XN-550), with thrombocytopenia defined as platelet count <150×10^9/L and anemia as hemoglobin <110 g/L. Biochemical analyses were conducted using an automated chemistry analyzer (Architect c4000), with hepatic dysfunction characterized by transaminase levels ≥40 U/L.

Parasitological diagnosis employed both immunochromatographic rapid diagnostic tests (CareStart™ Malaria Pf/Pv Combo) and microscopic examination of peripheral blood smears. Parasite density was semi-quantitatively categorized using the plus system: (+) for 1-10 parasites per 100 high-power fields; (++) for 11-100 parasites per 100 high-power fields; (+++) for 1-10 parasites per single high-power field; and (++++) for >10 parasites per single high-power field.

2.5. Statistical Analysis

Data were analyzed using SPSS version 22.0. Continuous variables were expressed as means ± standard deviations and compared using Student's t-test. Categorical variables were presented as frequencies and percentages, with comparisons conducted using Pearson's chi-squared test. The association between prophylactic medication usage and clinical or laboratory parameters was quantified through odds ratios with 95% confidence intervals. Statistical significance was established at $p<0.05$.

For comparative analyses, participants were stratified into two cohorts based on prophylactic medication adherence: a prophylaxis group (encompassing both regular and irregular users, n=140) and a non-prophylaxis group (comprising those with minimal or no compliance, n=118).

2.6. Ethical Considerations

This investigation utilized data collected during routine patient care. The research protocol received approval from the hospital's commanding authority. All patient information was anonymized prior to analysis to ensure confidentiality. The study was conducted in accordance with the Declaration of Helsinki.

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3. Results

3.1. Demographic Characteristics and Prophylactic Medication Usage

Of 258 patients diagnosed with malaria, the mean age was 40.64 ± 9.02 years, with male predominance (87.6%). Occupational distribution included individual officers (36.0%), contingent members (34.9%), and local civilians (29.1%). Primary malaria infection accounted for 64.3% of cases, while 35.7% were recurrent episodes. Analysis of prophylactic medication usage revealed that 45.7% of participants reported no prophylaxis, 35.3% acknowledged irregular usage, and only 19.0% demonstrated consistent compliance. Among those utilizing prophylactic agents (n=140), mefloquine predominated (53.6%), followed by doxycycline (38.6%) and atovaquone-proguanil (7.8%). Comparative analysis revealed no significant differences in fever pattern distribution between prophylaxis users and non-users, with atypical presentations predominating in both cohorts (65.0% vs. 55.9%, p=0.14). Associated symptoms, including cephalgia, fatigue, and gastrointestinal disturbances, exhibited similar frequencies between the two groups (Table 1).

Table 1. Comparative Clinical Manifestations Based on Prophylactic Medication Usage.

Clinical Feature	Prophylaxis Group (n=140)	Non-Prophylaxis Group (n=118)	p-value
Atypical fever	91 (65.0%)	66 (55.9%)	0.14
Classical paroxysms	49 (35.0%)	52 (44.1%)	
Cephalgia	105 (75.0%)	85 (72.0%)	0.58
Fatigue	90 (64.3%)	80 (67.8%)	0.55
Musculoskeletal discomfort	50 (35.7%)	47 (39.8%)	0.49
Gastrointestinal symptoms	67 (47.9%)	61 (51.7%)	0.53

3.2. Laboratory Abnormalities Based on Prophylactic Compliance

Significant disparities were observed in hematological parameters between the two cohorts. The prophylaxis group demonstrated higher mean leukocyte counts (7.17 ± 3.73 vs. 6.31 ± 2.45×10^9/L, p=0.03) and platelet counts (125.26 ± 52.96 vs. 97.75 ± 34.27×10^9/L, p<0.01) compared to the non-prophylaxis group. Notably, non-adherence to prophylactic medication significantly increased the risk of anemia (OR=2.81, 95%CI 1.27-6.25, p<0.01) and severe thrombocytopenia (<100×10^9/L) (OR=3.76, 95%CI 2.24-6.31, p<0.01), as detailed in Table 2. Similarly, hepatic function parameters exhibited significant differences between the groups. The non-prophylaxis group demonstrated markedly elevated mean transaminase levels (AST: 65.52 ± 51.13 vs. 42.44 ± 25.98 U/L, p<0.001; ALT: 62.79 ± 54.97 vs. 43.46 ± 25.13 U/L, p<0.001). Prophylactic abstention was associated with increased risk of hepatic dysfunction, with OR=2.26 (95%CI 1.36-3.75, p<0.001) for AST elevation and OR=1.86 (95%CI 1.13-3.05, p<0.01) for ALT elevation, as shown in Table 3.

Table 2. Comparative Hematological Parameters Based on Prophylactic Medication Usage.

Parameter	Prophylaxis Group (n=140)	Non-Prophylaxis Group (n=118)	p-value	Odds Ratio (95% CI)
Leukocyte count (×10^9/L)	7.17 ± 3.73	6.31 ± 2.45	0.03	-
Hemoglobin <110 g/L	10 (7.1%)	21 (17.8%)	0.009	2.81 (1.27-6.25)
Platelet count (×10^9/L)	125.26 ± 52.96	97.75 ± 34.27	<0.001	-
Platelets <100×10^9/L	49 (35.0%)	79 (66.9%)	<0.001	3.76 (2.24-6.31)

Table 3. Comparative Biochemical Parameters Based on Prophylactic Medication Usage.

Parameter	Prophylaxis Group (n=140)	Non-Prophylaxis Group (n=118)	p-value	Odds Ratio (95% CI)
AST (U/L)	42.44 ± 25.98	65.52 ± 51.13	<0.001	-
AST ≥40 U/L	45 (32.1%)	61 (51.7%)	0.001	2.26 (1.36-3.75)
ALT (U/L)	43.46 ± 25.13	62.79 ± 54.97	<0.001	-

 doi:10.20944/preprints202509.0966.v1

Parameter	Prophylaxis Group (n=140)	Non-Prophylaxis Group (n=118)	p-value	Odds Ratio (95% CI)
ALT ≥40 U/L	58 (41.4%)	67 (56.8%)	0.01	1.86 (1.13-3.05)
Total bilirubin (μmol/L)	14.34 ± 5.44	15.16 ± 7.11	0.29	-
Bilirubin >17 μmol/L	38 (27.1%)	24 (20.3%)	0.20	-

3.3. Disease Severity and Parasitemia Based on Prophylactic Compliance and Treatment Outcomes

Most significantly, prophylactic medication usage substantially influenced disease severity and parasitemia levels. The non-prophylaxis group exhibited a higher proportion of malaria with warning signs (28.0% vs. 14.3%, p=0.007) and elevated parasite density (≥+++) (71.2% vs. 44.6%, p<0.001). The absence of prophylactic medication conferred an increased risk of developing malaria with warning signs (OR=2.33, 95%CI 1.25-4.34, p<0.01) and high-density parasitemia (OR=3.07, 95%CI 1.81-5.20, p<0.001), as indicated in Table 4. Despite the significant disparities in clinical and laboratory parameters between the two cohorts, therapeutic outcomes were universally favorable, with all patients in both groups achieving complete parasitological clearance by day three post-treatment initiation. No significant differences were observed in the frequency of inpatient management between prophylaxis users and non-users (34.3% vs. 39.8%, p=0.35).

Table 4. Comparative Disease Severity and Parasite Density Based on Prophylactic Medication Usage.

Characteristic	Subcategory	Prophylaxis Group (n=140)	Non-Prophylaxis Group (n=118)	p-value	Odds Ratio (95% CI)
Disease severity	Uncomplicated	120 (85.7%)	85 (72.0%)	0.007	2.33 (1.25-4.34)
	With warning signs	20 (14.3%)	33 (28.0%)		
Parasite density (n=248)	≤ ++	72 (55.4%)	34 (28.8%)	<0.001	3.07 (1.81-5.20)
	≥ +++	58 (44.6%)	84 (71.2%)		

4. Discussion

This prospective investigation conducted at a United Nations peacekeeping mission in South Sudan elucidates the profound impact of antimalarial prophylaxis compliance on disease manifestations. While chemoprophylaxis did not entirely preclude infection acquisition, it demonstrably attenuated parasitemia, mitigated hematological aberrations, preserved hepatic function, and diminished overall clinical severity [17-24].

The remarkable concordance in symptomatic presentation between prophylaxis-adherent and non-adherent cohorts merits scrutiny. Both groups exhibited comparable fever patterns and ancillary symptoms, suggesting prophylaxis may not substantially modify the symptomatologic profile that precipitates healthcare consultation [17,25]. However, the marked disparity in laboratory parameters between these cohorts furnishes compelling evidence of prophylaxis-mediated pathophysiological modulation [26,27].

Thrombocytopenia—quintessential in malarial infection—manifested with substantially greater severity in prophylaxis non-users. The nearly quadrupled risk of profound thrombocytopenia (<100×10^9/L) amongst this cohort intimates that prophylaxis may ameliorate platelet sequestration and immune-mediated destruction characteristic of malarial pathobiology [18,28,29]. This observation carries substantive clinical relevance, as multiple investigations have identified severe thrombocytopenia as an independent harbinger of complicated malaria and mortality [19,20,30].

The prophylaxis-associated preservation of hepatic function exemplifies another facet of disease attenuation. Hepatocellular injury in malaria stems from multifarious mechanisms, including erythrocyte sequestration within sinusoids, proinflammatory cytokine cascades, and microvascular occlusion [21,31,32]. Our documentation of attenuated transaminase elevations in prophylaxis users signifies partial hepatoprotection despite breakthrough infection [22,33].

 doi:10.20944/preprints202509.0966.v1

Significantly, prophylaxis adherence correlated with diminished parasite density and reduced frequency of advanced clinical stages. The threefold elevated risk of high-density parasitemia among non-users suggests that even suboptimal prophylaxis compliance may constrain parasite replication through residual sub-therapeutic drug concentrations [23,34,35]. This parasitemia reduction plausibly contributes to the reduced incidence of warning signs observed in the prophylaxis cohort, consistent with the established correlation between parasite burden and clinical severity [24,36].

Therapeutic outcomes remained uniformly favorable across both cohorts, with universal parasitological clearance by day three post-treatment initiation. This observation affirms that while prophylaxis modifies disease manifestations, artemisinin-based combination therapies maintain exceptional efficacy irrespective of prior prophylactic exposure [37,38], a particularly reassuring finding given emerging concerns regarding artemisinin resistance in Southeast Asia [39,40].

The clinical implications of our findings are manifold. First, the demonstrated benefits of even irregular prophylaxis adherence suggest that partial compliance, while suboptimal, confers measurable protection against severe disease. Second, the comparable clinical presentations between prophylaxis users and non-users underscore the necessity of maintaining heightened vigilance for malaria in febrile patients regardless of prophylactic status. Finally, the substantial differences in laboratory parameters between cohorts indicate that prophylaxis should be particularly emphasized for individuals with pre-existing hematological or hepatic conditions.

Despite methodological strengths including prospective design, substantial sample size, comprehensive laboratory evaluation, and extended observation period, certain limitations warrant acknowledgment: self-reported prophylaxis usage, observational design precluding definitive causality establishment, predominance of military personnel potentially limiting generalizability, and possible confounding by acquired partial immunity in some participants..

5. Conclusions

While antimalarial chemoprophylaxis did not prevent infection in our cohort, it significantly reduced parasitemia, hematological abnormalities, hepatic dysfunction, and overall disease severity when breakthrough infections occurred. These findings emphasize the value of prophylactic medication compliance among non-immune individuals in high-transmission settings, even when perfect adherence cannot be achieved. Healthcare providers should encourage prophylaxis continuation or resumption after interruptions, given the demonstrated benefits of even imperfect compliance in mitigating disease severity.

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Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper, if applicable.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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