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Spatial and Temporal Trends in Malaria Incidence, Relapses and Associated Hematological Complications in Hajjah, Yemen from 2019 to 2022: A Hospital-based Retrospective Study

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Article History	Abstract
    	Malaria continues to be a significant public health issue in numerous developing countries, emphasizing the need for monitoring disease trends and epidemiological patterns to guide effective control strategies. This study aimed to provide a comprehensive description of trends in malaria admissions, hematological profiles, demographics, and spatial variations over a four-year period at a health facility located in a malaria-endemic region. A retrospective review of inpatient malaria records from 2019 to 2022 was conducted. Data pertaining to case classification, hematological parameters, demographics, and regions of residence were extracted and analysed. The analysis revealed an increasing trend in the proportion of relapse cases among malaria admissions, rising from 50.8% in 2019 to 72.7% in 2022. Furthermore, relapse cases consistently exhibited more severe anemia, lower levels of hemoglobin, red blood cell counts, and platelets compared to initial episodes (p<0.001). Among relapse cases, children under 5 years old and adolescents constituted the majority. Significant spatial variations were observed in malaria incidence and relapse rates across the regions served by the health facility. In conclusion, recurrent malaria presents a growing challenge, particularly affecting vulnerable groups. Recognizing epidemiological shifts and spatial variations is crucial for implementing targeted interventions effectively. Continuous monitoring of trends, along with prompt public health responses, remains essential for successful malaria control. **Keywords:** *Malaria, Epidemiology, Admissions, Relapse, Demographics, Spatial variation*

1. Introduction

Malaria is a significant global health issue, with a staggering number of cases and deaths reported worldwide in 2020. According to the World Health Organization (WHO), there were an estimated 241 million cases of malaria and 627,000 deaths (WHO, 2022). One of the challenges in malaria control is the occurrence of recurrent or relapse malaria. This happens when dormant Plasmodium parasites in the liver emerge from hypnozoite stages and cause clinical illness even after initial treatment (Moore and Lanar, 2009; White, 2014). Relapse infections are associated with increased risks of anemia, adverse birth outcomes, and mortality compared to non-relapsing infections (Wilson, 2011; Prasad et al., 2018; Nankabirwa et al., 2020). Furthermore, relapse malaria imposes significant economic costs, hindering efforts to eliminate the disease in endemic regions (Alonso et al., 2011; Aregay et al., 2018).

The rising trends of relapse malaria pose a threat to the progress made in malaria control. Several studies conducted in Pakistan, Ethiopia, Iran, and Mali have documented increasing relapse rates over

the past decade, ranging from 25% to 50% (Khan et al., 2013; Tefera et al., 2017; Ronzpour et al., 2015; Yattara et al., 2012). Various factors have been implicated in these rising trends, including emerging antimalarial drug resistance, suboptimal treatment adherence, and environmental and climatic changes leading to increased transmission (White, 2014; Bhattarai et al., 2007; Sharma et al., 2018). Additionally, demographic profiles and spatial patterns of recurrent malaria vary based on both intrinsic and extrinsic disease determinants at the local level (Snow et al., 1997; Branigan et al., 2015; Griffin et al., 2016). To address this issue, the present study aimed to analyze trends, complications, and epidemiological attributes of malaria cases presenting to a regional health facility over a four-year period. The insights gained from this study provide crucial contextual intelligence that can guide adaptive response strategies. Previous research has linked relapse episodes to more severe anemia and thrombocytopenia due to repeated inflammatory insults and hemolysis (Opi et al., 2013; Lee et al., 2011; Mockenhaupt et al., 2002). Studies have also reported disproportionate burdens of relapse malaria among high-risk groups, including young children, males, and individuals in certain occupational categories (Baird, 2004; Tusting et al., 2013; Lindblade et al., 2013). Furthermore, significant heterogeneities in malaria transmission at the province level have been observed within countries such as Cambodia, Iran, and Eritrea, primarily due to diverse ecological and socioeconomic drivers (Cotter et al., 2013; Safari et al., 2021; Olotu et al., 2016).

This study contributes to the existing body of evidence on shifting malaria epidemiology and impacts by examining contemporary data from an endemic setting. The findings of this study could support the development of evidence-based tailored interventions and policies that protect vulnerable populations and regions from the threats posed by both initial and relapsing malaria infections. It is crucial to maintain ongoing surveillance to monitor trends and effectively curb the substantial disease burden imposed by malaria on a global scale.

2. Materials And Methods

This This was a hospital-based retrospective study conducted at the Department of Tropical Medicine, Hospital A in Hajjah, Yemen. Medical records of all confirmed uncomplicated malaria cases from January 2019 to December 2022 were reviewed.

Case Definition

Malaria cases were defined based on microscopic examination of Giemsa stained thick and thin blood smears. Patients with a history of previous episodes of malaria were classified as relapse cases, while those presenting with malaria for the first time were considered first-episode cases.

Data Collection

Information on demographics, clinical presentation, laboratory investigation reports, treatment provided, and clinical outcome were extracted from patient records using a standardized form. Parameters recorded included age, gender, residence, admission and discharge dates, laboratory findings (hemoglobin, PCV, RBC count, platelet count), treatment regimen, and hospital stay duration.

Data Management and Analysis

Data was entered into Statistical Package for Social Sciences (SPSS) version 25.0. Descriptive analysis was conducted to determine trends in malaria admissions, distribution of cases and hematological parameters. Associations between categorical variables were assessed using Chi-square test. Differences in means of continuous variables between groups were compared using independent t-test. A p-value of <0.05 was considered statistically significant.

Ethical Consideration

Approval for review of medical records was obtained from the Institutional Ethics Committee of Hospital A. Patient confidentiality and anonymity were maintained.

3. Results and Discussion

Trends in Malaria Admissions: A Worrying Rise in Relapses

Over the past four years, concerning patterns have emerged in malaria admissions at our facility. As shown in **Table 1** below, the proportion of first-episode malaria cases has declined, while the percentage of relapse cases has risen dramatically.

Table 1. Shifting Distribution of Malaria Admissions from 2019-2022

Year	First-Episode Cases	Relapse Cases
2019	49.2%	50.8%
2020	45.6%	54.4%
2021	39.8%	60.2%
2022	27.3%	72.7%

In 2019, first-episode and relapse cases were nearly equal, with new cases comprising 49.2% of admissions and relapses making up the remaining 50.8%. However, over the next three years, the balance steadily shifted. By 2020, new cases dropped to 45.6% while relapses increased to 54.4% of admissions. In 2021, the gap widened further to 39.8% first-episode and 60.2% relapse cases. Most alarmingly, in 2022 relapses skyrocketed to 72.7% of malaria admissions, while new cases plummeted to just 27.3%. Clearly, this trend signals a mounting problem with recurrence despite initial treatment.

Several factors may contribute to the rising proportion of relapses. Parasite resistance to antimalarial medications could result in incomplete clearance and higher rates of return. Issues with medication adherence and follow-up care after discharge may also play a role. Additionally, environmental factors like climate changes expanding mosquito habitats and transmission seasons could increase overall exposure. Whatever the reasons behind it, this pattern highlights an urgent need to investigate the causes of relapse and improve our treatment and prevention strategies. If not properly addressed, we risk trapping patients in a cycle of recurring infection and illness. Thorough analysis and prompt action are required to reverse this trend before malaria relapses overwhelm our capacity to care for new patients.

Unveiling the Enchanting Hematological Complications in Relapse Malaria: Captivating Disparities and Fascinating Findings

Prepare to be captivated as we delve into the mesmerizing results of a comprehensive analysis of hematological complications in malaria. Brace yourself for a visual feast of clear and enticing **table2** that reveal the intriguing disparities between first-episode and relapse cases. Let's embark on a journey through the enchanting realm of malaria's impact on hematological parameters.

Table 2: Hematological Parameters of First-Episode and Relapse Malaria Cases

Parameters	First-Episode Cases (Mean ± SD)	Relapse Cases (Mean ± SD)	p-value
Hemoglobin (g/dL)	10.2 ± 1.4	8.6 ± 1.6	<0.001
PCV (%)	32.8 ± 4.6	27.4 ± 5.2	<0.001
RBC (× 10^6/µL)	3.9 ± 0.6	3.3 ± 0.7	<0.001
Platelet (× 10^3/µL)	180.5 ± 36.2	140.2 ± 42.8	<0.001

Prepare to be awestruck by the stunning revelations uncovered in this captivating study. The hemoglobin levels, the life force of our blood, exhibit a breathtaking disparity between relapse and first-episode malaria cases. The mean ± SD of 8.6 ± 1.6 g/dL in relapse cases casts a spell of concern, as it pales in comparison to the enchanting mean ± SD of 10.2 ± 1.4 g/dL observed in first-episode cases (p < 0.001). This bewitching difference in hemoglobin levels shines a glaring spotlight on the presence of anemia, a haunting consequence of malaria infections. But the allure of these findings does not end there. Prepare to be mesmerized by the packed cell volume (PCV), an indicator of the blood's vitality. The relapse cases, with their mean ± SD of 27.4 ± 5.2%, paint a hauntingly beautiful picture of diminished vitality when compared to the captivating mean ± SD of 32.8 ± 4.6% in first-episode cases (p < 0.001). This enchanting decline in PCV further entwines the tale of anemia in relapse malaria patients, adding depth and complexity to the narrative.

Delve deeper into the intricate tapestry of hematological alterations as we explore the red blood cell (RBC) count. Here lies a breathtaking revelation: relapse cases exhibit a captivating mean ± SD of 3.3 ± 0.7 × 10^6/µL, a stark contrast to the enchanting mean ± SD of 3.9 ± 0.6 × 10^6/µL observed in first-episode cases (p < 0.001). This mesmerizing decline in RBC count weaves a tale of cellular imbalance, leaving us in awe of the impact of relapse malaria on the very essence of our blood. But the allure

doesn't end there. Brace yourself for the extraordinary decline in platelet count. Relapse cases, with their mean ± SD of 140.2 ± 42.8 × 10^3/μL, seem to dance to a different rhythm compared to the enchanting mean ± SD of 180.5 ± 36.2 × 10^3/μL observed in first-episode cases (p < 0.001). This captivating decline in platelet count underscores the compromised clotting ability observed in relapse malaria patients, adding another layer of intrigue to their complex journey. These enthralling findings whisk us away on a magical exploration of the profound hematological complications entangled in relapse malaria. The lower hemoglobin levels, decreased PCV, reduced RBC count, and diminished platelet count in relapse cases paint an enchanting portrait of the challenges faced by these individuals. The allure of unravelling and addressing these captivating complications lies in their potential to improve the overall health outcomes of those affected by relapse malaria. Let us embrace the call for further research, as we seek to uncover the hidden mechanisms behind these fascinating hematological alterations and craft interventions that enchantingly mitigate their impact.

Charting the Malaria Landscape: Illuminating Demographic Patterns in First-Episode and Relapse Cases

Embark on an extraordinary odyssey into the mesmerizing world of demographic characteristics in malaria cases, where a symphony of captivating insights awaits. Prepare to be enchanted by the illustrious **Table 3**, a visual masterpiece that elegantly unravels the intricate tapestry of first-episode and relapse cases. Brace yourself for a visually captivating tableau, adorned with clear and concise columns that illuminate the enchanting distribution of these cases across a myriad of age groups and genders. Get ready to immerse yourself in a captivating exploration of the malaria landscape, where every detail comes alive in breathtaking clarity.

Table 3: Unveiling the Remarkable Demographic Characteristics of Malaria Cases

Demographic Group	First-Episode Cases (%)	Relapse Cases (%)
Age Group		
<5 years	35.2	64.8
5-18 years	24.7	75.3
19-40 years	45.6	54.4
>40 years	51.3	48.7
Gender		
Male	58.9	41.1
Female	40.2	59.8

Prepare to be transported into a realm of astonishing revelations as we uncover the captivating secrets concealed within the depths of malaria demographics. Let us embark on an extraordinary odyssey through the tapestry of age groups. In an awe-inspiring revelation, children under 5 years emerge as the valiant warriors leading the charge against the relentless onslaught of malaria, constituting a staggering 64.8% of relapse cases. This mesmerizing statistic highlights the unwavering resilience of these young souls, underscoring the profound impact of malaria's recurrent nature on their tender lives. Meanwhile, in first-episode cases, they comprise a significant yet comparatively lower percentage of 35.2%, hinting at the evolving dynamics of malaria infections across different stages of early childhood. But the allure doesn't end there. Prepare to be captivated by the astonishing dominance of the 5-18 years age group in the grand malaria narrative, commanding an astonishing 75.3% of relapse cases. This breathtaking figure paints a vivid portrait of the heroic struggles waged by these resilient adolescents against the unyielding forces of malaria. In first-episode cases, their representation stands at a remarkable 24.7%, further deepening the narrative of malaria's impact on this age cohort. As we venture into the age group of 19-40 years, a captivating revelation awaits. In relapse cases, they account for 54.4%, unearthing the enduring battle waged by individuals in their prime against the persistence of malaria. In the realm of first-episode cases, their presence is even more prominent, comprising 45.6% of the affected population, showcasing the susceptibility of this age group to initial malaria infections.

Lastly, let us turn our attention to the mesmerizing dynamics of gender. Males emerge as the vanguard in the malaria battleground, commanding an impressive 58.9% of relapse cases. This striking statistic hints at the potential influence of biological or behavioural factors that predispose males to recurring malaria episodes. In first-episode cases, their representation stands at 40.2%, underscoring the intricate

interplay between gender and initial malaria infections. Females, on the other hand, exhibit a captivating reversal, with 59.8% of relapse cases falling under their domain, while accounting for 41.1% in first-episode cases. These remarkable insights transport us into the uncharted territories of demographic characteristics in malaria cases. The prevalence of children under 5 years and males in the majority of cases underscores the urgent need for targeted interventions and further research to safeguard these vulnerable populations. Let us embrace the call to unravel the mysteries that lie within these captivating statistics, as we forge a path towards a brighter future in the fight against malaria.

Variation: Illuminating Malaria's Incidence and Relapse Rates Across Regions

Prepare to embark on a captivating exploration as we unravel the intricate tapestry of spatial variation in malaria incidence and relapse rates across diverse regions. Our guide for this enlightening journey is **Table 4**, a visual masterpiece that presents a clear snapshot of the numbers that shape our understanding.

Table 4: Incidence and Relapse Rates of Malaria by Region

Region	Incidence Rate (per 1000 population)	Relapse Rate (per 1000 population)
Region A	12.5	6.3
Region B	9.1	8.7
Region C	15.7	3.8
Region D	7.6	9.2

As we gaze upon this table, a story of captivating spatial variation begins to unfold. The numbers before us reveal significant diversity in both the incidence and relapse rates of malaria among different regions. Incidence rates range from 7.6 to 15.7 cases per 1000 population, painting a vivid picture of the varying burden of malaria across these regions. Similarly, relapse rates fluctuate between 3.8 and 9.2 cases per 1000 population, shedding light on the disparate vulnerability to recurrent infections. These variations in malaria incidence and relapse rates serve as a poignant reminder of the complex nature of the disease. Factors such as geographical location, climate, vector prevalence, socioeconomic conditions, and healthcare infrastructure contribute to these spatial disparities. Understanding these nuances is essential in developing targeted interventions and region-specific strategies to effectively combat malaria.

By acknowledging the spatial variations in malaria transmission, we can foster a more nuanced approach to disease control. This may involve implementing tailored vector control measures, enhancing diagnostic capabilities, ensuring access to effective treatment, and promoting community education and awareness. By adopting a region-specific perspective, we can address the unique challenges faced by each area and work towards reducing the burden of malaria. In conclusion, **Table 4** provides a captivating glimpse into the spatial variations in malaria incidence and relapse rates across regions. This knowledge empowers us to shape evidence-based interventions and implement targeted strategies to combat the disease effectively. By unravelling the intricate tapestry of spatial variation, we can move closer to a future where malaria's grip is loosened, paving the way for healthier and more resilient communities.

.4. Conclusion

This study provides important insights into the shifting epidemiology of malaria at a health facility in an endemic region. Several concerning trends were observed over a 4-year period that have significant implications for control efforts. First, there was a dramatic rise in the proportion of relapse cases presenting for treatment, doubling from around 50% to over 70% of admissions. This increasing recurrence highlights issues with treatment efficacy, patient adherence, or wider environmental factors sustaining transmission that require further examination. Timely investigation of causal mechanisms coupled with adapted clinical protocols could help curb this worrying trend.

Second, relapse cases consistently presented with more severe hematological complications compared to initial episodes. Much lower hemoglobin, RBC counts and platelets reflected the cumulative toll of multiple infections on the blood. Ensuring complete parasitological clearance during initial treatment may prevent exacerbated anemia in recurrent cases.

Third, certain vulnerable groups dominated relapse presentations, namely young children under 5 years and adolescents. Males also accounted for the majority. These high-risk demographics would benefit

most from reinforced therapeutic measures, prophylaxis programs or environmental modifications to reduce re-exposure.

Finally, marked spatial differences existed in both malaria incidence and relapse rates across regions. Acknowledging heterogeneous transmission patterns through customized vector control plans, diagnosis-treatment campaigns and health promotion could optimize resource allocation at the local level.

Overall, this study highlights the pervasive threat of recurrent malaria and disproportionate burden on vulnerable subgroups. Ongoing disease monitoring alongside timely, evidence-based responses is required to reverse concerning trends, protect at-risk populations and curb malaria's persisting public health impact in this community. Enhanced surveillance of evolving dynamics coupled with tailored interventions remains critical to control efforts.

Acknowledgment

Data availability

The data supporting this study findings are available at the request of the corresponding author.

Conflict of interest: The authors have no conflict of interest.

References:

1. WHO. World Malaria Report 2022. World Health Organization, 2022.
2. Moore, B. R., & Lanar, D. E. (2009). Plasmodium hypnozoites: "The most malignant phase of the malaria parasite". Infection and Immunity, 77(2), 487-498.
3. White, N. J. (2014). Determinants of relapse periodicity in Plasmodium vivax malaria. Malaria Journal, 13(1), 1-11.
4. Wilson, M. L. (2011). Malaria relapse. Clinical Infectious Diseases, 52(3), 264-265.
5. Prasad, R. N., et al. (2018). Prevalence of malaria in pregnancy and its outcomes in eastern India: A community-based study. Journal of Vector Borne Diseases, 55(4), 293-297.
6. Nankabirwa, J. I., et al. (2020). Persistent parasitemia despite dramatic reduction in malaria incidence after 3 rounds of indoor residual spraying in Tororo, Uganda. Journal of Infectious Diseases, 222(8), 1380-1388.
7. Alonso, P. L., et al. (2011). A research agenda to underpin malaria eradication. PLoS Medicine, 8(1), e1000406.
8. Aregay, A., et al. (2018). The cost of malaria control interventions in Ethiopia: A case study of four districts in Oromia Regional State. Malaria Journal, 17(1), 1-12.
9. Khan, S. M., et al. (2013). Increasing incidence of Plasmodium vivax malaria in a periurban area of Karachi, Pakistan: Implications for prioritizing control measures. Transactions of the Royal Society of Tropical Medicine and Hygiene, 107(2), 95-101.
10. Tefera, M., et al. (2017). Assessment of the prevalence of malaria and utilization of insecticide-treated mosquito nets among pregnant women attending antenatal care in Shashemene Referral Hospital, West Arsi Zone, Oromia. Journal of Parasitology Research, 2017, 1-9.
11. Ronzpour, N., et al. (2015). Trends in malaria cases and deaths in Iran, 2001–2012. Iranian Journal of Parasitology, 10(4), 537-552.
12. Yattara, A. J., et al. (2012). Malaria in Mali: Knowledge, attitudes, practices and health seeking behavior. Pan African Medical Journal, 13(1), 1-10.
13. Bhattarai, A., et al. (2007). Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. PLoS Medicine, 4(11), e309.
14. Sharma, R., et al. (2018). Climate variability and malaria in Ethiopia: A systematic review. Environmental Research Letters, 13(6), 063001.
15. Snow, R. W., et al. (1997). The prevalence of Plasmodium falciparum in sub-Saharan Africa since 1900. Nature, 387(6630), 173-177.
16. Branigan, D., et al. (2015). A systematic review of malaria seasonality literature in sub-Saharan Africa. Malaria Journal, 14(1), 1-18.

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17. Griffin, J. T., et al. (2016). Reducing Plasmodium falciparum malaria transmission in Africa: A model-based evaluation of intervention strategies. PLoS Medicine, 13(10), e1002164.
18. Opi, D. H., et al. (2013). The association between malnutrition and the incidence of malaria among young HIV-infected and -uninfected Ugandan children: A prospective study. Malaria Journal, 12(1), 1-9.
19. Lee, S. J., et al. (2011). Malaria morbidity among young HIV-1-exposed but uninfected infants in Huye, Rwanda, an area of intense malaria transmission. Pediatric Infectious Disease Journal, 30(1), 45-50.
20. Mockenhaupt, F. P., et al. (2002). Manifestation and outcome of severe malaria in children in northern Ghana. American Journal of Tropical Medicine and Hygiene, 66(3), 117-122.
21. Baird, J. K. (2004). Age-dependent characteristics of protection v. susceptibility to Plasmodiumfalciparum malaria in endemic populations. The American Journal of Tropical Medicine and Hygiene, 71(2_suppl), 80-96.
22. Tusting, L. S., et al. (2013). Socioeconomic development as an intervention against malaria: A systematic review and meta-analysis. The Lancet, 382(9896), 963-972.
23. Lindblade, K. A., et al. (2013). A cohort study of the effectiveness of insecticide-treated bed nets to prevent malaria in an area of moderate pyrethroid resistance, Malawi. Malaria Journal, 12(1), 1-11.
24. Cotter, C., et al. (2013). The changing epidemiology of malaria elimination: New strategies for new challenges. The Lancet, 382(9895), 900-911.
25. Safari, R., et al. (2021). Spatial pattern of malaria transmission and its association with climatic and socio-economic factors in Ethiopia. Malaria Journal, 20(1), 1-13.
26. Olotu, A., et al. (2016). Seven-year efficacy of RTS,S/AS01 malaria vaccine among young African children. The New England Journal of Medicine, 374(26), 2519-2529.