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Medical Research Paper

Malaria is a long-term problem in public-health review

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Abstract

Malaria is one of the life-threatening diseases that have been the worst globally. It is among the greatest causes of death. It is a leading cause of illness in most developing countries, especially among young children and pregnant women. In fact, new antibiotics and even possible vaccines are necessary, but the fact that working antibiotics exist is important. It is compulsory to control and educate the community in terms of Anopheles 'mosquitoes. Malaria is the norm worldwide, with 3000 children dying due to this malaria. Pakistan records half a million cases of malaria each year, and Khyber is worse afflicted compared to others in the Khyber Pakhtunkhwa provinces. He indicated that 50000 people die due to malaria every year in the entire global population, and most of these cases are among infants, children, and pregnant mothers. Women in the malaria-endemic countries have 4 times higher chances of exposure to malaria attacks when they are in their pregnant conditions and deliver low-weight and stillborn children. Not only this, but also malaria is also one of the causes of about 60 per cent of the miscarriages in hyperendemic areas. Morocco is an example of the capacity to reduce the transmission of malaria by conducting a well-coordinated vector-control programme as a state with a majority of its people being Muslim. This was attained courtesy of a culmination of various factors: steadfast political dedication, direct involvement of local people, and a well-structured people-well-being style of infrastructure. The synergy that occurred allowed the country to transform very high incidence rates into eradication. On the other hand, malaria has persistently been a thorn in the flesh of Pakistan due to the lack of awareness of the general population about the disease and also the lack of well-developed sewage systems. Therefore, there is the imminent need to break several silos and package and implement evidence-based preventative and therapeutic measures, which are patient-friendly, clinician-efficient, and would yield positive socio-economic impact.

Keywords: Malaria, life threatening, mosquitoes, Distribution, Pakistan

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1. OVERVIEW

The phylum Apicomplexa represents one of the most diverse and medically significant groups of protozoan parasites. This phylum includes a wide range of obligate intracellular parasites, among which the Plasmodium genus holds particular importance due to its role in causing malaria, a life-threatening vector-borne disease. Globally, over 250 distinct Plasmodium species have been identified, but only five are known to infect humans and lead to clinical malaria. These are Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, Plasmodium knowlesi, and Plasmodium ovale (A. Q. Khan et al., 2023). Each of these species exhibits distinct epidemiological patterns, life cycle characteristics, and clinical manifestations, with P. falciparum and P. vivax being the most prevalent and medically significant, particularly in tropical and subtropical regions.

Malaria remains a primary cause of morbidity and mortality, especially in low- and middle-income countries. The profound socioeconomic consequences of malaria compound its medical impact, affecting productivity, increasing healthcare burdens, and perpetuating cycles of poverty in endemic regions. In Pakistan, malaria poses a persistent public health challenge. Among the five human-infecting species, P. vivax and P. falciparum are

the most dominant, contributing significantly to the national disease burden. These species are not only widespread across various provinces but also exhibit seasonal surges influenced by climatic factors, vector ecology, and population mobility. While P. vivax tends to cause relapsing infections due to dormant liver stages (hypnozoites), P. falciparum is notorious for its potential to cause severe and often fatal complications.

According to the 2021 World Malaria Report, a substantial portion of the global population continues to reside in malaria-endemic regions. Alarmingly, nearly half of the world's population is at risk, as many malaria-prone countries and territories remain vulnerable to the disease's transmission and resurgence (M. I. Khan et al., 2023). This points to the importance of sustained surveillance, robust vector control strategies, and equitable access to diagnosis and treatment. In the broader context of global health, malaria is not merely a tropical disease; it is a socio-environmental challenge that requires integrated public health interventions and long-term investment in health infrastructure, especially in countries like Pakistan, where both biological and environmental factors favour its persistence.

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2. Morphology of Plasmodium

Plasmodium parasites, the causative agents of malaria, are complex unicellular eukaryotic organisms that undergo a series of morphologically distinct developmental stages throughout their life cycle. These stages are finely adapted to various environments, including both invertebrate and vertebrate hosts, as well as specific cell types such as hepatocytes and erythrocytes. The morphological and physiological diversity of Plasmodium across its life cycle is a hallmark of its survival strategy, enabling it to evade host immune responses, adapt to changing environments, and complete transmission cycles. This developmental plasticity is orchestrated by tight regulation of a compact and relatively small genome, which, despite its size, encodes a large number of proteins essential for parasite survival and pathogenicity.

However, approximately 40% of the genes in the Plasmodium genome remain uncharacterized, and their biological roles are still unknown. This presents a major barrier to the rational design of antimalarial drugs and vaccines, as researchers are often working with an incomplete understanding of the parasite's biology. The functional obscurity of a significant portion of its genome slows down the discovery of therapeutic targets and hinders the identification of molecular mechanisms responsible for drug resistance, immune evasion, and life cycle regulation.

Recently, the advent of single-cell RNA sequencing (scRNA-seq) has offered transformative potential in the study of Plasmodium biology. Unlike bulk transcriptomics, scRNA-seq enables researchers to dissect gene expression at the level of individual parasites, offering an unprecedented resolution of cellular heterogeneity, lineage specification, and transcriptional dynamics. This method is particularly valuable for unicellular organisms like Plasmodium, where population-level studies can mask critical functional differences between cells at various life stages or under different environmental pressures. By applying scRNA-seq to Plasmodium, scientists are beginning to reveal novel insights into the developmental transitions, cell-type diversity, and regulatory networks that drive its complex life cycle (Howick et al., 2019).

Ultimately, the use of high-throughput, high-resolution technologies such as scRNA-seq represents a significant leap forward in malaria research. Not only does it enhance our understanding of the fundamental biology of the parasite, but it also contributes to the broader goals of target discovery, vaccine development, and the design of more effective malaria control strategies.

3. Epidemiology of Malaria

In the year 2020, malaria continued to pose a severe global health threat, with an estimated 241 million clinical cases and approximately 627,000 associated fatalities recorded worldwide. Despite decades of intervention and scientific advancement, the disease remains endemic in many parts of the world, particularly within humid and subtropical regions, where environmental conditions are conducive to the survival and breeding of the Anopheles mosquito vector. These regions experience consistent challenges in managing transmission due to climatic suitability, socio-economic barriers, limited healthcare infrastructure, and vector resistance to insecticides.

According to the World Health Organisation (WHO), Pakistan is among the seven countries in the Eastern Mediterranean Region contributing to a staggering 98% of the region's total malaria burden. This alarming statistic highlights the disproportionate impact malaria has on specific geographical zones and underscores the need for context-sensitive and sustained public health interventions. Within Pakistan, the risk is widespread: approximately 217 million individuals are classified as being at intermediate risk, while a further 63 million people fall into the high-risk category. In 2020 alone, Pakistan reported an estimated 470,000 malaria cases and 800 deaths, demonstrating that the disease remains a major public health concern within the country (Organisation, 2023).

Malaria is caused by five main Plasmodium species capable of infecting humans: Plasmodium falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi. Each species exhibits unique epidemiological characteristics, geographic distribution, and clinical implications. P. falciparum, the most lethal of the species, was responsible for 99.7% of malaria infections in Africa as of 2018 and notably accounted for 71% of malaria cases in the Eastern Mediterranean region. Conversely, P. vivax

holds the broadest geographical distribution globally, accounting for 53% of global malaria prevalence. Its highest concentration is observed in India, which represents 47% of all P. vivax cases, followed by 11% in Afghanistan and 8% in Pakistan, making South Asia a critical focal point for vivax malaria (Karim et al., 2021).

Despite ongoing progress in malaria elimination initiatives, particularly through immunisation strategies and antimalarial chemotherapy, the effective management of malaria infections continues to be a complex challenge. Factors such as drug resistance, delayed diagnosis, inconsistent access to healthcare, and the resilience of mosquito vectors hinder the success of control programmes. Therefore, while technological and medical advances offer hope, a sustained and coordinated effort involving surveillance, education, treatment, and vector control remains essential to reduce malaria morbidity and mortality, especially in high-burden countries like Pakistan.

4. Transmission Factors of Malaria

The transmission dynamics of malaria in Pakistan are strongly influenced by seasonal variations and regional ecological conditions, leading to periodic epidemic outbreaks, particularly in certain high-risk provinces. Among the most vulnerable areas are Khyber Pakhtunkhwa, Sindh, and Baluchistan, where malaria remains endemic and poses an ongoing threat to public health. These provinces are characterised by a combination of favourable climatic conditions, socio-economic challenges, and limited access to quality healthcare services, which collectively contribute to sustained transmission and difficulty controlling the disease.

In Khyber Pakhtunkhwa, three districts—Bannu, Dera Ismail Khan, and Lakki Marwat—have been identified as key malaria hotspots. These districts consistently report high incidence rates, and malaria remains a major contributor to febrile illnesses among the local population. The topography, climatic conditions, and mobility patterns in these areas create an ideal environment for the breeding of Anopheles mosquitoes and the ongoing circulation of Plasmodium species.

The seasonality of transmission in Pakistan is particularly relevant for the two most prevalent Plasmodium species: P. vivax and P. falciparum. The transmission of P. vivax typically peaks between June and September, coinciding with the monsoon season, and again from April to June, largely due to the reactivation of dormant hypnozoites in the liver from infections acquired in the previous season. These seasonal relapses make P. vivax particularly challenging to eliminate, as the parasite can remain undetected and reemerge under favourable conditions without new mosquito transmission.

On the other hand, P. falciparum—associated with more severe clinical outcomes and drug resistance—has its primary transmission window from August to December, a period that overlaps with post-monsoon conditions, when stagnant water serves as breeding sites for mosquitoes and human-vector contact is intensified. These distinct seasonal patterns demand tailored intervention strategies that align with the life cycles of the parasites and vector populations (Qureshi, Khan, Ambachew, Pan, & Ye, 2020).

Understanding the spatiotemporal dynamics of malaria transmission in Pakistan is essential for implementing effective surveillance, vector control, and treatment protocols. It also points out the need for region-specific public health planning, resource allocation, and education campaigns to mitigate outbreaks during known high-transmission periods.

5. Signs and symptoms of malaria

The manifestation of malaria frequently mimics that of prevalent viral illnesses, perhaps resulting in a diagnostic delay. Most patients exhibit fever (over 92% of cases), chills (79%), headaches (70%), and diaphoresis (64%). Additional prevalent symptoms encompass dizziness, fatigue, myalgia, stomach discomfort, nausea, vomiting, moderate diarrhoea, and dry cough. Physical manifestations include fever, tachycardia, jaundice, pallor, orthostatic hypotension, hepatomegaly, and splenomegaly. Clinical examination in non-immune individuals may be entirely normal, even in the absence of fever (Kotepui, Kotepui, De Jesus Milanez, & Masangkay, 2020).

6. Global Health Issue

Malaria is a significant global public health issue. Approximately three billion individuals are at risk of contracting malaria, with 212 million cases and 429,000 associated fatalities reported in 2015. Malaria is a significant worldwide public health issue. Malaria is among the most catastrophic parasite infections in Pakistan, with a greater mortality rate than any other nation in Asia. Plasmodium falciparum and P. vivax are two prevalent species responsible for significant morbidity and death rates.

Malaria is a predominant source of illness and mortality in Pakistan, as in several other nations. It poses a health danger to millions of individuals and is classified as one of the six priority communicable illnesses. Pakistan is a high-burden nation for malaria, with an estimated one million infections and 300,000 confirmed cases yearly. The distribution favours Plasmodium vivax over Plasmodium falciparum in mixed cases. Malaria is a seasonal illness, making epidemic breakouts common in locations like the Khyber Pakhtunkhwa, Sindh, and Baluchistan provinces. Khyber Pakhtunkhwa comprises three endemic districts: Bannu, Lakki Marwat, and D.I.

Khan. From June to September, there are peaks in P. vivax cases, whereas relapse cases occur from April to June. Plasmodium falciparum peaks from August to December in these locations (Naqvi et al., 2020).

7. Lifecycle of Parasite

In the parasite human life cycle the plasmodial species pass through at least ten different morphological stages, have divisions of reproduction which have passed the 10,000 cell divisions and have a complete final population of 1 to greater than a million organisms in the end. In spite of the fact that the accurate quantitative distribution of malaria parasites is not yet determined, individual morphological forms are always known to cause clinically apparent disease. Most of the infections produce small or insignificant symptoms. The interaction of the species of the parasites with the physiology of the organism clinically is commonly exerted in a variety of manifestations exhibited by human hosts. They include such expressions as fever, which are caused by the actuation of innate and adaptive immunological processes. Fever, which is also noticed in the progression of malaria, is episodic, and it occurs during the haematological phase. Irrespective of this clinical feature, the malarial parasite has a standard life cycle as well as a standard morphological development process. Therefore, this is to be explained by the severity of the disease to be an immune-mediated hyper-response to an antigen of a parasite, a situation that is enhanced in the case of immunocompromised people. (Watt, 2023)

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7.1 Mosquito Stage

In-depth understanding of the malaria biology and pathology requires profound insight concerning the causative agent, which is the parasite Plasmodium. There are five known species of the Plasmodium which infects human beings; these are Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium knowlesi and Plasmodium malariae. The malaria life cycle exists within two hosts and three stages of development. The initial phase is in the Anopheles mosquito that is the main amplifier and becomes affected by a blood meal from an infected human. Thereafter, the gametocytes in the mosquito will differentiate to gametes, where fertilisation occurs, leading to zygotes. These zygotes will then attain the oocyst stage, after which the sporozoites are released back into the salivary glands. (Monroe, Williams, Ogoma, Karema, & Okumu, 2022). Whenever a female Anopheles mosquito takes a blood meal, transmission of Plasmodium to human beings commences as a gametocyte is taken up by the female Anopheles mosquito. In the midgut of the mosquito, the gametocyte reproduces asexually, and the sporogonic cycle in the mosquito commences (Beier et al., 2019). It is during a blood meal that female mosquitoes take up male gametocytes (microgametes). These microgametes travel into the circulatory system of the mosquito, and they face the macrogametes, which are found in the circulatory system, which are the female gametocytes. The subsequent interaction between microgametes and macrogametes leads to the development of the resulting zygotes transforming to oocysts through penetration of midgut epithelium. These oocysts get swollen, rupture and discharge sporozoites into the haemocoel. Thereafter the sporozoites travel towards the salivary glands of the mosquito. When a human blood-feeding occurs, the Anopheles mosquito releases saliva into the body and delivers the sporozoites to the host. The anopheline gene complex present in the mosquito salivary gland is expressed to produce proteins that are released into the host vertebrate during blood feeding to bind with thrombin and serve as anticoagulants, which also prevent processes of coagulation. At the same time with this process, the sporozoites harboured in the saliva are inoculated into the cutaneous vasculature, which allows the next stages of the parasite's life cycle.

7.2 Lifecycle of Parasite: Human Stages

Upon injection of saliva and sporozoites into the human host, the sporozoites are localised inside the dermis. The sporozoites must traverse dermal fibroblasts and endothelial cells to get to the circulation. Upon entering the circulation, the sporozoites migrate to the liver, where they infect hepatocytes and undergo replication; this phase is referred to as the liver stage. Subsequently, the sporozoites infiltrate hepatocytes and engage in asexual reproduction termed exo-erythrocytic schizogony. The method by which the hepatocyte is invaded is poorly comprehended. The thrombospondin domains on the sporozoite facilitate hepatocyte invasion by binding to heparan sulphate proteoglycans present on hepatocytes. The replication of sporozoites results in the formation of multi-nucleated cells termed schizonts. The schizonts produce merozoites within the hepatocyte. Following schizont rupture, merozoites are liberated into infected red blood cells (RBCs), initiating the human blood stage. The clinical signs of malaria result from the blood stage. During the blood stage, merozoites invade red blood cells as a trophozoite develops into a schizont by successive nuclear divisions. Subsequently, the adult schizont ruptures, releasing more merozoites; this rupture transpires following the lysis of the red blood cells, enabling the merozoites to infiltrate more uninfected red blood cells. This release corresponds with the elevation in body temperature as the illness advances. The substances produced during red blood cell lysis induce the synthesis of cytokines that are accountable for the clinical signs of malaria. This cycle of invasion, replication, and release persists. To perpetuate the cycle, a fraction

of the merozoites within the RBCs develop into microgametocytes or macrogametocytes, which are crucial for the transmission of infection to new female Anopheles mosquitoes. The production of gametocytes in this process may take up to two weeks, with time varying according to the type of Plasmodium. Upon ingestion of a gametocyte by a female Anopheles, the mosquito might subsequently consume another blood meal from a human, so perpetuating the cycle (Chauhan & Tuteja, 2019).

Pre-patent and the period of incubation

In nonimmune people infected with P. falciparum, the median pre-patent period (duration from sporozoite inoculation to observable parasitemia) is 10 days (range 5–10 days), whereas the median incubation period (duration from sporozoite inoculation to symptom onset) is 11 days (range 6–14 days). The incubation time may be considerably extended by the degree of immunity gained from past exposures, antimalarial prophylaxis, or previous partial treatment, which may reduce but not eliminate the illness (Ebi, Hess, & Watkiss, 2017). Most non-immune visitors exhibit signs of falciparum malaria within one month of leaving a malaria-endemic region (median 10 days); nonetheless, cases of falciparum malaria have been documented to manifest up to four years later. The incubation time for non-falciparum malaria is often extended (median 15–16 days), and both P. vivax and P. ovale malaria can recur months or years post-exposure due to the existence of hypnozoites in the liver. The maximum documented incubation time for P. vivax is 30 years. (Omondi et al., 2024).

8. Uncomplicated Malaria

The most prevalent and least severe kind of malaria is referred to as uncomplicated malaria. Uncomplicated malaria is characterised by symptoms like fever, chills, nausea, headaches, myalgia, and vomiting, without clinical indications indicative of severity or crucial organ failure. A severe infection typically manifests with cognitive impairment, pronounced anaemia, and respiratory failure; its severity is largely contingent upon the specific Plasmodium species and the host's immunological response. The symptoms of malaria start at the rupture of the first liver schizont, resulting in the release of merozoites that subsequently infect red blood cells. This event is typically asymptomatic in the majority of individuals who will subsequently develop illness, despite being the initial chance for symptoms to manifest. In the course of this first infection, cytokines, including tumour necrosis factor (TNF-α), induce fever. Uncomplicated malaria is often managed with antimalarial medicine throughout each symptomatic episode. The malaria parasites can be eradicated from the body by administration of antimalarial therapy. The plasmodial species responsible for simple malaria include Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium knowlesi, and Plasmodium malariae (Watt, 2023).

9. Laboratory findings

Thrombocytopenia—a condition marked by a significant reduction in platelet count—is the most commonly observed laboratory abnormality in patients diagnosed with malaria, occurring in approximately 60% of cases. This haematological finding is particularly important, as it not only aids in clinical suspicion of the disease but also reflects the pathophysiological impact of Plasmodium infection on the host's haematopoietic system. Following thrombocytopenia, hyperbilirubinemia is reported in around 40% of patients, likely due to the increased breakdown of red blood cells and resultant haemolysis associated with malaria infection. Anaemia, another hallmark of severe and chronic malarial episodes, is present in approximately 30% of individuals, reflecting sustained destruction of erythrocytes and impaired erythropoiesis. Additionally, elevated hepatic aminotransferase levels, seen in 25% of cases, point to hepatic involvement and potential liver dysfunction, which may complicate clinical management, especially in severe P. falciparum infections.

The white blood cell (WBC) count in malaria patients typically remains within normal limits or may even appear reduced. However, a closer look often reveals neutrophilia, with a pronounced left shift, indicating an increase in immature neutrophil forms such as bands. This phenomenon suggests an active inflammatory response, often seen in moderate to severe infections. Moreover, inflammatory markers such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin levels tend to be consistently elevated, further confirming the systemic inflammatory nature of malarial infections. These laboratory indicators, while non-specific, provide valuable insight into disease severity and systemic involvement.

Crucially, the degree of abnormality in these laboratory tests has been shown to correlate with the clinical severity of malaria. As parasitemia increases and organ systems become more involved, markers of inflammation and organ dysfunction rise accordingly, often serving as early warning signs for clinicians. In one notable study involving tourists returning from malaria-endemic tropical regions, it was found that the combination of thrombocytopenia and hyperbilirubinemia had a positive predictive value of 95% for malaria, underscoring the diagnostic utility of routine laboratory investigations in settings where malaria is suspected but not initially confirmed (Thakur, Joshi, & Kaur, 2020).

In light of these findings, integrating standard haematological and biochemical markers into diagnostic

protocols can enhance early detection and guide timely intervention. Moreover, recognising these laboratory signatures is especially crucial in non-endemic areas where clinical familiarity with malaria may be limited, yet imported cases continue to occur due to global travel and migration.

10. CONCLUSION

In Pakistan, malaria remains a significant public health challenge, continuing to exact a toll on the healthcare system, economy, and vulnerable populations. Despite various national and international efforts, the disease persists as a high-profile concern, especially in endemic provinces and districts with limited access to health infrastructure. The effective management of malaria in the country necessitates a rigorous, inter-sectoral partnership that brings together health authorities, policymakers, research institutions, civil society, and international health bodies. Such partnerships must be grounded in a long-term strategic framework, supported by sustained political will, consistent funding, and clear accountability mechanisms. Central to this effort is the establishment of a comprehensive monitoring and evaluation system, which ensures that ongoing malaria control programmes are regularly assessed for their effectiveness, adaptability, and alignment with epidemiological realities.

To close existing knowledge gaps and support evidence-based interventions, the formulation of metacentric, interdisciplinary research projects is vital. These projects should be designed with a clear focus on the epidemiological, entomological, and socio-behavioural dimensions of malaria transmission. By doing so, they can yield insights that are contextually relevant and inform targeted interventions across diverse ecological zones in Pakistan. The launch phase of such initiatives must be underpinned by a rigorous situation analysis, through which the current state of malaria transmission, health system capacity, and community-level challenges are thoroughly assessed. This phase should also anticipate and outline potential logistical, operational, and infrastructural barriers that may arise during implementation. Addressing these issues proactively can significantly improve the likelihood of programmatic success.

In reviewing the broader picture, it becomes clear that Pakistan continues to experience an extended period of high malaria transmission. Factors such as population displacement, climate variability, and limited access to vector control tools have prolonged the country's position in the transmission phase. Nevertheless, with the right combination of political commitment, community engagement, data-driven planning, and robust health systems, Pakistan may transition to the pre-elimination stage in the foreseeable future. This transition is achievable, particularly if preventive and curative measures are executed proactively, rather than reactively. Strategic investments in diagnostic services, vector control, public awareness campaigns, and health worker training will be pivotal in shifting the country from disease management to elimination preparedness.

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