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NARRATIVE REVIEW: CURRENT UPDATES IN THE TREATMENT OF MALARIA

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Abstract

Malaria is an infectious disease caused by the Plasmodium parasite and transmitted through the bite of female Anopheles mosquitoes. Although global efforts to control the disease have increased, malaria remains a major health threat, especially in developing countries. This study aims to identify recent developments in malaria treatment methods. This study uses a narrative review method. Data collection was carried out through a literature review by searching for relevant research articles, reports, and books from various scientific databases. The collected data were then analyzed in three stages, namely data reduction, data presentation, and drawing conclusions. The results showed that updates in malaria treatment include the development of new drugs and combination therapies, prevention efforts through vaccines, more individualized treatment approaches, and community involvement in treatment programs. These initiatives provide new hope in the fight against malaria.

Keywords: *Current treatment, Treatment, Malaria.*

INTRODUCTION

Malaria is a disease caused by protozoa from the Plasmodium parasite and is one of the leading causes of death and morbidity in many developing countries. It is estimated that around 3.3 billion people worldwide are at risk of contracting this disease. Malaria is also a significant health problem in tropical and subtropical regions (Kendie et al., 2021). Globally, there are 247 million positive cases of malaria reported in 84 malaria-endemic countries. Indonesia is one of the malaria-endemic countries with a total of 443,530 cases, of which 89% of positive cases come from Papua Province (Ministry of Health, 2023).

The government is targeting national malaria elimination by 2030. Based on the 2020-2024 National Medium-Term Development Plan (RPJMN), the target is for 408 districts/cities in Indonesia to be free from malaria. By 2023, 389 districts/cities have reached the maintenance stage or have been declared malaria-free. There are five strategies implemented together with local governments, related agencies, and community elements. First, the implementation of comprehensive policies, including increasing detection, case finding, and diagnostics. Second, strengthening surveillance.

Third, providing treatment. Fourth, controlling risk factors. Fifth, empowering the role of the private sector and society (Indonesia, 2020).

Since 2000, the development and widespread rollout of rapid diagnostic tools (RDTs), insecticide-treated bed nets (ITNs), and artemisinin-based combination therapies (ACTs) have been the cornerstones of malaria control efforts. Continued investment in the development and deployment of next-generation tools is critical to achieving the global malaria elimination target by 2030. Several malaria vaccines are currently in development. Like the RTS,S vaccine, many of these vaccines target the malaria parasite before it enters the human liver, where it can multiply rapidly. The most advanced vaccine candidate is R21, which has completed Phase 3 clinical trials. In addition, there are other vaccines that focus on preventing parasite transmission, as well as vaccines specifically designed to protect women during pregnancy (WHO, 2023).

Previous research by (Hanboonkunupakarn & White, 2022) showed that targeted malaria eradication using focal mass treatment with dihydroartemisinin-piperaquine has been proven to be a safe and effective malaria elimination accelerator, but overall progress towards malaria elimination has been slow. Since 2015, the number of malaria cases globally has increased. Since new drugs will not be widely available in the near future, active measures to conserve current antimalarials should be the highest priority. Another study by (Daily, Minuti, & Khan, 2022) showed that malaria prevention and treatment depend on the species and drug sensitivity of the parasite from the area of transmission. Intravenous artesunate is the first-line therapy for severe malaria.

This study enriches the theory in clinical epidemiology by highlighting the latest developments in malaria treatment and disease distribution patterns and their impact on public health management strategies. So that it can help in formulating a more comprehensive theory about the relationship between treatment, drug resistance, and case management at the population level. This study aims to identify the latest developments in malaria treatment methods.

RESEARCH METHOD

This study uses a narrative review method. Narrative is a research method in social sciences that functions to describe or explain an event, incident, or series of events that are chronologically interconnected (Yusri, 2020). Data collection was carried out through a literature review by searching for relevant research articles, reports, and books from various scientific databases. Data collection was carried out through a literature review by searching for relevant research articles, reports, and books from various scientific databases, such as PubMed, Google Scholar, and health journals related to malaria treatment. The data that has been collected is then analyzed in three stages, namely data reduction, data presentation and drawing conclusions. These three stages are carried out repeatedly to produce a comprehensive and accountable analysis.

RESULT AND DISCUSSION

The disease mechanism of malaria occurs through the relationship between two main hosts, the female Anopheles mosquito and humans. When a female mosquito bites a human, the parasite's life cycle begins. The mosquito draws blood while introducing sporozoites from its saliva into the human body. The malaria parasite then invades red blood cells (RBCs), resulting in a decrease in hemoglobin, and releases acid digestion vacuoles due to heme digestion, which are toxic to the parasite itself (Nureye & Assefa, 2020). Malaria is a health problem that can also have a significant economic impact, especially because the disease is widespread in countries and regions experiencing poverty, hindering social and economic development in the area (Lukwa, Mawoyo, Zablon, Siya, & Alaba, 2019). In addition to infecting humans, malaria parasites can also infect other animals, such as reptiles, birds and mammals. To date, more than 200 Plasmodium species have been formally identified, with each species having a different host (Nandal et al., 2024).

However, despite malaria being a major challenge, developments in medical research and technology have brought advances in the management and treatment of the disease. In recent decades, malaria treatment development programs have progressed through partnerships in pharmaceutical development, aiming to find more effective and efficient therapies in the fight against malaria (Ashley & Phyo, 2018). One of the main reasons for the importance of malaria treatment updates is due to the increasing parasite resistance to existing drugs. Malaria parasites, particularly Plasmodium falciparum, have shown increasing resistance to many antimalarial drugs. This resistance poses a serious threat to malaria control efforts (Ippolito, Moser, Kabuya, Cunningham, & Juliano, 2021).

Over the past two decades, malaria treatment updates have focused on responding to the problem of drug resistance, particularly to Plasmodium falciparum. This parasite has now become highly resistant to most of the antimalarial drugs that were once effective, so the medical world's attention is focused on developing new drugs. This approach aims to combat parasite resistance more effectively and prevent the return of malaria outbreaks in tropical regions (Nandal et al., 2024). Given the complexity of malaria and the growing challenge of drug resistance, treatment renewal efforts are urgently needed. More innovative and diverse approaches need to be implemented to address the problem of drug resistance, including by introducing new antimalarials that are more effective and resistant to mutated parasites (Monroe, Williams, Ogoma, Karema, & Okumu, 2022).

In addition to resistance, updates in malaria treatment are also important because they have the primary goal of improving treatment success and bringing malaria closer to global elimination. Providing more appropriate and effective treatment will result in improved patient recovery rates. Better treatment can lead to faster treatment and fewer complications, thereby reducing morbidity and mortality from malaria. Achieving these cure rates allows populations vulnerable to infection, especially in endemic areas, to be

better protected from long-term health impacts. Thus, continuously updating and improving treatment methods are steps towards a more achievable malaria elimination.

With these reasons in mind, updates in malaria treatment have been a major focus. This includes several important aspects, including the development of new drugs and more effective drug combinations. Artemisinin remains the main foundation in malaria treatment to date. However, with the increasing risk of parasite resistance, researchers are constantly working to develop more effective drug combinations. Artemisinin-based combination therapy (ACT) is one of the most important steps in treating malaria, especially when combined with vector control interventions. This strategy has significantly reduced the burden of malaria caused by Plasmodium falciparum worldwide (Bhatt et al., 2015).

ACTs remain the only widely used treatment for uncomplicated falciparum malaria. This is even true in regions such as the Greater Mekong Subregion (GMS), where artemisinin resistance (ART-R) is widespread. Currently, there are five ACT combinations recommended by WHO for the treatment of malaria, namely artemether-lumefantrine, artesunate-mefloquine (ASMQ), dihydroartemisinin-piperaquine, artesunate-amodiaquine, and artesunate-sulphadoxine-pyrimethamine (WHO, 2015). These combinations rely on fast-acting artemisinin derivatives, combined with slower-acting drugs that last longer in the body to ensure the remaining parasites are eliminated.

ACTs consist of artemisinin derivatives such as artemether, artesunate, or dihydroartemisinin which are very potent and fast-acting, but have a short plasma half-life. Therefore, ACTs are combined with slower-acting partner drugs such as lumefantrine, amodiacuine, mefloquine, piperacuine, sulfadoxine-pyrimethamine, or pyronaridine. These partner drugs last longer in the blood, so elimination of parasites that may persist after artemisinin clears most of the parasites in the body. Treatment of malaria with artemisinin can reduce the parasite load by 10,000-fold every 48 hours, or one parasite life cycle. After a three-day course of ACT treatment, the remaining parasites are then cleared by the partner drug (Dhorda, Amaratunga, & Dondorp, 2021).

However, in some areas, resistance to ACTs has begun to emerge. Malaria parasites, such as Plasmodium falciparum, show the ability to mutate and survive despite appropriate treatment. This resistance refers to the ability of the parasite to survive or multiply despite being given a dose of a drug that is normally effective (Alaithan, Kumar, Islam, Liappis, & Nava, 2023). This phenomenon has encouraged researchers to develop new drugs that aim to overcome the increasing drug resistance. The development of these new drugs aims to maintain the effectiveness of malaria treatment in the long term.

Several promising new antimalarial drugs are currently in the clinical development stage (Dhorda et al., 2021). Among these drugs are cipargamine (KAE609) and ganaplacide (KAF156). Cipargamine is a spiroindolone compound that has a higher speed of action than artemisinin, while ganaplacide is an imidazolopiperazine that works at different stages of the parasite life cycle. Despite

these new drugs, there are other compounds, such as 4-aminoquinoline ferroquine, which are not a new class of compounds. Currently, these new drugs are undergoing phase II clinical trials and are not expected to be available for rapid use in areas where artemisinin resistance (ART-R) is common or emerging (Ashley & Phyo, 2018; Tse, Korsik, & Todd, 2019).

AstraZeneca has also discovered a new antimalarial drug known as ZY-19489, which is currently in phase I clinical trials. ZY-19489, previously known as MMV 253 or compound 12, is part of the triaminopyrimidine group. Although the exact mechanism of action of this drug is not yet known, ZY-19489 showed potent antimalarial activity against asexual blood stages of Plasmodium falciparum, both in in vitro assays and in mouse models. However, it did not show significant activity against the form of the parasite present in the liver or its sexual phase.

Results from the first phase 1 trial in healthy volunteers showed that the drug has good efficacy and safety. No resistance was detected in cases of relapse, indicating that the problem was due to insufficient exposure to the drug rather than the presence of a genetic mutation. Therefore, further studies are needed to explore the potential of ZY-19489 in combination with partner drugs, to treat the liver stage and sexual phase of the parasite and prevent infection recurrence and resistance (Barber et al., 2022). In this regard, the Medicines for Malaria Venture (MMV) plans to study ZY-19489 in combination with ferroquine, which is a 4-aminoquinoline that inhibits heme detoxification (Alaithan et al., 2023).

In addition to the development of new drugs and combinations, progress in malaria treatment can also be seen from prevention efforts, including through malaria vaccines. The administration of malaria vaccines aims to reduce the burden of infection in endemic areas. Currently, two promising malaria vaccines, RTS,S/AS01 and R21/MM, are available and are being evaluated for their performance in the field (González-Sanz, Berzosa, & Norman, 2023).

The RTS,S/AS01 vaccine is a recombinant protein-based vaccine that uses T epitope repeats of the P. falciparum sporozoite surface antigen. The vaccine also contains hepatitis B surface antigen (HBsAg) and proprietary adjuvant AS01. In phase III trials, the RTS, S/AS01 vaccine demonstrated partial protection against clinical malaria in children aged 5 to 17 months who received three doses, plus a booster given at 20 months of age. The efficacy of this vaccine was recorded at 36% (95% CI 32-40), providing new hope in malaria prevention efforts among children (González-Sanz et al., 2023).

Meanwhile, the R21/MM vaccine is a virus-like particle based on the P. falciparum circumsporozoite and fused with N-terminal HBsAg, and uses the patented M matrix as an adjuvant. In phase II trials, the vaccine showed impressive efficacy of 74% (95% CI 63-82%) with the use of low-dose MM adjuvant, and increased to 77% (95% CI 67-84%) when combined with high-dose MM adjuvant. The R21/MM trial was implemented alongside other malaria prevention strategies, such as passive and active

case detection, bed net use, SMC (comprehensive management strategy), and indoor residual spraying (Butler & Stricker, 2019).

Although both vaccines have shown promising results, data on the protective resistance of the vaccines are limited, and neither has met the expected baseline requirements. Currently, there is also a lack of data comparing the use of R21/MM and RTS,S/AS01 vaccines directly. There is no fully effective malaria vaccine, so research continues to develop safe and effective vaccines to prevent malaria.

There are several other vaccines currently under research, including the attenuated sporozoite vaccine known as PfSPZ (Butler & Stricker, 2019). In addition, there are also protein-based vaccines designed to target other stages in the parasite's life cycle, such as Rh5, Pfs35, and Pfs230 (Minassian et al., 2021). In addition, research is also exploring DNA- and mRNA-based vaccines (Mallory et al., 2021).

Furthermore, malaria treatment updates are also increasingly personalized with the arrival of a rapid and accurate diagnostic test, the Rapid Diagnostic Test (RDT). RDT for malaria is an examination method that measures a patient's antibodies against specific antigens from one or more plasmodium species. According to Aryani (2023), RDTs have become an important tool in efficiently detecting malaria infections.

The World Health Organization (WHO) recommends increasing the use of RDTs as an integral part of the management and surveillance of malaria infection. RDTs offer several advantages, including high sensitivity, rapid results, and affordable cost. This convenience makes them a commonly used option in malaria testing. The use of RDTs helps doctors quickly identify the type of malaria parasite infecting a patient. This aids in more precise treatment adjustments, thereby improving the effectiveness of therapy and patient outcomes. This approach represents a significant advance in malaria diagnosis and treatment strategies, leading to more efficient management that is responsive to individual needs.

Following on from the prevention approach, there has also been a renewal of the direct community engagement approach. Globally, malaria control programs have adopted a community-based approach known as community engagement (ACE) to design and implement malaria interventions. According to Awasthi et al. (2024), this approach emphasizes the importance of working with communities in the design and implementation of culturally appropriate interventions. In this way, wider acceptance and participation among at-risk groups is expected, while also developing a sense of local ownership to improve the sustainability of malaria prevention efforts.

Increasing public awareness is one of the main focuses through health campaigns, where communities are given a better understanding of malaria prevention and treatment. Intervention activities include promoting the use of long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), and environmental management to control vectors, which includes larviciding and chemoprophylaxis as preventive measures. In addition, the program also emphasizes the importance of early diagnosis and prompt treatment of positive cases, which is essential for disease control and strengthening surveillance.

Furthermore, community involvement in the malaria elimination program is emphasized. Communities are encouraged to actively report malaria cases and follow recommended treatment procedures. This approach not only strengthens malaria elimination efforts, but also builds communities that are more responsive and proactive in facing the threat of malaria. Active community involvement is expected to strengthen public health programs and achieve better results in controlling the disease.

However, despite continued advances in malaria treatment, a number of challenges remain that affect the effectiveness of efforts to treat the disease. One of the main challenges is access to treatment. In some areas, especially in remote or less developed areas, access to quality malaria medicines is still very limited. In addition, the cost of malaria treatment is also a burden for communities, especially in developing countries. Low-income communities often struggle to afford treatment, even for treatment that is necessary to save lives. Further complicating the challenge is climate change. Climate change can expand the distribution areas of Anopheles mosquitoes, which are the main vectors of malaria. As temperatures rise and rainfall patterns change, new areas that were previously unaffected can become breeding grounds for these mosquitoes. Thus, efforts must be made to overcome these challenges so that malaria treatment reforms can be effective. To ensure the effectiveness of malaria treatment reforms, concrete measures are needed to overcome these barriers.

From the results obtained, it can be concluded that updates in malaria treatment include the development of new drugs as well as combination therapies, prevention efforts through vaccines, more individualized treatment approaches, and community involvement in treatment programs. These initiatives provide new hope in the fight against malaria. However, many challenges remain. Limited access to quality treatment, high costs, and environmental factors that influence the spread of malaria are some of the issues that need to be addressed. Therefore, close collaboration between governments, health institutions, researchers and communities is necessary to achieve the goal of reform in malaria treatment and to effectively achieve elimination of the disease.

CONCLUSSION

Therefore, this research provides a compelling story of what leaders have done and how they have enacted COVID-19 and its impacts on organisations through the lens of adaptive leadership. In light of the adaptive leadership theory by DeRue, our results depict the dynamic nature of leadership actions and environment—especially work arrangements in a pandemic. We have now identified a new kind of leadership practice that can be best described as hybrid, collaborative, and inclusive leadership. This hybrid approach represents a change from the conventional leadership paradigm that was centred on anticipatory responses to uncertainty.

As the author also quoted from the book of Paul Hersey and Kenneth Blanchard about situational leadership may still be relevant: “There is no single ‘best’ style of

leadership. The most effective leaders are those who can change their style to meet the needs of their followers and the demands of the situation."

The quote above has reiterated the need for flexibility and adaptive-ability in leadership rather than to stick with the fixed method. By elaborating more on this, the authors conclude that adaptive leadership in the midst of changing eras, specifically pandemics, has gone hand in hand to prove that leadership in many practices has a back and forth correlation both from the individual leader contingency plan and its circumstances readiness.

Moreover, our study highlights the leading actors' significance in building organizational capacity and effectiveness in the post-COVID-19 era. The case can therefore be made that by changing their leadership styles to suit the new environment, leaders can effectively manage the complexities of the post-pandemic team environment. Hybrid, collaborative, and inclusive leadership is a new era in leadership concept and practice that The results show that updates in malaria treatment include the development of new drugs as well as combination therapies, prevention efforts through vaccines, more individualized treatment approaches, and community involvement in treatment programs. The findings show that there have been advances in malaria treatment, which include the development of new drugs and more effective combination therapies. In addition, malaria vaccines such as RTS,S/AS01 and R21/MM are now available as an additional preventive measure, although challenges related to vaccine effectiveness and availability still need to be addressed. A more individualized approach is also key, with the use of rapid diagnostic tests (RDTs) facilitating more precise detection and treatment based on the type of infecting parasite. Furthermore, the importance of community involvement is also increasingly recognized in malaria treatment programs. Community-based approaches help increase awareness, case reporting and active participation in prevention efforts through the use of long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) activities. However, despite significant progress, challenges such as limited access to treatment, the high cost of treatment, and the impact of climate change expanding the distribution areas of Anopheles mosquitoes remain a major barrier. Therefore, based on these findings, further collaboration between governments, health organizations, researchers and communities is needed to overcome these challenges and achieve sustainable malaria elimination.

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