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Differences in the Life Cycle and Growth of Plasmodium Knowlesi, Inui, Vivax, Malariae, Falciparum, Ovale

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ABSTRACT
Plasmodium is a parasite that causes malaria in humans. Various Plasmodium species have differences in their life cycles and growth, which influence the clinical characteristics and management of malaria. This article explains the differences in the life and growth cycles of the six Plasmodium species most commonly found in humans, namely Plasmodium knowlesi, Plasmodium inui, Plasmodium vivax, Plasmodium malariae, Plasmodium falciparum, and Plasmodium ovale. Each species has differences in its life cycle, including pre-erythrocytic, erythrocytic, and extracellular duration. In addition, these differences also influence clinical symptoms, disease severity, and response to treatment. A thorough understanding of these differences is important for accurate diagnosis and effective treatment of malaria.

Keywords: *Inui, , Malariae, Vivax*

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INTRODUCTION

In the field of medicine and parasitology, research on the variations in the life cycle and growth of several Plasmodium species, such as Plasmodium knowlesi, Plasmodium inoui, Plasmodium vivax, Plasmodium malariae, Plasmodium falciparum, and Plasmodium ovale, is essential for discussion and investigation. Each Plasmodium species has a unique life cycle and growth mechanism. A deep understanding of these differences is crucial in efforts to prevent, diagnose, and treat malaria caused by various Plasmodium species. Therefore, this research aims to gain a deeper understanding of the differences in the life cycles and growth of Plasmodium species to make a significant contribution to malaria management.

Malaria is a disease caused by obligate intracellular protozoa of the genus Plasmodium. Malaria in humans can be caused by Plasmodium malariae, Plasmodium

vivax, Plasmodium falciparum, and Plasmodium ovale. The spread of malaria is determined by three factors known as the host, agent, and environment (Irianto, 2013). Malaria is a major public health problem that can cause death, especially among high-risk groups such as infants, young children, and pregnant women. Malaria can also cause anemia and reduce work productivity. In 2010, 65% of districts in Indonesia were endemic, resulting in approximately 45% of the population in those districts being at risk of contracting malaria. Based on community survey results from 2007 to 2010, the prevalence of malaria in Indonesia decreased from 1.39% (Riskesdas 2007) to 0.6% (Riskesdas 2010). Malaria morbidity rates also declined from 3.62 per 1,000 population in 2000 to 1.85 per 1,000 population in 2009 and 1.96 in 2010, while the mortality rate due to malaria reached 1.3%.

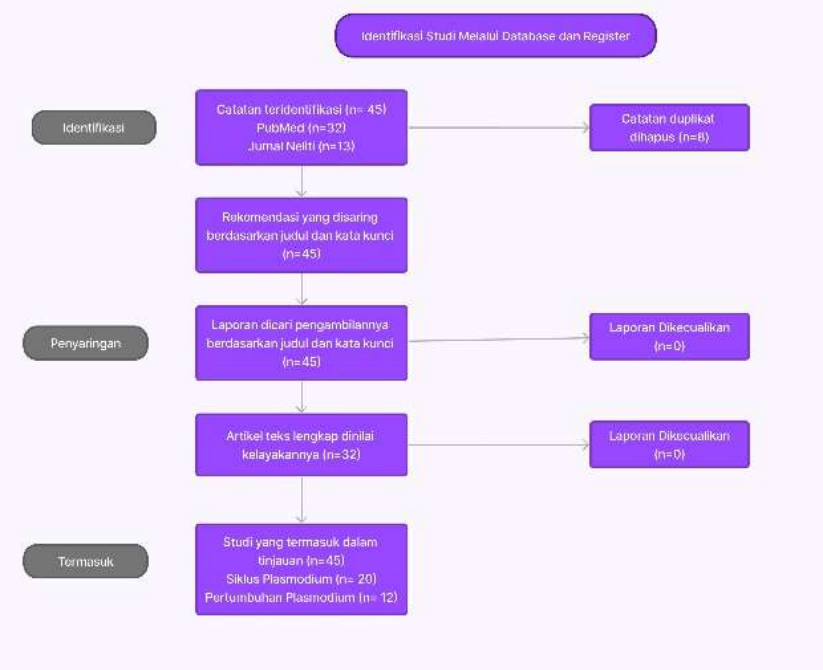
Although the Annual Parasite Incidence (API) has decreased nationally, the API in certain areas remains significantly higher than the national average. Additionally, in areas with relatively low malaria cases, outbreaks often occur due to imported cases. In 2011, the reported number of malaria-related deaths reached 388 cases. The national prevalence of malaria based on the 2010 Basic Health Research (Riskesdas) was 0.6%, with several provinces exceeding the national average API, including West Nusa Tenggara, Maluku, North Maluku, Central Kalimantan, Bangka Belitung, Riau Islands, Bengkulu, Jambi, Central Sulawesi, Gorontalo, and Aceh. The highest prevalence rates were found in eastern Indonesia, specifically West Papua (10.6%), Papua (10.1%), and East Nusa Tenggara (4.4%). Efforts to reduce malaria morbidity and mortality are carried out through malaria eradication programs, including early diagnosis, rapid and accurate treatment, and surveillance and vector control through community education and environmental health understanding, all aimed at breaking the transmission chain of malaria.

The first recorded case of malaria parasite resistance to chloroquine was in East Kalimantan in 1973 for Plasmodium falciparum, and in 1991 for Plasmodium vivax in Nias. Since 1990, such resistance has been increasingly reported throughout Indonesia's provinces. Additionally, there have been reports of resistance to Sulfadoxine-Pyrimethamine (SP) in several parts of Indonesia. This situation can increase the morbidity and mortality of malaria. Therefore, to address the issue of resistance (multiple drug resistance) and the development of more effective antimalarial drugs, the government has recommended the use of alternative treatments for chloroquine and SP, namely the combination of Artemisinin with antimalarial drugs known as Artemisinin-based Combination Therapy (ACT).

RESEARCH METHODOLOGY

This research employs a descriptive-analytical approach by collecting data from relevant scientific literature, including journals, articles, and textbooks. The information obtained will be used to develop a deep understanding of the life cycle and growth of each Plasmodium species. Additionally, the clinical characteristics associated with each species will be investigated, such as clinical symptoms, disease severity, and response to

treatment. This data will be critically analyzed to identify the key differences among the Plasmodium species studied. This research will make a significant contribution to the scientific understanding of the biological differences between various Plasmodium species, which can aid in more accurate diagnosis and more effective management of malaria. The results of this study are expected to provide guidance for global efforts in malaria control and prevention.



RESULT AND DISCUSSION

The analysis results indicate differences in the life cycle and growth of various Plasmodium species, namely Plasmodium knowlesi, Plasmodium inui, Plasmodium vivax, Plasmodium malariae, Plasmodium falciparum, and Plasmodium ovale. Each species has unique characteristics that influence clinical symptoms, disease prognosis, and malaria control strategies. Plasmodium is a protozoan parasite that causes malaria in humans. Although all Plasmodium species share a general life cycle involving stages in the Anopheles mosquito vector and the human body, there are differences in the life cycle and growth of each species. The following are the differences in the life cycle and growth of the different Plasmodium species:

a. Plasmodium knowlesi

The life cycle is similar to that of P. vivax and P. malariae. It has a life cycle with the gametocyte stage (formation of sex cells) in humans which is spread by the bite of the Anopheles mosquito. The life cycle of the parasite P. knowlesi involves the mosquito An. leucosphyrus and An. latens as vector and definitive host, as well as monkeys (M. fascicularis, M. nemestrina) and humans as intermediate hosts. In the mosquito's body, the parasite will experience an exogenous sexual phase or form sporozoites (sporogony), whereas in the bodies of

monkeys and humans, the parasite will experience an asexual phase or form schizonts (schizogony) and an endogenous sexual phase or form gametes (gametogony).

The life cycle of P. knowlesi is generally similar to other Plasmodium species, but there are slight differences, such as the duration of the phases in the cycle. In P. knowlesi, the extrinsic incubation period required in the body of the Anopheles mosquito is around 9–10 days and at a temperature of 25oC, almost the same as P. malariae; both are long-lived agents. When entering the body of an intermediate host, P. knowlesi will first undergo an exoerythrocytic cycle in the liver and will only form sporozoites which are immediately active in hepatocytes; Hypnozoites are not formed. This means that P. knowlesi cannot cause recurrence or relapse. Then, the parasite will enter the erythrocyte cycle, namely in the red blood cells. The erythrocyte cycle in P. knowlesi is the shortest, namely every 24 hours. As this erythrocyte cycle progresses, the patient's clinical symptoms begin to appear and form a fever pattern. In P. knowlesi, the fever pattern that occurs is quotidian fever (every 24 hours). The formation of gametocytes will occur after experiencing several asexual cycles (sprogony), around 3-5 times. The formation of P. knowlesi gametocytes occurs relatively slowly, approximately 48 hours (Singh & Daneshvar, 2013).

Plasmodium knowlesi has a morphology that is very similar to other Plasmodium parasites, making it difficult to differentiate only with the help of a microscopic examination involving blood smear preparations. On blood smear examination, three stages can be identified, namely the trophozoite, schizont and gametocyte stages (Jeremiah et al., 2014). The young trophozoite stage of P. knowlesi is very similar to P. falciparum, while the other stages are similar to P. malariae. P. knowlesi gametocytes are rarely found (only around 40%) because they are influenced by the formation of gametocytes which occurs later, after going through 3-5 erythrocyte cycles, plus the development of gametocytes which takes quite a long time, around 48 hours, to mature in erythrocytes. If the patient is treated late, then these gametocytes will form and can be found in blood tests. Because of this similarity and to reduce errors in diagnosis, in microscopic examination, if the parasite P. malariae is found, it will be written as "P. malariae/P. knowlesi". Currently, additional examinations using molecular techniques such as PCR can be used to detect malaria parasite species more accurately and with certainty (Angelika et al., 2021).

b. Plasmodium inui

Its life cycle is similar to that of Plasmodium falciparum and Plasmodium malariae. Through the bite of the Anopheles mosquito, Plasmodium inoui infects humans. P. inui infection in humans occurs approximately 31 days after the bite of an infectious mosquito (Coatney et al., 1966). This study highlights that the life cycle of P. inui in the human body lasts for 72 hours, resulting in quartan fever.

However, P. inui infections in humans are self-limiting because the parasite was not detected in certain case patients after about 8 months of exposure. P. inui infection in humans appears likely to occur naturally, but low parasite counts and sharp fluctuations between negative and moderate parasitemia via microscopy hinder detection by standard methods such as PCR. Sporozoites of Plasmodium inui have been observed naturally in the Anopheles cracens mosquito. Apart from that, mosquitoes from the Leucosphyrus group have also been proven to be able to transmit P. inui naturally.

Laboratory experiments show that P. inui is able to adapt well to the Anopheles mosquito species which is its natural vector. Geographically, P. inui has a wide distribution in Asia, including southern India, Southeast Asia and Taiwan. A surveillance study revealed a high prevalence of P. inui in wild macaques in Pahang, with the majority of infections being co-infections with other Plasmodium species. Due to the high prevalence of P. inui among macaques and the Anopheles mosquito vector, humans are at risk of contracting P. inui through vector-borne transmission from infected macaques, especially in areas where humans, macaques, and the mosquito vector coexist. Studies also report the simultaneous occurrence of P. inui with other species such as P. knowlesi and P. cynomolgi in monkeys and mosquitoes. Humans are frequently exposed to a mixture of non-human primate malaria sporozoites. Since P. inui infections in humans often cause no symptoms, this raises the possibility of the evolution of P. inui to efficiently infect humans, especially since patent infections in humans can be caused by only a few parasites. Patterns of P. inui infection can vary depending on geographic location. Therefore, epidemiological and entomological research on simian malaria transmission must be carried out using highly sensitive detection methods, especially in efforts to eliminate malaria in Malaysia and other countries (Liew et al., 2021).

c. Plasmodium vivax

Life Cycle It has a complex life cycle involving an asexual stage in the liver and a sexual stage in the Anopheles mosquito. Has a dormant (sleeping) form which can cause relapse. exoerythrocytic cycle for 8 - 27 days. P. vivax ametocytes are known for their very early appearance during the course of infection. This may be due to their rapid development, with gametocytes often detected within 3 days after asexual parasites are first observed (Bousema & Drakeley, 2011). In controlled experimental infections, gametocytes appeared in peripheral blood within 7 days after direct infection with P. vivax sporozoites, indicating that mosquito transmission may occur before the appearance of clinical symptoms. Although early transmission can lead to rapid spread and rapid outbreaks, the positive impact of this phenomenon is to limit the spread of drug resistance to P. vivax. It is important to note that because transmission usually occurs before the infection is treated, a vaccine that is effective in inhibiting

transmission will help overcome infections that recur due to failure of radical treatment (Bousema & Drakeley, 2011).

However, a hallmark of P. vivax biology is its ability to form long-lasting liver stages, called hypnozoites. Upon entry to the liver, P. vivax sporozoites can follow two different pathways. Some develop directly into hepatic schizonts, which after 8 days, release merozoites to initiate an asexual cycle in the blood, while others, namely hypnozoites, enter the dormant phase around the third day after infection. Although hypnozoites may be metabolically active, they do not undergo division and remain in a dormant state for weeks or even months before becoming active again. The frequency and time of recurrence of this disease varies globally, with the longest recurrence periods occurring in strains in temperate climates, indicating that the periodicity of recurrence is influenced by natural selection. Although the mechanisms underlying commitment to dormancy and reactivation are still not completely understood, it is clear that relapses caused by hypnozoites may account for up to 80% of all P. vivax blood stage infections. The common parasitemia of vivax malaria is relatively low because the infection is limited to reticulocytes, so often requires the use of a thick smear to obtain an accurate diagnosis (Galinski & Barnwell, 2008).

d. Plasmodium malariae

The life cycle has asexual and sexual stages in the human body and the Anopheles mosquito. Tends to cause chronic infections and persists in the blood for long periods of time. exoerythrocytic cycle for 15 - 30 days. The life cycle of Plasmodium malariae begins when an infected Anopheles mosquito bites a human and injects sporozoites into the bloodstream. These sporozoites then move to the liver, where they develop into merozoites in liver cells. Thereafter, merozoites are released into the bloodstream, where they attack red blood cells, undergo asexual reproduction, and induce malaria symptoms (Mendis et al., 2001).

Transmission of Plasmodium malariae in the human body occurs through the bite of an infected Anopheles mosquito. When a mosquito looks for human blood to suck, it injects Plasmodium sporozoites into the human bloodstream. These sporozoites then reach the liver, where they multiply and release merozoites into the bloodstream, leading to malaria infection. Next, the released merozoites attack and infect human red blood cells, causing malaria symptoms. Some merozoites can undergo development into the sexual form of the parasite, called gametocytes, and when an Anopheles mosquito bites an infected human, these gametocytes can be reabsorbed by the mosquito, starting a new infection cycle in the mosquito's body and helping the spread of disease (Langhorne et al., 2008).

e. Plasmodium falciparum

Plasmodium falciparum has the most complex life cycle among the Plasmodium species that cause malaria. The asexual stage occurs in the human body and the sexual stage occurs in the Anopheles mosquito, the exoerythrocytic cycle lasts 8 – 25 days. The asexual cycle of plasmodium begins when

plasmodium sporozoites, transmitted by Anopheles mosquitoes through saliva, enter the human bloodstream and migrate to the liver to multiply to form schizogony sporozoites, also known as merozoites. After this formation, merozoites are released into the bloodstream through hepatocyte vesicles. The merozoites released are called merosomes. This process takes around 6 days in Plasmodium falciparum (Chrismayanti & Veronica, 2020). Merosomes then infect red blood cells and multiply into "ring stage" trophozites and then into mature trophozoites.

In the final trophozoite phase, schizonts are formed with a formation duration of between 36-48 hours in Plasmodium falciparum. Each schizont consists of a variable number of merozoites depending on the type of plasmodium. These schizonts cause lysis of erythrocytes, which results in fever symptoms and the release of hemozoin as a breakdown product of heme by the plasmodium. The sexual phase occurs when the Anopheles mosquito sucks plasmodium gametocytes when it bites a human. Gametocytes mature in the intestines of the Anopheles mosquito, then undergo fertilization by previously formed male and female gametes, forming a zygote. The zygote then develops into ookinetes and oocysts, and finally forms sporozoites which then migrate to the mosquito's salivary glands to be transmitted to other hosts (Chrismayanti & Veronica, 2020)

It is known as the most deadly Plasmodium species because it can cause severe and fatal complications, including cerebral malaria. Fever usually appears irregularly. Symptoms of malaria include weakness, lethargy, abdominal discomfort, headache, muscle aches, fever, anemia, and splenomegaly. Fever in malaria occurs due to an inflammatory reaction due to rupture of erythrocytes which releases cellular debris, hemozoin, and plasmodium metabolic waste. These symptoms usually appear except during the primary attack phase (Avisha and Utami, 2018). Anemia occurs due to damage to erythrocytes due to heme resulting from the breakdown of hemoglobin which is toxic to tissues. The decrease in the number of erythrocytes in the body also occurs due to suppression of erythropoietin, which is a factor that makes erythrocytes, as well as because many erythrocytes are destroyed by macrophages and Rupture Parasitized RBC (pRBC) (Avisha & Utami, 2018).

f. Plasmodium ovale

Its Life Cycle is Similar to P. vivax. It has a life cycle with an asexual stage in the liver and a sexual stage in the Anopheles mosquito. Has a dormant form that can cause relapse. exoerythrocytic cycle for 9 - 17 days. Just like P. vivax, relapse can occur due to dormant forms that survive in the human liver and then become active again. The life cycle of P. ovale involves the hypnozoite stage which is an inactive phase in the liver. This stage can be reactivated several weeks, months, or years after the initial infection, causing a recurrence of the disease. Malaria parasites in their microscopic form quickly move through the bloodstream to the liver. In the liver, they invade liver parenchymal cells and initiate asexual

reproduction in a period called the intrahepatic or pre-erythrocytic stage. Typically, P. ovale spends about nine days in this pre-erythrocytic stage, which results in the formation of sporozoites.

In the erythrocyte cycle, P. ovale spends about 50 hours. By the end of this period, the parasite has consumed almost all the hemoglobin and filled most of the red blood cells (Tomar et al., 2015). This stage is called schizont. One P. ovale sporozoite can produce approximately 15,000 daughter merozoites per infected hepatocyte. Some P. ovale schizonts will rupture, releasing merozoites into the circulation. The merozoites then attack red blood cells, develop from a ring shape into trophozoites, and then into multinucleated schizonts. This stage is called the erythrocytic stage. Some schizonts remain inactive and are called hypnozoites. Hypnozoites are inactive stages in the liver that are silent and do not show clinical symptoms. Reactivation and release of hypnozoites into the circulation can cause relapses of disease that may occur several months after the initial malaria infection (Facer & Rouse, 1991). After being released from the liver, some merozoites develop into morphologically distinct male or female gametocytes and can transmit malaria infection. Anopheles mosquitoes ingest these cells while sucking blood. Male and female gametocytes mature and form zygotes in the midgut of the mosquito. The zygote then develops through asexual division and eventually releases sporozoites. The sporozoites then move to the mosquito's salivary glands, completing the transmission cycle by infecting another human at the next feeding (Okafor & Finnigan, 2024).

Each Plasmodium species has unique characteristics in its life cycle and growth that influence the clinical symptoms and prognosis of the malaria disease it causes. A better understanding of these differences is important for the proper diagnosis and management of malaria infections. P. ovale generally infects reticulocytes, i.e. young red blood cells, which can be identified by Schuffner's dots when viewed under a light microscope after Giemsa staining (Baird et al., 1990). Infected red blood cells are usually larger than normal, and their shape can be round, oval, or fimbriated. P. ovale trophozoites can be dense or irregular in shape with dense cytoplasm and a large nucleus. P. ovale gametocytes are usually round to oval in shape, while P. ovale schizonts contain 4 to 16 merozoites with dark brown pigment.

The life cycle of P. ovale involves the hypnozoite stage, which is a stationary phase that occurs in the liver and does not cause systemic infection. Relapse symptoms occur when reactivated hypnozoites are released into the systemic blood circulation. Although P. ovale malaria is not resistant to chloroquine, relapses caused by it are rare and can be prevented with anti-relapse therapy such as primaquine.

The following is a brief explanation of the 5 plasmodium cycles in brief

- Plasmodium is a protozoan parasite that causes malaria in humans. Although all Plasmodium species have a common life cycle involving the internal phase of the

Anopheles vector mosquito and the internal phase of the human body, there are differences in the life cycle and growth of each species, such as Plasmodium knowlesi, Plasmodium inui, Plasmodium vivax, Plasmodium malariae, Plasmodium falciparum, and Plasmodium ovale .

- Plasmodium knowlesi has a life cycle similar to P. vivax and P. malariae. This parasite develops in the bodies of humans and monkeys as an intermediate host, with an asexual and sexual cycle that takes place in the body of the Anopheles mosquito. P. knowlesi has a relatively short incubation period and a quotidian fever pattern (every 24 hours).
- Plasmodium inui has a life cycle similar to P. falciparum and P. malariae. Infections in humans often cause no symptoms and are self-limiting, but can be transmitted via mosquito vectors from infected monkeys. P. inui has a wide distribution in Asia and can coexist with other species of monkeys and mosquitoes.
- Plasmodium vivax has a complex life cycle involving an asexual stage in the liver and a sexual stage in the Anopheles mosquito. One of its distinctive characteristics is the ability to form hypnozoites which can cause relapse. P. vivax infection often occurs before clinical symptoms appear and can cause serious complications.
- Plasmodium malariae has a life cycle with asexual and sexual stages in the human body and Anopheles mosquitoes. These parasites tend to cause chronic infections and persist in the blood for long periods of time. Symptoms of malaria produced by P. malariae are often mild, but chronic infection can cause long-term organ damage.
- Plasmodium falciparum has the most complex life cycle among other Plasmodium species. This parasite causes severe and fatal malaria symptoms, including cerebral malaria. Its life cycle involves asexual and sexual stages in the human body and the Anopheles mosquito.
- Plasmodium ovale has a life cycle similar to P. vivax, with the ability to form hypnozoites that can cause relapse. Its life cycle involves an asexual stage in the liver and a sexual stage in the Anopheles mosquito. Relapse symptoms occur when hypnozoites are reactivated after the initial infection.

A good understanding of the differences in the life cycle and growth of Plasmodium helps in the diagnosis and proper management of malaria infections. Accurate diagnostic methods and effective treatment are essential in efforts to control and eradicate malaria

CONCLUSION

From the results of this analysis it can be concluded that Plasmodium, the cause of malaria in humans including Plasmodium knowlesi, Plasmodium inui, Plasmodium vivax, Plasmodium malariae, Plasmodium falciparum, and Plasmodium ovale, have differences in their life cycle and growth. These differences include the incubation period, complexity of the life cycle, the ability to form asexual and sexual stages, and the ability to form dormant forms that cause relapse. has unique life cycle characteristics. A good understanding of these differences is important for the proper diagnosis and management

of malaria infection. Accurate diagnosis and effective treatment are very necessary in efforts to control and eradicate malaria.

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