# Plasmodium Ovale Malaria: Endemic Areas in Indonesia

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## ABSTRACT

*Plasmodium ovale consists of two subspecies – P. ovale wallikeri and P. ovale curtisi. Increased reports of imported malaria ovale in non-endemic regions and mixed infection of P. ovale with other Plasmodium species suggest that P. ovale might be under-detected during routine surveillance. Areas endemic with P. ovale have mostly been reported in African and Western Pacific countries. A recent case report in Indonesia indicated that regions with P. ovale endemicity are not only distributed in Lesser Sunda and Papua, but also in North Sumatra.*

***Keywords:*** *Plasmodium ovale, Indonesia, Endemic Area, Malaria, Molecular Tests.*

## INTRODUCTION

Malaria is caused by *Plasmodium* parasites. *Plasmodium* can infect humans and animals, such as mammals. Many factors contribute to this infectious disease in humans, such as demography, environment, population mobility, and economic and sociocultural reasons.[1] Malaria is a preventable and treatable infectious disease, and intensive prevention efforts in various endemic areas have reduced the burden of this disease. Endemicity and vector distribution are based on environment, climate, and season among the five *Plasmodium* species, which vary in their distribution. Ovale malaria was seldom reported except in Sub-Saharan Africa and on some islands of the western Pacific.[2] In 2015, 106 countries were reported as sources of malaria transmission. Between 2010 and 2015, the incidence of malaria in the at-risk population (rate of new cases) was 21%. In the same period, the global mortality rate for the at-risk population was 29% in all age groups and 35% in children under 5 years.[3,4] The WHO Global Technical Strategy (GTS) launched in 2015, which aimed to eradicate 90% of the global burden of malaria in 2030, would likely be unmet.[5] Therefore, programs directed at combating malaria in endemic areas should be strengthened, specifically considering the ongoing Covid-19 pandemic.

Although *P. falciparum* is generally considered to cause severe disease and death, a recent meta-analysis reported that *P. ovale* can lead to severe illness with jaundice, anemia, and respiratory failure.[6,7] Thus, it is important to recognize the severity of *P. ovale* infection in order to prevent rare complications. Diagnosis relies on molecular examination using polymerase chain reaction (PCR). Published case reports have shown that all *Plasmodium* species can cause severe malaria.[8-11]

Malaria in Indonesia is still a public health problem. Malaria endemic areas in Indonesia cover several provinces, including the province of North Sumatra. Five species of plasmodium in humans were found with different species in

each endemic area, and the most common was *P. falciparum* species. So far, ovale malaria endemic areas in Indonesia have only been reported in two provinces, namely Papua and East Nusa Tenggara.[6] The limited reports of ovale malaria endemic areas in Indonesia are thought to be influenced by the diagnostic methods used in the field. For malaria blood surveys in the field, a rapid diagnostic test (RDT) is always used, because it is easy, cheap, fast and does not require special skills such as microscopic examination. RDT examination can only differentiate diagnostic *P. falciparum* and non-*P. falciparum* infections (*P. vivax, P. malariae, P. ovale,* and *P. knowlesi* cannot be distinguished). To ascertain the morphology of the five plasmodium species, the gold standard is microscopic examination of thick and thin blood with good staining and the microscopic skill and experience of the examiner. Other possible misdiagnostic factors for determining *P. ovale* species on microscopic examination are the presence of mixed infection, low parasite density, and the subspecies of *P. ovale*, namely *P. ovale wallikeri* and *P. ovale curtisi* which can only be distinguished by RT-PCR examination by sequencing.

The discovery of one case of ovale malaria in Gerunggang Village, Langkat Regency, North Sumatra Province which was reported in 2017, is the basis for making this review. Previously the case was diagnosed as mixed-infection with *P. falciparum* and *P. vivax*. It was not previously thought that *P. ovale* might be found, because malaria endemic areas in Langkat Regency have been reported only *P. falciparum* and *P. vivax*. After re-observation of the patient's blood smear, and confirmed by the parasitologist, it was confirmed that the morphology found was typical for *P. ovale*. Unfortunately, due to limited laboratory facilities, we could not proceed with RT-PCR and sequencing to determine the subspecies of *P. ovale* found.[12]

## REPORTS OF *PLASMODIUM OVALE* MALARIA WORLDWIDE

*P. ovale* was the fourth known cause of malaria before the discovery of *Plasmodium knowlesi* in Sarawak, Malaysia in 2004.[13,14] In 1969, Lysenko and Beljaev conducted a geographical analysis of published cases of ovale malaria across the Western Pacific countries, including India, Nigeria, Philippines, Southern China, Iraq, Pakistan, New Guinea, Solomon Island, Bulgaria, Columbia, Venezuela, Macedonia, S. Epirus, Iran, USSR (Armenia, Georgia, Bashkiria), Palestine, Egypt, South America, Duke of York Island, and Indonesia.[15] Sporadic spread and alteration trends in the prevalence of the four *Plasmodium* species were reported, except *for P. falciparum*. Several countries across the African continent, including Ethiopia, Uganda, Equatorial Guinea, and Kenya have recorded cases with *P. ovale curtisi* and *P. ovale wallikeri*.[16]

An imported case of infection by two species (*P. ovale* and *P. falciparum*) in an Indonesian patient working in Cameroon was reported in north Sumatera.[17] Prakash et al. reported a case of ovale malaria from Assa District, India, which was initially diagnosed as vivax malaria.[18] In Southern Bangladesh, Fuchrer et al. reported the first cases of *P. ovale* infection with a percentage of 1.6% in 189 patients using the species-specific nested PCR technique, targeting the small subunit ribosomal RNA (SSU tRNA) gene from 379 patient samples.[19] Singh et al. in 2010 reported regarding 256 patients with *P. falciparum* malaria who were hospitalized in central India and diagnosed microscopically; three cases (1.2%) of *P. ovale* malaria were detected for the first time using species-specific nested PCR with 18s rRNA.[20] Cao et al. identified 98 cases of ovale malaria out of 1,268 malaria cases from Jiangsu Province, China, from 2011 to 2014, most of which were imported from Sub-Saharan Africa.[21] Mitchel et al. reported that *P. ovale* was widely distributed in the Democratic Republic of the Congo, especially *P. ovale curtisi* and *P. ovale wallikeri* in 2013.[22]

Lim et al. reported the first imported malaria case, which was initially diagnosed as *P. vivax* malaria microscopically.[23] Likewise, a case report from Gujarat, India in 2006, showed that the parasite seemed to be *P. vivax* in a thick smear stained with Leishman stain. However, it was revealed as *P. ovale* in a thin smear using standard microscopic and morphological

evaluation.[2] Misidentification of *P. ovale* can occur microscopically when the parasite density is low and other types of *Plasmodium* infection occur concurrently. The morphology of *P. ovale* is similar to *that of P. vivax*, which can lead to an error in the estimation of the current prevalence of ovale malaria and endemic areas by species. Because *P. ovale* possesses a hypnozoite stage in liver cells similar to that found in *P. vivax*, a relapsing course of infection can ensue. Furthermore, both *P. ovale* species, *P. ovale curtisi* and *P. ovale wallikeri,* are sympatric but distinct species, based on the analysis of the MSP-1 (merozoite surface protein-1) sequence in Thailand.[24] Diversity in PocMSP-1 and PowMSP-1 by the MSP-1 sequences from the isolate sample resulted in a low level of sequence, suggesting that *P. ovale curtisi* and *P. ovale wallikeri* originate from a persistently low prevalence. *P. ovale* infections cannot be diagnosed by SSU rRNA-based PCR if coinfection with other *Plasmodium* species is present at a very low parasite density. Hence, the burden of *P. ovale* infection could be underestimated.

An imported case of ovale malaria was reported in 2011[25] in Brazil, which was later confirmed by standard microscopy and PCR. Based on the patient's travel history, it was concluded that the parasite was in the latent hypnozoite form for a minimum of 2 years. It was difficult to ascertain the relationship between the time of exposure to the parasite and the onset of symptoms because of the relatively long incubation period of *P. ovale.* Asymptomatic *P. ovale* infection is usually found in areas endemic with ovale malaria. Additionally, a report [26] in Senegal showed that there was no risk of fever when the parasitemia was 80–799 parasites/mL of blood. The risk of fever increased 11-fold in mixed infections or 93-fold for *P. ovale* when the parasite count was 800–8000 parasites/mL of blood.

Multiple infections of *Plasmodium* species often occur in certain endemic areas because of the presence of several species in the same area. Microscopic findings of multiple infections of *P. falciparum* and *P. malariae* in two children were reported in Central African Republic.[27] Three species were found (*P. falciparum*, *P. malariae*, and *P. ovale*) in real-time PCR examination of the first blood sample after treatment follow-up. *P. ovale* infection was still found in one child after re-examination on day 28, suggesting a delayed appearance of ovale malaria in this mixed infection. The proportion of imported cases due to *P. ovale* and the difference between *P. ovale curtisi* and *P. ovale wallikeri* are important. A descriptive study to analyze the prevalence, proportion, distribution, and origin of *P. ovale curtisi* and *P. ovale wallikeri* in Henan Province was collected from 2010 to 2017 by Zhou et al.[28], and their findings showed that the proportion of imported cases of *P. ovale* was larger than that of *P. vivax.* The latency period of *P. ovale curtisi* was significantly longer than that of *P. ovale wallikeri* in these two subspecies imported into China. Nolder et al. [29] reported the results of PCR examination of *P. ovale curtisi* and *P. ovale wallikeri* infections in blood samples of a British traveler who had malaria. The suspected asymptomatic period between the time of diagnosis was determined, and the time of the patient entering the UK was compared between the two groups. Showed that there are epidemiologically significant differences between the two cases of ovale malaria, suggesting that targeted treatment for *P. falciparum* may not be sufficient to reduce the malaria burden caused by *P. ovale.*

## MALARIA MAP IN INDONESIA

One of the Millennium Development Goals (MDGs) was to eradicate malaria in 2015. This commitment was strengthened by the Sustainable Development Goals (SDGs). In the SDGs, the malaria control program is in the third objective, namely, ensuring the health and welfare of all people, with the specific aim of ending the malaria epidemic and neglected infectious diseases by the end of the year 2030. The level of morbidity due to malaria in an area is determined by the annual parasite index (API), which is the number of malaria cases per 1,000 population in a certain country or territorial area in a year. The API in Indonesia has declined since 2011, indicating the success of the malaria prevention program conducted by the central, regional,

community, and related partners in Indonesia.[4]

To date, there has been no mapping of endemic areas for *P. ovale* malaria in Indonesia. The existing mapping considers all malaria cases without specifying the *Plasmodium* species. The existence of *P. ovale* malaria in Indonesia from Belu (East Nusa Tenggara) was reported by Gundelfinger et al., in 1975.[6] Baird et al. reported 34 cases of ovale malaria infection found in 15,806 peripheral slide smear samples examined from 1973 to 1989 from various islands in Indonesia. Of the 514 samples, 25 were obtained from Owi, Irian Jaya (Papua). Other *P. ovale* infection cases originated in two areas in East Flores. However, there were no cases of *P. ovale* malaria in samples from Sumatra, Kalimantan, Sulawesi, and Java.[30] Reports on parasite surveys in Indonesia were recorded between 1900 and 2008 at 2,366 locations with an uneven distribution of locations; 63% of the surveys were conducted in Eastern Indonesia, namely, Maluku, East Nusa Tenggara, and Papua. Of the 16 survey locations, *P. ovale* was only found in East Nusa Tenggara Province and Papua Province, with a prevalence of 0.003% and 0.02%, respectively.[6]

However, a 2017 case report revealed non-imported *P. ovale* mixed with *P. falciparum* infection in North Sumatra Province, which was confirmed by microscopic examination.[12] The endemicity of ovale malaria in three provinces in Indonesia is shown in Figure 1. The distribution of *P. ovale* in people in Indonesia is presented in **Table 1**.


**Figure 1.** Three Provinces of Endemic Area Ovale Malaria in Indonesia. *Plasmodium ovale* infection has been reported in three provinces, including North Sumatra, East Nusa Tenggara, and Papua

**Table 1.** The Distribution of Plasmodium ovale in Indonesia.

| Province | Year of sample | No. site | No. exams | No. *Pf* (%) | No. *Pv* (%) | No. *Pm* (%) | No. *Po* (%) |
|---|---|---|---|---|---|---|---|
| **North Sumatra** | 2015 | 1 | 75 | 2 (0.02) | 2 (0.02) | - | **1 (1.33)** |
| **East Nusa Tenggara** | 1975–2009 | 609 | 383,950 | 23,502 (6.1) | 19,401 (5.1) | 157 (0.04) | 11 (0.003) |
| **Papua** | 1929–2009 | 694 | 193,043 | 19,848 (10.3) | 9343 (4.8) | 1395 (0.7) | 40 (0.02) |
| **Indonesia** | 1900–2021 | 2366 | 1,062,259 | 61,415 (5.8) | 52,336 (4.9) | 2299 (0.2) | 52 **(1.36)** |

*Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; *Pm*, *Plasmodium malariae*; *Po, Plasmodium ovale*. Modified from Elyazar et al.[6]

## CONCLUSION

The mapping of malaria-endemic areas in Indonesia needs to be reviewed because of the detection of various *Plasmodium* species that have not been previously reported. The report of cases of *P. ovale* malaria by the current author and colleagues in North Sumatra needs to be followed up by the government and related sectors to conduct a widespread blood survey with microscopic examination, followed by nested PCR confirmation. This should yield a new map of malaria-endemic areas in Indonesia in general, and in North Sumatra in particular. The endemicity map may provide a rational basis for future malaria management strategies.

## AUTHORS' CONTRIBUTIONS

All authors have helped draft the manuscript. All authors have read and approved the final manuscript.

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The authors declare that they have no competing interests.

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