

## Seleksi Mutan dan Identifikasi Gen Molekuler Plasmodium berghei Resisten terhadap Artemisinin, Sulfadoksin, dan Piperakuin = Selection and Identification of Plasmodium berghei Resistant to Artemisinin, Sulfadoxine, and Piperaquine

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### Abstrak

Kemunculan resistensi parasit terhadap obat antimalaria, seperti artemisinin, sulfadoksin, dan piperakuin, menjadi tantangan besar dalam eliminasi malaria di negara-negara endemik, termasuk Indonesia. Hal ini meningkatkan urgensi pengembangan obat antimalaria baru yang dapat membunuh parasit sensitif dan resisten. Penggunaan model parasit Plasmodium berghei resisten diperlukan untuk merepresentasikan keberagaman populasi alami parasit ke skala laboratorium. Seleksi P.berghei resisten dilakukan melalui Repeated Incomplete Treatment (RIcT) dengan memaparkan dosis terapeutik obat pada parasit tanpa menyelesaikan pengobatan. Metode ini menyerupai kondisi kegagalan pengobatan berulang yang memicu terbentuknya resistensi pada parasit. Siklus pengobatan mencit dan pemulihan parasit dilakukan berulang sampai fenotipik resisten parasit teramati. Setelah empat regimen RIcT berbeda dilakukan, fenotipik resisten P.berghei terhadap artemisinin belum ditemukan. Pertumbuhan parasit tidak dapat ditekan selama pemberian obat pada siklus 2 berlangsung. Namun analisis molekuler target gen k13 tidak menunjukkan terbentuknya mutasi. Fenotipik resisten parasit terhadap sulfadoksin belum diperoleh setelah 3-4 siklus RIcT. RIcT sub-klon parasit menemui kondisi yang sama. Analisis molekuler target gen dhps tidak menunjukkan keberadaan mutasi. Menariknya, gametositemia terjadi pada siklus terakhir RIcT. Kondisi ini meningkatkan risiko transmisi parasit ke nyamuk. RIcT piperakuin tidak dapat dilanjutkan setelah 2 siklus berlalu dikarenakan parasit habis selama pengobatan. Fenotipik resisten parasit tiga obat antimalaria pada eksperimen RIcT belum ditemukan

.....The emergence of antimalarial drug resistance, such as artemisinin, sulfadoxine, and piperaquine, is an enormous hindrance to malaria elimination in endemic countries, including Indonesia. This increases the urgency in novel antimalarial drug development to obtain antimalarial drugs that are effective in clearing sensitive and resistant parasites. The use of a resistant Plasmodium berghei parasite model can represent the variety of parasites spreading in natural populations to a laboratory scale. The selection of P.berghei-resistant model was done through Repeated Incomplete Treatment (RIcT) by exposing a therapeutic dosage of the antimalarial drug to the parasites without finishing the treatment. This method mimics repeated treatment failure that induces resistance in parasites. The cycles of drug treatment and parasite recovery were repeated until phenotypic resistance was observed. After four different RIcT regimens, the parasite's phenotypic resistance to artemisinin has not yet been observed. The parasite growth keeps rising during treatment in cycle 2. However, no mutation was found in k13 gene. Parasite phenotypic resistance to sulfadoxine has not been identified after 3-4 RIcT cycles. RIcT in sub-clone parasite faced the same situation. Molecular analysis at the target gene dhps did not show any mutation. Interestingly, gametocytemia was observed at the last cycle of RIcT. This condition increases the risk of parasite transmission into the mosquitoes. RIcT piperaquine could not be continued after 2 cycles due to parasite clearance during drug treatment. Phenotypic resistance of the parasite to 3 of the antimalarial drugs used in

this RICT experiment is not yet observed.