論文の内容の要旨

論文題目 Temporal patterns in the dynamics of molecular markers for anti-malarial resistance in Myanmar
(ミャンマーにおける抗マラリア剤耐性分子マーカーの時間的ダイナミクス)

氏名　　ウィン ジン ゼーヤ　Win Zin Zayar

Understanding the dynamics of *Plasmodium falciparum* parasite population in terms of drug resistance is of paramount importance especially in Myanmar, a country with increasing prevalence of artemisinin resistance and the greatest burden of malaria in the Greater Mekhong Sub-region. Here, I attempt to clarify how change of drug treatment policy in Myanmar, particularly dramatic increase in artemisinin usage, affected population dynamics of *P. falciparum*.

Blood samples from patients infected with *P. falciparum* were collected from four areas in two periods; before (2002-5) and after (2013), the official implementation of artemisinin combination therapies (ACTs) in Myanmar. I determined variants of newly identified artemisinin-resistant gene (*kelch 13*) and well-known chloroquine and pyrimethamine/sulfadoxine resistant genes (*pfcrt*, *pfmdr1*, *dhfr*, and *dhps*). To clarify the evolutionary lineages of anti-malarial resistant parasites, microsatellite markers flanking *pfcrt*, *dhfr* and *dhps* were assessed and compared to those in the other endemic regions.

In artemisinin resistance, a significant increase in the prevalence of parasites harboring *kelch 13* mutation was observed from 8.6% in 2002-2005 to 24% in 2013 ($p = 0.0031$). One novel mutation (Y511H) was observed in the 14.8% of samples in 2013, suggesting potential selection after the ACTs initiation. In contrast, three SNPs (G449A, R561H and C580Y) that have been reported to be associated with artemisinin resistance in the Greater Mekhong Sub-region were not identified. Almost all fixation of *pfcrt* K76T and overwhelming of highly resistant types of *dhfr* and *dhps* mutant parasites persisted even after the withdrawal of official chloroquine and pyrimethamine/sulfadoxine usage. Lineages of chloroquine and pyrimethamine/sulfadoxine resistant parasites were shared between Myanmar and other endemic countries in Asia and Africa.

This study suggests that artemisinin resistance arose independently and was selected in Myanmar, in sharp contrast to chloroquine and pyrimethamine/sulfadoxine resistance. Change of malaria

treatment regime has not induced any sign of reduction of chloroquine and SP resistant *P. falciparum*. These molecular epidemiological observations regarding the dynamics of molecular markers for anti-malarial resistance after the introduction of ACTs in Myanmar will provide an insight into future policy making for implementing a strategy to prevent and control artemisinin resistance, initially in the Mekong subregion, expanding worldwide and utilising multi-drug regimens with different ACTs.