CHAPTER VII
CONCLUSION

1. *In vitro* drug susceptibility of *P. falciparum* isolates to quinoline-containing antimalarials and artesunate

1.1 CQ susceptibility

The sensitivity to CQ in these Thai isolates of *P. falciparum* remains in the resistant level which has been partially CQ pressured from national drug use policy.

1.2 QN susceptibility

All *P. falciparum* isolates collected were shown to be sensitive to QN and absence of influence of antimalarial drug pressure from clinical use.

1.3 MQ susceptibility

These *in vitro* sensitivity data was decreased (increased IC_{50} values) continuously from 1988 to 2003 because of continuous MQ drug pressure from clinical use which would be expected.

1.4 ARS susceptibility

Our *in vitro* results showed good sensitivity of *P. falciparum* isolates in Thailand during the study periods and should be closely monitored.

2. *In vitro* cross resistance

Positive correlation of sensitivity of *P. falciparum* isolates to CQ and QN. In addition, the expected strong correlation between MQ and QN. No correlation between sensitivity to ARS and any of the quinoline antimalarials was observed. The discrepancy of *in vitro* results reported from different studies could be accounted for by several factors including number of isolates studied, origin of isolated collected and history of antimalarials treatment in each area.

3. Association between genetic polymorphisms of *pfcrt* and *pfmdr1* with period of Time

3.1 *pfcrt* polymorphism

Our observation indicates no influence of drug pressure resulting from antimalarials usage during the study periods on the stability of *pfcrt* gene mutation level.

3.2 *pfmdr1* polymorphism

In our study, it was found that the prevalence of *pfmdr1* polymorphisms of the wild type S1034C and D1042D were significantly influenced by drug pressure produced by antimalarials usage during different periods of time. Additionally, there was influenced the patterns of *pfmdr1* polymorphism in such a way to increase the level of resistance to MQ, while reversing CQ sensitivity.

4. Association between gene copy number and time periods

MQ pressure from nation drug policy in these time periods has not influenced the number of *pfmdr1* gene copy number in these isolates.

5. Association between gene copy number, allelic polymorphisms of the *pfmdr1* gene and the *in vitro* susceptibility

5.1. CQ

Our data showed that the copy number of the *pfmdr1* gene was the only predictor of the level of CQ resistance, thus the *pfmdr1* gene play a role in modulating levels of resistance and confirm a link between the *pfmdr1* gene and CQ sensitivity.

5.2 QN

QN sensitivity seems not to be associated with the *pfmdr1* gene copy number and Post hoc analysis showed no significant difference between parasites with and without these mutation. QN susceptibility could be influenced by multiple genes.

5.3 MQ

There was no association between amplification of *pfmdr1* gene and MQ sensitivity. Our data suggest that SNP of codon 1042 should be considered for MQ resistance monitoring in addition to copy number of the *pfmdr1* gene.

5.4 ARS

Artesunate susceptibility of the parasite isolates in the present study was not influenced by the *pfmdr1* gene both of amplification and allelic polymorphism due to no suspicious resistant isolates.