

Therapeutic efficacy of Amodiaquine (AQ),
Sulfadoxine-Pyrimethamine (SP), and the
combination of AQ + SP in treatment of
uncomplicated *falciparum* malaria in Cameroon

Akaragwe Ateh Isabel

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Malaria: Management

- Interventions

 - Interrupt Transmission*

 - Prevent Infection*

 - Prompt diagnosis and treatment with the appropriate antimalarial drug*

- Bednet Trials

 - 30% - 60 % Reduction in Mortality*

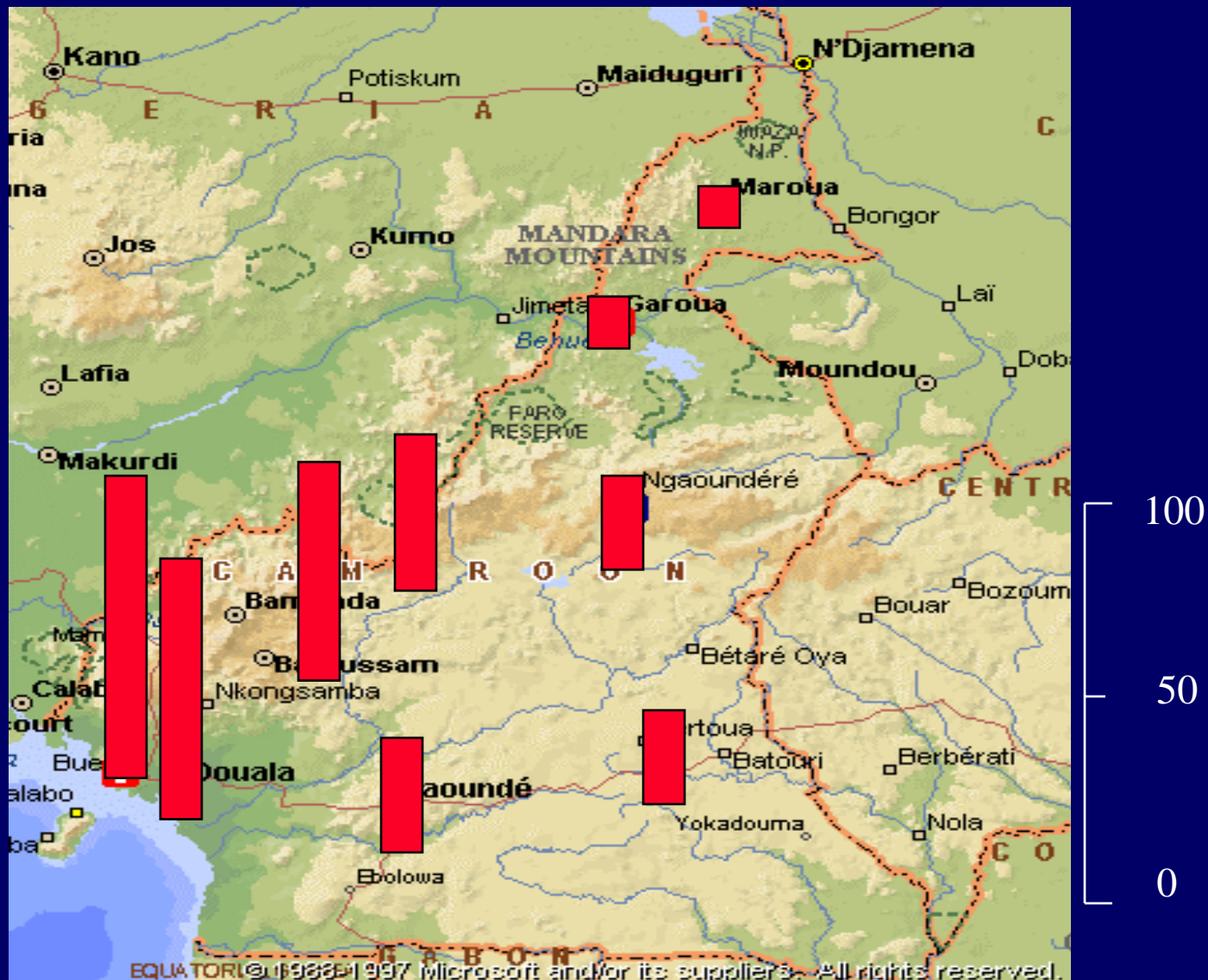
 - Weight Gain*

 - Reduction in anemia*

Background

- High mortality to malaria is due to emergence and spread of drug resistant parasites
- High levels of CQ resistance- interim policy of AQ as the 1st line drug
- Therapeutic efficacy studies conducted in Cameroon b/w 1999 – 2002 to assess the efficacy of SP and AQ showed rising levels of resistance to antifolates (6-14%) and AQ (0 – 6%)

Chloroquine Resistance: Cameroon - 2002



Objectives

- **Demonstrating the efficacy and safety of the alternatives to CQ- AQ, SP and a combination of the two drugs, AQ and SP in Limbe, Yaounde and Garoua.**
- **Determining the prevalence of known and newly discovered molecular markers associated with resistance to CQ, AQ and SP in these sites.**

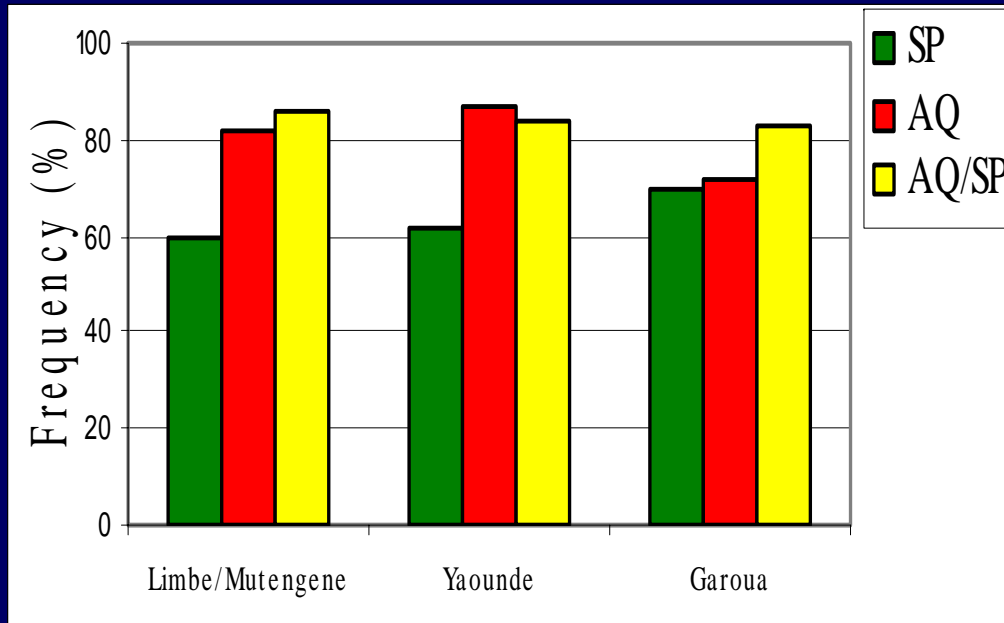
Methodology

- **Study design: Randomised double-blind placebo controlled trial**
- **Sample size: Limbe/Mut(260), Yde(260), Garoua(240)**
- **Sample collection**
 - **January to December, 2004**
 - **Ethical clearance Ministry of Public Health**
 - **Informed parental consent**
 - **Febrile children**
 - 6 to 59 months (2000 – 200000p/μl blood + other inclusion criteria)
 - Filter paper blood sample
 - Drug Administration (randomization into 3 drug arms)

Methodology cont.

- Follow-up (days 3, 7, 14 and subsequently, day 28)
- Therapeutic responses (scored using the WHO 2002 protocol for assessing clinical and parasitological outcome)
- Recurrence of parasitaemia and fever (filter paper blood sample). Treated with quinine
- Day 3 blood filter paper samples were analysed for whole blood drug concentrations by HPLC
- Molecular markers, investigated by PCR-RFLP on dhfr (51, 59, 108), dhps(437, 540), pfcr(76), pfmdr1(86) genes

Results

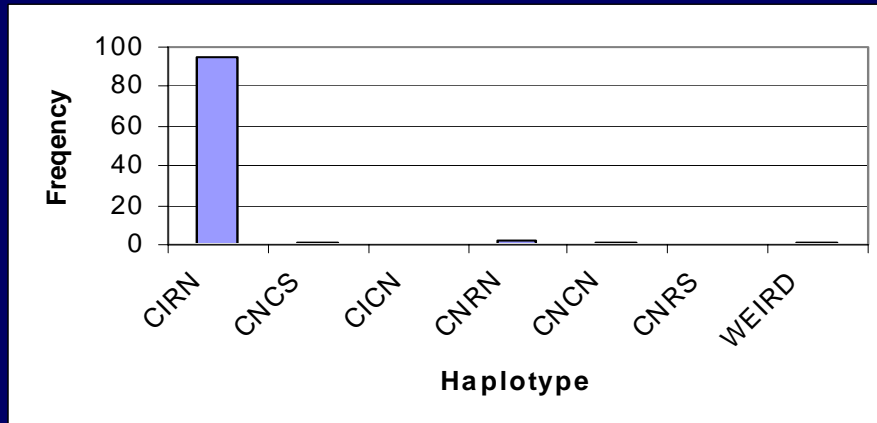


-AQ/SP was the most effective treatment than AQ and SP alone in all three sites

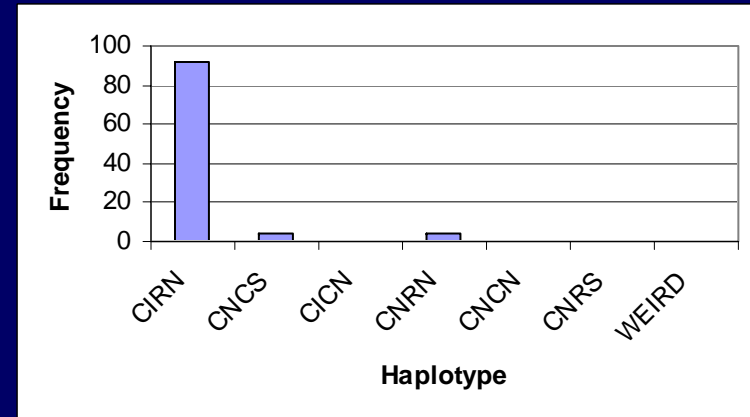
-SP was the least effective treatment in all three sites

Adequate Clinical and Parasitological Responses on day 14

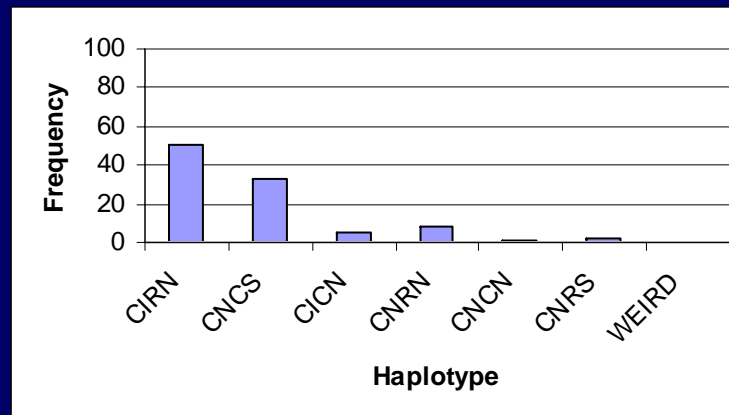
dhfr haplotypes



Limbe/Mutengene (n = 223)

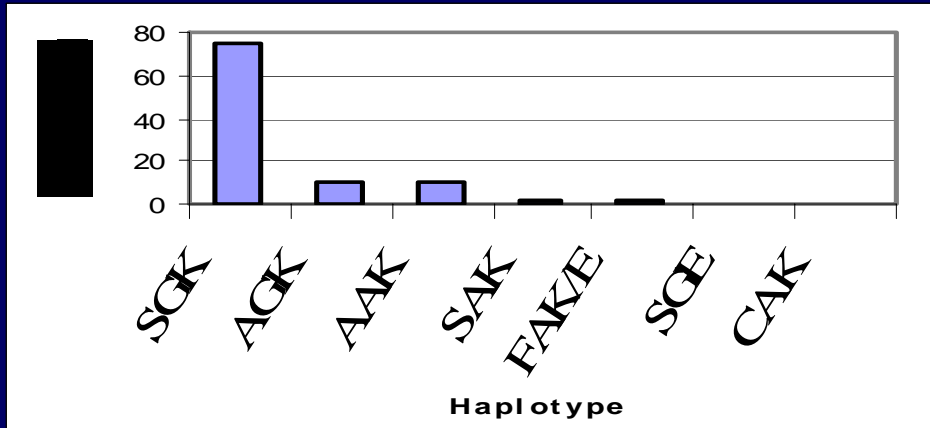


Yaounde (n = 203)

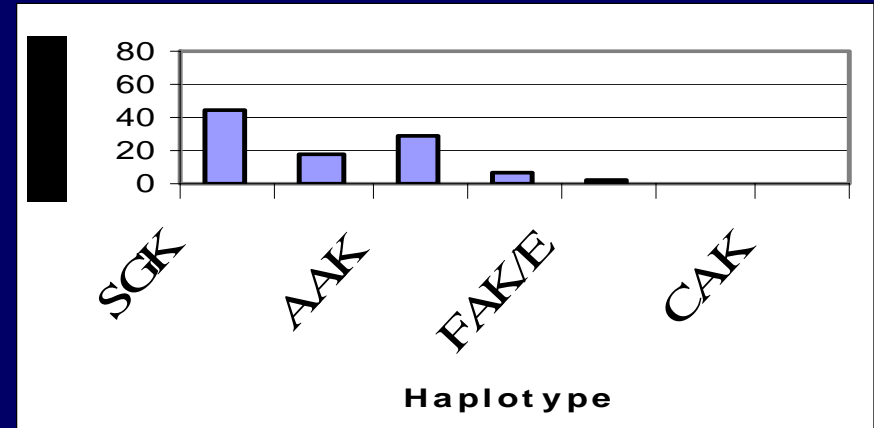


■ Garoua (n = 102)

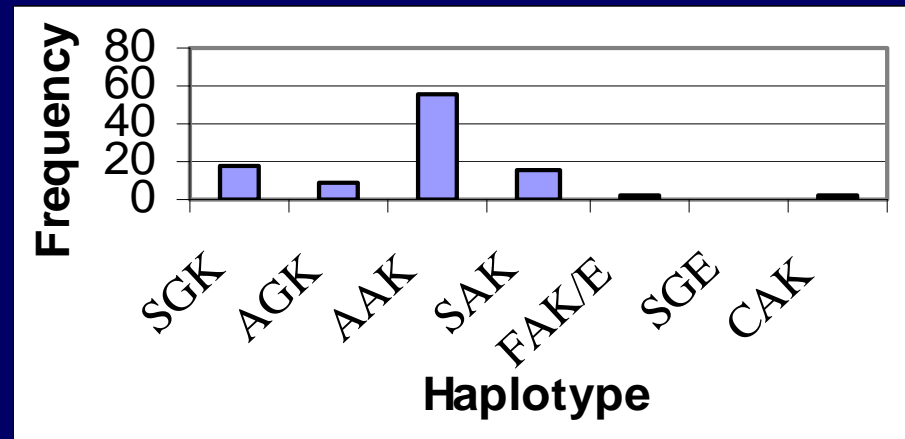
dhps haplotypes



Limbe/Mutengene (n=223)

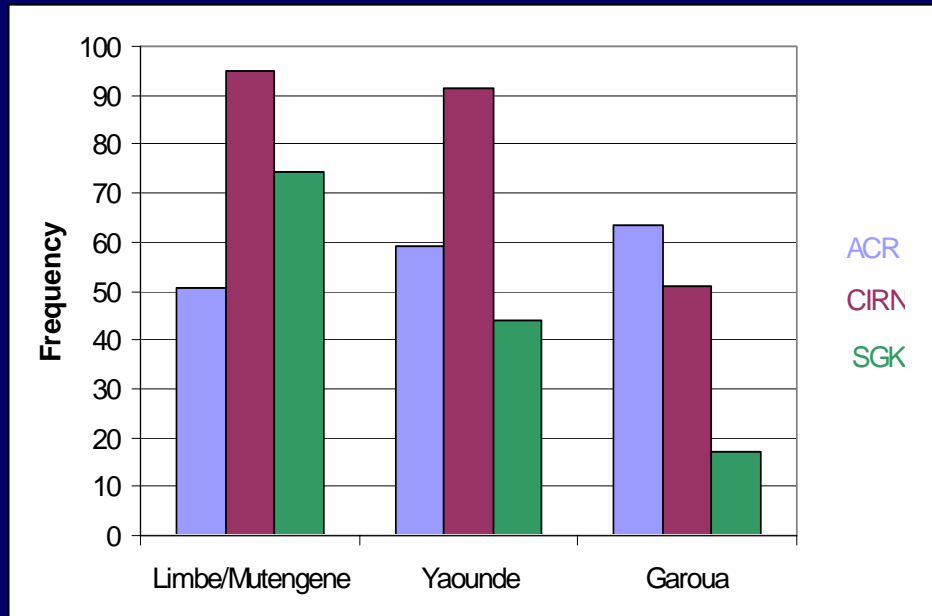


Yaounde (n=203)



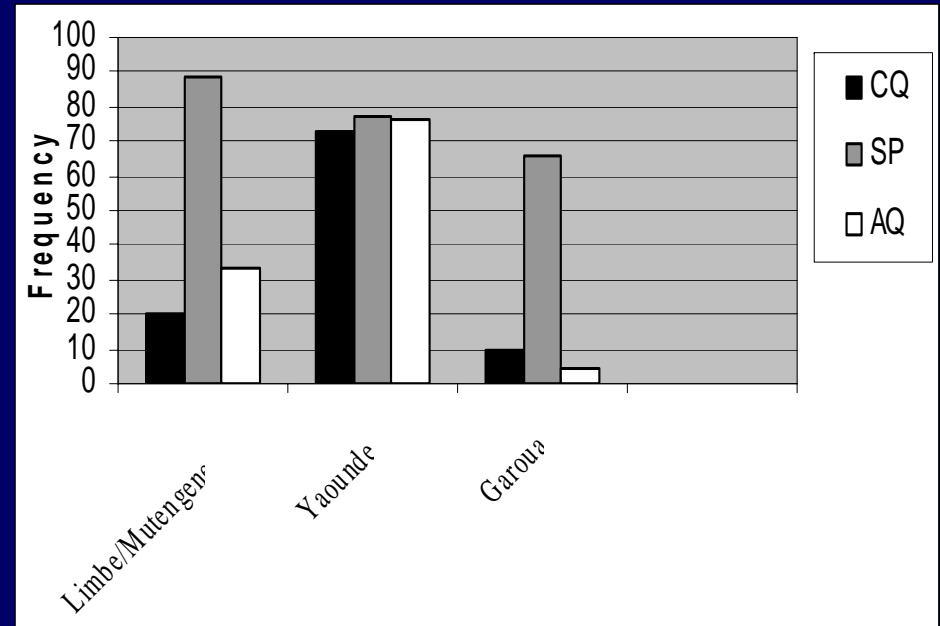
Garoua (n=192)

Results cont.



ACR and Molecular markers

- ACR is inversely related to the frequency of dhfr CIRN (51, 59, 108) and dhps SGK (437) haplotypes
- The highest frequency is in Limbe/Mutengene which is hyperendemic for malaria, and lowest in Garoua, a hypoendemic zone
- Molecular markers for mutations on *pfert* and *pfmdr1* are still being analysed



Level of drug pressure in study sites

- High drug pressure (due to self medication) on SP in all three sites
- Self treatment with AQ and CQ is highest in Yaounde and lowest in Garoua

Conclusions

- *P. falciparum* population in all three sites carry the resistance genes to sulfadoxine-pyrimethamine
- Frequencies of the resistance alleles in Limbe/Mutengene were highest but also very high in Yaounde, therefore efficacy to SP is deteriorating and has policy implications and the need to adopt a strategy that includes artemisinin-based drugs in the combination
- About 1/3 of the malaria parasites in Garoua are still sensitive to SP

- Ranking of the 3 sites according to efficacy and with respect to molecular markers show consistency. This implies that the higher the frequency of the triple *dhfr* (CIRN mutant) and the SGK (437) haplotype, the more resistant the parasites are to SP, in that population.
- We found other *dhps* alleles apart from SGK, SAK (sensitive), AAK (single mutant) and AGK (double mutant) and other rare mutant alleles like FAK and CAK. Only the SGK showed a relationship with resistance.
- Self medication with SP is highest in Limbe/Mutengene, but also very high in Yde as well as with CQ and AQ. This may also be a strong driving force to drug resistance in these sites.

Acknowledgements

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**THANKS FOR YOUR KIND
ATTENTION**