Health problems in the forested mountains of southern Viet Nam

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Summary
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The studies presented in this thesis are the result of a long-standing collaboration in medical research between Cho Ray Hospital in Ho Chi Minh City, the Center for Malaria & Goitre Control of Binh Thuan Province and the Academic Medical Center in Amsterdam. The author and his team carried out a series of studies in Binh Thuan province, a province in southern Viet Nam. The early malaria treatment studies were soon complemented by malaria control studies and this led to studies into malnutrition, intestinal parasite infections, anemia and other health problems of the vulnerable ethnic minority population of Binh Thuan province.

Chapter 1, the introduction, describes the burden of malaria and other diseases in the rural and remote areas of Viet Nam. At the end of the 1980s and early 1990s, malaria was a great health problem in Viet Nam with an increasing incidence of malaria, complicated and fatal cases and increasing frequency of local outbreaks. Binh Thuan, was highly endemic for malaria in that time.

The research group was involved in malaria treatment studies at the primary health care level in Binh Thuan but, it was realised that the largest burden of disease was not presented to the health services. The majority of the population of Binh Thuan belongs to the group of ethnic Vietnamese, but the ethnic minority groups in Binh Thuan suffered the most from malaria. Phan Tien was an isolated ethnic minority village, at the foot of the Truong Son mountains, with a very high perennial malaria transmission but without health facility. The health needs of the population and our scientific objective of studying the effects of the Vietnamese malaria control program were complementary. The entire population of Phan Tien was included in a dynamic cohort study, looking at the prevalence of malaria, malnutrition, intestinal helminth infections, anemia and the longitudinal effects of control measures.

Chapter 2 describes a malaria treatment study of artesunate with mefloquine at various intervals in non-severe falciparum malaria. The efficacy, tolerance, population pharmacokinetics and pharmacodynamics of artesunate followed by mefloquine at various intervals were studied in 360 patients with falciparum malaria. They received 4 mg/kg artesunate and 15 mg/kg mefloquine either simultaneously (A), or after 8 h (B) or 24 h(C). Each patient received 3 doses of "mefloquine", one being the real drug, the other 2 being placebo. Follow up was 28 days.

All patients recovered rapidly except one case of failure within the first 24 h. Mefloquine pharmacokinetics was similar in the three regimens. Parasites reappeared in 26%, 26% and 33% of patients in groups A, B and C respectively. Early recrudescence was associated with high initial parasite density, slow parasite clearance and rapid mefloquine clearance and low plasma concentrations at day 28. Mefloquine plasma concentrations all reached therapeutic ranges, suggesting reduced parasite sensitivity.

It was concluded that there is no interaction between artesunate and mefloquine with respect to tolerance, efficacy and pharmacokinetics. Single dose combination therapy with artemisinin drugs and 15 mg/kg mefloquine does not completely prevent parasite recurrence and may not prevent mefloquine resistance. There is probably
already some reduced mefloquine sensitivity prevalent in Viet Nam, and therefore a regimen of three days of artesunate with a higher dose of mefloquine is recommended. The national drug policy changed in the meantime. The regimen of first choice, for the treatment of uncomplicated malaria is nowadays CV8.

Chapter 3, describes the first randomized clinical trial with a new combination drug based on dihydroartemisinin and piperaquine (CV8®) in Viet Nam and atovaquone/proguanil (Malarone®) for treatment of uncomplicated falciparum malaria in Viet Nam. Vietnamese adults with falciparum malaria were allocated randomly to treatment with dihydroartemisinin/piperaquine/trimethoprim/primaquine 256/2560/720/40 mg (CV8®, n = 84) or atovaquone/proguanil 3000/1200 mg (Malarone®, n = 81), both over 3 days. Patients were followed-up for 28 days.

All patients recovered rapidly. The mean (95% CI) parasite elimination half-life of CV8 was 6.8 h (6.2–7.4) and of Malarone 6.5 h (6.1–6.9) (p = 0.4). Complete parasite clearance time was 35 (31–39) and 34 h (31–38) (p = 0.9). The 28-day cure rate was 94% and 95%, respectively (odds ratio 0.84, 95% CI 0.18–3.81). No significant side-effects were found.

It was concluded that CV8 and Malarone are effective combinations against multi-drug resistant falciparum malaria. CV8 has the advantage of a low price.

In chapter 4, the control of malaria in Phan Tien is described as a successful example of the Vietnamese national malaria control program, which includes prevention with insecticide treated bed nets (ITBNs) and early diagnosis and treatment (EDT) of symptomatic patients. A combination of these strategies is often advocated but its effectiveness had not been studied extensively. When a decade ago the malaria situation in Viet Nam deteriorated dramatically a nation wide malaria control strategy was adopted based on a combination of ITBNs, EDT at the primary health care level with artemisinin drugs and community involvement with health education.

We prospectively followed malaria in Phan Tien during interventions with ITBNs and EDT. From 1994 onwards the following interventions were applied: distribution of ITBNs to all households with biannual reimpregnation; construction of a health post and appointment of staff trained in microscopic diagnosis and treatment of malaria; ensuring regular supply of materials and drugs; annual cross-sectional malaria surveys with treatment of all parasitaemic subjects, and a programme of community involvement and health education. Surveys were held yearly at the end of the rainy season. During the surveys demographic data were updated. Diagnosis and treatment of malaria were free of charge. Plasmodium falciparum infection was treated with artesunate and P. vivax infection with chloroquine plus primaquine.

In 1994, when the baseline survey was held, there were 716 inhabitants. Among children under two years of age, 37% were parasitemic; 56% of children aged 2 to 10 and 35 % of the remaining population were parasitemic. P. falciparum contributed 73% to 79% of these. The respective splenomegaly rates were 20%, 56% and 32%. In 1998, only one parasite carrier was detected, a visitor from outside the village. In 1999 there was slight increase probably by re-introduction of malaria by workers on the road and electric grid. The proportions of parasitemic subjects were
4%, 7% and 1% respectively of which *P. falciparum* contributed 56%. Splenomegaly rates were 0%, 5% and 2% respectively.

A combination of ITBNs and EDT, free of charge, complemented by annual diagnosis and treatment during malaria surveys and community involvement with health education successfully brought malaria under control. This approach can be applied to other regions in the south of Viet Nam and provides a solid basis for further studies in other areas with different epidemiology of malaria.

**Chapter 5** describes the nutritional status in Phan Tien following malaria control. A cross-sectional study with annual surveys from 1995 to 2000 was conducted in Phan Tien to study the nutritional status and trends of growth. All people ≥ 1 year were examined. Height and weight were measured annually from 1995 until 2000. Skinfold thickness and middle upper arm circumference (MUAC) were only measured in 1995. Z-scores for height, weight and BMI for age and weight-for-height were determined by using NCHS 1978 and CDC 2000 reference tables (called US Z-scores) and by the LMS method, which was also used to draw growth charts. Longitudinal analysis was based on mixed effects modeling of the time course of the repeated Z-scores.

During the first measurement, based on US Z-scores, the prevalence of moderate/severe stunting was 53% / 24%; for wasting this was 27% / 9%. This would indicate severe malnutrition in the population of Phan Tien. However, it did not accurately reflect the good physical condition and normal daily activities of most inhabitants, although almost all subjects were very thin, with a very low BMI and with very little subcutaneous fat. LMS Z-scores accurately described the distribution of anthropometric parameters in the population, and showed a significant catch up growth of height, especially during puberty. Consequently, weight-for-height and BMI-for-age decreased. It is argued that the control of malaria was the most significant health intervention during the last decade, and probably contributed significantly to the recovery of stunting.

It was concluded that in a marginally nourished Asian population, the standard anthropometric indicators have little diagnostic and prognostic value. Analysis of repeated Z-scores, generated with the LMS method, is a sensitive tool to detect secular trends over a relatively short period, in small populations. Catch up of stunted growth may falsely suggest increase of wasting in a population.

**Chapter 6**, “Intestinal helminth infections in an ethnic minority commune in southern Viet Nam”, describes a program to control intestinal helminth infections. This control program was based on stool surveys, albendazole mass treatment in children below 17 years, targeted use of praziquantel, and sanitation and health education. At baseline, over 28% of the studied children were infected with intestinal helminths. Hookworm infection was the commonest (23%) followed by *Trichuris trichiura* (1.9%), *Hymenolepis nana* (1.9%), *Enterobius vermicularis* (0.9%), *Ascaris lumbricoides* (0.5%), and multiple helminths infections (0.5%); *Strongyloides stercoralis* was not detected. Poor sanitation, lack of personal hygiene, and walking barefoot, were considered the main risk factors for intestinal helminth infections.
Summary

The success of 400 mg albendazol single dose mass treatment was initially frustrated by poor quality of the used drug formulation, only containing half of the indicated amount of albendazole. Using another formulation quickly reduced the prevalence of hookworm infections. Praziquantel was used at a dose of 50mg/kg for subjects infected with H. nana only. The program was strengthened by the distribution of plastic sandals to all children, health education, ensuring safe drinking water by drilling wells and the construction of five pit latrines, as an example to follow.

After three years of intervention, the overall intestinal parasitic rate had decreased to 3.3% (p<0.001). We conclude that interventions which combine health education, improved sanitation and albendazole mass treatment, can effectively control intestinal helminth infections but that the quality of the used drugs is an important factor.

Chapter 7, “Anemia, malaria and hookworm infections in a Vietnamese ethnic minority” describes the prevalence of anemia and the relationship with malaria and intestinal helminth infections in Phan Tien.

This longitudinal study was performed from April 1997 to 2000 by measuring the hemoglobin concentration of all people who participated in annual surveys at the end of the rainy seasons. Ferritin concentration was measured in 2000 to evaluate the proportion of iron deficiency anemia. The relation between malaria and intestinal helminth infections with anemia was investigated.

2767 blood samples were collected and measured for Hb concentration during six surveys. Anemia was always over 43% and mainly associated with iron deficiency (80.1%). Using generalized estimating equations, a small but significant decline of the anemia prevalence was detected (OR: 0.805; p < 0.0001). Malaria was significantly associated with anemia (OR: 2.408; p = 0.0006). There was no significant effect of the control of intestinal helminth infections on the time course of anemia (95% CI: -0.1548 to 0.1651).

It was concluded that, in ethnic minority communes in Viet Nam, anemia is highly prevalent but it cannot serve as a proxy indicator of malaria, and not of hookworm infections. This is probably caused by the marginal nutritional status of those who are at risk of malaria and helminth infections. Since micronutrient deficiency is common in the vulnerable populations of South-east Asia, infectious disease control programs should be accompanied by monitoring iron deficiency and, when needed, supplementation can be organized through the helminthiasis or malaria control programs.