Health problems in the forested mountains of southern Viet Nam

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Chapter 1

General introduction
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BACKGROUND

Malaria

Malaria continues to be a major health problem in endemic countries and remains a matter of global concern. It is endemic in 91 countries. Over 40% of the world’s human inhabitants live in areas where there is a (varying) risk of malarial infection. According to a WHO report there may be around 500 million clinical cases of malaria and up to 2.7 million malaria-attributable deaths each year. (1)

Malaria is also a social issue. In addition to the high mortality rate, it also causes economic losses to individuals, communities and developing nations. In the past several studies were conducted to calculate the economic loss due to malaria based on many different categories, such as the number of days lost (from work or school), income lost, cost of saving a life or preventing illness...etc. For example, a study in India concluded that malaria causes an annual economic loss from 0.5 to 1 billion US dollars. (2) Picard and Mills showed that attacks of falciparum malaria caused 10 days of total disability and a further 2.5 days of partial disability while an attack of P. vivax caused 5 days of disability and 1 day of partial disability. (3)

Generally, one may conclude that so long as malaria is not under control, it has a negative impact on the individuals and society in general. To call malaria to a halt, many meetings were held throughout the last decades, and new strategies of malaria control were developed (Roll Back Malaria). Notwithstanding these initiatives, the global malaria incidence is still very high.

In Viet Nam, after the re-unification in 1975, the population suffered from hard living conditions due to several reasons such as the consequences of the long period of war, reduction and later complete interruption of aid from the socialist countries and the influence of the economic embargo by the United States. The extreme shortage of medicines, medical materials and insecticides, added to the poor socio-economic condition and high prevalence of multi-drug resistant parasites led to a dramatic increase of malaria at the late 1980’s and early 1990’s. For example, in 5 years time (1989 – 1993) 5.221.000 cases of uncomplicated malaria, 97.964 of severe malaria, 4.650 death cases and 459 outbreaks were reported. (4) Malaria was really a very big problem of Viet Nam at that time.

Cho Ray hospital, in Ho Chi Minh City, is directed from the Ministry of Health. It has the responsibility of taking care of the patients of and supporting the medical network of 37 provinces in the south of Viet Nam. Since the introduction of the open-door policy of the Vietnamese government in the late 1980s, several medical organizations (national and international, government and non-government) cooperated with Cho Ray hospital in its malaria control programs, and this probably contributed to the decrease of malaria in Viet Nam. The scientific cooperation with Sanya Traditional Medicine Institute (STMD) from China, and with the Academic Medical Center (AMC) from Amsterdam, the Netherlands, was the longest lasting and considered the most successful.
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The scientific work mostly focused on the development and application of chemotherapy for malaria, based on artemisinin drugs, thereby contributing to evidence based national drug policy. Initially, most of the artemisinin was supplied by STMD and was quickly accepted for the use in Viet Nam in the early nineteen nineties. At the same time, mefloquine was supplied to the Vietnamese government by international donors to treat malaria cases. In a situation of drug resistance, both new drugs were important assets in the antimalarial armamentarium. Initially monotherapy with artemisinin drugs was studied, but soon compelling arguments were put forward to apply artemisinin based combination therapy (ACT).

Mefloquine with its long elimination half-life is vulnerable to the development of drug resistance. In Thailand, mefloquine resistance rapidly emerged when it was used as monotherapy and the dosage of mefloquine had to be increased quickly from 15mg/kg to 25mg/kg. (5) In contrast, artemisinin resistance has not been observed in vivo. The class of artemisinin and its derivatives are the most potent antimalarial drugs available.(6) They have the potency to quickly reduce a large initial parasite load and they inhibit gametocyte production.(7-9) Furthermore, all artemisinin drugs have a short elimination half life which may protect the drugs from developing resistance. These characteristics can also be employed in combination regimens to protect drugs with longer elimination half lifes from development of resistance. However, the appropriate dose of the respective drugs in the ACT regimens in Viet Nam was not known clearly and the data from Thailand could not readily be extrapolated.

In Thailand mefloquine resistance had developed after several years of applying mefloquine monotherapy so that nowadays an artesunate dose of 4mg/kg/day for three days plus 25mg/kg of mefloquine is required.(10;11) In Viet Nam mefloquine monotherapy was never applied and mefloquine resistance was not confirmed. Adverse effects of mefloquine were feared and the drug was relatively expensive. Thus a low dose of mefloquine was used in combination with artemisinin. To evaluate the effect of combination regimens of artemisinin/mefloquine with different doses, many studies were conducted in Cho Ray hospital and in provincial hospitals under supervision of the Scientific Committee of Cho Ray hospital.

However, an interaction between artesunate and mefloquine could not be ruled out. A study in Thailand concluded that the timing of the mefloquine administration in the artemisinin/mefloquine regimen plays an important role in efficacy.(12) To re-evaluate the efficacy of a combination regimen of 4 tablets artesunate of 50 mg plus 3 tablets of mefloquine, of 250 mg – a favourite regimen in Viet Nam in that time - and to define tolerance, pharmacokinetics and pharmacodynamics of different timing of the mefloquine dose as well as the interaction between artesunate and mefloquine, a controlled randomized double blind study was performed in Binh Thuan province. The results are discussed in chapter 2.

Despite the comfortable experience from Thailand, showing a high effectiveness of the combination regimens with artemisinin and a high dose of
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mefloquine, and the apparent absence of mefloquine resistance in Viet Nam, the search for alternative antimalarial drug regimens was still promoted by the cooperation between Cho Ray hospital and the Sanya Traditional Medicine Institute. Many combinations based on dihydroartemisinin and piperaquine, with the code name “CV”, China - Viet Nam, were tested in Cho Ray hospital and Binh Thuan province. They showed excellent effectiveness, eliminated the initial parasitemia in a short time and also prevented recrudescence. The first randomized clinical trial with this drug combination is described in chapter 3.

During our clinical research in Binh Thuan province, we appreciated the fact that a majority of our patient population concentrated in remote rural areas. It was recognized that the new potent antimalarial combinations play an important role in the treatment of malaria patients, but that in order to reduce malaria prevalence in the community, a different strategy was required.

In Amsterdam in 1992, the assembled ministers of health of developing and developed countries, agreed on a malaria control strategy based on the following four principles: 1) early diagnosis and treatment of symptomatic malaria; 2) preventive measures including insecticide treated bed nets (ITBNs) and selective residual spraying; 3) prediction, containment and if possible prevention of epidemics and, 4), strengthening of local capacities. This strategy was adopted by WHO and endorsed by the World Health Assembly in 1993. It became the basis of WHO’s Roll Back Malaria programme.(13)

Early diagnosis and treatment (EDT), is considered an important strategy to prevent the progress of symptomatic malaria into complicated and potentially fatal stages. This can be achieved by a good system of microscope posts and availability of proper treatment (P.T. Giao, Thesis, September 20, 2004, University of Amsterdam). However, the contribution of EDT to the control of malaria is not yet fully clear. In several African studies treatment at health post and district level did not reduce mortality and involvement of community health workers did not improve this.(14-17) Declining treatment efficacy of chloroquine, by increasing resistance, was significantly associated with increased mortality and there are other studies indicating that ensuring prompt adequate treatment of malaria decreases mortality.(18;19)

The efficacy of ITBNs has been demonstrated in many endemic areas in the world, especially in Africa.(20-23) They can reduce mortality in children less than 5 years of age with varying results (from 15 to 63%) but in any case, this preventive measure should be backed up by adequate facilities for prompt diagnosis and treatment.(24;25)

The strategies of RBM have resulted in reduction of malaria in some parts of the world. The contribution of the individual components of the control strategies is difficult to unravel; studies comparing different intervention strategies and various combinations are lacking.
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When the implementation of the National Malaria Control Program in Vietnam, based on a combined approach of ITBNs, EDT and health education, started in Binh Thuan province, this offered the opportunity to follow and study this in detail. This was the start of a series of health intervention studies in Phan Tien, an ethnic minority commune in Binh Thuan.

Figure 1: The map of Viet Nam with Binh Thuan province.

Binh Thuan is a province in the south of Viet Nam with an area of 7992 km² including a narrow delta near the capital Phan Thiet, the shore at the South Chinese Sea in the East and the Truong Son mountains in the West (figure 1). Binh Thuan
province has 9 districts and 115 communes. The population increased from 770,000 in 1991 to approximately one million in 2001. The majority of the population (88%) is of Kinh (ethnic Vietnamese) origin and there are 26 ethnic minorities of varying population size. Hot, humid and a long rainy season are the characteristics of the weather in Binh Thuan. The rainy season lasts from May until October-November with an average annual rain fall between 100 and 1400 mm. Average air temperature is 27°C and the average relative humidity is 81%. (Source: Statistical Yearbook – Binh Thuan Statistics Office, Phan Thiet).

In the late 1980s and early 1990s, Binh Thuan was known as highly endemic for malaria. In 1991, 6506 malaria cases were reported with 501 complicated cases and 106 deaths. Malaria due to Plasmodium falciparum accounted for 70% of the cases and the remaining were infected with Plasmodium vivax. Anopheles dirus and Anopheles minimus were the major transmitting vectors (Reports of Binh Thuan Provincial Malaria Station).

Figure 2: The map of Binh Thuan province. Phan Tien village is shown in black.

Phan Tien village, an ethnic minority community, belongs to Bac Binh district and is located in a mountainous part of Binh Thuan province (figure 2). Ambient temperature ranges from 20 to 35°C and humidity is high. The population was composed of eight ethnic minority groups and few Kinh people. Phan Tien exists approximately 20 years as one of the areas for resettlement of members of the hill tribes who had become displaced during the war. There is still some influx of families now. In the early 1990's Phan Tien was isolated: during the rainy season it could not be reached by car and in the dry season only after a several hours drive by terrain vehicle. Since mid 1999 the village can be reached via a permanent, gravel road which has increased the movement of people to and from Phan Tien substantially.
In October 1994, 716 persons lived in Phan Tien village in 128 houses. The population increased to 1088 persons in 2000. Approximately 50% of the population was younger than 15 years. The local economy was simple, based on small-scale slash and burn subsistence farming and on what the forest offered as food. Governmental support included a program of nutrient supplementation for vulnerable groups, such as pregnant women and children, but in fact this was shared within families.

People lived family wise with 5 to 6 persons in one house made of clay walls, thatched roofs and without toilets or bathrooms. Knowledge and practice of sanitation was limited and walking barefoot was common especially in infants and children. Domestic animals like chicken, goats, cattle, dogs and cats, stayed in the same compound and house with man. Excrements were disseminated in and around the village. People and cattle shared a small river as their water source for consumption, washing and agricultural irrigation.

Before 1994 water supply was mainly from a small river surrounding the village which dropped to very low levels and became turbid in the dry season. In 1994, three wells were drilled with the aid of UNICEF. Those wells did not produce enough water for the entire village and by the end of 1996 two wells were broken, so that many inhabitants remained dependent on water from the river. At the end of 1997 with the help of the AMC – the Netherlands, a safe water supply program was initiated, providing new wells as well as fixing the old wells so that 8 functioning wells were available supplying enough clean water to the population. Five latrines and bathrooms were also built at public places such as the health post, the school and the office of the people’s committee. There was no electricity until the end of 2000.

In the early 1990's malaria was considered a great problem but of unknown magnitude. In the first half year of 1994 thirty persons of a population of about 750 had died, many of them with fever. Most deaths were children. Before 1994 there was no health care facility and surveys for malaria as well as other common tropical diseases had not been performed. Anopheles dirus and Anopheles minimus were the principle vectors in that part of the province. The transmission intensity in Phan Tien was thought to be very high but exact data, including the entomological inoculation rate, were not available. P. falciparum and P. vivax were both present in the region (approximately 70% and 30%, respectively). Peaks of reported cases are from October through December/January (year reports Binh Tan health post and Malaria Station), that means, during and after the rainy season that starts about April and continues through October/November. Transmission, however, continues throughout the year in the forested regions around Phan Tien.

The studies of the effects of malaria control in Phan Tien are described in chapter 4 of this thesis.
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Nutrition

Malnutrition is a big problem of human health, especially in the poor countries. Based on a report of WHO nearly 30% of people of all ages suffer from some form of malnutrition and 49% of the 10.7 million annual deaths on this globe, are associated with malnutrition in the developing countries. (26) Malnutrition causes reduction of physical growth, mental retardation, vulnerability to infectious diseases, loss of workdays, disabilities or even death. As an apodictic result, the socio-economic development of a country will be influenced.

Less than one decade ago, malnutrition was very common in Viet Nam, especially among the rural and ethnic minority populations, who also suffered the most from malaria. Clearly, health intervention programs had to combine control of malaria and malnutrition. The government supported food donation programs to the most vulnerable populations. However, in contrast to malaria, of which the prevalence can be measured quite accurately, the prevalence of malnutrition and its severity were not accurately known. The main reason was that no good reference data existed for the most vulnerable population. In addition, the rapid socioeconomic changes of the last decade in Viet Nam paralleled great changes in food supply. Similar to other countries in the region, the prevalence of overweight and obesity increased rapidly. Analogous to studies in malnourished populations, studies into overweight showed that body dimensions are extremely variable, that reference values are difficult to obtain and that it is extremely difficult if not impossible to determine general cut off points for healthy body dimension.

Anthropometric measurements are considered simple effective methods for public health assessment and are used worldwide. (27) The health and nutritional status of an individual, a community or a nation are estimated by these methods. Collection and assessment of anthropometric data at population level can help in the identification of the status of health and nutrition and even socioeconomic problems. Risk factors can be derived or predicted and appropriate interventions can be planned. In addition, anthropometric longitudinal datasets can evaluate the efficacy of the interventions and the trend of growth of a community, especially of infants, children and adolescents. (27;28)

Anthropometric dimensions include indices like weight, height, body mass index, middle arm circumferences, body fat, etc. Of these, common indices are derived from body height and weight with reference curves or cut off points: height-for-age (HA); weight for age (WA), weight-for-height (WH) and body mass index (BMI). Although these are related, each has a specific meaning in terms of the process or outcome of growth impairment as described below.

Height-for-age (HA) reflects linear growth and its deficit indicates long term cumulative inadequacy of health or nutrition. The term “height” covers two terms: length and stature. “Length” refers to the measurement in the recumbent position and it is often used for children less than 3 years old because they can not stand well. For older children and adults, the term “stature” is used and it refers to measurement of
the height in the standing position. Low HA may refer to shortness or stunting. “Shortness” does not imply a reason for an individual being short and may reflect either normal variation or a pathological process. “Stunting” reflects a process of failure to reach linear growth as a result of inadequate health or nutritional conditions. The socioeconomic level of a community in the past or in the present time can be considered as poor if the rate of stunting is high in the studied population. High HA is less important in public health.

Weight-for-height (WH) reflects body weight relative to height irrespective of age. Low weight-for-height is covered by terms of: "thinness" or "wasting". “Thinness” does not imply a pathological process whereas “wasting” refers to a recent and severe process that has led to significant weight loss. Even though high weight-for-height can be used in identification both of overweight and obesity, it is nowadays less used to define obesity because BMI or skinfolds are more appropriate indices. The rate of low and high weight-for-height in a population can help in evaluation of the health and nutritional conditions or socioeconomic level in the recent or present period.

Weight-for-age (WA) reflects body mass relative to the chronological age. It is influenced by both the height of the child (HA) and his/her weight (WA), and its composite nature makes interpretation complex. However in the absence of significant wasting in a population, similar information is provided by WA and HA, in that both reflect the long term health and nutritional experience of the individual or population. “Lightness” has been proposed as a descriptive term for low WA, while “underweight” has been used to refer to the underlying pathological process. High WA is seldom used for public health purposes because other indicators such as weight-for-height are more useful.

Body mass index (BMI) is calculated by dividing weight in kilograms by the height in square meters. High BMI indicates overweight or obesity and low BMI reveals different levels of thinness. BMI is mostly used for adults, older children and adolescents but is not widely used for young children because of its variation with age.

Skinfold measurement is another commonly used index of body dimensions. Skinfold measurement assesses the thickness of subcutaneous tissues and is widely used for assessing obesity among adults. However, it has limited value for assessing the degree of wasting because of failure to take into account changes in muscle mass.

Anthropometric data are commonly reported as Z-scores (standard deviation scores), percentiles or percentages of median values. In this thesis Z-scores are reported and data are considered abnormal at values below -2 Z-scores or above +2 Z-scores relative to the reference median. Evaluation of anthropometric measurements requires the use of growth standards or references. Local references can be used but unfortunately these are often not available in developing countries so the references of industrialized countries are used instead. However the body dimensions or growth standards of different nations may be different. (29;30) Moreover most references in
developed countries are adjusted repeatedly because of changing body dimensions over time.(31-35)

Therefore there is a clear need for an international reference to allow for comparison of the nutritional status of populations in different parts of the world. For that reason, WHO recommended the use of the 1978 references of the US National Center for Health Statistics (NCHS/WHO references) as international references. However, it is not clear if extrapolation of criteria for optimal or hazardous body dimensions from one population to other populations is justified.(36;37) Thus questions are raised about the appropriateness of international references for all nations in the world, especially for the members of the Vietnamese ethnic minority groups, who are often very small. If international references are not appropriate, which methods have to be used?

The LMS method is used to analyse anthropometric data. It generates smooth centile curves of data sets that do not necessarily show a normal distribution.(38-40) Calculation of centiles is based on establishing smooth curves for skewness (L), the median (M) and the coefficient of variation (S). Although the LMS method was not designed to analyse data from small populations and it also does not provide cut off points for normal body dimensions, it is helpful in generating Z-scores which can be analysed as repeated measures.

In chapter 5 of this thesis the author discusses the role of anthropometric measurements from the perspective of the population of an ethnic minority commune in southern Viet Nam, while using the LMS method.

Anemia

In the first year of our malaria studies in an ethnic minority community in southern Viet Nam, 15% of the population had signs of anemia. Despite the fact that malaria was brought under control relatively quickly, anemia prevalence remained high.(41) Thus further studies to evaluate the prevalence and cause of anemia were undertaken. In view of the poor environmental and sanitary condition in the village it seemed logical to study the prevalence of helminth infections and their possible relation to anemia.

Anemia is a significant health problem in many parts of the world especially in regions of low socio-economic status. In 1996 it was estimated that about 2 billion people suffer from anemia and most of them are young children and women. If not treated, anemia can lead to increased susceptibility to infection, retarded growth in children, reduced work performance and increased accident rate.(42;43)

Anemia has many causes, including nutrient deficiencies, chronic blood loss for which several causes should be considered, hemolytic diseases, chronic conditions that suppress erythropoiesis, toxic exposures and hemoglobinopathies. Anemia occurs everywhere in the world, but in different regions the main causes of anemia are different. In developing countries, many studies have shown that the main causes of
anemia are dietary iron deficiency, hemolytic diseases such as malaria and chronic blood loss due to intestinal parasitic infections. Iron deficiency is believed to cause the largest part of anemia globally.(44)

Measurement of the hemoglobin concentration is the most reliable method to assess the anemia status in a population. Cut off values of hemoglobin concentration may be different in several studies but most authors define anemia as a hemoglobin level lower than 110 g/l and severe anemia as a hemoglobin level lower than 70 g/l as recommended by WHO.(44)

The serum ferritin level is the most specific biochemical test that correlates with relative total body iron stores. A low ferritin level reflects depleted iron stores and is a marker of iron deficiency in the absence of infections. Serum apoferritin is an acute phase reactant protein and is elevated in response to any infectious or inflammatory process. Consequently, a serum ferritin level in the normal range only reflects iron sufficiency in the absence of these conditions. In general, iron deficiency is determined by ferritin levels lower than the cut off value of 12 μg/l.(44)

Intestinal helminth infections

After three years of malaria control in Phan Tien, the prevalence of malaria was significantly reduced. However, the anemia rate did not clearly improve. This led us to suspect that intestinal helminth infections, notably hookworm infections, were quite prevalent in Phan Tien. Helminth infections are among the commonest infections of humans worldwide and are recognized as an important public health problem, especially in poor countries. In 1996 it was estimated that there were 1.4 billion, 1.3 billion and 1 billion people in the world infected with *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*, respectively.(45) Even though people of all age groups are exposed to infection by helminths, school age children and women bear the greatest disease burden. Most clinicians and medical workers however, do not recognize helminth infections to be an important problem and therefore infected people are often not appropriately treated for their worm infections. This may lead to anemia and other complications or even be related to death.(46-48)

The control of intestinal helminth infections, from 1997 to 1999, is discussed in chapter 6 of this thesis. The relation between malaria, hookworm infections and anemia in Phan Tien is discussed in chapter 7.

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