MANAGING CHILDHOOD MALARIA IN RURAL TANZANIA
FOCUSING ON DRUG USE AND RESISTANCE

Jaran Eriksen

Stockholm 2006
All previously published papers were reproduced with permission from the publisher.

Published and printed by Karolinska University Press
Box 200, SE-171 77 Stockholm, Sweden
© Jaran Eriksen, 2006
ISBN 91-7140-678-6
ABSTRACT

Background: Malaria is a leading cause of death in underfive children in Africa. Due to the spread of chloroquine (CQ) resistance, sub-Saharan African countries such as Tanzania have changed their malaria treatment policies. In 2001 Tanzania replaced CQ with sulfadoxine/pyrimethamine (SP) as first line malaria treatment. Resistance to SP is known to develop fast and little is known about how a new policy is adopted.

Main aim: The aim was to explore the influence of the national malaria policy change on malaria case management of children under five and development of resistance to antimalarials in rural Tanzania.

Methods: The thesis consists of five cross-sectional studies performed in three different rural districts of Tanzania. During data collection, the national malaria treatment policy was changed and our studies were patterned accordingly: two studies were conducted before (I & II) and three studies after (III, IV & V) the policy change. Four studies were conducted at health facility level (I, II, IV & V) and one was conducted in the community (III). Consultations of 652 and 117 underfives, attending all public primary health facilities in Kibaha district (I) and eight health facilities in Mkuranga district (IV), respectively, were observed and mothers/guardians were interviewed upon exit. Caretakers in 729 randomly selected households in Kibaha district were interviewed about knowledge of the new malaria treatment policy and FGDs were performed with caretakers and health professionals (III). In Kilosa district we assessed efficacy of SP and CQ before the policy change (II) and SP and Amodiaquine (AQ) after the policy change (V). In study II and V, 117 and 96 underfives with malaria, respectively, were treated with the mentioned drugs. Clinical status, parasite densities, blood drug levels, haemoglobin levels and parasite mutations were monitored for 28 days. In all studies (I-V), blood was sampled from children and analysed for antimalarial content.

Results: Before the policy change, quality of care was poor in terms of history taking, physical examination and prescribing. Self-treatment was common as 98% of children had detectable CQ in blood prior to seeking formal health care (I). Clinical failure rates with CQ and SP were only 10% and 2%, respectively, despite high drug pressure in the community (II). Six months after the policy change, 51% of caretakers knew that SP was the new first line treatment. Interviewees reported seeking care at public health facilities instead of self-treatment and only 18% of children had measurable levels of SP in blood (III). Although quality of care was still poor and health workers scored 18% when performance was assessed by quality indicators, most febrile children (89%) received antimalarial treatment, in line with guideline recommendations (IV). SP resistance levels had not increased and drug pressure was lower than before the policy change (V).

Discussion: Progression of resistance to SP was not seen despite its use as first line treatment for three years (II & V), probably caused by changed drug use and thereby decreased drug pressure (I-V). Although the thesis mainly consists of data from health facilities, the findings indicate that the Tanzanian policy diffused well to the studied community (III). Quality of diagnosis at health facilities was poor (I & IV). Future malaria treatment policies include challenges such as high drug costs and poor compliance. In this aspect, inhibited drug resistance and changed patterns of drug use is positive, but quality of care at health facilities needs to be improved.

Key Words: Malaria, Policy change, Sulfadoxine-pyrimethamine, Chloroquine, Tanzania, Health workers, Drug resistance
LIST OF PUBLICATIONS

I. Nsimba SED, Massele AY, **Eriksen J**, Gustafsson LL, Tomson G and Warsame M. Case management of malaria in underfives at primary health care facilities in a Tanzanian district. Tropical Medicine & International Health (2002) 7, 3:201-209


The papers will be referred to in the text by their roman numerals (I–V).
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACPR</td>
<td>Adequate Clinical and Parasitological Response</td>
</tr>
<tr>
<td>ACT</td>
<td>Artemisinine-based Combination Therapy</td>
</tr>
<tr>
<td>AQ</td>
<td>Amodiaquine</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>ETF (early treatment failure) + LCF (late clinical failure)</td>
</tr>
<tr>
<td>CQ</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>DHFR</td>
<td>Dihydrofolate reductase</td>
</tr>
<tr>
<td>DHPS</td>
<td>Dihydropteroate synthase</td>
</tr>
<tr>
<td>ETF</td>
<td>Early Treatment Failure</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FGD</td>
<td>Focus Group Discussion</td>
</tr>
<tr>
<td>HBMF</td>
<td>Home-Based Management of Fever</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Pressure Liquid Chromatography</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illnesses</td>
</tr>
<tr>
<td>LCF</td>
<td>Late Clinical Failure</td>
</tr>
<tr>
<td>LPF</td>
<td>Late Parasitological Failure</td>
</tr>
<tr>
<td>LTF</td>
<td>Late Treatment Failure</td>
</tr>
<tr>
<td>MAMOP</td>
<td>“Improving the management of childhood MAlaria: an experiment to bridge the gap between MOthers and healthcare Providers” – EU funded project</td>
</tr>
<tr>
<td>MCH</td>
<td>Mother and Child Health</td>
</tr>
<tr>
<td>MoH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>MSD</td>
<td>Medical Stores Department</td>
</tr>
<tr>
<td>MUCHS</td>
<td>Muhimbili University College of Health Sciences</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-Governmental Organisation</td>
</tr>
<tr>
<td>NIMR</td>
<td>National Institute for Medical Research</td>
</tr>
<tr>
<td>NMCP</td>
<td>National Malaria Control Programme</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>pfdhfr</td>
<td><em>Plasmodium falciparum</em> dihydrofolate reductase gene</td>
</tr>
<tr>
<td>pfdhps</td>
<td><em>Plasmodium falciparum</em> dihydropteroate synthase gene</td>
</tr>
<tr>
<td>PHF</td>
<td>Primary Health care Facilities</td>
</tr>
<tr>
<td>RBM</td>
<td>Roll Back Malaria</td>
</tr>
<tr>
<td>RI</td>
<td>Resistance grade I</td>
</tr>
<tr>
<td>RII</td>
<td>Resistance grade II</td>
</tr>
<tr>
<td>RIII</td>
<td>Resistance grade III</td>
</tr>
<tr>
<td>S</td>
<td>Sensitive (to an antimalarial)</td>
</tr>
<tr>
<td>SP</td>
<td>Sulfadoxine-pyrimethamine</td>
</tr>
<tr>
<td>TTF</td>
<td>Total treatment failure (= clinical failure + LPF)</td>
</tr>
<tr>
<td>UNDP</td>
<td>United Nations’ Development Programme</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations’ Children Fund</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1 BACKGROUND

1.1 BURDEN OF MALARIA

Malaria is, together with acute respiratory infections and diarrhoea, one of the three infections killing the majority of children in sub-Saharan Africa, each contributing to about one-fourth of the mortality (Black et al., 2003; Bryce et al., 2005). A study reports that the proportion of deaths due to malaria has increased during the last decade (Korenromp et al., 2003). Malaria is now categorised as a re-emerging disease and a major threat to global health in the coming decades. About 40% of the world’s population lives in a malaria endemic area and 300 to 500 million cases occur yearly. In malaria high-transmission areas children and pregnant women have the highest morbidity and mortality rates. Despite control attempts about 1.1 million people die from malaria worldwide, 90% of them are underfives living in sub-Saharan Africa (WHO, 1993b; Breman, 2001). It is difficult to know exactly how many people die from malaria and in Tanzania the annual estimates range from 40,000 (Schellenberg et al., 2000) to about 100,000 deaths (MoH-Tanzania, 1999), 95% of which are children under five years of age.

Malaria is transmitted through a bite of an infected female anopheline mosquito. Four types of malaria parasites affect humans; *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax* and *Plasmodium malariae*. *Plasmodium falciparum* is the major cause of malaria related deaths. It is also the most common plasmodium species and accounts for more than 90% of infections worldwide with an even higher proportion in Tanzania.

1.2 STRATEGIES FOR MALARIA CONTROL

Following two decades of unsuccessful attempts to eradicate malaria in the 1950s and in the 1960s, a re-orientation towards control of the disease ensued. For several reasons these strategies were largely unsuccessful, including financial, technical and operational constraints. An additional backlash was the development of resistance to the existing antimalarial drugs and insecticides.

**Global Malaria Control Strategy**

The malaria situation worsened in the 1980s with an alarming rise in the incidence of *P. falciparum* malaria, causing increasing mortality rates. Malaria epidemics were reported in many countries, with an increase in urban as well as cross-border malaria. At the Ministerial Conference on Malaria organized by WHO in 1992, a global strategy was endorsed (WHO, 1993b) that intended to prevent mortality and reduce morbidity, as well as social and economic loss (WHO South-East Asia, 2001).

The Global Malaria Control Strategy consisted of four basic elements:

1. To provide early diagnosis and prompt and effective treatment
2. To plan and implement selective and sustainable preventive measures
including vector control
3. To detect epidemics, as well as containing or preventing them
4. To strengthen local capacities in basic and applied research in order to permit and promote the regular assessment of a country’s malaria situation, in particular the ecological, social and economic determinants of the disease

These elements were chosen because early treatment of malaria can prevent its progression to a severe disease and death (Koram et al., 1995). A large proportion of underfives die at home every years without visiting a health facility (Kondrachine and Trigg, 1997; Garg et al., 2001). Despite the efforts, access to effective drugs has remained problematic. Moreover, adequate response to malaria epidemics is often delayed and has caused high mortality in countries such as Burundi, Ethiopia, Somalia and Kenya (Myers et al., 2000; Hay et al., 2001).

Roll Back Malaria initiative (RBM)
Malaria morbidity and mortality continued to increase in the 1990s and the Global Malaria Control Strategy of 1992 was complemented in 1998 with an initiative by the Director General of WHO, Dr Gro Harlem Brundtland, to roll back malaria (RBM). The initiative was different from previous efforts to fight malaria in that it not only aimed to work through new tools for controlling malaria but also by strengthening the health services to affected populations. RBM would implement its activities through partnerships with international organizations, governments in endemic and non-endemic countries, academic institutions, the private sector and nongovernmental organizations. Above all, it was a united effort by WHO, UNDP, UNICEF and the World Bank (WHO/OMS, 30 October 1998). Its objective has been to reduce by half the burden of malaria for the world’s people by the year 2010 by reducing poverty, boosting school attendance, using the available drugs, tools and control measures and by improving health care services and systems. The focus has been on the people living in Africa (Trigg and Kondrachine, 1998).

The RBM strategy focuses on the following aspects (WHO/TDR, 2002):

1. Early diagnosis and prompt, effective treatment of malaria
2. Prevention of malaria through the use of insecticide-treated materials and other vector control measures including residual indoor spraying, larvaciding and environmental management
3. Prevention of malaria in pregnancy (intermittent treatment, insecticide-treated bednets)
4. Early detection and prevention of epidemics, and rapid response to epidemics (through monitoring, surveillance, preparedness and timely action)
5. Development of new tools, strategies and methodologies, and improvement in delivery of existing tools through research and development
6. Coordinated action through establishing partnerships that utilize an optimal mix of measures adapted to local situations

Integrated Management of Childhood Illness (IMCI)
One of the most notable strategies to improve child health is the WHO/UNICEF initiative, Integrated Management of Childhood Illness (IMCI). Building on the
experiences from a number of disease-specific programmes since the early 1980s, IMCI aims to integrate the management of sick children at health facilities (Gove, 1997;WHO, 1997). Children may suffer from more than one condition at the same time and symptoms for diseases may be similar. E.g. the symptoms of uncomplicated malaria overlap with those of many other acute febrile illnesses, making exact diagnosis difficult (Redd et al., 1992;O'Dempsy et al., 1993;Källander et al., 2004). Thus, IMCI’s first objective has been to train first-level health workers, i.e. prescribers in primary health care facilities, to use a symptom-based algorithm for assessing, classifying and treating the most common childhood illnesses, such as malaria, pneumonia, diarrhoea, measles and malnutrition (WHO , 1997). Under the IMCI algorithm, “malaria” is defined as presence or history of fever in countries where malaria is endemic.

IMCI has now been implemented or is being implemented in more than 80 countries and a recent evaluation from Tanzania showed reduced child mortality by 13% (Armstrong Schellenberg et al., 2004). However, previous studies did not show such an impact (Perkins et al., 1997;Weber et al., 1997). They furthermore stress that the main challenge of the IMCI algorithms is for the diagnosis of malaria, for which its current definition leads to substantial over-treatment (Weber et al., 1997).

A key factor in the IMCI guidelines is referral of children who are classified as having severe illness (WHO, 1997). Completion of referral has been shown to be a problem in Africa (Macintyre and Hotchkiss, 1999), due to a number of constraints such as lack of money, transport problems and other responsibilities at home (Peterson et al., 2004). It has therefore been suggested that first level health workers should be empowered to care more effectively for severely ill children at their health facilities (Peterson et al., 2004).

Home and community based management strategies
When IMCI was implemented in Tanzania in 1995 the focus was on improving care at primary health facilities. During the first global assessment of IMCI in 1997, delegates acknowledged that improving care at health facilities would not by itself result in a reduction in child mortality and morbidity, because many caretakers never sought care at formal health facilities (Garg et al., 2001). Improvement of family and community childcare practices have now been officially designated as essential components of IMCI, so-called community IMCI (c-IMCI) (Ford et al., 2005).

A study from Ethiopia demonstrated a 40% underfive mortality reduction through presumptive treatment of malaria using community volunteers holding drugs for neighbouring mothers/guardians (Kidane and Morrow, 2000). Also, evidence of the capacity of mothers in Guinea Bissau to adequately administer antimalarial treatment to children in the home (Kofoed et al., 2003) has lead many policy makers and financers to support the undertaking and implementation of this strategy in communities, although integration of c-IMCI into health systems in low-income countries has been slow (Task force on Health Systems Reserach, 2004). A commitment from the African summit on RBM held in Abuja in 2000 was to ensure that by 2005 at least 60% of malaria episodes would have access to correct, affordable and appropriate treatment within 24 hours of symptom onset (WHO, 2000a). This has further prompted home
based malarial management strategies. Far from the Abuja target, a study conducted in rural Uganda in 2002 found an effectiveness of malaria treatment of only 7%, but that almost half of the caregivers treated febrile children within 24 hours (Nsungwa-Sabiiti et al., 2005). The same research group highlighted local understandings and perceptions of febrile illness as a key factor in community effectiveness of fever treatment (Nsungwa-Sabiiti et al., 2004). This stresses the importance of considering the local context when implementing treatment strategies.

A main challenge for the malaria treatment strategies is the balance between prompt, effective treatment and ensuring that the antimalarials have a maximum useful therapeutic life. These two essential components should complement each other in policy decisions (WHO, 2001a). Ensuring adequate regulation and control of drug use should allow for equity and rational use of antimalarial drugs leading to reduction of mortality and at the same time reducing or delaying resistance development (WHO, 2001a).

**Figure 1.** Balance between provision of early diagnosis, prompt, effective treatment and minimising the development of antimalarial drug resistance. Modified from WHO (WHO, 2001a).

This thesis uses clinical pharmacology, health systems research and malariology in an attempt to address these issues by looking at how a health system adopts a new malaria treatment policy and how health workers and caretakers are influenced. At the same time we assess the development of drug resistance.

### 1.3 MALARIA CASE MANAGEMENT INCLUDING DRUG TREATMENT

Presently, a limited number of drugs exist for the prevention and treatment of malaria. In Africa the drugs must be affordable and efficacious. The most widely used drugs are quinine and its derivatives and antifolate combination drugs. The most recent addition to the list of drugs is the artemisinine compounds (Rang et al., 2004).

Quinine was first used for fever treatment in “modern medicine” in Peru in 1630, and soon thereafter introduced in Europe (Black et al., 1986). It is still used as a last resort
for treating malaria, especially severe disease (Bloland, 2001). Chloroquine (CQ) is a derivative of quinine first synthesised in 1934 and that quickly became the most widely used antimalarial drug. This has changed with spreading resistance to the drug. Amodiaquine (AQ), closely related to CQ, is another effective antimalarial but has been used to a lesser extent because of adverse reactions in the form of agranulocytosis (CDC/MMWR, 1986; Hatton et al., 1986). With the emergence of CQ-resistance, AQ is again increasingly used for malaria treatment in low-resource settings (Olliaro and Mussano, 2003). Other commonly used quinine derivatives include mefloquine and primaquine.

The antifolate combination drugs consist of DHFR (Dihydrofolate Reductase) inhibitors (e.g. pyrimethamine, trimethoprim, proguanil and chlorproguanil) and sulfonamides (e.g. sulfadoxine, sulfamethoxazole, dapsone) that inhibit DHPS (Dihydropteroate Synthetase). When used alone, resistance to these drugs develops fast, which is why they are used in combinations achieving synergistic effects.

Although artemisinine was first isolated in pure form as late as 1972 from the herb Quinghaosu (*Artemisia annua*), it has been used in Chinese traditional medicine for fever treatment for more than 2000 years (Abdi et al., 1995). In addition to the extremely rapid parasite clearance times and fever resolutions seen, it also has low toxicity. So far there are few reports of resistance to artemisinine derivatives. The most commonly used derivatives are artesunate, artemether and arteether. These drugs, when used in combination with other compounds, have been reported to inhibit progress of drug resistance and to decrease malaria transmission, the latter due to its gametocidal effects (White et al., 1999; Barnes et al., 2005).

**Case management of malaria**

Case management can be defined in different ways. A traditional definition is “the assignment of a healthcare provider to assist a patient in assessing health and social service systems and to assure that all required services are obtained” (Mosby, 1994). This view is too narrow for the case management of malaria discussed in this thesis. Malaria management in Tanzania starts at home with caretakers recognising and responding to a sick child with fever (Mwenesi et al., 1995; McCombie, 2002). The subsequent actions taken depend on numerous factors, discussed in chapter 1.4. It has been shown that a large proportion of febrile children are never treated at health facilities (McCombie, 1996). For the patients who do seek health care services, case management is performed by health workers. Studies have shown poor health worker performance in terms of history taking, prescribing practices, physical examination and consultation time at primary health care facilities (Gilson et al., 1993; Krause et al., 1998). Inadequate clinical assessment could cause incorrect diagnosis and inappropriate treatment of malaria episodes, as well as other conditions.

In this thesis we have measured case management at health facilities based on certain minimum criteria regarding history taking, physical examination, diagnosis, treatment and counselling (see studies I & IV).
Figure 2. The malaria parasite life cycle and the site of action of antimalarial drugs (figure modified from *Principles of Clinical Pharmacology* (Rang et al., 2004)).

A: Site of action of drugs used to treat the acute attack (= blood schizonticidal) (e.g. quinine, mefloquine, chloroquine, sulfadoxine, pyrimethamine, artemisinine, amodiaquine, doxycycline)

B: Site of action of drugs used for radical cure, i.e. kills parasites “hibernating” in liver cells, so-called hypnozoits (*Plasmodium vivax* and *Plasmodium ovale* only) (e.g. primaquine)

C: Site of action of drugs used for chemoprophylaxis (e.g. chloroquine, mefloquine, pyrimethamine, doxycycline)

D: Site of action of drugs that prevent transmission (= gametocidal) (e.g. artemisinine)
**Table 1. Pharmacological properties of the antimalarials most commonly used in Tanzania.**

<table>
<thead>
<tr>
<th></th>
<th>Chloroquine</th>
<th>Sulfadoxine</th>
<th>Pyrimethamine</th>
<th>Amodiaquine</th>
<th>Quinine</th>
<th>Artemisinine derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
<td>Inhibits haeme polymerase → accumulation of toxic haeme</td>
<td>Inhibits DHPS</td>
<td>Inhibits DHFR</td>
<td>Inhibits haeme polymerase</td>
<td>Inhibits haeme polymerase</td>
<td>Damages parasite membranes by accumulating toxic free radicals</td>
</tr>
<tr>
<td><strong>T ½</strong> (hrs)</td>
<td>1220 (41-50 days) (multi-step)</td>
<td>125</td>
<td>80-95</td>
<td>240 (1-10 days) (2 phases)</td>
<td>7-11</td>
<td>Artemisinine: 4 Artesunate: 0.75 Artemether: 4-11</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>1x1 for 3 days</td>
<td>Single dose combining the drugs.</td>
<td>1x1 for 3 days</td>
<td>1x3-4 for 5-10 days*</td>
<td>Usually in combinations, different regimens</td>
<td></td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>Blood schizonticide</td>
<td>Blood schizonticide</td>
<td>Blood schizonticide</td>
<td>Blood schizonticide</td>
<td>Blood schizonticide + gametocide</td>
<td></td>
</tr>
<tr>
<td><strong>Cost (USD)</strong></td>
<td>0.44 /course</td>
<td>0.38</td>
<td>0.76</td>
<td>3.20</td>
<td>7.11 ‡</td>
<td></td>
</tr>
<tr>
<td><strong>Drug-drug Interactions †</strong></td>
<td>Unusual but risk for: Arrhythmia with halofantrine, convulsions with mefloquine. Reduces bioavailability of ampicillin</td>
<td>Co-admin. with other folate antagonists may exacerbate bone marrow depression because of folic acid synthesis impairment</td>
<td>Insufficient data</td>
<td>Avoid anti-arrhythmics and halofantrine, rifampicine → low plasma conc.</td>
<td>None known</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Gastro intestinal, pruritus, retinopathy, cardiovascular effects (iv)</td>
<td>Stevens-Johnson, hepatitis, haemolysis</td>
<td>Skin rashes, megaloblastic anaemia</td>
<td>Agranulocytosis (1:1000-5000 in prophylaxis)</td>
<td>Hypoglycemia (1:2 pregnant), blood dyscrasia, cinchonism **</td>
<td>Few</td>
</tr>
</tbody>
</table>

*depends on severity of disease and immunity of patient, **cinchonism=tinnitus, headache, nausea, hearing impairment, ***cost for adult dose (Amin and Snow, 2005)
†(WHO, 2006), ‡ WHO and Novartis have signed an agreement for provision of Coartem at a non-profit price of USD 2.40 (The Global Fund, 2004)
Drug treatment in children

Age is often an important factor in drug metabolism with several physiological parameters contributing to differences in treatment between adults and children. Bioavailability (affected by e.g. gastric pH and gut motility), metabolism and elimination (affected by e.g. immaturity of kidneys) vary between age groups (Rane, 2005), but the clinical importance of this is not always given (Atkinson, 2001). Malnutrition could potentially lead to changes in pharmacokinetics of antimalarials. There have been reports of increased risk of treatment failure with sulfadoxine/pyrimethamine in malnourished children, but these have not studied drug pharmacokinetics (Wolday et al., 1995; Hamel et al., 2005). Quinine is the only antimalarial drug for which there have been sufficient studies on pharmacokinetics in malnourished children, but no change in dosage schedules has been recommended (WHO, 2006). The older antimalarials, such as sulfadoxine, quinine and chloroquine have been used and studied extensively and paediatric dosages have been well-established (Abdi et al., 1995). Artemisinine, on the other hand, is relatively new but the drug combination of artemether and lumefantrine (Coartem®) has been registered for use in children with a bodyweight from 5 kg (The Global Fund, 2004).

1.4 CARE-SEEKING BEHAVIOUR AND DRUG USE IN THE COMMUNITY

A recent review of fever treatment in sub-Saharan Africa found that about 60% of fever cases were taken to a modern medical provider (Filmer, 2005). This varied across the continent from less than 25% of fever cases in Burkina Faso to 85% in Côte D’Ivoire. In Tanzania one study reported about 60% of febrile cases were taken to formal health care (private or public) (Filmer, 2005). This is an example of the importance of considering the local context when implementing strategies to improve drug use and treatment strategies.

There are numerous sources from which care is sought in resource limited settings, such as in Tanzania. Home treatment is, as mentioned above, very common in several African countries. Outside the home, caretakers can choose to seek care at formal health facilities (private, non-governmental or public), different drug selling facilities (drug vendors, ordinary shops of drug stores) or traditional healers. Treatment-seeking choices are influenced by a number of factors. Caretakers at the household level have their own knowledge, perception and beliefs about illness causation and the efficacy of different treatments, leading to numerous paths of care-seeking for febrile children (Mackian et al., 2004; Nsungwa-Sabiiti et al., 2005). Other factors affecting care-seeking are availability of services, accessibility and economy (Peterson et al., 2004; Ahmed, 2005).

Care-seeking behaviour varies between contexts. A study from Tanzania showed that convulsions, which in biomedical terms could be a symptom of severe malaria, is traditionally diagnosed as degedege, possession of evil spirits, a disease that requires traditional healing with e.g. smoke from elephant dung or urinating on the child (Comoro et al., 2003). In Kilifi, Kenya, on the other hand, 72% of interviewed mothers/guardians bought drugs from shops for treating fever in children, mainly
chloroquine (CQ) and antipyretics (Williams et al., 1999). Drug sellers have been seen to play an important role as the main sources of most antimalarials in many rural communities in Africa (Snow et al., 1992; Foster, 1995; McCombie, 1996; WHO, 2000b). In addition, care-seeking varies even within communities. In a study performed as a baseline for the IMCI multi country evaluation in several Tanzanian districts close to the study areas of this thesis it was shown that poor families were less prone to bringing their children to formal health care facilities as compared to relatively richer families (Schellenberg et al., 2003b). Similar findings were reported from a review of several sub-Saharan countries (Filmer, 2005).

The complex and context-specific responses to an illness episode might greatly affect illness outcome (Krause and Sauerborn, 2000; Amin et al., 2003; Nsungwa-Sabiiti et al., 2005). In order to reduce mortality and morbidity in underfives, a model in which all steps of the health care system, including families and communities, and care-seeking are included had been suggested (Kalter et al., 2004). This model is called “the Pathway to Survival” and is meant to help identify biological and socio-cultural factors that contribute to death in a certain community.

1.5 ANTIMALARIAL DRUG RESISTANCE

Antimalarial drug resistance has been defined as the “ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject” (WHO, 1973). In addition, the drug in question must “gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action” (Bruce-Chwatt et al., 1986).

Numerous factors contribute to the spread and intensification of drug resistance. These vary widely from human behaviour and vector and parasite biology to pharmacokinetics and economics (Bloland, 2001). Drug pressure is considered one of the most important factors in drug resistance development (Payne, 1988; Wernsdorfer, 1994; Bloland, 2001). Drug pressure is here defined as the number of humans with residual drug levels in their blood that exposes inoculated parasites to sub-therapeutic drug levels (Watkins et al., 2005). The two main components of drug pressure are the average number of drug treatments per person per year and the proportion of infections treated (Watkins et al., 2005).

After two decades of use of CQ, resistant *P. falciparum* was first reported simultaneously in 1960-61 in South America and South East Asia (Moore and Lanier, 1961; Harinasuta et al., 1962) and has now reached high levels in both areas. In the early 80s, CQ resistance emerged even in East Africa and has now spread to most malarious areas of the world (Bloland et al., 1993). SP was successfully introduced in South East Asia as malaria treatment in areas with high CQ resistance, but after 10 years treatment failure had already reached high levels (Doberstyn et al., 1976; Pinichpongse et al., 1982). A similar pattern has been seen in all areas after the introduction of SP, and since the early 1980s increasing SP resistance
has limited the provision of adequate malaria treatment in East Africa (EANMAT, 2001). In many places rapid and massive development of resistance against SP has been seen after a period of intense drug pressure. One example is a trial from Muheza, northern Tanzania, where children were given presumptive intermittent dapsone-pyrimethamine treatment for a year, resulting in 74% RII/RIII resistance levels to SP after only one year (Ronn et al., 1996).

1.6 MOLECULAR MARKERS FOR RESISTANCE

Both drugs in the sulfadoxine/pyrimethamine combination act by synergistic inhibition of two key enzymes involved in the synthesis of folic acid, dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR), respectively. It was previously thought that for both DHPS and DHFR a single mutation alone was needed for the development of resistance against sulfadoxine and pyrimethamine, whereas multiple mutations are thought to be needed for development of resistance against CQ (Masimirembwa et al., 1999; Wellems and Plowe, 2001). This difference has been considered as one of the causes for the rapid development of resistance to SP as compared to CQ. However, it has now been shown that multiple mutations in the \textit{dhfr} and \textit{dhps} genes are needed for SP resistance development (Kublin et al., 2002).

Variant sequences of \textit{P. falciparum} dihydrofolate reductase (DHFR), the target enzyme of Pyrimethamine, were first described in 1988 (Wang et al., 1997). More recently mutations have also been reported in the gene coding for dihydropteroate synthase (DHPS), the target of sulfadoxine. It is now established that the worldwide spread of resistance towards these two drugs in combination results from the accumulation of mutations in their target enzymes’ genes (Plowe et al., 1997). Variant genotypic sequences of DHFR and DHPS have been seen in different parts of the world correlating to the drug pressure of SP in these areas (Gregson and Plowe, 2005).

Point mutations at codons 108, 51, 59 and 164 in the \textit{dhfr} gene (which encodes for the DHFR enzyme) alter the binding active-site cavity where the drug binds to the enzyme (Cowman et al., 1988). Point mutations in the gene coding for DHPS have also been studied, and mutations at codons 436, 437, 581 and 540 have been associated to \textit{in vitro} resistance to sulfadoxine (Triglia et al., 1997). It has been suggested that the sequence of the mutations occur in a stepwise fashion with selection for mutations in the \textit{dhfr} gene probably occurring first, followed by mutations in the \textit{dhps} gene (Sibley et al., 2001; Talisuna et al., 2004). In Tanzania, the mutations that have been found are those at codons 108, 51 and 59 for \textit{dhfr} and 437 and 540 for \textit{dhps}.

For SP resistance there have been findings from East Africa that show the \textit{dhfr} triple mutations (at positions 108, 51 and 59), with or without \textit{dhps} mutations, can predict treatment failure (Nzila et al., 2000; Mutabingwa et al., 2001). Contrary to this, a study in Malawi (Kublin et al., 2002) showed a stronger correlation between a quintuple mutant (\textit{dhfr} mutations at positions 51, 59 and 108 and \textit{dhps} mutations at positions 437 and 540) and SP treatment failure than for the triple mutant. However, there is an inconsistency in the results (Talisuna et al., 2004) and there is a need to find a relationship between specific mutations and \textit{in-vivo} resistance to SP in order to be able to monitor the further development of resistance towards the drug.
1.7 MEASURING DRUG RESISTANCE

In general, four basic methods have been routinely used to study or measure antimalarial drug resistance: in vivo tests, in vitro tests, animal model studies and molecular characterisation (Bloland, 2001). This thesis focuses on in vivo tests. An in vivo test is the treatment of a group of malaria patients with known doses of drug and the subsequent monitoring of the parasitological and/or clinical response over time. One of the key characteristics of in vivo tests is the interplay between host and parasite. Reduced therapeutic efficacy of a drug can be masked by immune system clearance of parasites in patients with a high degree of acquired immunity (White, 1997). A high degree of acquired immunity is seen in populations in holo-endemic areas for malaria, such as the study populations of this thesis.

A standardised method for assessing efficacy of chloroquine in vivo was first developed in 1965. This was later revised twice, in 1967 and 1972 (WHO, 2003a). This method was quite demanding and over time, the focus of research changed from the initial parasitological focus to clinical outcome and efficacy in the most vulnerable patient groups. Therefore, a workshop was arranged that resulted in the development of a new standardised protocol for assessing efficacy of antimalarial drugs (WHO, 1996). This protocol emphasised clinical response over parasitological response and after several years of use, a new workshop was arranged to revise it. In 2003 the revised protocol was published, defining drug efficacy as combined parasitological and clinical outcome (WHO, 2003a). Both of the protocols, from 1996 and 2003, have been used in this thesis.

1.8 HEALTH SYSTEMS AND HEALTH WORKERS

The WHO defines health systems as those which “include all actors, organizations, institutions and resources whose primary purpose is to promote, restore or maintain health” (WHO, 2000c). In most countries a health system has public, private, traditional and informal sectors. The task of a health system is to improve health and to distribute the services equitably to the population it serves. The effectiveness, efficiency and equity of a health system are critical determinants of a population health status (Travis et al., 2004). The performance of the health system is determined by the way it is designed, managed and financed (Muir Gray, 2001) and in the World Health Report 2000, the performance of the health system was for the first time addressed as a determinant of health (WHO, 2000c).

The World Health Report 2000 (WHO, 2000c) also identifies four key functions of a health system: (i) service provision, (ii) resource generation and development, (iii) mobilisation and channelling of financing and (iv) stewardship (i.e. ensuring that the individuals and organisations within the system act as good stewards of the trust and resources given into their care (Muir Gray, 2001)). Human resources, a critical component of all four key functions mentioned above, is increasingly seen as a key issue in health systems (Travis et al., 2004). Thus, we need to know the determinants for health worker performance in order to improve the health system and the services it delivers.
In Tanzania, health care is delivered by the public and private sector as well as by non-governmental organisations (NGOs) and informal services. Tanzania is one of the countries in sub-Saharan Africa with the best health system infrastructure. It has well-established and evenly distributed primary health facilities (PHF), most of them accessible within a 5-10 km walking distance from the rural communities (Gilson, 1995). The formal health care in Tanzania is delivered at four different levels:

**Table 2. The four levels of formal health care services in Tanzania.**

<table>
<thead>
<tr>
<th>Type of facility</th>
<th>Population served</th>
<th>Staff qualifications</th>
<th>Services provided</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong></td>
<td>Village health workers</td>
<td>2 health workers/village (pop. 2,500)</td>
<td>Primary school, courses in preventive care</td>
</tr>
<tr>
<td><strong>Level II</strong></td>
<td>Dispensary</td>
<td>5,000–10,000</td>
<td>Clinical officers, MCH aids/nurses, nurse assistants</td>
</tr>
<tr>
<td><strong>Level III</strong></td>
<td>Health Centre</td>
<td>50,000–80,000</td>
<td>As above + medical officers, midwives, lab technicians, pharmaceutical assistants</td>
</tr>
<tr>
<td><strong>Level IV</strong></td>
<td>Hospital (district/regional)</td>
<td>250,000</td>
<td>As above + medical doctors and pharmacists</td>
</tr>
</tbody>
</table>

All three study districts in which the studies of this thesis were performed follow the formal health care system described above. They are all densely populated with the majority of the population living within a one hour walk from the nearest health facility.

1.9 POLICY CHANGE
Policy change is a complex process involving several interconnected steps: (i) policy problem identification, (ii) policy formulation, (iii) policy implementation and (iv) policy evaluation (Walt, 1994). Although these steps have been described in different ways, there is little disagreement about them between policy analysts. The disagreement concerns whether the policy cycle follows a rational or incremental process from problem identification to evaluation (Walt, 1994; Buse et al., 2005). The rational process is often described as “prescriptive” or the way policy decisions ought to be made whereas the incremental process is “descriptive” of how policy decisions are actually made (Buse et al., 2005). Results from a doctoral thesis on pharmaceutical policies, including the Lao National Drug Policy, showed that although the formulation of the policies may be relatively trouble free, it does not necessarily lead to the policy being translated as anticipated (Jönsson, 2002). The Lao National Drug Policy is an
example of an incremental process where stepwise preparatory work clearly influenced the decisions to policy formulation (Paphassarang et al., 1995).

The steps of the policy process can be seen as a cycle, constantly requiring feed-back leading to change (Walt, 1994). Most of the research done on policy change is related to the first steps of the policy cycle, up to policy formulation and the political implementation of the policy. Little is known about what happens after the implementation or about how a policy diffuses into a system (Williams et al., 2004). Most of the information available in this area is from high-income settings, creating an additional knowledge gap with regards to resource-poor settings.

A policy change can be said to be an innovation and several factors are known to be important for the diffusion of innovations. These factors include the perceptions of the innovation, the characteristics of the people who may adopt the innovation, and the contextual and managerial factors (Berwick, 2003). The context varies between high- and low-income settings, making it difficult to uncritically transfer the knowledge we have from one setting to the other. Most studies on the effects of innovations/interventions have been directed towards professionals and the change in their practices. This might be sufficient for health care reforms in high-income countries where health services, including drug prescriptions, are controlled and all patients see a health care professional. However, in low-income countries, such as Tanzania, people can to a great extent choose to treat themselves outside the formal health care system. An intervention will therefore need to be implemented at household level as well as in the formal health care system in order to have a large impact. This makes it essential to disseminate information to all levels of society, with informing the public as a crucial element.

1.10 MALARIA TREATMENT POLICY

Effective treatment of malaria episodes is a fundamental pillar of the malaria control strategy. This is why it is important to constantly monitor the efficacy and effectiveness of antimalarials. The WHO and WHO/AFRO have proposed criteria for changing treatment policy based on the resistance development. Three levels of resistance are described:

I. Total treatment failure <5%: Grace period: At this level, regular monitoring of antimalarial efficacy is recommended.

II. Total treatment failure 6-15%: Alert period: At this level the control programme needs to define alternative treatment, initiate mechanisms for the change, attempt to forecast the time for change and the cost and start advocacy for change.

III. Total treatment failure 16-24%: Action period: The control programme can focus on the operational plan for drug replacement and detailed considerations for cost and implementation.

Implementation of the new policy is recommended at total treatment failure rates above 25% (WHO, 2001b;WHO, 2001a). Recently, the WHO published new guidelines for the treatment of malaria. In this document, the policy change threshold has been revised to 10% total treatment failure. The reasons for the change are the availability of highly
effective drugs and recognition of the consequences of drug resistance in terms of morbidity and mortality, as well as the importance of high cure rates in malaria control (WHO, 2006). The guidelines also state that the average cure rate should be at least 95% for an antimalarial introduced as treatment policy. However, the guidelines acknowledge that a decision to change might be influenced by a number of additional factors, including prevalence and geographical distribution of reported treatment failures, patient and health worker dissatisfaction with the treatment, political and economical factors, and the availability of affordable alternatives to the commonly used treatment (WHO, 2006).

Because of rapidly spreading resistance, many African countries changed their malaria treatment policies from chloroquine (CQ) to the sulfadoxine/pyrimethamine (SP) drug combination. Malawi was the first in 1993, followed by South Africa and Kenya (Shretta et al., 2000). Tanzania, faced with an average CQ treatment failure rate of 42% already in 1999 (Kitua et al., 1999), changed its national malaria treatment policy from CQ to SP as first line treatment in August 2001. Amodiaquine was introduced as the new second line treatment, with quinine as third line, and as treatment for severe malaria (NMCP, 2001).

**Box 1.** The Tanzanian National anti-malarial Drug Policy (Msengi et al., 2001)

```
Implemented on August 1st 2001

**Treatment for uncomplicated malaria:**
1. Sulfadoxine/Pyrimethamine (SP)
2. Amodiaquine
3. Quinine

**Treatment for complicated malaria:**
- Quinine, preferably i.v.

**Treatment for children aged one week to two months:**
- Quinine, i.v.

**Intermittent presumptive treatment (IPT) in pregnant women:**
- Full treatment dose of SP in week 20 and week 30 of pregnancy

**Malaria chemoprophylaxis:**
- Patients with sickle cell anaemia: Chloroquine once weekly
- Non-immune travellers: Mefloquine once weekly
```

1.11 RATIONALE OF THE STUDIES

The rapid development of antimalarial drug resistance makes it important to monitor the resistance levels and thereby guide policy changes and ensure effective treatment. When the data collection for this thesis began SP, because it was affordable and relatively safe, was considered the only possible option for replacing CQ as malaria treatment in Tanzania. We had the possibility of assessing the drug efficacy in the same
geographical area before and after the policy change. Extensive research has tried to
find a way of predicting development of SP resistance and DHFR/DHPS genotypes
have been seen as possible markers. However, there is an inconsistency in the results
(Talisuna et al., 2004) and there is a need to find a relationship between specific
mutations and in-vivo resistance to SP in order to be able to monitor the further
development of resistance towards the drug. Studying drug efficacy over time may
teach us how resistance develops on a molecular level, but also how it is influenced by
community behaviour.

The change on August 1st 2001 to the Tanzania national malaria treatment policy
replacing CQ as the first line drug with SP provided an opportunity to study the policy
diffusion and community perceptions of SP in our study area shortly after the policy
change. The process of policy change has previously been poorly studied in sub-
Saharan Africa. Furthermore, most research describes the theory of the policy cycle up
to policy implementation (Williams et al., 2004). Our study focuses on how people in
resource-limited settings adopt a new policy and how this affects their behaviour.

Health personnel, such as prescribing nurses and clinical officers working in peripheral
dispensaries and health centres, provide the first contact with formal health care
services. Studies have shown their poor performance in terms of history taking,
-prescribing practices, physical examination and consultation time at primary health care
facilities (Gilson et al., 1993; Krause et al., 1998). Inadequate clinical assessment could
cause incorrect diagnosis and inappropriate treatment of malaria episodes and other
conditions. This is an important factor in the balance between prompt, effective
treatment and reducing spread of drug resistance.

As discussed previously, one of the main aims of the current strategies for controlling
malaria is to integrate knowledge from different fields of malaria research. The sub-
 studies in this thesis therefore triangulate findings from clinical pharmacology, health
 systems research, malariology and paediatrics, to explore how management of malaria
has been affected by the change of malaria treatment policy.
2 OBJECTIVES

2.1 GENERAL OBJECTIVE
The aim was to explore the influence of the national malaria policy change on malaria case management of children younger than five years of age and the development of resistance to antimalarials in rural Tanzania.

2.2 SPECIFIC OBJECTIVES
In rural Tanzania we wanted to study the following:

1. The resistance patterns of the most commonly used antimalarials (sulfadoxine/pyrimethamine, chloroquine and amodiaquine) and the value of using DHFR/DHPS mutations in determining clinical resistance before (study II) and after (study V) the implementation of the new malaria treatment policy.

2. The quality of case management of malaria in children under five years of age at health facilities and evaluate the accuracy of self-reported mothers'/guardians’ information on chloroquine use in children before (study I) and after (study IV) the implementation of the new malaria treatment policy.

3. The management of malaria in homes and the use of antimalarials for self-treatment before (study I) and after (study IV) the implementation of the new malaria treatment policy.

4. The diffusion of the Tanzanian malaria treatment policy by surveying the availability, the use of and knowledge about antimalarial drugs in households (study III).
3 MATERIALS AND METHODS

3.1 DESIGN AND SAMPLING

The thesis consists of five cross-sectional studies performed in three different rural district of Tanzania. During the course of data collection for this thesis, the national malaria treatment policy changed on August 1st 2001. All studies are therefore described in relation to this policy shift. One study on the quality of care at health facilities and one about the efficacy of the current antimalarials was performed both before (studies I & II) and after (studies IV & V) the policy shift. In addition a fifth sub-study concerning the policy adoption itself was performed just six months after the policy shift (study III).

Details of the sampling and design are described in each sub-study and a summary is given in section 3.6.

Data collection timeline:

<table>
<thead>
<tr>
<th>1997</th>
<th>1999</th>
<th>1st August 2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
<td>Treatment Policy shift from CQ to SP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>HF</td>
<td>Community HF HF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Facility (HF)</td>
<td>Quality of care/case management</td>
<td>Efficacy study</td>
<td>Household survey</td>
<td>Policy adoption</td>
<td>Quality of care/case mgmt.</td>
</tr>
</tbody>
</table>

3.2 STUDY AREAS AND POPULATION

The five sub-studies were performed in three different Tanzanian districts. All the districts are rural and so-called high-transmission areas for malaria, i.e. transmission occurs the whole year around. The short rains fall from November to December and the long rains from March to June, giving two peak malaria transmission periods in December/January and in June.
Figure 3. Map of study area.

Table 3. Populations in the study districts of this thesis (NBoST, 2003):

<table>
<thead>
<tr>
<th>Name of district</th>
<th>Region</th>
<th>Population</th>
<th>Average household size</th>
<th>Annual population growth</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mkuranga</td>
<td>Pwani (Coast)</td>
<td>187,428</td>
<td>4.4</td>
<td>2.4%</td>
<td>IV</td>
</tr>
<tr>
<td>Kibaha</td>
<td>Pwani (Coast)</td>
<td>132,045</td>
<td>4.4</td>
<td>2.4%</td>
<td>I, III</td>
</tr>
<tr>
<td>Kilosa</td>
<td>Morogoro</td>
<td>489,513</td>
<td>4.6</td>
<td>2.6%</td>
<td>II, V</td>
</tr>
</tbody>
</table>

*Kibaha district* is located about 40 km northwest of Dar es Salaam. Studies I & III were performed in Kibaha. The district had, at the time of study III, 9 wards, of which 4 were classified as urban and 5 as rural. There was no district hospital in the district at the time of data collection, but eight dispensaries and two health centres were available. The Kibaha district was the study site of a SAREC funded project in which study I & III were part.
**Box 2.** Description of the Sida/SAREC funded malaria management project.

The Kibaha study site is part of an ongoing Sida/SAREC funded bilateral project, a collaboration between the Muhimbili University College of Health Sciences (MUCHS) and Karolinska Institutet (KI). The collaboration started in 1992 with the department of Clinical Pharmacology as the core on the MUCHS side. It has facilitated interactions between Tanzanian and Swedish PhD students and between Tanzanian students from different departments, so-called twinning. This contributes to bridging the gap between disciplines at both KI and MUCHS. The collaboration now involves a number of different departments, such as Clinical Pharmacology, Public Health, Parasitology and Paediatrics at MUCHS and Clinical Pharmacology, Infectious diseases and International Health (Swedish coordinator) at KI. Several PhD students have graduated from both MUCHS and KI. A drug analysis laboratory has been established at MUCHS as part of the collaboration and some of the blood drug level analyses in studies III & IV were performed there. The project itself explores different aspects of malaria management. It covers methods for drug analysis of antimalarials, genetic and environmental control of drug metabolism, and quality of drugs from different producers and health systems research and quality of care at health facilities. Most recently it has launched an intervention of studying impact of diagnostic tests on fever management in the community.

*Kilosa district* is located in the Morogoro region about 300 km west of Dar es Salaam. Studies II & V were both performed in Tindiga village, about 25 km south of Kilosa town. Tindiga is quite poorly accessible, far from busy trading routes and thus rather isolated. There were also no drug stores in the village at the time of data collection. Study II was performed as part of the baseline of the “Rectocap” project, a TDR/WHO funded project run under NIMR, based in Kilosa district. We decided to perform the follow-up (study V) in the same area.

*Mkuranga district* is located about 60 km south of Dar es Salaam, along the coast. The district was chosen as the study site for an EU-funded intervention called the MAMOP project and study IV was part of its baseline survey. All health facilities (n=9) in the wards selected for the MAMOP intervention were included in study IV. These included 7 dispensaries (one government, one mission and five private), one government health centre and one government hospital. However, during our fieldwork, we realized that one of the (private) dispensaries did not treat any underfives at all. This unit was thus excluded, leaving us with 8 health facilities.

**Box 3.** Description of the MAMOP project.

The MAMOP project is a controlled malaria community intervention with a pre-post design conducted in rural Burkina Faso and Tanzania in 2002-2004. The overall objective of the MAMOP study was to evaluate the feasibility and effectiveness of an intervention aimed at improving case management of malaria in underfive children through the primary caretakers in collaboration with local women groups and existing health centres.

Ninety percent of global child deaths occur in 42 countries (Black et al., 2003), one of which is Tanzania. The underfive mortality rate in Tanzania is, according to the official
records from 1995-1999, 147:1000 (WHO, 2005). However, estimates from 2003 gave figures around 165:1000 (WHO, 2005). This underfive mortality rate ranks Tanzania as the 23rd worst globally and ninth in absolute number of child deaths (Black et al., 2003). The five most common causes of underfive deaths are pneumonia, malaria, neonatal disorders, diarrhoea and AIDS. The proportion accounted for by each of these causes is often described as homogenous for countries in sub-Saharan Africa, sometimes misleading because of differences between individual countries. Black et al. propose a grouping of countries into five different profiles depending of the proportion of the different illnesses (Black et al., 2003). According to this grouping, Tanzania belongs to profile 4, where malaria accounts for 26% and pneumonia and diarrhoea each account for 17-19% of deaths. AIDS account for at least 10%.

3.3 DATA COLLECTION METHODS

3.3.1 Triangulation

One of the strengths of this thesis is that it has used triangulations for a more comprehensive picture of malaria case management. Triangulation broadly means using multiple methods in research. There are four types of triangulation: data triangulation (using different sources of data), theory triangulation (applying different perspectives to the same data source), investigator triangulation (using different researchers) and methodological triangulation (using multiple methods) (Patton, 1987). The approach of combining different methods in data collection and analysis as performed in studies I, III and IV could be considered methodological triangulation (Dootson, 1995; Begley, 1996; Foss and Ellefsen, 2002) where research adopts the advantage of seeing different realities. For example, a participant of an FGD might, within the comfortable environment of a group, reveal points that he/she would not have dared to nor have had the possibility to express in an interview. This way of seeing different views of a topic provides a greater perspective and might also serve as a way of confirming (validating) the quantitative and completeness (credibility) of qualitative data (Breitmayer et al., 1993; Begley, 1996; Foss and Ellefsen, 2002). The overall conclusions of this thesis are drawn from data collected in the different sub-studies and could be considered data triangulation in itself. Furthermore, triangulation from the different perspectives of clinical pharmacology, health systems research, malariology and paediatrics can give additional strength to the conclusions.

3.3.2 Interviews

Interviews with questionnaires are commonly used research techniques in Health Systems Research (Varkevisser et al., 1991). The interviews are then structured in the sense that there are fixed sets of questions to be asked. Questions can be asked using open-ended or closed questions (Hordon et al., 2001a). Open-ended questions are useful in obtaining information on facts with which the researcher is not familiar, such as opinions, attitudes and suggestions from the informants, or sensitive issues, whereas closed questions offer a list of possible options or answers from which the respondents must choose. Closed questions are useful if the range of possible responses is known (e.g. marital status). An advantage of these types of interviews includes the possibility to get many views or answers, to perceive peoples’ views and experiences, and the
possibility to ask several questions while recording and studying the participants’ responses to questions. This instrument does not allow freedom to adjust any of its elements, such as contents, wording or order of the questions during the interview itself. The questionnaires imply strict adherence to the questions and instructions. In all our studies, interviews were conducted with individuals and not in groups.

Interviews in the household study (III) were conducted using questionnaires with heads of households and mothers/guardians of underfive children (Appendix 2). The questionnaire focused on the treatment strategies of malaria in underfives, home stocking of drugs, knowledge of dosages for malaria treatment, perceptions about SP, knowledge of the new treatment policy and policy diffusion. The interviews were conducted on a house-to-house basis and the village chairmen or secretaries escorted the researchers. In the Tanzanian context, the presence of village leaders is an advantage when it comes to building a trustful relationship with the interviewee. The village leaders were not allowed to listen to the interview itself. Allowing the researcher to be the interviewer enabled first-hand control of the data.

Interviews were also performed in studies I & IV. These were exit interviews with mothers/guardians of underfives conducted after a consultation and they concerned the mothers’ understanding of treatment and counselling given (Appendices 1 and 4). Interviews in study I were performed by a clinical pharmacologist or one of four experienced public health nurses trained for the data collection. In study IV the author of this thesis together with an interpreter performed the interviews. Two PhD students from MUCHS, Dar es Salaam, performed the interviews of the household survey (study III).

3.3.3 Direct observation

By definition, observation (participant or non-participant) is a technique that involves systematically watching and recording the behaviour and other characteristics of living beings or phenomena (Robson, 1993). Observational methods usually refer to a number of techniques aimed at forming direct observations about peoples’ own behaviour. Observation has an advantage of collecting detailed first-hand data on phenomena as it occurs. Furthermore, this technique can be used to collect information to complete or complement the data collected by other techniques.

We used two slightly different methods of observation in study I and study IV. In study I the investigator was sitting outside the consultation room, but could observe the patient-provider interaction through a window. This did not allow a very detailed record of history taking, physical examination and consultation. Instead a child was considered physically examined if touched by the health worker. Observations in study I were performed by a clinical pharmacologist from MUCHS, Dar es Salaam.

In study IV, we decided to record more details from the patient-provider interaction. The observer thus sat inside the consultation room checking off points in a detailed check list concerning history taking, physical examination and counselling (Appendix 4). All observations were performed by the author of this thesis and one of three junior physicians from Muhimbili National Hospital, Dar es Salaam.
3.3.4 Focus Group Discussions

This method has a wide application in qualitative/behavioural research (Murphy et al., 1992; Hardon et al., 2001b) and Health Systems Research (Varkevisser et al., 1991). FGDs are low-cost and can be conducted rapidly. Because discussions are performed in groups, interactions tend to be lively with synergistic effects where one person builds on what another person has said. The method is open and flexible, and this allows more probing/exploration of opinions, feelings, attitudes, previous experiences and other behaviours, which may not be possible to obtain through quantitative methods. In addition, FGDs can handle topics that are sensitive or controversial because participants feel more comfortable or secure when expressing certain views when they are in a group as compared to individual interviews. FGD as a qualitative method can stand on its own and can be used to explore or confirm hypotheses and research questions in conjunction with other research methods, such as interviews, surveys and observations. FGDs are often processes that reveal social norms as opposed to interviews, which highlight the views and attitudes of individuals (Lunt and Livingstone, 1996; Hardon et al., 2001b).

Disadvantages of FGDs include that minority opinions may not always be expressed and there may be dominant participants. Furthermore, the facilitator may sometimes visibly react favourably or unfavourably to comments given by participants. FGD results are qualitative in nature and may be difficult to interpret. Other limitations with FGDs are: they can be driven by the researcher’s interests, there is always some residual uncertainty about the accuracy of what participants say and as the moderator tries to maintain the discussions in focus, he/she can influence the group’s interactions which can affect the quality of the data. The group itself can also influence the nature of data it produces (Hardon et al., 2001b). Thus, the selection of participants needs to represent, among other things, education level, gender and other characteristic similarities, so as to minimise some of these cited problems that can occur when conducting FGDs. In study III (Appendix 3), FGDs were used to explore the knowledge and perceptions of the new Tanzanian malaria treatment policy.

Following the household interviews, thematic guides for the FGDs were developed, including self-treatment practices with antimalarials, perceptions of SP and the antimalarial drug policy change. The discussions were moderated by one of the co-authors, a sociologist. Two note takers and one observer from the research team were also present (the author of this thesis or the second author of the study III).

3.3.5 Filter paper of blood drug levels and genetic markers

In all sub-studies of this thesis, blood samples were collected from children under five years of age in order to measure blood levels of antimalarials. In addition, in studies II & V, samples were taken for analysis of DHFR/DHPS genotypes.

In the study settings, the community often shows reluctance to participating in venous blood sampling. In addition, no facilities are available for cold storage of blood samples. Thus, a field adapted method has been developed for simple blood collection and storage (Lindström et al., 1985). All blood samples in the sub-studies are capillary
samples collected after a finger prick. For the blood drug levels, 100 µL of blood is collected by a heparinized capillary tube and dried on filter paper (Whatman 3MM chromatography). For analysis of DHFR/DHPS genotypes, a blood drop (10-50 µL) is taken directly from the pricked finger and dried on filter paper (Whatman 3MM chromatography or Whatman GF/C glass fibre filter). All samples need to be wrapped individually to avoid contamination, but once collected they can be stored for several years without affecting the quality of the analysis (Lindström et al., 1985; Bergqvist et al., 1986).

3.4 LABORATORY METHODS

3.4.1 Microscopy

To detect malaria parasites, conventional microscopy was used. From a capillary blood sample drawn by a single finger prick, thick and thin blood smears were taken and Giemsa stained for detection and determination of malaria parasites. The numbers of asexual parasites per 200 WBC in thick films were counted. Parasite densities (asexual parasites/µl blood) were calculated assuming a leukocyte count of 8000 WBC/µl blood. A blood film was classified as negative when examination of 100 fields failed to show the presence of asexual forms of *P. falciparum*.

3.4.2 Genotyping

**Study II:** For the genetic mutations, 10 to 50 µL of blood was collected from the SP patient group, dried on filter paper, and analysed using PCR (Polymerase Chain Reaction). Variation in *pf dhfr* at positions 51, 59, 108 and 164 was detected using the method described by (Masimirembwa et al., 1999) with mutation specific primers. The mutation specific PCR for position 59 mutations, was done using pre-mixed reagents in Alpha Helix Reagent Cartridges (AlphaHelix, Uppsala, Sweden). Variation in DHPS genotypes at positions 437 and 540 was detected using the primers specified in (Masimirembwa et al., 1999) for nested PCR. The PCR products were subjected to restriction enzyme cleavage. AvaII (New England Biolabs, Beverly, MA, USA) was used to detect Gly (mutation) at position 437. FokI (New England Biolabs, Beverly, MA, USA) was used to detect Glu (mutation) at position 540.

**Study V:** The genotype of DHFR SNPs was made as described by Veiga et al (Veiga et al., 2006). For the genotype of *pf dhps* SNPs, a set of first and nested PCR amplifications were designed for DNA fragments containing *pf dhps* A437G and K540E a conventional PCR-RFLP method was developed. The primers were synthesized by Thermo Electron Corporation (Ulm, Germany) and, *Taq* polymerase, MgCl2 and dNTPs were purchased from Promega (Madison, WI, USA). The restriction was performed with 7µL of amplified product with a respective enzyme for each SNP in a final volume of 25µL.

3.4.3 Haemoglobin levels

Haemoglobin levels were measured using the HemoCue® technique (Von Schenck et al., 1986; Kwant et al., 1987). Capillary blood was sampled from the patient using a special cuvette. The cuvette was inserted into the HemoCue® apparatus and analysed
within a few seconds. For every haemoglobin value in each patient we used the average value of two consecutive measurements.

### 3.4.4 HPLC

Blood drug levels of antimalarials were measured using High Pressure Liquid Chromatography (HPLC) for analyzing the capillary blood sampled on filterpaper (see section 3.2.4). CQ concentrations were determined by the HPLC method developed by (Lindström et al., 1985). SP was measured using sulfadoxine as a proxy sample. The HPLC method used for analysing sulfadoxine was the one developed by (Bergqvist et al., 1987). Because of the long terminal half-life of chloroquine, it can be measured in the blood of a patient much longer following drug intake as compared to sulfadoxine.

We controlled the validity of the measurements by calculating the coefficient of variation (CV) for the accuracy and the precision in each round of analysis. Whereas the accuracy is a control of the quality or correctness of the results, the precision relates to the quality of the methods and instruments used (the performance).

### 3.5 STATISTICAL ANALYSIS

The statistical methods used for analyses were:

i. **Chi-square test** was used to compare two groups of categorical data such as the proportion of children with adequate clinical response by drug treatment group.

ii. **Student’s t-test** was used to compare independent samples in a normally distributed data set. This was used in studies II and V to test statistical significance of continuous data such as haemoglobin levels and parasite densities.

iii. **Logistic regression** was used to estimate the effect of several independent variables while controlling for a number of confounding factors and allowing for interaction between variables. In study III, it was used to determine predictors (such as level of education, sex, location of residence, underfives living in a household) for e.g. knowledge of the policy change and care – seeking behaviour.

iv. **Intraclass correlation** To perform an analysis of intra- and inter-facility variation of the quality scores, we calculated an intraclass correlation coefficient (ICC). This was also done for health workers (study IV).

v. **Geometric mean** is useful when, as opposed to situations where the arithmetic mean is used, the measurement scale is not linear. We have used the geometric mean in all analysis of parasite densities.

vi. **ANOVA** (multivariate) has been used to analyse potential differences in mutation rates between parasite populations on different days.
3.6 SUMMARY OF METHODS

Table 4. Summary of the methods used in the five sub-studies.

<table>
<thead>
<tr>
<th>Title of study</th>
<th>Methods</th>
<th>Study population and sample size</th>
<th>Study Period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Case management of malaria in underfives at primary health care facilities in a Tanzanian district</strong></td>
<td>Interviews with mothers/guardians of underfives, observation of consultations, malaria microscopy, HPLC of dried blood filter papers for CQ</td>
<td>- Mothers/guardians with sick underfives (n=652)</td>
<td>Aug-Sept 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Health workers (n=10)</td>
<td></td>
</tr>
<tr>
<td><strong>II. Patterns of resistance and DHFR/DHPS genotypes of Plasmodium falciparum in rural Tanzania prior to the adoption of sulfadoxine/pyrimethamine as first-line treatment.</strong></td>
<td>Malaria microscopy and HPLC for dried blood filter papers for CQ and SP, PCR for detection of DHFR/DHPS mutations</td>
<td>- Underfive malaria patients treated with SP (n=58)</td>
<td>Oct-Nov 1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Underfive malaria patients treated with CQ (n=59)</td>
<td></td>
</tr>
<tr>
<td><strong>III. Household adoption of the new antimalarial drug policy in Tanzania – implications for future policy changes</strong></td>
<td>Household survey with questionnaires, Focus group discussions (FGDs), HPLC of dried blood filter papers for CQ and SP</td>
<td>- No. of households (HH) (n=729), - HH with underfives (n=397) - 12 FGDs: -- 4 with 6-11 mothers/guardians per groups -- 4 with 6-11 fathers per group -- 4 with 6-11 health workers per group</td>
<td>Jan-Feb + Aug 2002</td>
</tr>
<tr>
<td><strong>IV. Assessing health worker performance in malaria case management of underfives at health care facilities in rural Tanzania</strong></td>
<td>Interviews with mothers/guardians of underfives, observations of consultations, malaria microscopy and HPLC of dried filter paper for SP and CQ</td>
<td>- Interviews with mothers/guardians (n=115) - Observations (n=117)</td>
<td>June-Aug 2003</td>
</tr>
<tr>
<td><strong>V. Three years with sulfadoxine/pyrimethamine as first-line treatment of uncomplicated falciparum malaria in rural Tanzania – efficacy unchanged.</strong></td>
<td>Malaria microscopy and HPLC for dried blood filter papers for CQ and SP, PCR for detection of DHFR/DHPS mutations</td>
<td>- Underfive malaria patients treated with SP (n=66) - Underfive malaria patients treated with AQ (n=30)</td>
<td>May-June 2004</td>
</tr>
</tbody>
</table>
4 ETHICAL CONSIDERATIONS

Human research ethics committees in Tanzania and Sweden approved all the studies.

Study I: Approval obtained from Muhimbili University college of Health Sciences (MUCHS) (MU/PGS/AEC/VOL.4) in Dar es Salaam and Karolinska Institute (KI) (D-nr 309/03).

Study II: Approval obtained from the National Institute of Medical Research (NIMR) (NIMR/R.8a/Vol.VII/85) and KI (D-nr 444/03).

Study III: Approval obtained from MUCHS (MU/PGS/AEC/VOL.4) and KI (D-nr 01-426).

Study IV: Approval obtained from NIMR (NIMR/HQ/R.8a/Vol.IX/253) and KI (D-nr 03-206).

Study V: Approval obtained from NIMR (NIMR/HQ/R.8a/Vol.IX/278) and KI (D-nr 310/03).

For all studies, permission was granted from district authorities, village authorities and all health staff, patients and caretakers involved. Informed consent was obtained from all guardians of under-aged children.
5 RESULTS

5.1 DEVELOPMENT OF ANTIMALARIAL RESISTANCE (II & V)

We assessed the pattern of resistance to the first and second line antimalarials used in Tanzania before (1999 – study II) and after (2004 – study V) the malaria treatment policy change.

Clinical and parasitological resistance

In study II, 117 children were treated with either CQ (n=59) or SP (n=58). In study V, 96 children were given either SP (n=66) or AQ (n=30). The baseline characteristics of the enrolled patients are shown in Table 4.

Table 5. A comparison of the baseline characteristics of the enrolled patients in the studies from 1999 (n=117) and 2004 (n=96).

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>1999</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CQ n=59</td>
<td>SP n=58</td>
</tr>
<tr>
<td>Age (mean ± SD) (months)</td>
<td>21 ± 12</td>
<td>20 ± 15</td>
</tr>
<tr>
<td>Percentage females</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>Haemoglobin at enrolment (mean ± SD) (g/L)</td>
<td>83.1 ± 17.9</td>
<td>82.8 ± 19.8</td>
</tr>
<tr>
<td>Mean parasitaemia at enrolment (geometric means)</td>
<td>9315</td>
<td>9467</td>
</tr>
<tr>
<td>Temperature (% ≥38 °C day 0) at enrolment</td>
<td>20%</td>
<td>26%</td>
</tr>
</tbody>
</table>

The classification of treatment responses in the WHO protocols for assessing the efficacy of antimalarials of 1996 (WHO, 1996) and 2003 (WHO, 2003a) differ and we used the two protocols in study II and V, respectively. In Table 5, results from both studies are presented according to the 2003-protocol to simplify comparison.

Total treatment failure is equal to the sum of early treatment failure (ETF), late clinical failure (LCF) and late parasitological failure (LPF) (WHO, 2003a). In 1999 this was 33% for SP and 61% for CQ. In 2004 total treatment failure was 18% for SP and 27% for AQ (using a 14 day follow-up). When comparing the total treatment failure for SP in 1999 and 2004, there was no statistically significant difference ($\chi^2=3.50$, p=0.06).
Table 6. Comparison of treatment outcomes in 1999 and 2004. Outcome based on the WHO protocol for assessing therapeutic efficacy of antimalarials (WHO, 2003a). For the criteria of the different outcome definitions, see Box 1 in paper V.

<table>
<thead>
<tr>
<th>Outcome according to the 2003 WHO protocol</th>
<th>1999</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CQ %</td>
<td>SP %</td>
</tr>
<tr>
<td>1999</td>
<td>n=59</td>
<td>n=58</td>
</tr>
<tr>
<td>ACPR (adequate clinical and parasitological response)</td>
<td>39</td>
<td>67</td>
</tr>
<tr>
<td>TTF (total treatment failure = Clinical failure + LPF)</td>
<td>61</td>
<td>33</td>
</tr>
<tr>
<td>Clinical failure (ETF + LCF)</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>ETF (early treatment failure)</td>
<td>3.5</td>
<td>-</td>
</tr>
<tr>
<td>LCF (late clinical failure)</td>
<td>6.5</td>
<td>2</td>
</tr>
<tr>
<td>LPF (late parasitological failure)</td>
<td>51</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

DHFR/DHPS genotypes

In study II, pre-treatment samples of the patients treated with SP (n=58) were analysed for pf\textit{dfr} and pf\textit{dhs} mutations. Post-treatment, 19 patients still had detectable parasites and could be analysed for mutations.

The presence of mutations in DHFR was high for positions 51 (84%), 59 (86%) and 108 (91%) before treatment. Of these genotypes, 65-70% were mixed with wild-type alleles. The number of pure mutants in samples on day 14 as compared to day 0 was higher for mutations at position 108, while no clear trends were detected for mutations in positions 51 and 59. Five of the 17 samples analysed on day 14 were pure mutants in all three positions (108, 51 and 59), and 15 samples contained mutants at all positions if mixed samples were included.

The results for DHPS analysis in study II were surprising in that on day 0, all alleles at position 437 were wild-type and all at position 540 were mutated. In contrast, on day 14 all except one of the samples analysed were of wild type. The remaining sample was mixed wild-type/mutant at both positions. There were no quintuple mutants (having mutations in positions 108, 51 and 59 of \textit{pf\textit{dfr}} combined with mutations in positions 437 and 540 of \textit{pf\textit{dhs}}) on day 0, but several patients had mutations in both position 59 of \textit{pf\textit{dfr}} and position 540 of \textit{pf\textit{dhs}}. These two mutations can obviously persist together with wild-type alleles at other \textit{pf\textit{dfr}} and \textit{pf\textit{dhs}} positions.
In study V, pre-treatment samples from 94 patients were analysed for DHFR and DHPS mutations. Post-treatment, samples from 11 patients (8 were treated with SP and three with AQ) were successfully analysed for the same mutations after 14 days of follow-up. Most of these patients (n=8) were classified as late parasitological failures (LPF), two of them were late clinical failures (LCF) and one had an adequate clinical and parasitological response (ACPR).

The frequency of point mutations in\textit{pfdhfr} was high for Ile51 (85%), Arg59 (82%) and Ser108 (92%) before treatment. Of these, 63-77% were pure mutants, the rest of the samples contained mixed genotypes. The presence of mutations at position 51 and position 108 rose to 100% on day 14 if mixed samples are included. Position 59 remained unchanged. Nine of the 11 samples analysed on day 14 were pure mutants in all three positions of\textit{dhfr} (51, 59 and 108).

The frequency of\textit{pfdhps} mutations were not altered significantly after treatment, Gly437 changing from 56% to 60% and Glu540 from 64% to 70%. There was no statistical difference between the AQ and SP groups.

In the overall study population, as many as 44% of the patients were quintuple mutants (having mutations in positions 51, 59 and 108 of\textit{pfdhfr} combined with mutations in positions 437 and 540 of\textit{pfdhps}) before receiving treatment. Seven of the 11 patients followed from day 0 to day 14 were quintuple mutant on day 0 (one of them had an ACPR – i.e. no parasites seen with microscopy, but detected by PCR) and five were still quintuple mutants on day 14. Nine percent of patients had mutations in both position 59 of\textit{pfdhfr} and position 540 of\textit{pfdhps} and had wild-type alleles at other positions. Using a multivariate ANOVA including all the five point mutations no significant differences between the mutation rates at day 0, 7 and 14 were found (multivariate test and Bonferroni-adjusted 5% test level for pairwise contrasts).

On day 7, only parasites from five patients could be analysed for mutations. Three of these were quintuple mutants. Of the quintuple mutants, one had an ACPR, one was a LPF and one was a LCF.

In summary, we were unable to demonstrate a causal relationship between clinical outcome and number of point mutations. However, the number of quintuple mutants on day 0 was higher in 2004 than in 1999. The frequency of mutations in both positions of\textit{dhps} was higher in 2004 as compared to 1999. In addition, we saw an indication of a selection of more mutated parasites on day 7 and 14 following treatment in study V.

5.2 DRUG PRESSURE IN THE COMMUNITIES (I, II, III, IV & V)

We measured the drug pressure as blood drug levels in children in all five sub-studies, four of them facility based and one community based, and after the policy change saw a decrease in blood drug levels of the first line antimalarial.

In studies I, II, IV & V, the population studied comprised of ill underfives seeking care at health facilities. Pre-treatment blood drug levels were measured in all children.

\textit{In study V, pre-treatment samples from 94 patients were analysed for DHFR and DHPS mutations. Post-treatment, samples from 11 patients (8 were treated with SP and three with AQ) were successfully analysed for the same mutations after 14 days of follow-up. Most of these patients (n=8) were classified as late parasitological failures (LPF), two of them were late clinical failures (LCF) and one had an adequate clinical and parasitological response (ACPR). The frequency of point mutations in\textit{pfdhfr} was high for Ile51 (85%), Arg59 (82%) and Ser108 (92%) before treatment. Of these, 63-77% were pure mutants, the rest of the samples contained mixed genotypes. The presence of mutations at position 51 and position 108 rose to 100% on day 14 if mixed samples are included. Position 59 remained unchanged. Nine of the 11 samples analysed on day 14 were pure mutants in all three positions of\textit{dhfr} (51, 59 and 108). The frequency of\textit{pfdhps} mutations were not altered significantly after treatment, Gly437 changing from 56% to 60% and Glu540 from 64% to 70%. There was no statistical difference between the AQ and SP groups.

In the overall study population, as many as 44% of the patients were quintuple mutants (having mutations in positions 51, 59 and 108 of\textit{pfdhfr} combined with mutations in positions 437 and 540 of\textit{pfdhps}) before receiving treatment. Seven of the 11 patients followed from day 0 to day 14 were quintuple mutant on day 0 (one of them had an ACPR – i.e. no parasites seen with microscopy, but detected by PCR) and five were still quintuple mutants on day 14. Nine percent of patients had mutations in both position 59 of\textit{pfdhfr} and position 540 of\textit{pfdhps} and had wild-type alleles at other positions. Using a multivariate ANOVA including all the five point mutations no significant differences between the mutation rates at day 0, 7 and 14 were found (multivariate test and Bonferroni-adjusted 5% test level for pairwise contrasts).

On day 7, only parasites from five patients could be analysed for mutations. Three of these were quintuple mutants. Of the quintuple mutants, one had an ACPR, one was a LPF and one was a LCF.

In summary, we were unable to demonstrate a causal relationship between clinical outcome and number of point mutations. However, the number of quintuple mutants on day 0 was higher in 2004 than in 1999. The frequency of mutations in both positions of\textit{dhps} was higher in 2004 as compared to 1999. In addition, we saw an indication of a selection of more mutated parasites on day 7 and 14 following treatment in study V.}

5.2 DRUG PRESSURE IN THE COMMUNITIES (I, II, III, IV & V)

We measured the drug pressure as blood drug levels in children in all five sub-studies, four of them facility based and one community based, and after the policy change saw a decrease in blood drug levels of the first line antimalarial.

In studies I, II, IV & V, the population studied comprised of ill underfives seeking care at health facilities. Pre-treatment blood drug levels were measured in all children.
Studies I & II were performed before the policy change in August 2001, when CQ was still the first line treatment. In study I we successfully analysed blood drug levels in 529 children. Of these, 98% had detectable blood levels of CQ, 11% had high (≥1000 nmol/L) levels. The results in study II were similar. Of the 59 children in the CQ group, 92% had detectable CQ blood levels and 10% of 58 children in the SP group had detectable sulfadoxine levels.

Studies IV & V were performed after the policy change when SP was the first line treatment and CQ had been banned. From the 117 children seen at the health facilities in study IV, we analysed 110 blood samples for CQ and 99 for sulfadoxine. Only 12% of the children had detectable sulfadoxine levels, none of them high, and 2% had CQ. In study V, 24% of the children had detectable sulfadoxine in the blood.

The population in study III comprised of healthy children in the community and we were able to analyse 321 samples for sulfadoxine content and 320 for CQ. Eighteen and five percent had detectable levels of S and CQ, respectively.

Table 7. The proportion of children with detectable blood levels of sulfadoxine and CQ in the five sub-studies before and after the malaria policy change.

<table>
<thead>
<tr>
<th>Drug analysed</th>
<th>Children with detectable blood drug levels (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before policy change</td>
</tr>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td><strong>Study year</strong></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>1997</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>Health facility (HF)</td>
</tr>
<tr>
<td><strong>Sulfadoxine</strong></td>
<td>*</td>
</tr>
<tr>
<td><strong>Chloroquine</strong></td>
<td>98</td>
</tr>
</tbody>
</table>

*not analysed

Stated self-treatment

Pre-policy change, in study I, 54% of the mothers/guardians reported giving medication at home, 21% having taken the children to another health facility prior to the current visit and 3% visiting traditional healers. The remaining 22% reportedly did not do anything prior to this visit. Antipyretics (45%) and antimalarials (24%), mostly chloroquine, were the most common drugs reported for self-treatment.

Post-policy change, in study IV, the main difference compared to study I was the decrease in self-treatment with antimalarials. Although 68% of the caretakers stated to have given their children some kind of treatment at home prior to coming to the health facilities this treatment was mostly antipyretic drugs (81%). Antimalarials (Quinine and SP) were reportedly given only by 4%. The sole community based study (III) also showed a decrease in self-treatment for febrile episodes with only 4% of children being given an antimalarial at home.
In summary, frequency of chloroquine in blood decreased markedly after the policy change, both in the study populations at the health facilities and in the community based survey. Detected sulfadoxine/pyrimethamine levels increased after the policy change, but did not reach the high levels of chloroquine seen before the policy change. Similarly, caretakers stated less frequent self-treatment after the policy change.

5.3 QUALITY OF CARE AT HEALTH FACILITIES (I & IV)

Quality of care was studied in 1997 (I) and 2003 (IV). For the study in 2003, we used a more detailed checklist during our observations and assessed the quality of care in terms of indicator scores.

In study I, the average consultation time was 3.8 minutes, 75% of the consultations lasted less than five minutes and none lasted more than ten minutes. Physical examination defined as touching the child was performed in 39% of the children with significant inter-facility differences. This was not more favourable in study IV where no more than 29% of the children were physically examined. The mean consultation time was 4.8 minutes (SD = 2.4). In study IV, we used nine indicators to assess quality of history taking, counselling and prescription. History taking was poorest with an average score of only 18% of what was considered optimal. Regarding prescriptions, only 28% of the febrile children received malaria treatment according the national guidelines (i.e. SP in correct dosage). However, as many as 74% of the febrile children received an effective antimalarial, the second line drug AQ being the most common choice. There was no obvious reason for not choosing the first line treatment in any of these cases. Only 20% of the health workers counselled the caretaker on how to take the medication they prescribed.

In study I, 71% of the children were presumptively diagnosed with malaria either as a single condition or in combination with other diagnoses. Respiratory problems accounted for 29% of the diagnoses and were the leading over-lapping condition. Diarrhoea alone or in combination with other conditions accounted for 9% of the diagnoses. A similar picture was seen in study IV, with 76% of the diagnoses given to the children by the health workers were malaria or “fever” alone or in combination with other conditions. Six percent were diagnosed with respiratory problems alone or with other conditions (except malaria).

To compare presumptive diagnoses of malaria with an objective diagnosis of malaria, we measured the parasite densities in the blood. In study I, this parasite count was performed only in the children who had been given a presumptive malaria diagnosis by the health worker, i.e. 449 children were screened for malaria parasites. Only 38% of these patients had parasites in their blood. In study IV, we defined malaria as a history of fever in combination with ≥2000 parasites/µL blood. Sixty-one percent of those treated with an antimalarial had ≥2000 parasites/µL blood. Among the febrile children, the proportion that was treated with antimalarials was almost the same for those with or without malaria.
Surprisingly, health workers did not take advantage of microscopy as a diagnostic tool even in the facilities where it was available. Seventy-one children sought care at a facility with a functioning microscope. Of these, 55 had fever or a history of fever. Microscopy was performed for 36 children and one-third of these had no malaria. However, almost all of them were prescribed an antimalarial.

In summary, in terms of physical examination and prescription, quality of care was poor both in studies I and IV. Despite this, most children seeking care for febrile illness were treated with an antimalarial as recommended in the guidelines. Of those presumptively treated as malaria, 38% and 61% were parasitaemic in studies I and IV, respectively. In study IV, several children sought care at facilities with microscopes. These were, however, not used in determining diagnosis or treatment.

5.4 DIFFUSION OF THE NATIONAL MALARIA POLICY (III)

Only 8% [4.7 – 12.1] of the households presented home-stocked antimalarials, mostly quinine, SP and CQ, although as many as 42% of households stated having previously stocked antimalarials. In the households, 51% correctly stated that the current first line treatment against malaria was SP and 41% explained that CQ was not used anymore because of drug resistance (using the word “sugu” = resistant). Seventy-four percent of those who had an opinion of use of SP perceived it to be a good drug.

Children with recent febrile episode

One hundred and sixteen underfives were reported to have had febrile episodes during the last 4-week period, consistent with the expected prevalence (Schellenberg et al., 2003a). Eighty percent [68% – 91%] of the children were estimated to have been given drugs at home; mostly analgesics and a small proportion (4% [0.2 – 7.2]) antimalarials. Most mothers (88%) reported also to have sought care outside the home, mainly from public health facilities. Among the children whose mothers stated to have sought care outside the home, 30% had detectable levels of SP in the blood.

Focus Group Discussions

In all FGDs, almost all the participants claimed to know that the current first line antimalarial was SP. They also knew that the new drug had been implemented because of malaria resistance against CQ. Participants mentioned having heard about SP on the radio or from staff or posters at health facilities. The FGDs also revealed that CQ is not readily available but some participants said that they would like to continue using CQ, as they believed it to be effective.

Contrary to the rather positive attitude toward SP expressed in the household survey, many of the statements made in the FGDs were negative. Most participants in the FGDs with mothers and fathers expressed fear of using SP due to adverse reactions although few had actual experience of such reactions. Most FGD participants had also heard about people who died after using SP. Most commonly, newspapers and radio were reported information sources.
Because of the fear of SP, health workers explained that they have to give the drug under observation in the health facility to avoid that the mothers throw away the tablets instead of giving them to their children. The health workers did not think that the number of patient visits due to fever in underfives had changed since the introduction of the new drug. At the same time there was never a shortage of the first line antimalarial in the health facilities.

In summary, more than half of the caretakers knew SP was the new first line drug 6 months after the policy change. Only 4% claimed to treat their children with antimalarials at home and the majority stated seeking care at health facilities for febrile illness. Poster campaigns and mass media were reported as the main sources of information about SP and FGD participants expressed fear of side-effects from the drug.
6 DISCUSSION

Total treatment failure with SP was low and had not increased during the five years that passed between study II and V. This is surprising considering previous reports from both Africa and Asia of rapid development of SP resistance with its extensive use (Doberstyn et al., 1976; Pinichpongse et al., 1982; Ronn et al., 1996). A possible explanation could be the occurrence of low drug pressure, indicating less frequent use of the first line antimalarial following the policy change as compared to before the change.

Around half of the interviewed caretakers knew about the policy change 6 months after SP had replaced CQ as first line treatment. Policy change has been poorly studied, especially in low-income settings, but it has been suggested that at least 24 months is needed for implementation (Williams et al., 2004). Considering the relatively short time that had passed between policy implementation and study III, our findings indicate a rapid shift. This could be because of the large campaigns and the fact that malaria plays an important role in most peoples’ lives in Tanzania.

Contrary to the findings before the policy shift (study I), following August 2001 caretakers reported seeking care at health facilities instead of self-treatment for fever. This was supported by low detection rates of antimalarials in blood seen after the policy change. Four of the five sub-studies of the thesis are from health facilities, but the findings from the community-based study (III) were similar to the facility-based, indicating that people have altered their practices for treatment of febrile illness. This contrasts previous data from sub-Saharan Africa reporting that most children with malaria are never seen at health facilities but get treatment at home instead (Foster, 1995; Mwenesi et al., 1995; Breman, 2001), findings that have subsequently lead to advocacy for home based management of fever (HBMF) (WHO, 2000a; Källander et al., 2004; Peterson et al., 2004; Ford et al., 2005). The HBMF strategy is spearheaded by Uganda where antimalarials for treatment of fevers, so-called “homapak”, are distributed by community volunteers (MoH-Uganda, 2002). Although this strategy may lead to treating non-parasitaemic children in addition to those with malaria, it ensures that few malaria cases progress to a more severe form and hopefully improves malaria management compared to home treatment by caretakers. The drawback is that it could also greatly enhance drug pressure and subsequent resistance development to the drugs used (Bloland, 2001). The aim for prompt effective treatment must be balanced with limiting the spread of resistance to the treatment, especially with introduction of new, expensive combination therapies for malaria (WHO, 2001a).

A way of decreasing drug pressure is to sharpen diagnostics, e.g. by using microscopy or rapid diagnostic tests (Barat et al., 1999; Bloland et al., 2003). Although microscopy was available in several health facilities in study IV, it was not used in deciding treatment, leading to 86% of the non-parasitaemic children getting antimalarial treatment. In study IV quality of care at health facilities was measured using a scoring system based on IMCI indicators. Despite quality of care being poor according to indicator scores, most febrile children did get treatment with an effective antimalarial drug – in line with guideline recommendations (MoH-Tanzania, 2005). For the
individual patient, measuring quality of care by indicators is less important than receiving an effective antimalarial to prevent progress to severe disease. However, with few malaria treatment options left, in the long run improved diagnosis to prolong the useful therapeutic life of drugs is also important (WHO, 2001a), and in this aspect determining diagnostic quality is indeed relevant.

6.1 FIELDWORK AND THE CONTEXT

Real world research involves taking advantage of the actual context where whatever we are interested in occurs (Robson, 1993). Fieldwork is therefore sometimes the only way of exploring certain aspects of a topic (Hardon et al., 2001a). The sub-studies of this thesis were performed over a time span of 7 years and logistics and basic conditions sometimes affected field research in unpredictable ways. Weather affected our data collection in study V: 2003 had unusually dry rainy seasons, resulting in decreased malaria transmission whereas the long rainy season of 2004 was so wet it was impossible to reach the dispensary in Tindiga. Although this delayed our data collection in ways that might have been preventable in a well-controlled setting, our findings probably lead to results that are relevant to the study populations.

Performing fieldwork in settings with limited resources, such as rural Tanzania, requires careful planning building on feasibility. Literature discussing this is rare and plans must always be adapted to the local context. Important before starting data collection in the field, is to get the community involved – at all levels. After obtaining ethical clearance and research permission from the universities and appropriate ethics committees, we first contacted the regional authorities. From the regional level we had to work our way down the hierarchy of the society. In Tanzania the administrative structure of the society is very well defined. This is largely because of the system built up by the former President Nyerere, in which the society was sub-divided into units down to groups of 10 households. This makes it relatively easy to access key persons.

In the fieldwork of this thesis, the village chairmen have been crucial partners. With their help we have invited hamlet (sub-village) leaders for information meetings. These hamlet leaders, in turn, have helped us inform the community and helped us gain access to the study population during surveys. Being aware of the influence of the hamlet leaders, we always took particular care in informing the potential volunteers in a location separate from the hamlet leader, making sure they knew their participation was completely voluntary. The process of accessing the community has taken just as much, or even more, time than the data collection itself. However, it is well spent time for obtaining relevant data. Gaining the trust of the study population is also important because science depends on public support (Nature, 2005), especially if findings should lead to interventions in the community. Because one of the co-supervisors of this thesis was principle investigator of a WHO/TDR funded clinical trial of malaria treatment in Kilosa district, we had the opportunity of conducting the efficacy studies (II & V) there. The study community was already familiar with parts of the research team and felt safe enrolling in our studies. It could be argued that it would have been better to perform all five sub-studies in the same district. Although spreading data collection to
three districts makes certain comparisons difficult, the results might be considered applicable to a larger population.

Many of the steps described might seem self-evident, but can be difficult to grasp when starting work in a new setting. However, although the details might differ between settings, gaining the community’s trust at all levels is the key for a successful field study (Dahlgren et al., 2004). Apart from help in recruiting study participants and key informants, the ethical aspect is an important reason for involving the community. Especially in disadvantaged populations, partners in the community can help researchers by highlighting flaws in study design and strengthening the informed-consent process (Nature, 2005). In our case, the well informed hamlet leaders that introduced us to the villagers hopefully helped give thorough information to the potential volunteers. Malaria research has been criticised for not being practically applicable or really benefiting those exposed to malaria (Cot, 2005). Others claim that ethics committees adapt their standards to the local (often inadequate) conditions, leading to poor quality research (Kent et al., 2004). Taking these aspects into account, it becomes even more important to involve the community and making sure that the research is connected to real life.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Study design

All five studies presented here are cross-sectional studies measuring an outcome at a certain point in time. Cross-sectional studies are helpful in assessing health care needs of a population (Beaglehole et al., 1993) but less so in studying how a community and drug resistance is affected by the implementation of a policy. A more ideal way of studying this would be to conduct a longitudinal survey where outcome in the same population is measured over time.

Cross-sectional studies are faster and cheaper than longitudinal studies, making this approach attractive. It is often tempting to interpret the results of a cross-sectional study as though they came from a longitudinal study, but we have tried to take the study design into consideration in our interpretations of the results. Even longitudinal studies must be interpreted with caution. Effects seen over the short term may not continue over a longer period (Dallal, 1998). This could be the case with the implementation of innovations where the adoption varies over time (Rogers, 1995).

6.2.2 Sampling

Four of the studies were performed at health facility level (I, II, IV & V) and one in the community (III). This might bias our findings towards information from a population prone to seeking care at health facilities and this should be considered when interpreting the data. The main objectives of the facility based studies were to study efficacy of drugs and quality of care at health facilities, making the facility a natural study site to achieve adequate data. Community adoption of the policy was studied at community level. The interpretational challenges concern the drug pressure changes in the community, here studied as blood drug levels in children. Whereas drug pressure in
children seeking care at facilities can easily be compared before and after the policy change, community based drug pressure was only measured post policy change. However, the low blood levels of antimalarial drugs seen in the community are matched by equally low levels seen at health facilities after the policy change.

In study I a non-proportional cluster sampling procedure was used. During data collection each health facility was visited for five days and every second patient was asked to participate. We thus later performed weighted analyses taking the different population sizes into account. The potential clustering was assessed, but was found to be negligible. Likewise, the sample selection of the population in study III was non-proportional to the population size. In the data analysis all the reported results have been calculated by weighted analysis to compensate for this.

In study I, the data was collected by obtaining a random sample of mothers visiting one of the 10 public health facilities with sick underfives, after excluding severely sick children. Thus, the findings can be extrapolated only to children with non-severe diseases. Due to practical and economical reasons, the study duration was to be five working days per facility. A sufficiently large number of underfive children to describe the drug prescribing situation, according to the WHO/DAP 93.1 protocol (WHO, 1993a), was sampled. In study IV we aimed for a qualitative approach to assess the quality of care at health care facilities. The study was performed as part of the MAMOP project and all health facilities in the MAMOP area were included. Searching the literature we found several other similar observational studies. The different choices of sampling varied from observing health workers during 14 days per facility (Krause et al., 1998) to observing 2 patient-provider interactions per condition (Ehiri et al., 2005). One study had observed six cases at each facility (Armstrong Schellenberg et al., 2004) and another spent three days observing each facility (Arifeen et al., 2005). However, none of the studies gave a reference as to why they had chosen these sampling procedures. We observed the case management of children during three days at each facility. These three days were chosen as we thought this would reflect the variations in behaviour of a health worker. A challenge encountered was the fact that the number of patients seen at each facility varied considerably. One of the facilities only saw three underfives (one per day) during our observations, whereas one facility saw 36 patients (an average of 12 per day). The sample size was still big enough to perform analysis of intra- and inter-facility variations of the performance, giving a picture of the difference in behaviour between health workers.

In study V, the enrolled study-children were randomised to treatment with either SP or AQ. The required calculated study population was 61 children in each study arm (73 including potential drop-outs). After one week of enrolment we realised that we would not get 146 patients. It was considered most important to fulfil the SP study arm in order to compare the data to our findings from study II. Therefore the treatment randomisation was stopped and all children were treated with SP from that point on. Thus, the planned number of study children was included in the SP group, but only 31 children in the AQ group. Stopping a randomisation might lead to the two treatment groups differing in baseline characteristics, potentially affecting the outcome and leading to misinterpretation of results. However, no difference could be seen in the baseline characteristics of the study patients.
6.2.3 Recall bias

Interviews depending on people’s memory and recall bias pose both reliability and validity issues (Last, 1983; Kroeger, 1985). Especially in proxy reporting by parents, where sources of error might be created by missed reporting of minor incidences. Severe symptoms are remembered longer than mild ones (Linder, 1965; Mechanic and Newton, 1965) while minor problems may be under-reported during a two week (Roghmann and Haggerty, 1974), or even one week recall period (Martorell et al., 1976).

The recall period may be a source of bias in studies I, III & IV as in most studies involving interviews on morbidity and drug use (Kroeger, 1985; Klungel et al., 2000). Recall periods tend to vary between studies of outpatient morbidity recall, ranging from one to four weeks, while recall of hospitalisation usually ranges from one month to a year, its importance making it likely to be accurately recalled (Nordberg, 1988; Mechanic, 1989). A number of factors that affect the accuracy of recalling medical information have been proposed, such as the severity of the condition, interval between illness and the interview, and whether or not the illness required hospitalisation or a physicians’ visit (Ley, 1972; Kroeger, 1983). Shorter recall periods capture more mild and brief episodes and are reported more accurately (Nchinda, 1977; Roberts et al., 1996). Recent illnesses are reportedly over-estimated and previous events are easily forgotten. It is suggested that in a two week recall period both over and under-reporting largely cancel each other out (Freij et al., 1977). In study III, the interview data concerning actions taken for the last febrile episode was divided into time periods of 0-7 days, 8-14 days and 15-28 days. When comparing reported drug intake 0-14 days before the interview to the drug intake 15-28 days earlier, no major differences were found. This may be an indication that the use of a four-week recall period was adequate for the studies.

6.2.4 Observation bias

The presence of study teams may affect the health workers’ performance by making them nervous or by motivating them to perform better as they are actively aware that they are being observed. This is referred to as the Hawthorne effect (the observer influencing the performance or behaviour of the study subject). Influence of the Hawthorne effect seems unlikely to have improved results in studies I & IV as the performance was still poor.

6.2.5 Ethical considerations

In order to improve the standard of treatment and quality of care, it is critical to know how health workers interact with patients, including their attitudes to parents. Studying health worker performance through non-participant observation (I & IV) could be understood as a violation of their integrity. However, as it did not impose any risk or harm to them, it was considered that the benefits outweighed the risks. The results were furthermore presented without naming the health facilities.

Obtaining capillary blood samples from children is part of ordinary clinical practice
and, provided that hygienic practices are followed, it imposes no risks. The blood samples were obtained after explaining the objectives of the studies to the mothers and obtaining informed consent.

6.2.6 Triangulation

In triangulation, results can support, complement or contradict each other (Mays and Pope, 2000). An example of methodological triangulation where results support each other is found in study III, where only a few mothers of underfives in households stated that they stocked and self-treated their sick children with CQ. This was supported by analysis of blood samples that proved that only 6% of the children had detectable CQ levels. Another example of supporting data is from study IV where 4% of mothers stated to have given an antimalarial at home and also very few (13%) children had blood levels of SP. The “conflicting” results in study III where not more that one-third of the children with fever had measurable blood levels (SP), despite claiming to have received an antimalarial at health facilities, could be due to the health workers perceiving them as not having malaria and consequently giving them another treatment. Another example of “conflicting” results is from study I where mothers during interviews reported not having administered CQ at home, whereas in 75% of the children CQ was detected. This could be due to recall bias or mothers being afraid to inform what drug had been administered, fearing that the child may not receive drug treatment at the health facilities. The above mentioned examples all show triangulation of data within a study. Simultaneously triangulating data obtained by different methods within sub-studies with data from different sub-studies has been used in studying drug use: in pre-policy change studies (I & II) a large proportion of caretakers stated self-treatment, supported by high levels of antimalarials in blood. In studies performed both at the community level and at the health facility level after the policy change (III-V), few caretakers reported self-treatment and few children had detectable levels of antimalarials in their blood.

6.2.7 Assessing efficacy

The minimum recommended length of follow-up of patients in efficacy studies in high transmission areas is 14 days (WHO, 2003a). However, a significant proportion of treatment failures do not appear until after day 14, which means that a shorter observation period can lead to overestimation of drug efficacy (WHO, 2006). It is therefore recommended that follow-up for assessing drug efficacy of antimalarials should be 28 days in areas of intense transmission. At 28 days of follow-up molecular assessment of msp-2 (merozoite surface protein 2) by PCR must be performed to distinguish reinfections from recrudescence. Studies have shown an overestimation of total treatment failures when day 28 results are presented without PCR correction (Magesa et al., 2001; Mugittu et al., 2005). In a study from Tanzania, the resistance levels at day 28 were estimated to be around 15% higher before PCR We did not have the possibility of performing PCR controls and thus chose to present only the day 14 follow-up results.

6.2.8 Drug analysis

Handling blood samples in the field can be difficult and care was taken to avoid the
contamination of the samples by using gloves and storing each blood sample separately. It has been documented that neither transportation, length of storage nor tropical temperatures affects chloroquine or sulfadoxine content in blood samples dried on filter papers (Bergqvist et al., 1986). The blood samples were collected from underfives in the field (studies I-V) under the supervision of the author of this thesis, dried on filter paper, transported from the field site and stored separately in room temperature and later analysed using a high performance liquid chromatography (HPLC). Experienced personnel conducted the analyses under controlled conditions.

We have only analysed blood for concentration of SP and CQ. In study IV, more than half of the children were prescribed AQ. There was no clear reason for choosing AQ instead of SP (such as treatment failure with the first line treatment) and it could be due to patients preferring this drug. Self-treatment with AQ and/or other drugs would go unnoticed by our laboratory analyses.

6.3 ANTIMALARIAL DRUG RESISTANCE

In 1999, the resistance level (measured as total treatment failure) was 33% for SP and 61% for CQ. In 2004, this level was 18% for SP and 27% for AQ. The difference in SP resistance was not statistically significant between the two studies. Experiences from other countries have shown rapid development of SP resistance when the drug was introduced (Schapira et al., 1993; Nzila et al., 2000) and a study from northern Tanzania reported RII/RIII resistance rates of 74% for SP after only one year of dapsone-pyrimethamine weekly treatment of children (Ronn et al., 1996). This makes the unchanged resistance rates in our studies quite surprising, but consistent with findings from Malawi (Plowe et al., 2004).

The study from Malawi showed a sustained clinical SP efficacy as long as 10 years after the drug was introduced as first line treatment there (Plowe et al., 2004). This was explained by the low drug pressure seen in high malaria transmission country Malawi as compared to, e.g., South-East Asia, where resistance development has been fast. In a high-transmission area a relatively low proportion of parasites are under drug pressure because the population is semi-immune which means that most infections are asymptomatic and are left untreated. The findings from Malawi have been debated intensely (Barnes et al., 2004; Greenwood, 2004; Ringwald, 2004; White, 2004). Although the validity of the data has not been questioned, the recommendation of SP as an interim policy in African countries was. The stable, but high clinical failure rates (14% early treatment failures) were considered too high for this conclusion.

Two of the most important factors for preventing drug resistance progression are the reduction of the drug pressure and improving the way drugs are used, i.e. improving prescribing, follow-up practices, and patient compliance (Bloland, 2001). With the introduction of the new malaria treatment policy in Tanzania these two factors were affected. Because SP is a single dose treatment, compliance is high and there are no leftovers from the treatment that can be stored in the home for later self-medication. Furthermore, health workers in study III reported giving SP as direct observed treatment (DOT) in health facilities. In addition, because of a miscalculation of the drug
need, all Tanzanian health facilities were supplied with SP in abundance (Nderimo, 2005, May 10th). The fear of SP adverse reactions reported (III) in combination with the knowledge that SP was available at health facilities whenever needed might have led to the change in care-seeking behaviour from self-treatment to seeking care for febrile illness, supported by infrequent detection of SP in blood after the policy change. All these factors could have led to less use of the SP, thus preventing the increase in drug resistance.

It has been shown that cross-resistance might develop between trimethoprim (in co-trimoxazole) and pyrimethamine (in SP) (Iyer et al., 2001). Co-trimoxazole (trimethoprim/sulfamethoxazole) is an antibiotic combination commonly used for treatment of respiratory tract infections and gastroenteritis (and also malaria) in most sub-Saharan countries. Decreased use of this drug could also contribute to inhibiting spread of SP resistance.

In neither study II nor study V could we see a clear relationship between the DHFR/DHPS genotypes and clinical outcome. Previous studies have suggested that molecular markers can be used to monitor SP resistance and thereby help when developing malaria treatment policies (Talisuna et al., 2004). Variant patterns of genotypic sequences of DHFR and DHPS have been seen in different parts of the world, but it has been difficult to correlate these resistance markers to treatment outcomes. A study from Malawi (Kublin et al., 2002) showed correlations between mutation patterns and clinical failures. One of the findings was that a quintuple mutant (carrying DHFR mutations at positions 51, 59 and 108 and DHPS mutations at positions 437 and 540) is associated with SP treatment failure and that the presence of a single DHFR mutation (Arg-59) combined with a single DHPS mutation (Glu-540) accurately predicts the presence of a quintuple mutant. In study II, all patients who still had parasites on day 14 had an adequate clinical response. In study V, one patient was a quintuple mutant on day 14, but still had an adequate clinical and parasitological response. One of these patients had all five mutations on day 14, but still had an adequate clinical response, contrary to the findings in the Malawi-study (Kublin et al., 2002). All our patients had a Glu-540 mutation on day 0; many of these together with the Arg-59 mutation, though only one of them was a quintuple mutant. This contrasts the findings of Kublin et al. (2002) on the value of these mutations to predict quintuple mutations, but agrees with findings in another recent study in Malawi (Bwijo et al., 2003).

A surprising finding in study II was that on day 14 all samples except one contained parasites with wild type at position 540 although all samples were mutated on day 0. The most plausible explanation for this could is reinfections on day 14, but another possibility could be that parasite populations in minority might not have been detected on day 0 but were then selected and multiplied by day 14. Daily dynamics of concurrent parasite genotypes have been reported. These have shown multiple infections with different alleles being detected on consecutive days, suggesting synchronised 48 hour cycles of parasite-populations (Farnert et al., 1997). It is now recommended that msp-2 analysis should be performed to distinguish between recrudescence and re-infection (WHO, 2003a).
Although we could not see a clear relation between clinical outcome and number of mutations, the pre-treatment frequencies of point mutations were higher among the patients who still had parasites on day 14 as compared to the overall frequency. A study from Uganda reported high frequencies of \textit{pf}dhfr/\textit{pf}dhps mutations after 3 years of using SP+CQ as first line treatment but also found low clinical failure rates (Sendagire et al., 2005). The reason why the causal relationship between mutations and clinical outcome in our studies is not very clear is most probably because the parasite population already had high frequencies of mutations in almost all positions of the DHFR/DHPS genes. The frequency of point mutations in \textit{pf}dhfr in study \textbf{V} was very similar to the results from study \textbf{II}, consistent with the findings in total treatment failure rates. The situation for DHPS was different; whereas all patients were wild-type in position 437 in study \textbf{II}, 54\% were mutated in study \textbf{V}. This is an indication that parasites with higher frequencies of mutations have been selected with the increased SP use. During regular use of SP, treated people will carry residual levels of sulfadoxine in the blood, which may explain the selection of \textit{pf}dhps mutations that has occurred after the drug policy change. A review of mechanisms of resistance to antifolates has similarly showed that when there are three mutations present in DHFR, there will be selection pressure on DHPS, and that DHPS then decides treatment outcome (Gregson and Plowe, 2005).

In semi-immune patients, the host defence mechanisms can help the patients achieve adequate clinical response despite presence of parasites exhibiting high-degree resistance (White, 2002). Moreover, a study performed in Colombia, showed that DHFR mutations that are insufficient to cause clinical failure may nevertheless increase malaria transmission and promote the spread of drug resistance (Mendez et al., 2002).

\subsection*{6.4 CARE-SEEKING BEHAVIOUR}

In studies \textbf{III} and \textbf{IV}, patients claimed to seek care at health facilities as a first action when their children become ill, often giving an antipyretic at home first. In study \textbf{III}, only 4\% reported having given an antimalarial at home before seeking care, statements confirmed by low blood drug levels of SP and CQ. This is a dramatic difference compared to study \textbf{I} and \textbf{II} where more than half of the parents reported trying some kind of treatment at home prior to seeking formal health care and more than 92\% of the children had blood levels of CQ. It also differs from many other studies reporting self-treatment with antimalarials (Mwenesi et al., 1995;McCombie, 1996) where the majority of children had detectable antimalarials in blood (Greenberg et al., 1989;Hellgren et al., 1994).

These findings indicate a change in behaviour from self-treatment to seeking care at formal health facilities. Several factors could have influenced a change in behaviour. First of all, a dramatic change in drug supply took place after the policy change. All drugs for Tanzanian public health facilities are sent in drug “kits” from Medical Stores Department (MSD) in Dar es Salaam. Because of a miscalculation of the amount of SP needed, too much SP was sent to the facilities making SP available in abundance at health facilities after the policy change (Nderimo, 2005, May 10th). The knowledge that SP was widely available, which was not the case before the policy, could have
persuaded caretakers to take their children to health facilities where they would get treatment free of charge. SP is a single dose treatment and at the facilities SP was given as direct observed treatment (DOT) which means there were no leftover drugs that could be stored in the homes for treatment at a later illness episode. In addition, the FGDs in study III revealed negative perceptions of SP. Although few persons had experienced adverse reactions to SP, most people had heard about people who died from using the drug. This turned out to results from stories in the mass media and the majority of the household interviewees actually perceived SP to be a good drug. This is supported by findings in Zambia where caregivers recognised the greater efficacy of SP but feared that its “potency” could be dangerous (Bloland and Ettling, 1999). Studies from Uganda have shown contrasting behaviour among pregnant women where presumptive intermittent treatment (IPT) compliance was high with perceived better health using SP (Mbonye et al., 2005;Mbonye et al., 2006). The fear of side-effects might have made people more restrictive in their SP use and prompted them to seek care for a firm diagnosis before taking SP treatment. Furthermore, several persons seeking care asked for second or third line treatment, claiming allergy to SP (III). As all these treatments were free of charge for children at the health facilities, this might have been another reason for seeking care there. Yet another factor possibly influencing the behaviour is SP’s lack of antipyretic effect. This means patients do not feel the quick symptom relief that they previously got from CQ treatment. The massive campaigns for the new antimalarial policy seen in mass media and at health facilities all over Tanzania might also actually have made an impact on people’s attitudes toward malaria treatment and in turn affected their care-seeking behaviour.

Our design makes it difficult to offer a firm statement about a change in care-seeking behaviour. Only in study III did we interview a randomly selected village population, biasing our selection toward a population prone to seeking care at health facilities (where we selected the study subjects in studies I, II, IV and V). However, even the interviewees in study III claimed to seek care at health facilities rather than self-treatment, and few children had blood levels of antimalarials, corresponding well to the findings from the facility-based studies. Even though there was a discrepancy in study III between the reported intake of antimalarials and the blood drug levels, the correlation was in fact good compared to study I where 97% of those stating not to have taken CQ actually had detectable levels of the drug in their blood (Nsimba et al., 2002).

Our findings of most caretakers seeking care at health facilities for febrile illness contrasts previous data from sub-Saharan Africa, reporting that most children with malaria are never seen at health facilities but get treatment at home instead and that most malaria deaths occur at home (Foster, 1995;Mwenesi et al., 1995;Breman, 2001). These data have lead to advocacy for home-based management of fever (WHO, 2000a;Ford et al., 2005). This strategy is spearheaded by Uganda where antimalarials for treatment of fevers, so-called “homapak”, are distributed by community volunteers (MoH-Uganda, 2002). Home-based management of fever is meant to ensure prompt treatment of malaria and reduce progression to a more severe form, possibly avoiding difficult referrals (Peterson et al., 2004). The drawback is that it may also lead to enhanced drug pressure and subsequently to resistance development to the drugs used (Bloland, 2001;WHO, 2001a). Furthermore, diseases with symptoms similar to those of
malaria, such as respiratory tract infections, might get incorrect treatment leading to death (Källander et al., 2004).

There were no reports of an increasing patient load at the health facilities. This could be due to unreported self-treatment with drugs not detected in our analyses or a more restrictive attitude among caretakers to seeking care with febrile children. It could also be due to a decreased incidence of malaria due to a more effective treatment. In any case, this raises the question whether all children who need it actually get antimalarial treatment. This effect of the new policy leads to potential risk for the children and must be studied further.

6.5 QUALITY OF CARE AND CASE MANAGEMENT

Quality of care, measured as history taking, physical examination, prescription practices and counselling was poor in both studies I and IV. Similar findings have been reported in several other studies (Krause et al., 1998; Arifeen et al., 2005). However, almost all children with fever were prescribed an effective antimalarial, in line with recommendations in the Tanzanian national malaria policy (NMCP, 2001) and the IMCI (WHO, 1997). In this respect, the case management could paradoxically be said to be good. This raises the question of how we define quality of care and what we study with our evaluation tools.

Early evaluations of the IMCI showed good performance of the algorithms, but also stressed that this should not be read as evidence that it will improve child survival (Perkins et al., 1997; Weber et al., 1997). One of the studies (Weber et al., 1997) also found that the main challenges of the algorithm was the diagnosis of malaria, as the current recommendation that fever warrants an antimalarial drug leads to massive overtreatment. Quality of care should be measured in outcome for the patients, not how well health workers perform according to indicators. Although microscopy was available in several health facilities in study IV, it was not used in deciding treatment, leading to 86% of the children without malaria getting antimalarial treatment. In study IV quality of care at health facilities was measured using a scoring system based on IMCI indicators. Despite quality of care being poor according to indicator scores, most febrile children did get treatment with an effective antimalarial drug – in line with guideline recommendations (MoH-Tanzania, 2005).

A recent IMCI evaluation from Bangladesh reports generally poor quality of care and that most children received incorrect treatment despite availability of equipment and treatment for non-severe disease (Arifeen et al., 2005). That study concluded that case management would benefit from interventions aiming at improving health worker performance. Supporting this, a Tanzanian study showed 13% lower mortality rates in the intervention district after the introduction of IMCI (Armstrong Schellenberg et al., 2004).

As mentioned in the introduction, human resources is increasingly seen as a key issue in health systems (Travis et al., 2004) as health workers are essential for delivering health interventions (Rowe et al., 2005). We need to know the reasons for their poor
performance, as exemplified here by the poor quality indicator scores, in order to improve the situation. Training, skills, supervision and health facility resources obviously influences performance but factors such as motivation, job satisfaction, cultural factors and financial incentives are probably more important (Wyss, 2004; Rowe et al., 2005; Manongi et al., 2006). In our study the health workers complained of poor remuneration and introduction of new guidelines without follow-up, possibly affecting their performance. This should be considered when the next malaria treatment policy is introduced.

The current IMCI algorithm leads to over-treatment of fevers with antimalarials. Although the sensitivity (true malaria cases treated with an antimalarial) could be as high as 100% with this approach, the specificity (proportion non-malaria ill patients not given a malaria diagnosis) is sometimes as low as 0% (Perkins et al., 1997; Weber et al., 1997). Treating non-malaria ill patients with antimalarials increases drug pressure and leads to concurrent resistance development. It is therefore important to improve diagnostic facilities to be able to give a firm diagnosis. One means of doing this is by using Rapid Diagnostic Tests (RDT). These have been shown to have high specificity and sensitivity (Moody, 2002) and could potentially be used close to the homes. The drawback is the relatively high cost not affordable in malaria endemic countries. Another, less expensive diagnostic tool, but not so easy to use in the community, is microscopy. The impact of RDTs on fever management in the community is currently being studied in the SAREC funded KI-MUCHS project described in the “study areas and population” section.

Some of the health facilities in study IV had the possibility of performing microscopy for confirming malaria diagnosis. Surprisingly, not all children who sought care for fever at these health facilities were examined for malaria parasites in blood. Furthermore, the results from the microscopy were not used to decide whether or not one should prescribe an antimalarial, leading to an unnecessary overtreatment with these drugs. This has also been seen in Zambia (Barat et al., 1999). With cheap and relatively safe antimalarials, such as CQ and SP, this might not be very problematic (Bloland et al., 2003). However, with the introduction of expensive drugs with more complex dosage regimens, as with the Artemisinine-based Combination Therapies (ACT) soon to be introduced in Tanzania (MoH-Tanzania, 2005), a more restrictive drug use is needed. Basing treatment on a diagnostic test, such as microscopy or RDTs would result in the greatest reduction of unnecessary treatment (Barat et al., 1999; Bloland, 2001). Apart from reducing costs and adverse drug reactions, this would also decrease the probability that parasites are exposed to subtherapeutic blood levels of drug, possibly reducing resistance development (Bloland, 2001; Laufer and Plowe, 2004).

When resources are scarce, history taking and physical examination are the means available for making differential diagnoses. These tools then become important factors for improving diagnostic precision and correctness of treatment. This could improve patient care and also drug use, possibly reducing drug pressure and thus prolonging life span of antimalarials (Bloland, 2001). As shown in the introduction (Fig. 1) two basic, sometimes conflicting, paradigms affect malaria treatment policy decisions; ensuring prompt, effective treatment on the one hand and limiting the spread of resistance on the
other (WHO, 2001a; Bloland et al., 2003). The first paradigm maintains that the best approach to reducing malaria mortality and morbidity is to make freely available effective treatment down to the most peripheral level, the household. This means that anyone with a small chance of being infected receives treatment. This approach is a fundamental part of the Global Malaria Control Strategy and RBM and is an important component of IMCI (Bloland et al., 2003). The alternative paradigm advocates limiting occurrence of drug resistance and prolonging the useful therapeutic life of antimalarials: because drug pressure is a leading cause of resistance spread (Payne, 1988; Wernsdorfer, 1994), this paradigm stresses that access to treatment should be restricted so that only those with a confirmed malaria diagnosis receive treatment (Bloland et al., 2003). For the individual patient, measuring quality of case management by indicators is less important than receiving an effective antimalarial to prevent progress to severe disease. However, in the long run, improved diagnosis to prolong the useful therapeutic life of drugs is also important (WHO, 2001a), and in this aspect determining diagnostic quality is indeed relevant.

6.6 POLICY CHANGE

About half a year after implementation, the malaria treatment policy had diffused well to our study community in the sense that more than half of the caretakers and all health workers knew that SP was the new first line treatment. At the same time, CQ had been replaced by SP in the health facilities. The malaria treatment policy process in Tanzania has been described as a good example of an incrementalist model where the decisions leading to change occurred in numerous steps and were influenced by a variety of factors (Williams et al., 2004). Although the incremental model of the policy process is considered realistic in describing how policies decisions are actually made (Buse et al., 2005), there are criticisms to this approach. The incremental model is more conservative than the rational model and decisions are often explorative steps on the existing policy. In this way few fundamental reforms are made which means the incremental process rarely leads to innovations (Buse et al., 2005).

Most research on policy change describes the theory of the policy cycle up to the policy implementation, as is the case even with the study by Williams et al. (Williams et al., 2004). The data from study III is from the implementation phase of the policy cycle, which is rarely studied. The stages of the policy change take time to pass through. Limited data have suggested that 18-24 months are necessary to change policy (WHO, 2003b). This lead-time to policy change was slightly longer in Tanzania, where efficacy data had been compiled already early 1999 (Kitua et al., 1999) and the policy was implemented in 2001. We have not been able to find any literature on lead-time for the implementation itself, although at least 24 months has been suggested as necessary (Williams et al., 2004). Our data was collected 6 – 11 months after the policy change, making the behavioural changes we found seem quite dramatic.

The diffusion of innovations, such as a policy shift, is a complex matter where three clusters of factors have been identified as important for the adoption: The perception of the innovation, characteristics of the individuals who may adopt the change and contextual factors (Berwick, 2003). Not much is known about the diffusion of
antimalarial drug policies and little research has been done on the adoption of medical innovations. Most studies on the effects of interventions have been directed towards professionals and the change in their practices. This might be sufficient in high-income settings where services, including drug prescriptions, are well-controlled, but in a setting such as the one in Tanzania, consumer actions need to be taken into consideration. One of the reasons why there is a lack of discussion about the diffusion part of the policy process is that innovations are introduced with the expectation that the effects will be perceived as something good. Quite often the results are different, partly because of the fact that it is hard to predict people’s perceptions of innovation (Rogers, 1995). This was seen in study III as people feared adverse reactions to SP and felt it was too strong for children, similar to findings among pregnant women in Uganda (Mbonye et al., 2006). Another factor that could have influenced our results was the characteristics of the individuals we studied (Berwick, 2003), such as innate curiosity, level of education and access to information (Chambers, 2001). Innovation diffusion has a characteristic S-shape, with few early and late adopters and a rapid spread in the middle phase (Rogers, 1995). As our study was cross-sectional, it is difficult to know at what point in this diffusion curve our studied community was during our data collection. In high-income countries, personality and behaviour of early and late adopters have been studied extensively. However, this is focused health professionals and does not consider adoption by caretakers (Chambers, 2001).

Mass media was reported as an important source of information about the policy change in study III. Indeed, mass media involvement, in addition to poster campaigns and health staff training, was an important part of the implementation process of SP as the first line antimalarial in Tanzania (Mubyazi, 2003). This use of social marketing has previously been found to be effective in campaigns for oral rehydration salts (Kenya et al., 1990) and bednets (Schellenberg et al., 2001; Holtz et al., 2002). This could be one of the reasons for the seemingly high impact of the policy.

Because of the changing resistance patterns to antimalarials, malaria treatment policies have to be reviewed and changed. Although we did not see an increase in SP resistance after the policy implementation, the therapeutic life of SP is known to be short compared to CQ. The implementation of SP in 2001 was therefore seen as an interim policy in Tanzania (Mubyazi and Gonzalez-Block, 2005). Combination therapy (CT), in particular artemisinin-based combinations (ACT), is ten times as expensive as SP and is currently the strongest option for improving cure of *falciparum* malaria (EANMAT, 2003). But introducing this treatment strategy in low-income countries is a great challenge to their inadequate health systems, not only from a financial point of view (White et al., 1999; Bloland et al., 2000; Snow et al., 2003; Attaran et al., 2004). One major challenge is that compliance may be lower than it is for SP, as ACT is usually administered as a six-dose treatment over 3 days (Snow et al., 2003).

Starting in the autumn of 2006, ACT will be introduced as first line treatment on mainland Tanzania (MoH-Tanzania, 2005). As shown in study III, implementation of the current malaria treatment policy went quite smoothly. Furthermore, in Tanzania, the infrastructure of the health system is relatively good with evenly distributed and accessible health facilities (Gilson et al., 1995). We have also seen indications that caretakers have changed behaviour from self-treatment to seeking care at health
facilities for febrile illnesses. This, at least in theory, makes correct diagnosis and treatment possible, thereby improving drug use and prolonging the life span of antimalarial drugs. However, for this to happen, quality of care and diagnostic resources have to be improved at health facilities and caretakers and children need to access care in time.
7 CONCLUSION AND POLICY IMPLICATIONS

• Sustained clinical efficacy of sulfadoxine/pyrimethamine (SP) for uncomplicated malaria was observed in Kilosa district despite use of the drug as first line treatment for three years, possibly explained by changed patterns of drug use and thereby decreased drug pressure (II, V).

• Drug pressure for the first line antimalarial drug (CQ before and SP after the policy change) decreased dramatically in the study communities after the policy change (I-V).

• The decreased drug pressure of first line malaria treatment and reported change from self-treatment to seeking care at formal health facilities (I, III, IV) indicates a change in care-seeking behaviour.

• No clear relationship could be seen between DHFR/DHPS genotypes and clinical and parasitological outcomes of SP treatment (II and V).

• The Tanzanian malaria treatment policy diffused well to the studied community in the sense that people knew of the new drug and that CQ use changed to SP in the community (III).

• Quality of care at health facilities in terms of history taking, physical examination and counselling was poor, but most febrile children were treated with antimalarials in line with guideline recommendations (I, IV).

To decide the appropriate time to change a malaria treatment policy, resistance levels need to be continuously monitored in different areas of a country. Drug pressure is one of the most important factors in resistance development and should be decreased when possible. As the resistance patterns often vary between different parts of a country, regional, rather than national, drug policies might be an option that could help prolong the therapeutic life of antimalarials.

Because of increasing drug resistance, policies are being re-evaluated and new policies will be introduced. Tanzania will introduce Artemisinine-based Combination Therapy (ACT) as first line treatment in the near future. The introduction of new treatment policies with ACT includes challenges such as high drug cost and treatment compliance. In some African countries home-based fever management strategies are implemented, but in Tanzania with changed health-seeking behaviour, this is an issue for discussion. If resources are put into improving diagnostics and case management of febrile illness at health facilities, the apparent change in care-seeking behaviour could be taken advantage of in improving use of antimalarials. Antimalarial drug policies should always take into consideration the balance between prompt, effective treatment and limiting the spread of drug resistance.
8 ACKNOWLEDGEMENTS

First of all I would like to express my gratitude and sincere thanks to all study-patients, volunteers and the communities in Kibaha, Kilosa and Mkuranga. Without you this thesis would not have existed.

I have had the privilege of being supervised by Professor Göran Tomson (main supervisor), Professor Lars L Gustafsson and Dr Marian Warsame. I realise now how fortunate I have been to have such enthusiastic, inspiring supervisors. These few words cannot express my gratitude. Thank you, Göran, for always being available and always daring to push me a little further. You have really made me grow! Lars, no-one dances on the table like you do. You are both impressive visionaries and you have taught me what research is all about. Marian, thank you for introducing me to Tanzania and the art of performing fieldwork in rural Africa. You welcomed me as a family member during my stay in Morogoro and I hope I will have the opportunity of travelling with you to Somalia one day.

Thank you, Margarita Mahindi. Without your encouragement and enthusiasm from the very beginning, I would never have started this PhD project. You introduced me to lab work and the rules of the research world. You have supported me in all aspects of life from lab-work in Huddinge to life-saving on Zanzibar. I hope I will someday be able to repay you.

I would also like to express my sincere gratitude to all other persons who have contributed to this thesis in various ways, some of whom are mentioned here:

My room-mate, Karin Källander, for sharing supervisor and ideas, for stimulating discussions and contagious, productive energy, and for being such a nice travel companion.

Stephen Nsimba, my Tanzanian “twin”, with whom I have shared both supervisors and fieldwork.

All friends and colleagues at Clinical Pharmacology, MUCHS: Amos Massele, James Fulgence, Walter Msangi, Omary Minzi, Jane Sayi, Mary Jande, Gerald Rimoy, Dyana, Jumannne and Saidi. For always warmly welcoming me to the department and for teaching me about Tanzania. Thank you for all your support, laughs and Kiswahili lessons. A number of other people at MUCHS/UDSM and NIMR have also been invaluable for my work in Tanzania, including Andrew Kitua, Zul Premji, Anku Sanga and Phare Mujinja.

All friends and colleagues at IHCAR, in particular Anna T, Anders, Helena, Jesper, Karin, Lotta, Nadia and Nina. It is such a pity that we are hardly ever in the same country at the same time.
All friends and colleagues at the division of Clinical Pharmacology, Karolinska University Hospital Huddinge, including the “Tropical group”: Annika, Agneta, Rajaa and Margarita.

Max Petzold for always having time to explain the mysteries of statistics.

Margit Ekström at Clinical Pharmacology and Kersti Rådmark at IHCAR – for always giving excellent support in administrative matters.

All my friends in Kilosa, especially Steve Ngatunga, Stephen Mduma, Samuel Mwankusye and Patience Lipingo. For always being enthusiastic and helpful and for pushing me through the mud. Asanteni sana!

My MAMOP family members in Burkina Faso, Germany, Sweden and Tanzania, for inspiration and shared experiences.

Göte Swedberg at BMC, Uppsala University. For teaching me PCR, introducing me to the world of molecular markers and for generously accepting me as a visitor in your lab.

Emilie Agardh, Nina Viberg, Birger Forsberg and Agneta Wennerholm for valuable comments in the early phase of the thesis writing.

Professor emeritus Folke Sjökvist and Professor Anders Rane for carefully reading and commenting on my thesis in the late stages of the writing.

Jesper Sundewall for helping me with last minute revisions.

Anna Färnert, Pedro Gil, Isabel Veiga and Anders Björkman at the Malaria unit for helping me through a lab crisis.

To “bok-klubben”: Anna B, Jakob and Niklas. Once you go back, there’s no way back.

Anders Ragnarsson, King of Dar, for added glamour and for making the midwives of Congo famous. Anna Drejenstam, my “oldest” friend in Stockholm, for always listening and for finally discovering what Africa is all about! Eva Lundgren – always “blending in” – after fishing with you, Anna and Octopus, Zanzibar will never feel the same again. Thank you all other friends who have distracted me from research.

Anna Blomquist, my fabulous neighbour and the best friend I could ever have in this world, for making sure I thought about other things than research (now you finally have the opportunity to discover what I have been working with for the past years!) – what would I have done without you?

Last, but not least, my parents Jorja and Pål, my sisters Julie and Mirja and my grandparents, Mone, Farfar, Mormor and Bestefar. For your love and support and for always being there for me.
The studies were generously supported by:

- Swedish Agency for Research Collaboration with Developing Countries (SAREC) at Swedish International Development Cooperation Agency (Sida) (grants Swe 2002-076 and Bil-Tz 16/98 75007059)
- European Union (EC-INCO-DEV), MAMOP project ICA4-CT-2001-10010
- Karolinska Institutet (Research internship (“forskar-AT”)).
9 REFERENCES


analysis of dihydropteroate synthetase and dihydrofolate reductase alleles in a large number of field samples of diverse origins. *Mol Biochem Parasitol*, **89**, 161-77.


10 APPENDICES

10.1 APPENDIX 1 - QUESTIONNAIRE FOR MOTHERS/GUARDIANS OF UNDERFIVES IN HEALTH FACILITIES IN 1997 (I)

1. Serial number_______________

Name of Health facility_______________

Any antimalarial drugs prescribed?
   (a) Yes    (b) No.

Age of the mother/guardian_______________years.

Sex of the mothers/guardians
   (a) Male     (b) Female

Marital Status:
   (a) Married (b) Single  (c) Widowed (d) Divorced (e) Separated.

Education Status:
   (a) No education (b) Adult education (c) Primary education (d) Secondary education.

Employment/Occupation: (a) Farmer (b) Teacher (c) Health worker (d) Civil servant (e) Business man/woman (f) Any other, name it _______________

Age of the child in months_______________

Sex of the child:
   (a) Male (b) Female

Total number of underfives you have_______________

What problem do you think your child has:
   (a)_______________ (b)_______________ (c)_______________ (d)_______________

How long or since when has your child experienced this/these problems? (1). 0-7 days (2). 8-14 days (3). 14-21 days (4). more than 21 days.

What actions/steps or measures did you take? (a)_______________
   (b)_______________ (c)_______________ (d)_______________
   (e)_______________

Parasite density (total parasite count per 8000 WBC) _______________
Chloroquine (type of antimalarial drug prescribed at PHC by clinical/assistant clinical officers):
(a) Yes=1 or (b) No=0

Co-trimoxazole prescribed by health care providers at health facilities:
(a) Yes=1 or (b) No=0

16. What treatment did you give? Name the drug which you gave or was given to your child: (a)_______________ (b)_______________ (c)_______________
(d)_______________ (e)_______________

17. For how long (duration) did this treatment last for your child?
(a)_______________ (b)_______________ (c)_______________
(d)_______________ (e)_______________

18. Where (source) did you obtain/get those drugs which you gave your child?
(a) From a friend/neighbour (b) From the doctor (c) From the nurse/health worker (d) Any other source mention_______________

19. Observe whether the doctor has performed thorough physical examination of the child:
(a) Yes (b) No

20. Note the consultation time the doctor takes per one patient:_______________ in minutes.

21. Name all the symptoms of mild malaria your child had when he/she developed this disease.

22. Name all the symptoms of severe/serious cases of malaria you know:
   (1). Convulsions (2). Cerebral malaria (3). Severe anaemia (low haemoglobin) (4). Any other specify_______________

23. Please can you mention any symptoms of pneumonia (ARI) your child had or any child under 5 years you have seen:

24. Please can you mention the symptoms of diarrhoea for a child under 5 years of age:
   (1). Passes frequent (many) loose stools (more than 3 times a day) (2). The child gets very thirsty (3). Child gets sunken eyes (4). The child may have fever (5). The child passes bloody stools (6). The child does not drink or eat warmly (well) (7). The child seems not to be getting better (8). Any other specify
25a. For a nurse please measure or take and record the axillary body temperature of
the each child_______________ °C.

25b. Please measure and record the weight of each child_______________ in Kgs.

26. Lastly for the researcher (technician) prick about 100 micro-litres of blood on
filter paper and at the same time take blood slide thick and thin films for
detection and identification of malaria parasites for any child who has
antimalarials prescribed for before getting the drugs.
10.2 APPENDIX 2 – QUESTIONNAIRE FOR THE HOUSEHOLD SURVEY
OF THE POLICY ADOPTION STUDY IN 2002 (III)

Questions 1-16: for heads of households and mothers/guardians:

1. Name of interviewer__________________

2. Serial number__________________

3. Ward name__________________

4. Village name__________________

5. Hamlet name__________________

6. Name of household__________________

7. Age in years of interviewee__________________

8. Sex:
   (a) Male           (b) Female

9. Marital status:
   (a) single    (b) married    (c) widowed/er    (d) divorced/separated

10. Educational status:
    (a) No formal education  (b) Madrasa    (c) Adult education
    (d) Primary education (completed √/not completed □)
    (e) Secondary education  (f) Post secondary education

11. Occupation:
    (a) Peasant    (b) Civil servant    (c) Health worker    (d) Businessman/woman
    (e) Others. Specify:__________________

12. Number of people living in the household__________________

13. Distance to the nearest health facility (km) _________________

14. Designation of the nearest health facility:
    (a) Public    (b) Private    (c) NGO    (d) Parastatal

15. Do you have underfive children in your household?
    (a) Yes (how many) (Please show us MCH-cards)  (b) No

16. When was the last time one of your children had malaria?:
    (a) This week    (b) 1-2 weeks ago    (c) 2 weeks - 4 weeks ago
    (d) 4 weeks - 2 months    (e)2 - 4 months ago    (f) More than 4 months ago
Record who is answering Q 17-33
(*this should be the person who took care of the child during the last illness episode*)

17. When was the last time one of your children had dege/dege/convulsions?
   (a) This week    (b) 1-2 weeks ago    (c) 2 weeks - 4 weeks ago
   (d) 4 weeks - 2 months    (e) 2 - 4 months ago    (f) More than 4 months ago

Questions 18-34: Only for those sick during the recall period (4 weeks)

18. Who cared for the child during the last malaria-episode?
   (a) sister    (b) brother    (c) mother    (d) father    (e) grandmother
   (f) neighbour    (g) others. Specify: __________________

19. Which symptoms did the child have during this last episode of malaria?
   __________________

20. Did the person who cared for the child do something for the child at home?
   (a) nothing    (b) sponging    (c) gave drug    (d) gave herbal treatment
   (e) other. Please specify: __________________

21. If drug was given:
   - which drug: _______________
   - age of child: _______________

22. How did you give the drug?

<table>
<thead>
<tr>
<th></th>
<th>Amount/No. of</th>
<th>How many times a day:</th>
<th>How many days:</th>
<th>When did you give the last dosage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syrup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23. Where did you get these drugs that you gave at home?
   (a) Pharmacy    (b) Drug stores    (c) Ordinary shops
   (d) Health facility (public □ private □)    (e) Traditional healer
   (f) Others. Please specify: __________________

24. Did you seek care outside the home for this malaria episode?
   (a) Yes    (b) No

25. If yes, where?
   (a) Pharmacy    (b) Drug stores    (c) Ordinary shops
   (d) Health facility (public □ private □)    (e) Traditional healer
   (f) Others. Specify: __________________

26. Did you get any treatment outside the home?
   (a) Yes    (b) No

27. If yes: What kind of treatment did you get? __________________
28. Where did you get this treatment?
   (a) Pharmacy  (b) Drug stores  (c) Ordinary shops
   (d) Health facility (public ☐ private ☐)  (e) Traditional healer
   (f) Others. Specify:

29. If you went to a health facility: Were drugs prescribed for or given to the child by
   the health care provider at the facility?
   (a) Yes  (b) No

30. If yes →
   Number of tablets: _______________
   How many times a day: _______________
   How many days: _______________

31. Did the health care provider explain how the drugs should be given?
   (a) Yes  (b) No

32. If yes →
   Number of tablets: _______________
   How many times a day: _______________
   How many days: _______________

33. How did you give the drugs?
   Number of tablets: _______________
   How many times a day: _______________
   How many days: _______________

   Please confirm using exercise book. Record actual data from book:
   No. of tablets: _______________
   How many times a day: _______________
   How many days: _______________

34. If the drugs were not given according to the prescriber’s instructions: Why not?
   _______________

35. Do you have any drugs left from the treatment?
   (a) Yes. Please show them to me  (b) No

   Write down number of tablets/amount of syrup/injections, name, how they were
   identified:
   ☐Labels _______________
   ☐Colour of tablet _______________
   ☐Not identified _______________

36. Do you usually keep drugs at home?
   (a) Yes  (b) No

37. If “yes”: what kinds of drugs? _______________
38. Do you usually keep antimalarial drugs in your households?  
   (a) Yes    (b) No

39. Which antimalarials do you buy? Please specify: _______________

40. Do you have any of them now?  
   (a) Names:    (b) Formulations:    (c) Amount of syrup/injections/number of tablets:    (d) No

   Identified how?  
   □ Labels ____________
   □ Colour of tablet ____________
   □ Not identified ____________

41. Where did you get these drugs you have shown us/me?  
   (a) Pharmacy    (b) Drug stores    (c) Ordinary shops    (d) Health facility public/private    (e) Traditional healer    (f) Others

42. Do you know that there have been changes in the recommendations for treating malaria?  
   (a) Yes    (b) No

43. Do you know when it changed? _______________

44. Do you know which antimalarial drug is currently recommended for treating malaria?  
   (a) Yes. Please specify _______________ (b) No

45. The new first-line drug for treating malaria is “SP” (Fansidar). Have you received any information about this drug?  
   (a) Yes    (b) No

46. If yes: Where did you get information about this drug? _______________

47. Do you know which drug was the old recommended drug for treating malaria?  
   (a) Yes. Please specify _______________ (b) No

48. Have you been told that CQ has been abandoned as malaria treatment?  
   (a) Yes    (b) No

49. Have you been told why CQ has been abandoned as malaria treatment?  
   (a) Yes    (b) No

50. If “yes”: why? _______________

51. Have you used “SP” (Fansidar) as malaria treatment for yourself or any members of your family? (The following are “SP” – ask for the names if interviewing person does not know “SP”: Falcidin, Fansidar, Malostat, Orodar, Laridox, Metakelfin)  
   (a) Yes    (b) No (If no [ ] jump to Q 56)
52. If yes: What is your experience of “SP” (Fansidar)?

53. Have you experienced any skin problems after using “SP” (Fansidar)?

54. If yes: what kind of skin problems (including rashes)?

55. Even if you said you have never used “SP”. Do you know the recommended dose of “SP” (Fansidar) for malaria fever for children aged 1-5 years of age?

56. Do you know the recommended adult dose of “SP” (Fansidar) for malaria fever?
10.3 APPENDIX 3 - GUIDED TOPICS FOR THE FGDs OF THE POLICY ADOPTION STUDY IN 2002 (III)

Topics - mothers/key informants/Health Care Professionals

- What antimalarial drugs are used now in treating malaria? (In this section we want the participants to discuss the policy change)
  
  Checklist for the moderator:
  - Have they heard about SP/ different brands?
  - Do they know how long the drug has been around? When the policy changed?
  - Have they used other antimalarial drugs, especially CQ?
  - Do they know the reasons for the policy change?
  - How have they heard about the policy change? Details of the information campaign.

- From the problems stated above – how do you think this could be improved in a future policy change? (In this section we want the participants to discuss how the situations could be improved concerning information spread, drug supply, information about the drug).

- In a household survey we recently performed, we found that few people self-treat with SP. Do you think people self-treat with SP and how do they feel about the drug? (In this section we want the participants to discuss reasons for using/not using SP and the rumours concerning side-effects)
  
  Checklist for moderator:
  - Reasons for not using SP (single dose not perceived to be enough? Lack of injections? It is too strong?)
  - Availability of drug? Price?
  - Compared to CQ – better or worse?
  - Who decides to use the drug at home?

- From what was stated in the last section – how do you think the situation can be improved? (In this section we want the participants to discuss how they think their situation can be improved concerning side-effects of drug/misconceptions of the drug)
  
  Checklist for moderator:
  - If they thought the drug was not effective – want higher dose? Lower dose? Suggest that they should combine with paracetamol?
  - Improve the availability?
  - Give more/better information to community?

Additional topic for fathers

- We have heard that you are usually not involved in the care of your children when they are ill. Is this true?
PART A: Observation Checklist

Observer Name: ____________________________________________

| District_________ | HW Category_______ | Date ______/_____/____ |
| Facility__________ | HW initials_________ | Child ID No.__________ |
| Name______________ | Facility Type________ | Child's Age (months)___ |

Begin Timing for the Observation:___________ Hrs__________ min (24 h time)

1. What reason does the caretaker give for bringing the child to the health facility? (Check all that apply.)
   ___Fever/malaria
   ___Diarrhoea/vomiting
   ___Difficulty breathing/cough/pneumonia
   ___Other specify_____________

<table>
<thead>
<tr>
<th>History taking</th>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the health worker <strong>ASK</strong> about (or does the caretaker REPORT)</td>
<td>Does the health worker perform these tasks-</td>
</tr>
<tr>
<td>Danger signs:</td>
<td>Y / N</td>
</tr>
<tr>
<td>2. Not able to drink or breastfeed?</td>
<td>Y / N</td>
</tr>
<tr>
<td>3. Vomits everything?</td>
<td>Y / N</td>
</tr>
<tr>
<td>4. Convulsions?</td>
<td>Y / N</td>
</tr>
<tr>
<td>5. Change in consciousness /lethargic/sleepy?</td>
<td>Y / N</td>
</tr>
<tr>
<td>6. a. Fever?</td>
<td>Y / N</td>
</tr>
<tr>
<td>b. For how long?</td>
<td>Y / N</td>
</tr>
<tr>
<td>7. Cough or difficult breathing?</td>
<td>Y / N</td>
</tr>
<tr>
<td>For how long?</td>
<td>Y / N</td>
</tr>
<tr>
<td>8. Diarrhoea?</td>
<td>Y / N</td>
</tr>
<tr>
<td>a. For how long?</td>
<td>Y / N</td>
</tr>
<tr>
<td>b. Is there blood in the stool</td>
<td>Y / N</td>
</tr>
</tbody>
</table>

11. Undressing the child | Y / N
12. Touching the child | Y / N
13. Check if the child is awake | Y / N
14. Check for neck stiffness | Y / N
15. Checking the temperature by:
   - touching | Y / N
   - using thermometer | Y / N
   - checking on paper (written by nurse) | Y / N
16. Undress the child | Y / N
17. **Count respiratory rate** | Y / N
18. Undress the child | Y / N
19. Pinch the skin on abdomen | Y / N
20. Other actions taken, specify:________________________
9. Ear problem?  
   a. If YES, for how long?  
   b. If YES, is there ear discharge?  
      If “b”YES, for how long?  

10. Others (relevant for the presenting condition). Specify:  

21. Look for pus from ear?  
22. Feel for swelling behind ear?  

23. Look for palmar pallor  
24. Look for conjunctival pallor?  
25. Others relevant for the presenting condition (specify):  

**Comments by the observer on assessment done by health worker**  
(Did the health worker do the history taking and examination, as you would expect from the presenting condition of the child?)  

**Counselling**  
26. Does the health worker explain to the caretaker how to administer the treatment?  
27. Does the HW ask an open-ended question to verify the caretaker’s comprehension of how to administer the treatment?  
28. Does the HW prescribe and explain when to return for follow-up  
29. Does the HW tell the caretaker to come back immediately in case of danger signs?  
30. Does the HW give the caretaker any advice on nutrition?  

**Referral**  
31. Was the child referred?  
32. If yes→ did the HW give the caretaker any pre-referral counselling?  
33. Did the HW use IMCI chart/standard treatment guidelines?  

**Check the time of the observation as the caretaker leaves Time:**  

____________ Hrs: __________ minutes
PART B: Exit interview

Observer Name: ____________________________________________________________

<table>
<thead>
<tr>
<th>District_________</th>
<th>HW Category_________</th>
<th>Date_____ / ____ / ____</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility Name_____</td>
<td>HW name_____________</td>
<td>Facility Status_________</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>Facility Type________</td>
<td>Child ID No._________</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Child's Age (months)____</td>
</tr>
</tbody>
</table>

Diagnosis (as recorded in the patient book)
1. ______________________________________________________________________
2. ______________________________________________________________________
3. ______________________________________________________________________

Laboratory examination requested (as recorded in the patient book)
1. ______________________________________________________________________
2. ______________________________________________________________________

Treatment (as recorded in the patient book)
1. ______________________________________________________________________
2. ______________________________________________________________________
3. ______________________________________________________________________
4. ______________________________________________________________________
5. ______________________________________________________________________

Other medication given (but not recorded in the book)
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Mothers’ understanding of the counselling
1. What do you think of the services for your sick child at this facility today? Read all options to the caretaker.
   a. Good as they are
   b. Should improve
   What should improve:
   ______________________________________________________________________
   c. Doesn’t know

2. How do you feel about the time you had to wait today before receiving attention for your child? Read all options to the caretaker.
   a. Definitely too long
   b. Long
   c. Acceptable
d. Short
  e. Doesn’t know

3. Did the health worker give you or prescribe any oral medicines for <CHILD> at the health facility today?
   a. Yes
   b. No skip to question # 8
   c. Doesn’t know skip to question # 8

4. Were antibiotics prescribed? (1) Yes (2) No Skip to question # 6
   If yes:
   a. How much will you give <CHILD> each time:
   __________________
   b. How many times will you give it to <CHILD> each day?
   ________ times
   c. How many days will you give the medicine to <CHILD>?
   ________ days

5. Was a second antibiotic prescribed or given? (1)Yes (2) No Skip to question # 6
   If yes:
   a. How much will you give <CHILD> each time:
   __________________
   b. How many times will you give it to <CHILD> each day?
   ________ times
   c. How many days will you give the medicine to <CHILD>?
   ________ days

6. Were antimalarials prescribed or given? (1) Yes (2) No Skip to question # 8
   If yes:
   a. How much will you give <CHILD> each time:
   __________________
   b. How many times will you give it to <CHILD> each day?
   ________ times
   c. How many days will you give the medicine to <CHILD>?
   ________ days

7. Was a second antimalarial prescribed or given? (1) Yes (2) No Skip to q # 8
   If yes:
   a. How much will you give <CHILD> each time:
   ____________________
b. How many times will you give it to <CHILD> each day?
__________ times

c. How many days will you give the medicine to <CHILD>?
________ days

8. Did the health worker give you a specific day when to come back to this facility?
   (1) Yes If yes ➔ In how many days? _____ days
   (2) No
   (8) Doesn’t know

9. Sometimes children condition may worsen and they should be taken immediately to a health facility: What types of symptoms would cause you to take your child to a health facility right away? Do not prompt - keep asking for more signs/symptoms until the caretaker cannot recall any additional ones.
   a. Child not able to drink or breastfeed  (1) Mentioned (2) Not mentioned
   b. Child becomes sicker  (1) Mentioned (2) Not mentioned
   c. Child develops a fever  (1) Mentioned (2) Not mentioned
   d. Child has fast breathing  (1) Mentioned (2) Not mentioned
   e. Child has difficult breathing/pneumonia(1) Mentioned (2) Not mentioned
   f. Child has blood in the stools  (1) Mentioned (2) Not mentioned
   g. Child is drinking poorly  (1) Mentioned (2) Not mentioned
   h. Other (specify):
      ______________________________________________________________
      ______________________________________________________________
      ______________________________________________________________