# A STUDY EVALUATING RATIONAL DRUG USE IN MALARIA MANAGEMENT AMONG PUBLIC AND PRIVATE HEALTHCARE FACILITIES AT TWO PAKISTAN CITIES

**by**

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# DEDICATION

I dedicate this thesis to my beloved parents (Mr Khalid Latif Malik & Mrs Neelofur) and Prof Dr Azhar Hussain who have always been a constant source of motivation and inspiration throughout my professional career to pursue and accomplish my goals. I owe all my success in life to these three people.

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| | |
|---|---|
| ACT | Artemisinin Combination Therapy |
| ANC | Antenatal Care |
| BHU | Basic Health Unit |
| DCO | Drug Control Organization |
| DHO | District Health Office |
| EDL | Essential Drug List |
| FEFO | First Expire First Out |
| FIFO | First In First Out |
| GDP | Gross Domestic Product |
| GNI | Growth National Income |
| GP | General Practitioners |
| HBFMS | Home Based Fever Management System |
| HMIS | Health Management Information System |
| IECT | Information Education & Communication Techniques |
| IMCI | Integrated Management of Childhood Illness |
| IM | Intramuscular |
| INRUD | International Network for Rational Use of Drugs |
| IPTP | Intermittent Preventive Treatment in Pregnancy |
| ITBN | Insecticidal Treated Bed Nets |
| IUGR | Intra Uterine Growth Retardation |
| IV | Intravenous |
| LBW | Low birth Weight |
| MCP | Malaria Control Program |
| MOH | Ministry of Health |
| NDP | National Drug Policy |
| NEML | National Essential Medicine List |
| NMCP | National Malaria Control Policy |
| OTC | Over The Counter |
| PCR | Polymerase Chain Reaction |
| *P.falciparum* | Plasmodium falciparum |
| PHC | Primary Health Center |

| | |
|---|---|
| PPA | Pakistan Pharmacists Association |
| *P.vivax* | Plasmodium vivax |
| PV.DHFS | Plasmodium vivax Dihydrofolate Synthetase |
| PV.DHFR | Plasmodium vivax Dihydrofolate Reductase |
| RBM | Roll Back Malaria |
| RDT | Rapid Diagnostic Test |
| RDU | Rational Drug Use |
| RHC | Rural Health Centre |
| SP | Sulphadoxine/Pyrimethamine |
| STG | Standard Treatment Guidelines |
| THQ | Tehsil Headquarter |
| UM | Uncomplicated malaria |
| USAID | United State Agency for International Development |
| WHO | World Health Organization |

## LIST OF APPENDICES

# LIST OF PUBLICATIONS AND COMMUNICATIONS

Publication and communications arising from this thesis:

## A. PUBLICATIONS

1. **Malik, M.,** Hassali, M.A., Shafies, A.A. and Hussian, A. (2011) Strategic Solution to Malaria Eradication in Pakistan. Journal of Pharmacy Practice and Research. 41 (1).
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3. **Malik, M.,** Hassali, M.A., Shafies, A.A. and Hussian, A. (2012) Prescribing practices for the treatment of malaria among public and private healthcare facilities: A comparative cross sectional study from Pakistan. Health Med. 6 (4), 1147-1154.
4. **Malik, M.,** Hassali, M.A., Shafies, A.A., Hussian, A. and Hisham, A. (2012) Availability of different strengths of anti-malarial preparations in Pakistan: Implication for patient safety. Journal of Pharmacological and Biomedical Analysis. 1(1), 1-2.
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7. **Malik, M.,** Hassali, M.A., Shafies, A.A. and Hussian, A. (2013) A qualitative study exploring perspectives towards rational use of medicines in Pakistan's Malaria Control Program (MCP). Brazilian Journal of Pharmaceutical Sciences. 49 (2),321-328.
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**B. CONFERENCES PRESENTATIONS**

1. **Malik M,** Hassali MA, Shafie AA, Hussian A**.** Role of Essential Drug List for Effective Anti Malarial Drug Management in Pakistan. 16th International Pharmacy Conference and Exhibition April 28- May 01, 2011 Lahore, Pakistan.
2. **Malik M,** Hassali MA, Shafie AA, Hussian A**.** Current prescribing trends in treatment of malaria in health care system of Pakistan. Malaysian Pharmaceutical Society Conference 21-23 October, 2011 Kuala Lumpur

Malaysia.

3. **Malik M,** Hassali MA, Shafie AA, Hussian A**.** Barriers to rational drug use in treatment of malaria in health care facilities in Pakistan: A qualitative study. Malaysian Pharmaceutical Society Conference 21-23 October, 2011 Kuala Lumpur Malaysia.
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5. **Malik M,** Hassali MA, Shafie AA, Hussian A**.** Is current role of pharmacist fulfilling the challenges of 21$^{st}$ century of effective management of anti-malarial drugs in Pakistan? 17$^{th}$ International Pharmacy conference and exhibition 19-21 April, 2012 Islamabad, Pakistan.
6. **Malik M,** Hassali MA, Shafie AA, Hussian A**.** Adherence to Standard Treatment Guidelines: A turning point in control of Malaria in Pakistan. Asia Pacific on National drug policies 26-29 May, 2012 Sydney, Australia.
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**SATU PENILAIAN PENGGUNAAN UBATAN SECARA RASIONAL DALAM PENGURUSAN MALARIA DIANTARA FASILITI KESIHATAN AWAM DAN SWASTA DI DUA BANDAR PAKISTAN**

## ABSTRAK

Malaria menjadi masalah kesihatan awam berterusan yang utama di Pakistan, disebabkan masalah sosioekonomi dan epidemiologi. Tesis ini bertujuan menilai senario semasa tentang penggunaan drug secara rasional, pengetahuan, persepsi dan kepatuhan terhadap preskriber-dengan garis panduan rawatan yang standard bagi malaria di kemudahan penjagaan kesihatan awan dan swasta di dua buah bandaraya di Pakistan, iaitu Islamabad (ibu negara Pakistan) dan Rawalpindi (bandaraya berkembar). Gabungan kaedah penyelidikan kuantitatif dan kualitatif digunakan bagi pengumpulan data. Persepsi daripada pegawai yang terlibat dalam program kawalan malaria, preskriber dan ahli farmasi hospital berhubung faktor yang memberi kesan terhadap amalan rawatan malaria secara rasional diteliti berdasarkan dapatan daripada temu bual separa–struktur. Teknik pensampelan rawak mudah digunakan untuk memperoleh sampel kemudahan penjagaan kesihatan awam dan swasta tertier (n = 20), sekunder (n = 10), dan bandaraya). Amalan preskripsi dinilai berdasarkan indikator preskripsi WHO, sementara itu, soal selidik berstruktur digunakan untuk menilai persepsi dan pengetahuan preskriber tentang garis panduan rawatan malaria yang standard. Borang USAID (United State Agency for International Development) dan soal selidik digunakan untuk meneliti ketersediaan dan proses pengurusan drug. Lawatan juga dilakukan di farmasi komuniti untuk memantau pengurusan kes-kes

penyakit malaria. Berdasarkan dapatan kajian kualitatif, secara rasminya, semua program kawalan malaria yang diadakan adalah berjaya. Kejayaan ini tercapai dengan adanya peningkatan kemudahan diagnostik dan latihan dalam kalangan preskriber di Pakistan. Namun demikian, disebabkan kekangan kewangan, kejayaan program ini hanya tercapai di kawasan endemik yang tinggi, iaitu di sembilan belas buah daerah. Semua responden berpendapat bahawa amalan preskripsi yang tidak rasional, pengurusan drug yang tidak efektif, kurangnya kesedaran dan kepatuhan pada arahan preskriber dan pengubatan-diri adalah faktor utama yang menyumbang terhadap amalan rawatan malaria yang tidak rasional di Pakistan.

Sementara itu, dapatan kuantitatif menunjukkan bahawa pengetahuan dan kepatuhan terhadap arahan preskriber adalah lemah atau tidak begitu baik. Daripada 1500 preskripsi, diagnosis dinyatakan dalam 49% (n = 35) pembilang, namun ujian parasit malaria hanyalah 7.3% (n = 110) daripada total kes. Drug anti-malaria yang betul berdasarkan garis panduan rawatan standard dipreskrib dalam 33.8 % (n = 507) daripada kes. Secara keseluruhan, pengetahuan preskriber tentang regimen rawatan standard bagi malaria adalah tidak mencukupi (skor sederhana = 10). Skor total adalah di antara 6-12, dengan skor rendah menunjukkan pengetahuan yang baik. Kebanyakan stok drug anti-malaria ditemui di kedua-dua kemudahan penjagaan kesihatan awam dan swasta, namun demikian, ia lebih ketara di sektor awam. Pengurusan kes yang lemah atau tidak baik serta amalan pendispensan berkaitan rawatan malaria di farmasi komuniti dilaporkan disebabkan kekurangan staf yang berkualiti. Sebagai kesimpulan, tesis ini mengesahkan wujudnya amalan rawatanyang tidak rasional bagi malaria di Pakistan. Namun demikian, adalah sukar untuk mengubah amalan sedia ada. Walau bagaimanapun,

intervensi pendidikan yang bersesuaian, penglibatan program kawalan malaria secara aktif, pemegang taruh atau pemegang amanah yang berbeza, dan pelaksanaan dasar kawalan malaria diperlukan untuk mencapai amalan rawatan yang rasional dan kawalan malaria dalam negara.

# A STUDY EVALUATING RATIONAL DRUG USE IN MALARIA MANAGEMENT AMONG PUBLIC AND PRIVATE HEALTHCARE FACILITIES AT TWO PAKISTAN CITIES


## ABSTRACT

Malaria continues to be a major public health issue in Pakistan, due to socioeconomic and epidemiological reasons. The thesis aimed to assess current scenario related to rational drug use, knowledge, perceptions and adherence of prescribers with standard treatment guidelines for malaria in public and private healthcare facilities in two cities of Pakistan; Islamabad (national capital) and Rawalpindi (twin city). A combination of quantitative and qualitative research methods were used for data collection. The perceptions' of malaria control program officials, prescribers and hospital pharmacists regarding factors affecting rational treatment practices for malaria were explored by conducting semi-structured interviews. Simple random sampling technique was used to draw the sample of public and private tertiary (n = 20), secondary (n = 10), primary (n = 20) healthcare facilities and community pharmacies from Islamabad (n = 118) and Rawalpindi (n=120) respectively. Besides that, a sample of 360 prescribers was selected randomly from the two cities (n = 180 each city). Prescribing practices were evaluated by assessing prescriptions for malaria using WHO prescribing indicator form while a structured questionnaire was used to assess the perceptions and knowledge of prescribers regarding standard treatment guidelines. United State Agency for International Development (USAID) stock out form and questionnaire were use to review drug availability and process of drug management respectively. Simulated visits were also performed to observe disease case management of malaria at community pharmacies. Based on the results of the qualitative study, all the malaria control program officials agreed on successful implementation of

the malaria control program by improving diagnostic facilities and case management through training of prescribers in Pakistan. But due to financial constraints, this has been true only for the targeted high endemic areas of nineteen different districts of the country by the malaria control program. All the respondents were of the view that irrational prescribing practices, ineffective drug management, lack of awareness and adherence of prescribers to standard treatment guidelines and self medication are the major factors contributing towards irrational treatment practices for malaria in Pakistan.

While the results of the quantitative findings revealed, poor knowledge and adherence of prescribers with the standard treatment guidelines for malaria in Pakistan. Out of 1500 prescriptions, diagnosis was mentioned in 49% (n = 735) of the encounters but malarial parasite test was referred in only 7.3% (n = 110) of the total cases. Correct anti-malarial drugs according to standard treatment guidelines were prescribed in 33.8 % (n = 507) of the cases. The overall knowledge of prescribers regarding standard treatment regimen for malaria was inadequate (median score = 10). The total score was between 6-12 with lower scores indicating better knowledge. Major anti-malarial drug stock outs were seen in both public and private healthcare facilities but more prevalent in the public sector. Poor case management and dispensing practices in relation to treatment of malaria at community pharmacies was reported due to low availability of qualified person. In conclusion, this thesis confirmed irrational treatment practices for malaria in Pakistan. Although, it might be difficult to change the current practices, however, appropriate educational interventions, active involvement of Malaria Control Program, different stakeholders and implementation of Malaria Control Policy are required to achieve rational treatment practices and control of malaria in the country.

# CHAPTER ONE

# GENERAL INTRODUCTION

## 1.1 Background

Malaria remained one of the major health challenges to be addressed in the developing world. Approximately over three billion people live under the threat of malaria globally and the disease kills more than one million people each year (World Health Organization, 2012). Around 1.1-1.3 million deaths due to malaria worldwide were reported and the incidence of malaria globally was documented between 350-500 million cases in 2004 (World Health Organization, 2005). Approximately 5 million confirmed cases of malaria are reported each year from countries outside Africa, out of which 3 million are from India and Pakistan (World Health Organization, 2005). Malaria risk is often related to population movements particularly in the forest areas of Southeast Asia and South America where variety of anti-malarial drugs are used irrationally. Resistance to multiple anti-malarial drugs was first documented in these areas (World Health Organization, 2002b).

Most of the cases of malaria are reported in the South and South Eastern Asia regions (Cotter et al., 2013). Approximately, 70% of the total population (1216 million people) of South Eastern Asia Region is at risk of malaria; of which approximately 29% of the population is at moderate to high risk of malaria while 71% is at low risk of malaria. More than 95% confirmed cases of malaria and deaths are reported from population of moderate to high risk of malaria living in Bangladesh, India, Pakistan, Indonesia, Myanmar and Thailand (World Health

Organization, 2011). The increase in malaria in these Asian countries was due to economic situation, migration of populations and low quality health services. The prevalence of malaria due to Plasmodium falciparum is rapid. The highest number of laboratory confirmed cases were reported from India (1,563,344) followed by Indonesia (544,470) and Myanmar (414,008) where as the lowest number of cases was reported from Sri Lanka (558) followed by Bhutan (972) and Nepal (3,335) (World Health Organization, 2011). There has been little success in malaria control over the last decade in Asia due to lack of funding and resistance to anti-malarial drugs (World Health Organization, 2005).

### 1.2 Barriers to malaria control: A brief overview

Malaria has always remained a major cause of mortality globally (World Health Organization, 2002b). Malaria can be controlled through early diagnosis and effective treatment. The emergence of high rates of resistance to anti-malarial drugs due to lack of adherence of practitioners with standard treatment regimen for malaria has been reported in several developing countries (Abdel Hameed, 2003, Abuaku et al., 2005, Chuma et al., 2009, Chandler et al., 2008b). The contribution of inappropriate prescribing of anti-malarial drugs on transmission of drug resistance highlights the need to improve malaria treatment practices (Gbotosho et al., 2009). Access to essential drugs should not only be seen as a component of malaria control but also as a fundamental right of all populations at risk of malaria (World Health Organization, 2006). Availability of limited number of new anti-malarial drugs and resistance to conventional drugs have increased difficulties in formulating anti-malarial treatment policies and have delayed provision of prompt and effective treatment (UNICEF, 2000). Malaria is usually over-diagnosed and anti-malarial

drugs are prescribed empirically to patients without laboratory confirmation of malaria parasitaemia (Font et al., 2001). Most of the malaria cases are usually self-treated. Reasons underlying this practice include difficulty with access to health centre facilities, lack of affordable anti-malarial drugs, perceived deficiencies in the performance of formal health services including poor clinical and diagnostics skills, attitude of health personnel and cultural beliefs. These shortcomings encourage treatment of malaria at home with inappropriate drugs including herbal preparations purchased from pharmacy outlets (Okeke and Uzochukwu, 2009). All these concerns calls for in-depth investigation of the factors underling the problems in the practice and designing appropriate interventions addressing the causative issues in the control of malaria (Okeke et al., 2006). Thus strategies must be designed to achieve significant improvements in knowledge, behavior, compliance, performance and practices of prescribers/pharmacists and drug sellers in hospitals and at retail pharmacies respectively, for promoting rational practices for the treatment and control of malaria (Grand et al., 1999).

### 1.3 Justification for the study

The rationale for malaria control is based on early diagnosis and effective treatment. Treatment is specific for the type of malaria and is based on different phases of the parasite cycle. This leads to complex treatment regimens. Appropriate prescribing practices, drug management, quality of patient care services and rational drug use are considered as key elements for control of malaria (Meremikwu et al., 2007, Osorio et al., 2009). Most of the high burden countries usually face financial constraints and lack of interest in exploring the underlying causes for the irrational use of drugs. Insufficient data regarding the health system performance, malaria

epidemiological profile, community dynamics, decision making and prioritizing health problems have been reported. This has been particularly true about the high burden country for malaria, like Pakistan which is the focus of this research undertaking**.** Given the malaria control program push for the control of malaria, it is important to ascertain the contributing factors responsible for irrational practices for the treatment and control of malaria in Pakistan. Indeed, the impact of different aspects of performance of malaria control program at central and district levels remain to be fully elucidated. Furthermore, no study has yet been conducted to assess the perceptions of healthcare professionals regarding irrational treatment practices for malaria. This study was therefore designed to investigate the perceptions of doctors and pharmacists regarding factors underlying irrational prescribing practices and procurement issues of anti-malarial drugs in Pakistan. In-depth interviews were conducted with the participants from each of these groups to explore their perceptions.

Based on the outcomes of the interviews, further studies were undertaken to investigate current prescribing patterns, knowledge and adherence of prescribers with standard treatment regimen for malaria, drug management practices offered in different public and private primary, secondary and tertiary healthcare facilities and case management of malaria at community pharmacies in two major cities of Pakistan. The current study will serve as baseline data for the policy makers, managers, researchers and other stakeholders to modify the existing interventions or design future interventions for improving irrational treatment practices developing methods of accountability and control for malaria in Pakistan.

### 1.4 Overview of thesis

Chapter 2, the literature review, starts with malaria as disease and risk groups. A brief discussion of important features of malaria including burden, manifestation, symptoms, treatment and control strategies has been discussed. Monitoring trends and treatment policy along with changes in the policy have also been included. Rational drug use and barriers related to workplace, prescribing, dispensing, currently available anti malarial drugs and patient are discussed in depth. The chapter continues with an overview of different strategies used for improving treatment practices globally. A brief discussion on the gaps identified in the current literature is also included in this chapter. Further discussion in this chapter involves malaria epidemiology, current scenario of malaria control, policy, treatment practices and role of malaria control program in Pakistan. A thorough review of literature relevant to the study, looking at adherence with standard treatment guidelines (STGs), resistance, diagnosis, prescribing practices and the views of prescribers, dispensers, community towards the drug use in the world forms the bulk of this chapter. Chapter 3 comprises a thorough discussion of the methodology used for the qualitative and quantitative studies undertaken.

Chapters 4, 5 and 6 are consolidated as Section A of the thesis, which details the findings from the qualitative interviews with conveniently sampled malaria control program officials, prescribers and pharmacists in Islamabad and Rawalpindi, Pakistan. Chapter 4 presents the findings from interviews conducted with malaria control program officials regarding their perceptions about the role of malaria control program in Pakistan.

Chapter 5 presents the findings from the interviews with prescribers regarding factors related with prescribing practices for the treatment of malaria in Pakistan. Chapter 6 presents the findings from interviews with the hospital pharmacists regarding issues related to the process of drug management including selection, procurement, inventory control and storage. Chapters 7, 8, 9 and 10 are consolidated as Section B of this thesis, which describes the findings from quantitative surveys assessing knowledge of prescribers regarding standard treatment guidelines, prescribing patterns and adherence to standard treatment guidelines, anti-malarial drugs management and case management of malaria at community pharmacies.

Chapter 7 describes an analysis of the knowledge and perceptions held by the prescribers regarding adherence to standard treatment guidelines. Chapter 8 describes the findings of prescribing patterns and adherence of prescribers with standard treatment guidelines for the treatment of malaria among public and private primary, secondary and tertiary healthcare facilities. Chapter 9 describes findings of the process of anti-malarial drug management including selection, procurement, inventory control and storage at public and private primary, secondary and tertiary healthcare facilities. Chapter 10 describes findings of case management of malaria including history taking and provision of advice at community pharmacies through simulated patients' visits. Chapters 11 illustrate the thesis to final conclusion along with recommendations for further research.

# CHAPTER TWO

# LITERATURE REVIEW

## 2.1 Malaria as disease

Malaria has been classified as “emerging infection” and major cause of morbidity and mortality in tropical and sub-tropical regions of the world (Conway, 2007). The early discoveries of malaria have been well known. In 1880, Charles Louis Alphonse Laveran was the one who saw the malaria parasite for the first time. While Ronald Ross in 1897, discovered the complete mosquito cycle and Giovanni Batista in 1898, recognized the anopheles transmission of malaria in human. All these discoveries are the basis of currently originated malaria treatment research in the world (Sherman, 1998).

## 2.2 Important features of malaria

### 2.2.1 Malaria endemic vs. epidemic

Malaria can have different appearances based on type of exposure. Malaria endemicity may impact disease presentation in the population (e.g., susceptibility of patients and percentage of febrile patients with malaria), diagnostic and treatments policies and procurement systems. Moreover, recent rigorous preventative measures are predictable to assist in shifting prevalence from endemic to epidemic manifestations (Cook, 1988).

### 2.2.2 Seasonality

Malaria has seasonal fluctuations in some areas, with increased cases during the rainy season (Cook, 1988).

### 2.2.3 Geography

Usually lower altitude, wetter and more dense foliage provide more hospitable environments for malaria-carrying mosquitoes. However, urban areas might be less susceptible of transmission than rural areas in different countries (Cook, 1988, Silva and Marshall, 2012).

### 2.2.4 Different species of malaria parasite

Five species of the plasmodium parasite can infect humans: the most serious forms of the disease are caused by Plasmodium falciparum, and Plasmodium vivax which accounts for nearly all cases of malaria in humans. Malaria caused by Plasmodium ovale, and Plasmodium malariae produces milder disease not generally fatal in humans. A fifth species, Plasmodium knowlesi, causes malaria in macaques and can infect humans (Hsiang et al., 2010).

### 2.2.5 Global burden of malaria caused by different species

The global malaria incidence and malaria-specific mortality rates were decreased by 17% and 26% respectively, between 2000 and 2010 (World Health Organization, 2011, Pigott et al., 2012). Many countries such as Armenia, Morocco, Turkmenistan, and the United Arab Emirates have been declared as malaria free countries in the past five years (Yangzom et al., 2012, Cotter et al., 2013). Malaria-eliminating countries have contributed significantly to the reduction of the global

malaria burden over the past decade (Cotter et al., 2013). The total caseload of these specific malaria eliminating countries has been reduced by 79% in the Asia Pacific region, 86% in Latin America, 92% in sub Saharan Africa, and 96% in the Middle East, Europe and central Asia. Increased funding, effective vector control, improved case management with more effective treatment regimens and better case reporting and surveillance were the main factors responsible for these successes (Cotter et al., 2013).

An estimated global burden of 451 million clinical cases caused by *P. falciparum* has been reported. Most of these cases occurred in India, Nigeria, The Democratic Republic of the Congo and Myanmar (Hay et al., 2010). The focus of malaria control has understandably been on *P. falciparum* in high endemic countries. Many malaria-endemic countries including all countries in Europe and central Asia, Argentina, Belize, Mexico, and large parts of China have been successful in eliminating *P. falciparum* from them (Gething et al., 2012).

However, *P. vivax* is still the remaining challenge for the malaria eliminating countries as been less responsive to control interventions than *P. falciparum* infections because of several unique features. It has a dormant liver stage that can result in relapses even after treatment and greater range of ecological receptivity unlike *P. falciparum* (Mueller et al., 2009). Out of the 34 malaria-eliminating countries, 26 of the countries have 76% of the malaria burden mainly due to *P. vivax* (Feachem et al., 2010). The global burden of malaria due to *P. vivax* is 70–80 million cases annually. Approximately 10–20% of the world's malaria cases caused by *P. vivax* infection occur in Africa and 1% of the cases in western and central Africa. However, about 80–90% of *P. vivax* cases occur outside of Africa in the Middle East, Asia, Western Pacific and 10–15% in Central and South America. *P. vivax* infections

usually affect people of all ages and is rarely fatal, but can have major harmful effects on personal well-being, growth and development along with economic performance at individual, family, community, and national levels (Mendis et al., 2001).

### 2.2.6 Pathophysiology of malaria

The plasmodium parasite that causes malaria is transmitted from mosquitos to men. The parasites spend part of their life cycle in the mosquito and part of it in the human host. The infective plasmodial sporozoites enter the bloodstream from the saliva of the female anopheles mosquito (White and Ho, 1992, Anstey et al., 2009). The sporozoites are cleared from the blood stream by the Kupfer cells of the liver, but few of the sporozoites manage to enter the hepatocytes. The parasites transform into schizonts, and after replication finally into merozites within the hepatocytes (White and Ho, 1992). These merozoites are then released into the bloodstream where they penetrate into red cells and change into ring form called trophozoites. Trophozoites metamorph into schizonts and produce new merozoites inside the red cells by using haemoglobin. The red cells eventually burst and release merozoites that can invade new red blood cells (White and Ho, 1992). Some of the trophozoites in the red cells changes into sexual form of parasite i.e. gametocytes and do no lyse the red blood cells (Anstey et al., 2009). These gametocytes are then acquired by the mosquito taking blood meal from the respective person and thus the sexual reproduction cycle then begins in the mosquito, and subsequently it transmits the parasite to other human host (White and Ho, 1992, Anstey et al., 2009) (Figure 2.1).

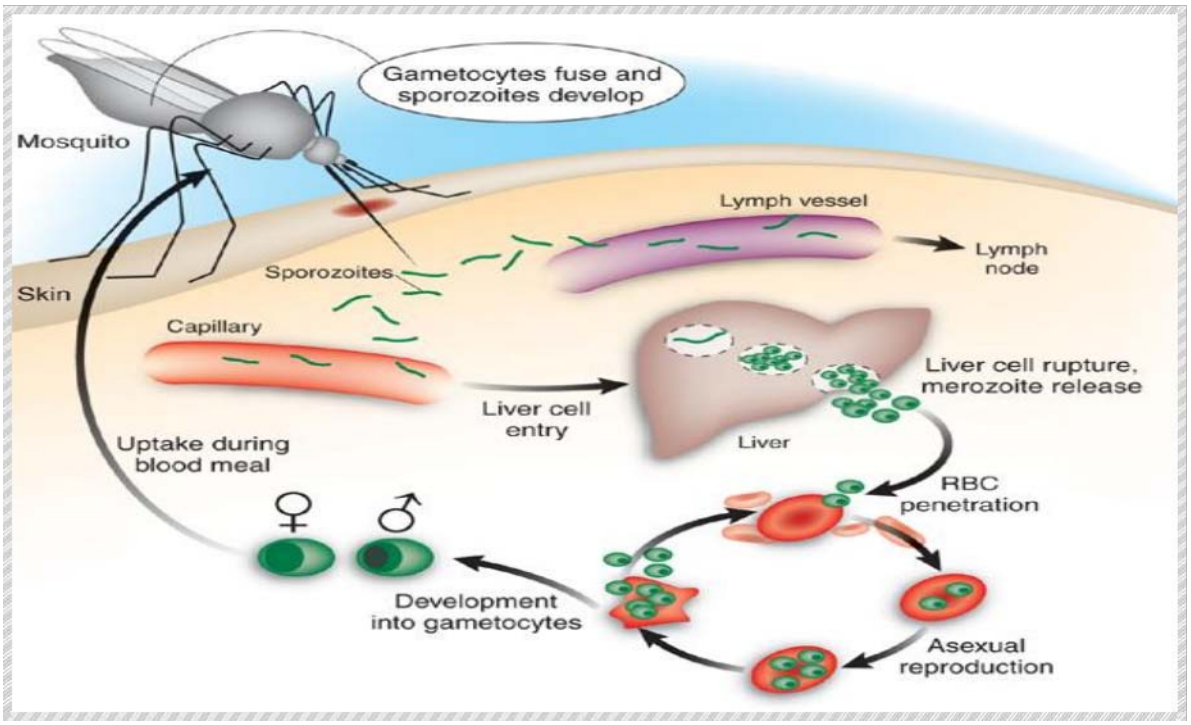


**Figure 2.1 Pathophysiology of malaria**
**Adapted from: Jones, M. K. & Good, M. F. (2006)**

### 2.2.7 Manifestation of malaria

Uncomplicated malaria is the most common form and may be intermittent or remittent but majority of patients can live with recurrences. However, cerebral or complicated malaria can be lethal if not treated immediately, especially among compromised patients, making children more vulnerable. To prevent development of complicated malaria, the WHO recommends using arteminsin combination treatment therapy within 24 hours onset of fever (Cook, 1988).

### 2.2.8 Malaria control strategy

### 2.2.8 (a) Prevention

Insecticide-treated bed nets and insecticide house spraying are the most commonly used preventive methods for malaria. A study conducted in South Africa

reported a significant reduction in malaria incidence in communities using treated bed nets than house spraying (Mnzava et al., 2001). Various studies have provided evidence of insecticide treated bed nets (ITBNs) special role in reducing severe morbidity in children under five years of age from malaria and as highly cost-effective intervention for control of malaria in resource constraints settings (Wiseman et al., 2003, Nevill et al., 1996). The focus of cleanup operations from 'waste' to 'breeding sources' including things and places that hold water in home based and major community based source elimination operations can also help in combating mosquitoes (Jamsheed, 2011).

### 2.2.8 (b) Environmental

Forest activity, abstaining from bed nets use, ethnicity, age and education are considered as risk factors for malaria infections. Control of malaria remains an extremely complex task that can only be accomplished by addressing the foremost risk determinants in malaria such as control of forest poverty-related risk factors including education, ethnicity and housing conditions (Thang et al., 2008). The numbers of malaria cases were reduced significantly between 1994 and 2011 in Sabah state, Malaysia but still an increasing proportion of malaria cases of adult men were reported due to their involvement in plantation work and forest activities which exposed them to outdoor biting vectors (Cotter et al., 2013). Similarly, occupational activities such as farming, forest clearing, hunting, and wood gathering were associated with increased chances of malaria infection in adult men in Bhutan, India, Sri Lanka and Philippines (Yangzom et al., 2012, Tobgay et al., 2010, Wangdi et al., 2011).

### 2.2.8 (c) Vector control

Insecticides are one of the cheapest and most effective methods of controlling malaria, but mosquitoes can rapidly evolve resistance. The use of existing chemical insecticides, bio-pesticides, and novel chemistry and one-off investment in a single insecticide can solve the problem of mosquito resistance forever. However, current strategies for dealing with resistance evolution are expensive and their sustainability has yet to be demonstrated (Read et al., 2009).

### 2.2.9 Diagnosis of malaria

Presumptive treatment with anti malarial drugs is a common practice by the public and private health care workers in malaria endemic regions. This has made malaria incidence difficult to be measured accurately. The diagnostic policies have shifted from predominantly clinical to laboratory diagnosis (rapid diagnostic test RDT or microscopy) in the recent years. The WHO recommends prompt parasitological confirmation to be obtained by microscopy or RDTs before starting treatment of patients suspected with malaria. Treatment based solely on clinical suspicion should be considered only when a parasitological diagnosis is not accessible. Light microscopy remains the gold standard in settings where many patients are to be tested but in peripheral settings it is usually less feasible or cost effective therefore, rapid diagnostic test (RDT) and clinical diagnosis based solely on fever are considered best options for diagnosis of malaria in these settings. Other approaches, such as polymerase chain reaction (PCR) and immunological tests for malaria are also available but are useful only for research purposes due to their high cost (Hammer, 1993).

### 2.2.10 Treatment of malaria

Development and testing of standard treatment guidelines for malaria have been initiated globally in various countries. Most countries are also updating their Integrated Management of Childhood Illness (IMCI) guidelines to align with WHO recommendations that confirmed diagnosis precede all treatment, even in children under the age of five. But still chloroquine and sulphadoxine/pyrimethamine (SP) are recommended as first line agents for uncomplicated malaria in several developing countries. SP is also used for intermittent preventive treatment in pregnancy (IPTp). Complicated or severe malaria is often treated with injectable artesunate or quinine (Acremont et al., 2009). Anti-malarial drugs are usually classified according to their action on the stage of the parasite cycle. Resistance has developed to several anti malarial drugs used as monotherapies, resulting in the current recommendation to use only combination therapies to treat uncomplicated malaria. Therefore, most of the countries have transitioned from monotherapies to Artemisinin Combination Therapy (ACT) as first-line treatment for uncomplicated malaria (Acremont et al., 2009). A detail classification of different anti-malarial drugs is given (Table 2.1).

**Table 2.1 Classification of different anti-malarial drugs***

| Therapeutic Class | Anti-malarial Drugs | Mode of Action |
|---|---|---|
| **Prophylactic Drugs** | Proguanil/Atovaquone, Pyrimethamine, Doxycycline, Mefloquine | Active against primary tissue schizontocides of *P.vivax* and *P.falciparum* |
| **Schizontocidal Drugs** | Quinine,Mepacrine,Chloroquine, Amodiaquine, Arteminsins deravatives | Acts on asexual erythrocytic form of all parasites |
| **Gametocytocidal Drugs** | Pamaquine, Primaquine, Plasmocide | Acts on asexual form of all malaria parasite especially *P.vivax* & *P.malariae* |
| **Sporontocidal Drugs** | Quinocide, Proguanil, Chloroproguanil, Pyrimethamine/ sulphadoxine | Inhibits sporogenic phase of *P.vivax* & *P. falciparum* |
| **Anti relapse Drugs** | Pamaquine, Primaquine, Quinocide | Acts on secondary exo-erythrocytic phase of *P.vivax* & *P.malariae* |

**** Directorate of Malaria Control and WHO, National Treatment Guidelines for Malaria. 2006***

## 2.3 Risk groups for malaria

### 2.3.1 Burden of malaria in pregnancy

Approximately, 75,000 to 200,000 infant deaths are associated with malaria infection in pregnancy every year, globally. Low birth weight (LBW) from prematurity and intrauterine growth retardation (IUGR) is the major determinants of infant mortality in malaria. Malaria-induced LBW kills 62,000–363,000 newborns annually. These malaria-induced medical problems poses major clinical, public health and research challenges which may contribute to increase mortality rate (Murphy and Breman, 2001). The failure of effective anti-malarial interventions through antenatal programs is significantly contributing to infant mortality worldwide. Less than 20% of the women use prophylactic regimen as per WHO recommendations in pregnancy which is due to low access and quality of antenatal care (ANC) services (TerKuile et al., 2003, Steketee et al., 2001, Menendez et al., 2007).

### 2.3.2 Child mortality in malaria

Approximately one million children under the age of five years die each year due to malaria globally, out of which 75 % are from Africa (Crawley, 2004). Anaemia usually affects more than half of all pregnant women and children less than five years old, and has serious consequences associated with an increased risk of death. Effective management of malaria in children under the age of 5 requires mothers to seek appropriate information regarding proper use of anti-malarial drugs. This is linked to timely decision, accessibility, correct use of the drugs and follow-up (Malik et al., 2006). Despite the magnitude of the problem of child mortality and constantly increasing research findings related to pathogenesis, risk factors and

efficacious interventions, child mortality in malaria-endemic countries still remains poor. This might be due to rapid spread of resistance to anti-malarial drugs, coupled with widespread poverty, weak health infrastructure and failure of currently available interventions to address child mortality from malaria (Singer and Teklahaimanot, 2003, Crawley, 2004).

### 2.4 Monitoring trends for malaria control

Mortality has always been considered as the primary indicator of a serious problem especially in vulnerable groups in malaria. Data from health facilities is a useful tool for monitoring trends in morbidity and mortality as well as the impact of control measures and other factors that affect malaria (United State Agency for International Development, 2011). But various limitations are seen while monitoring of malaria control. Reporting varies in its quality, comprehensiveness and appropriateness which might be due to lack of an accountable health information system or interest of concerned respective authorities in updating the data base in different developing countries. Data from non-governmental facilities or from the community where most cases of malaria illness and deaths occur is scarce. Thus, these factors contribute towards difficulties in developing standardized case definitions for malaria morbidity and mortality (UNICEF, 2000).

### 2.5 Treatment policy for malaria

It is the responsibility of national health programs to develop a treatment policy for malaria which should ideally be part of the national malaria control policy, covering prevention as well as case management (World Health Organization, 2005). Given the importance of the issues, the anti-malarial drug policy should be given

prominence within and supported by the National Drug policy (NDP) and National Malaria Control Policy (NMCP). The NMCP and the NDP should conform to the overall National Health Policy. It is recognized that anti-malarial treatment policies usually vary between countries depending on the epidemiology of the disease, transmission, patterns of drug resistance and political and economic contexts. In addition, significant variations in the therapeutic response to first-line anti-malarial drugs may exist in different geographical localities and regions of a country. Treatment policies in some countries have attempted to differentiate between localities with varying drug resistance (Worrall et al., 2005). Such decisions depend on whether countries are able to implement different drug policies for different regions and whether the health system can deliver the required drug successfully to end-users (World Health Organization, 2005).

As the available drugs become more expensive or less safe, dual policies for vulnerable and less vulnerable groups may need to be considered. One key challenge facing the development of anti-malarial treatment policies is achieving a balance between two essential purposes that:

- All populations at risk have access to prompt treatment with safe, good quality, effective, affordable and acceptable anti-malarial drugs.
- The approach should encourage rational drug use of currently available anti-malarial drugs in order to avoid unnecessary selection pressure favouring the development of drug resistance.

## 2.6 Changes in malaria treatment policy

The change in malaria control policy in various countries in favours of ACT became necessary with the prevalence of *P. falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine (Snow et al., 2006). Prescription practices have been shown to influence the emergence of resistance to anti-malarial drugs, thus the success of a new treatment policy would depend on the adherence of health providers and patients to treatment recommendations (Noranate et al., 2007). Several ACT drugs exist and others are in the pipeline and have the potential to reduce mortality from malaria substantially if properly targeted to the right people. Current evidence suggests that most of those who need the drugs do not get them while a high proportion of those who are given anti-malarial drugs in fact do not have malaria. Such irrational use of ACT could undermine the goal of combination therapy, which is to prevent the emergence of resistant against malaria parasites (Gbotosho et al., 2009). Financial and low accessibility to formal healthcare undermines the impact of provision of free anti- malarial drugs via this route. The higher cost of ACT creates a market for fake drugs (Whitty et al., 2008). Reliable data of the process of malaria treatment policy change are urgently required to address these issues to determine commonalities and optimize the efficiency of formulating and implementing malaria treatment policy changes in different countries (Durrheim et al., 2003).

## 2.7 Rational drug use, a component of good health care system

An efficient health care system can be achieved by promotion of rational drug use. Rational use of drugs necessitate that patients receive ‘medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an

adequate period of time and at the lowest cost to them and their community' (World Health Organization, 2005). Development of resistance to antibiotics, ineffective treatment, adverse effects, drug dependence and economic burden to the patient and society are the major dilemma of present medical practice in case of malaria (Juncosa, 2008). Enormous resources are reported to be wasted when drugs are prescribed, dispensed, administered and used in irrational way (Quick et al., 1991).

### 2.8 Different barriers to rational drug use in treating malaria

The major factors which contribute to irrational drug use and affects quality of health care system are combination of factors including patients, prescribers, dispensers, the workplace, the supply system, influences by the pharmaceutical industry, regulations, drug information and misinformation (Holloway, 2006, Maxwell, 2009).

#### 2.8.1 Workplace

#### 2.8.1 (a) Lack of availability and use of diagnostic tools

The use of microscopy and rapid diagnostic tests (RDTs) for malaria could improve the management of both malaria and other febrile illness. When diagnostic facilities are available, half or more of those with negative test results are still treated for malaria however, the proportion is even higher when these facilities are not present (Hamer et al., 2007, Reyburn et al., 2004, Zurovac et al., 2007). Diagnosis of malaria in the absence of microscopic confirmation was associated with significantly increased mortality in hospitalized patients in Uganda (Opoka et al., 2008). The need of employing trained technicians who are able to differentiate between different plasmodium species, constant supply of reagents and equipments is usually ignored

(Jonkman et al., 1995, Lubell et al., 2008). The quality of slides and stains is often poor and current tests being used are not heat stable (Chiodini et al., 2007). Various studies reported low use of diagnostic tools and poor quality blood smear staining leading to unreliable measurement of sensitivity and specificity and undermine the use of effective anti-malarial treatment (Morrow et al., 2008, Uzochukwu et al., 2010). However, directing resources towards improving diagnostic and treatment practices may provide a cost-effective measure for promoting rational use of anti-malarial therapy (Njama et al., 2007).

### 2.8.1 (b) Lack of availability and adherence to malaria diagnostics guidelines

Improving the accuracy of malaria diagnosis with rapid antigen-detection diagnostic tests (RDTs) has been proposed as a useful approach for reducing overtreatment of malaria in the current era. The reasons clinicians respond irrationally to diagnostic tests are complex and may be difficult or slow to change. Despite efforts to expand the provision of malaria diagnostics, they are underused and patients with negative test results frequently receive anti-malarials. This might be due to lack of availability of explicit diagnostic guidelines; training of technicians on these guidelines; feedback systems for results of quality control of RDTs and their use in routine practice are the missing components in the healthcare system (Hamer et al., 2007, Chandler et al., 2010).

### 2.8.2 Prescribing issues

### 2.8.2 (a) Inappropriate diagnosis of malaria by prescribers

Malaria is usually over-diagnosed at both healthcare centres and hospitals. Over diagnosis of malaria in the routine outpatient care system as compared to RDT

confirmed cases of malaria has been reported higher in developing countries (Reyburn et al., 2004, Mosha et al., 2010). More accurate diagnosis and management of febrile illnesses is significantly required, however, use of RDTs has shown improved health outcomes without increased cost per patient (Sievers et al., 2008, Rodrigues et al., 2008, Msellem et al., 2009, Okeke and Uzochukwu, 2009).

### 2.8.2 (b) Inappropriate case management of malaria

Appropriate case management of malaria is an important strategy to control malaria. Usually, the patients are not aware of the disease symptoms and even if familiar with malaria, they may find it difficult to identify fever pattern, especially when it is relatively low, as a result, several patients are missed for treatment (Ceesay et al., 2008, Diallo et al., 2006). Patients seek treatment from variety of sources including traditional healers, pharmacies retail outlets and public or private healthcare facilities. Self-treatment is regarded as one of the major factors that leads to delayed and poor diagnosis of malaria (Combie, 2002). On the other hand, patients with malaria are often treated empirically in the healthcare facilities without any laboratory investigation (Chandler et al., 2008a). As substantial overlap exists in clinical symptoms of malaria with several other diseases which can lead to incorrect diagnosis (Bojang et al., 2000). Non-availability of prescribed drugs at healthcare facilities is also one of the common factors relating to improper case management (Mumba et al., 2003). Various gaps such as lack of availability of ACTs, technical diagnostic skills and adherence to standard treatment regimen for malaria were reported in Sudan (Abdelgader et al., 2012). Parasitological diagnosis of malaria at all levels of the healthcare system was highlighted to be the part of the malaria case management policy in Sudan. Case management of malaria was more appropriate in

the private healthcare facilities as compared to public facilities of Sudan, as health workers from the private sector had extensive training in malaria case-management (Elmardi et al., 2011). Significant improvements in malaria case management were reported due to implementation of new treatment policies for malaria in Zambia (Zurovac et al., 2007).

### 2.8.2 (c) Prescribing patterns for malaria treatment

Major prescribing problems due to polypharmacy and irrational use of antibiotics and injections have been reported in various developing countries. Malaria treatments varied, but there were not large differences among the practice of public and private healthcare facilities (Ogwal et al., 2004). Most of the prescribers in developing countries usually prescribe monotherapy, either chloroquine, sulphadoxine-pyrimethamine or artemisinin derivatives alone. However, artemisinin combination treatments are prescribed only in few of the cases (Abuaku et al., 2005). Poor standards of prescribing of anti-malarial drugs, in terms of overprescribing of chloroquine tablets, broad spectrum antibiotics and incorrect regimens for intravenous administration of quinine have been reported (Kamat, 2009). Most of the medical practitioners tends to follow their own regimens to treat malaria in most of the developing countries (Yousif and Adeel, 2000). General practitioners who had attended less than two in-service training sessions in the past year have been reported to prescribe anti-malarial drugs and antibiotics without laboratory confirmation more frequently (Chandler et al., 2008a, Ogwal et al., 2004). Poor compliance of patients to their medication due to the absence of physicians and lack of oral/written counselling at primary healthcare facilities was highlighted in Brazil (Suarez et al., 2011).

### 2.8.2 (d) Availability and updating of standard treatment guidelines for malaria

Standard treatment guidelines (STGs) are the protocols for the most effective treatment of a specific clinical problem in a given setting, which is based on the consent of experts. STGs are developed on the most effective treatment which is also available at low cost. If healthcare providers adhere with STG, drugs demand is more predictable, facilitating more accurate forecasts and constant supply of drugs at healthcare facilities. The major issues highlighted for drug stock-outs in Sudan were lack of availability of STG's for malaria in healthcare facilities, continuous supervision, training and follow up of the guidelines and negative attitudes of hospital specialists towards the protocol following monitoring and updating of STGs. However, introducing STGs in pre-service training; thorough distribution of these guidelines to health workers, with close follow-up and supervision can improve prescribing practices for malaria (Ahmed and Yousif, 2004).

### 2.8.2 (e) Lack of knowledge and adherence of prescribers to malarial STGs

Influence of peers, pressure to conform with perceived patient preferences and quality of diagnostic support, involving resource management, personal motivations and lack of supervision are usually highlighted as the major reasons for lack of adherence of prescribers to STGs (Chandler et al., 2008b). Monitoring of drug advertising and promotional activities in the healthcare facilities by the hospital management can also improve compliance of prescribers with standard treatment guidelines (Chedi et al., 2010).

Intermittent Preventive Treatment of malaria in pregnancy (IPTp) is effective in preventing malaria in pregnancy but poor knowledge and compliance of prescribers with standard treatment guidelines was observed in Nigeria (Arulogun and Okereke, 2012). However, lack of adherence to national treatment guidelines, especially in the private sector, and a relationship between prescription practices and increase in anti-malarial drug resistance in Nigeria was reported (Gbotosho et al., 2009).

Prescribing practices of inappropriate doses of chloroquine due to lack of adherence of prescribers with standard treatment guidelines was found more prevalent in private than public health care facilities in Ghana (Abuaku et al., 2005). Similar situation was reported in India, where many practitioners were not legally qualified and majority of them adopted diagnostic and treatment practices that were not consistent with the guidelines of WHO and India's National Malaria Eradication Program. Medical journals were the most common source of information used by these practitioners. Improvement in access to information about new guidelines through IEC (information education communication) techniques or workshops was emphasized (Kamat, 2009).

A systematic organized education program for adherence to STGs with repeated feedback meetings showed improved performance of prescribers at healthcare facilities in Lao PDR. Thus, the audit–feedback model can be used and integrated into routine work, in order to improve the clinical performance of prescribers at healthcare facilities (Wahlstrom et al., 2003).