IMPACT OF DELAYED INTRODUCTION OF SULPHADOXINE-PYRIMETHAMINE AND ARTEMETHER-LUMEFANTRINE ON MALARIA EPIDEMIOLOGY IN KWAZULU-NATAL, SOUTH AFRICA

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DECLARATION

This is to certify that Mr Anyachebelu Emmanuel Junior has prepared this dissertation report entitled "Impact of delayed introduction of Sulphadoxine-Pyramethamine and Arthemeter-Lumefantrine on malaria epidemiology in KwaZulu-Natal, South Africa". This dissertation is my own work and all primary and secondary sources have been acknowledged. This dissertation has not been submitted to any other institution as part of an academic qualification.

This Dissertation is prepared in partial fulfilment of the requirement of the Master of Public Health degree at the School of Family and Public Health Medicine, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban South Africa.

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ABSTRACT

Background

The years 1985 to 1988 and 1997 to 2001, were periods of high morbidity and mortality due to malaria in KwaZulu-Natal, South Africa. One reason for the increased burden of disease was the emergence of drug resistant *Plasmodium falciparum.* The parasite was resistant initially to chloroquine and then to sulphadoxine-pyramethamine, the medication of choice for the treatment and prevention of malaria in different periods of time. The changing epidemiology of malaria in Africa was exacerbated by policy makers not making timely and rational change to the failing malaria drug regimens to newer and effective ones.

Purpose of the study

This study was conducted to determine the impact of delayed introduction of sulphadoxine-pyramethamine (Fansidar®) and artemether-lumefantrine (Coartem®) as a first-line drugs for malaria in KwaZulu-Natal from 1985 to 1988 and 1997 to 2001 respectively,

Study Design

Observational, Analytic, Ecological

Method

The incidence of malaria in KwaZulu-Natal was compared during different phases of the period when chloroquine was the first line treatment. The baseline phase (1982 to 1984) was taken when chloroquine correctly should have been used and this was compared with the delayed phase (1985 to 1988), when it should have been replaced by of sulphadoxine-pyramethamine. During the second period sulphadoxine-pyramethamine was the first line treatment of malaria, the baseline phase (1993 to 1996) when it correctly should have been used was compared to the delayed phase (1997 to 2001) of introduction of the alternate treatment of malaria with artemether-lumefantrine. Ethical approval for this study was obtained from the Biomedical Research Ethics Committee, of the University of KwaZulu-Natal.

Statistical Methods

The relative association of malaria infection during the chloroquine baseline and change phases and the sulphadoxine-pyramethamine baseline and change phases were compared with statistical significance at 0.05.

Results

The risk of malaria infection was 4.5 times (Incidence Risk Ratio = 4.5; 95% Confidence Interval: 4.1 to 5.0; $p < 0.0001$) higher in chloroquine change phase relative to the baseline phase. During the sulphadoxine-pyramethamine period, the malaria risk was 3.5 times greater (Incidence Risk Ratio = 3.50; 95% Confidence Interval: 3.40- 3.60; $p < 0.0001$) in the change phase. In the chloroquine period, the malaria mortality risk was 9.1 times higher (95% Confidence Interval: 2.1 to 38.5; $p=0.0003$) and the case fatality rate was increased 1.3 times more (95% Confidence Interval: 1.0 to 1.7; $p< 0.001$) in the change period. The risk of death during the sulphadoxine-pyramethamine change phase was 4.8 times (95% Confidence Interval: 3.3 to 7.0; $p<0.001$) and case fatality rate of 2 times (95% Confidence Interval: 1.5 to 2.7; $p <0.001$) relative to the baseline phase.

Conclusions

The dramatic change in the malaria epidemiology in Africa in recent times was exacerbated by delay in replacing first line failing antimalarial drugs. The establishment of sentinel sites for assessing drug resistance or failure and the application of World Health Organisation standards in drug resistance studies will go a long way to achieving the Roll Back Malaria target by 2010. (425 words)

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CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

High malaria morbidity and mortality was recorded in the province of KwaZulu-Natal between the periods 1985 to 1988 and 1997 to 2001 (MRC, 2006). One reason for this increased burden of disease was the emergence of drug resistant *Plasmodium falciparum* to the most affordable and cheapest drugs, chloroquine and sulphadoxine-pyramethamine (Fansidar ®) during the periods respectively. The aim of this study was to describe the impact of the policy which delayed introduction of first-line antimalarial drugs on malaria epidemiology in KwaZulu-Natal.

1.1.1 What is known so far?

The epidemics of malaria from 1985 to 1988 and from the 1997 to 2001 were contributed by a number of factors. These included agricultural practices, insecticide resistance, climatic changes, cross-border movements as well as *Plasmodium falciparum* resistance to chloroquine and sulphadoxine-pyramethamine respectively. In 1983, *in vivo* chloroquine resistance of 6 % (n=130) was detected during active case-finding in northern KwaZulu-Natal (Hansford, 1989). By 1985, resistance to chloroquine was 8% (n=77) (Herbst *et al.*, 1985). During the 1987/1988 malaria season, 75% of malaria parasite isolates obtained through surveillance were found to be resistant to chloroquine to varying degrees. Other studies showed 82% resistance in 1987 (n=11) and 100% in 1988 (n=14) (Freese *et al.*, 1988; Craig *et al.*, 2004).

Resistance to sulphadoxine-pyramethamine was exacerbated by its long half-life in the blood (Bredenkamp *et al.*, 2001). Sulphadoxine-pyramethamine was introduced in 1988 because of the unacceptable level of resistance to chloroquine. I*n vivo* studies conducted in 1997 and 2000 showed a 24% and 61 % parasitological failure to sulphadoxine-pyramethamine respectively (Bredenkamp *et al.*, 2001). Artemether-lumefantrine was officially introduced to replace sulphadoxine-pyramethamine as the first-line therapy for malaria in KwaZulu-Natal in February 2001. There was a marked reduction in malaria

morbidity and mortality immediately following the introduction of each new antimalarial drug.

1.1.2 What needs to be known?

Introducing new antimalarial treatment policies when resistant malaria is detected is a challenging process. Some key issues need to be considered before a change is made. These include following standardized procedures before changing malaria drug policy and using evidence informed methods to collect *in vivo* and *in vitro* drug resistance data (WHO 2001). Other issues include the availability of finance, having appropriate drug alternatives and the cost of replacement malaria drugs to both patients and providers (Williams *et al.*, 2004). Complex interactions and varying levels of drug resistance within and among countries have posed serious challenges to instituting a new malaria treatment policy (WHO/UNICEF, 2003). Whilst the malaria drug regimen change is delayed, the mosquito vectors are actively transmitting resistant parasites to affected populations (Buckling *et al.*, 1997; WHO 2006). This increases the chances of asymptomatic carriers resulting in illness and deaths in patients due to the ineffective prescription of medication (Zucker *et al.*, 2003).

1.1.3 What is the importance of this study?

During 1985 to 1988 and 1997 to 2001, the burden of malaria in KwaZulu-Natal increased multi fold compared to previous years. This was attributed to high rates of chloroquine resistant *Plasmodium falciparum* parasites in the 1980s and sulphadoxine-pyramethamine resistance *P. falciparum* in the 1990's together with insecticide resistance of the Anopheles mosquito vector in the community (Craig *et al.*, 2004). The malaria epidemics could also have been exacerbated by the delayed replacement of the recommended first line antimalarial treatments, which were already ineffective against the resistant malaria parasites. This study examined the increased morbidity and mortality due to malaria associated with the late replacement of recommended first line antimalarial medications.

1.1.4 How the study will solve the problem?

A range of studies have analysed the public health impact of using resistant antimalarial drugs against resistant *Plasmodium falciparum,* as well as issues around the changing policy of malaria parasite resistant drugs (Bredenkamp *et al.,* 2001; Laximinarayan, 2004; Nuwaha, 2001; Trape, 2001; 1998; White, 1999; Williams *et al.*, 2004; Zucker *et al.,* 2003). Little is published, however, on antimalarial treatment policy change, factors involved in policy change and the time taken to effect the change. No studies have indicated the duration taken to change malaria drug policy and its probable epidemiological implications. The findings of this study will provide evidence on the implications of late replacement of malaria drugs to key stakeholders, researchers and policy-makers. It emphasises the importance of prioritizing the lives of people when making decisions as to when policy changes need to be introduced.

1.2 STATEMENT OF THE PROBLEM

Some delays in changing failing antimalarial drugs regimens may have occurred on the African continent. The impact of these delays has not been adequately analysed. Research has reported on the nature of drug resistance, the effect on individuals of using chloroquine and sulphadoxine-pyramethamine after their efficacy in treatment has been nullified, on malaria control and on *in vivo* and *in vitro* drug resistance patterns. This study examined whether increased morbidity and mortality notified during the antimalarial treatment policy change processes in KwaZulu-Natal, South Africa were exacerbated by delays in the replacement of resistant antimalarial drugs.

1.2.1 Research Hypothesis

Policy delays in the introduction of sulphadoxine-pyramethamine and artemether-lumefantrine as new first line antimalarial therapy led to increased morbidity and mortality due to malaria during the change phases 1985 to 1988 and 1997 to 2001 respectively in KwaZulu-Natal.

1.2.2 Research Questions

- What proportion of reported malaria cases died during the chloroquine policy change phase (1985-88) and during the sulphadoxine-pyramethamine change phase (1997-2001)?
- What proportion of reported cases of malaria died during the baseline phase before the detection of malaria resistance to chloroquine (1982-85) and before resistance to sulphadoxine-pyramethamine was recognized (1993-1997)?
- What was the annual malaria morbidity risk during the phase of chloroquine policy change (1985-88) and during the sulphadoxine-pyramethamine change phase (1997-2001)?
- What was the annual malaria morbidity risk during the baseline phase before detection of chloroquine resistant parasites (1982-85) and before detection of sulphadoxine-pyramethamine resistance (1993-1997)?
- How long did it take to change the malaria treatment policy in the two periods?
- What recommendations concerning the malaria drug policy change should be given to health policy-makers, researchers and other stakeholders?

1.3 PURPOSE OF THE RESEARCH

The purpose of this study was to determine the impact of policy delays in the introduction of sulphadoxine-pyramethamine and artemether-lumefantrine as first-line drugs for malaria treatment in KwaZulu-Natal from (1985-88) and (1997-2001) respectively.

1.4 SPECIFIC OBJECTIVES OF THE RESEARCH

- To compare the reported incidence risk of malaria infection, mortality risk and case fatality risk in the baseline phases 1982 to 1985 before the detection of chloroquine resistant *P. falciparum;* 1993 to 1997 before the detection of sulphadoxine-pyramethamine resistance; during the phase of chloroquine antimalarial treatment regimen policy change (1985-88) and during the phase of sulphadoxine-pyramethamine treatment regimen policy change (1997-2001) respectively.

- To measure the time taken to effect the antimalarial treatment policy changes from chloroquine to sulphadoxine-pyramethamine and from sulphadoxine-pyramethamine to artemether-lumefantrine.
- To suggest recommendations to policy makers, health managers and health researchers

1.5 *ASSUMPTION UNDERLYING THE STUDY*

Studies reveal that delayed initiation of chemotherapy or other control interventions for a particular disease could result in an increased health burden from that disease (Budzar *et al.,* 1982; Heath *et al.*, 1996; Lodise, 2003). Delay in starting treatment especially against infectious disease increases the reservoir of disease, transmission to others, severity, complications and result in an increased cost in managing the condition (WHO, 2006; Spracklen and Whittaker, 1984; Greenwood *et al.,* 1987). In the worst case scenario, the patient dies. Delayed treatment in nosocomial infections was found to be an independent risk factor for related mortality (Lodise, 2003). Similarly, Heath *et al.,* (1996) found a significant association between delayed initiation of therapy and mortality among *Legionella* pneumonia patients. In the same way, the delayed introduction of newer and effective antimalarial drugs in the population especially in malaria endemic populations will inevitably lead to higher morbidity and mortality in the presence of *P. falciparum* resistance.

1.6 *OPERATIONAL DEFINITIONS USED IN THE STUDY*

Delayed introduction of antimalarial drugs / Change policy phase: This is the phase when replacement of failing antimalarial drug should have taken place. The change process begins when greater than 5% *Plasmodium* resistance is detected in the population and continues until the new therapeutic policy is fully introduced. More than 5% resistance is considered by WHO (2001) as an "alert period". This is the time when the process of change should be set in motion and discussions on the rate of change of drug efficacy to the current first-line drug and the timing of any change in policy be initiated. The change phase for chloroquine was February 1985 to January 1988 and for sulphadoxine-pyramethamine was February 1997 to January 2001.

Baseline phase: The phase when little or no *P. falciparum* resistance to antimalarial drugs was found. The baseline phase for chloroquine in this study was from February 1982 to January 1985 while that for sulphadoxine-pyramethamine was from February 1993 to January 1997.

Antimalarial drug resistance: is 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 (WHO 2001)

Antimalarial treatment policy: is a set of recommendations and regulations concerning the availability and rational use of antimalarial drugs in a country (WHO 2001).

Morbidity risk: is the number of new cases of a particular disease in a particular population during a particular time interval (DOH, KZN 2000).

Mortality risk: is the number of people dying from a particular disease during a given time interval, divided by the total number of people in the population (DOH, KZN 2000).

Malaria cases: a person who is found to have malaria parasites in his/her blood (DOH, KZN 2000).

Uncomplicated malaria case: A person presenting with a history of fever or having fever (axillary temperature >35°C and < 41°C) rigors and headache and confirmed as a malaria case (DOH, KZN 2000).

Active case-finding: When malaria control personnel actively test individuals in a malaria risk area to identify those with asymptomatic or mildly symptomatic disease (DOH, KZN 2000).

Surveillance: The collection of information in order to take early and appropriate action. The continuing watchfulness of occurrence and spread of disease that is pertinent to effective control (DOH, KZN 2000).

***In vivo* study**: The assessment of clinical and parasitological outcomes of treatment over a certain period following initiation of treatment, to check for the reappearance of parasites in the blood (WHO 2006).

***In vitro* study**: Study on the collected parasitized blood from patients and testing of parasite susceptibility to drugs in culture.

Treatment failure: A person with uncomplicated malaria who has taken a full course of antimalarial treatment and still presents at any time between 7 and 28 days after the start

of treatment with asexual forms of *P. falciparum,* in the absence of re-infection (DOH, KZN 2000

Case-fatality risk: The number of persons diagnosed as having a specific disease that die as a result of the illness, expressed as a percentage in a defined period (DOH, KZN 2000).

Passive case finding: When malaria diagnosis is confirmed by blood tests taken from persons presenting themselves at health facilities for whatever reasons (DOH, KZN 2000).

1.7 *SCOPE OF THE STUDY*

- The malaria morbidity and mortality data for KwaZulu-Natal available for the period 1982 to 1987 and 1993 to 2001.
- Secondary data was used to determine the mortality and morbidity data due to malaria.

2 CHAPTER 2: LITERATURE REVIEW

2.1 *PURPOSE OF THE LITERATURE REVIEW*

This chapter intends to explore issues around delayed introduction of sulphadoxine-pyramethamine and artemether-lumefantrine as first line drugs in malaria. These factors include the magnitude of *Plasmodium falciparum* resistance, incidence and prevalence associated with malaria resistance, malaria mortality and morbidity and factors associated with policy change and its delay in the introduction of new malaria drugs.

2.2 *SCOPE OF LITERATURE REVIEW*

Two methods were used in the literature search.

1) Printed materials such as journals and books. A search of the medical library of the University of KwaZulu-Natal, and materials from Medical Research Council, Durban.
2) Internet based search using Pub Med, Google-scholar and health related sites such as the WHO website.

Literature was also obtained from related studies cited in previous publications by authorities on malaria epidemiology. The search terms were "resistant malaria", "sulphadoxine-pyramethamine", "chloroquine", "artemether-lumefantrine", "malaria policy change", "malaria", "late replacement of malaria drugs". Only studies conducted in Africa and Asia were included in the literature review.

2.1.1 Theoretical Application

This section demonstrates the effect of trying to control malaria with continued use of ineffective drugs.

2.1.1.1 Concepts/ theories

The World Health Organization (WHO, 2006) stated that continued use of failing drugs would confer a selective transmission advantage to resistant parasites, which will lead to

high rates of transmission of drug resistant parasites. This could be due to two mechanisms. Firstly, higher numbers of circulating gametocytes would occur in those with resistant infections and secondly, gametocytes carrying resistant genes would be more infectious to mosquitoes, produce higher densities of parasites (oocytes) and infect more mosquitoes than parasites with drug sensitive genes (WHO, 2006).

To test the hypothesis that malaria infections treated with a sub-curative dose of chloroquine showed an earlier peak and a greater rate of gametocyte production relative to untreated controls. An experiment was conducted by Buckling *et al.* (1997) using a rodent malaria (*Plasmodium chabaudi*) model. It was observed that chloroquine treatment had a significant effect by reducing asexual parasitic stages to 20% of the control level and gametocytes to 50% of the control. The index of gametocytogenesis increased by 2.5 times when sub-curative levels of chloroquine treated infections than in control infections, with the peak gametocyte densities occurring approximately two or three days earlier in this group than in control infections. The proportion of mosquitoes infected were greater in chloroquine treated mice than control mice on day 6, but overall, no significant difference was found in mosquito infection (Buckling *et al.,* 1997). This experiment demonstrated that both the treated and untreated malaria infections have the same effect of continued transmission of malaria parasites in the population. Perhaps, initiation of a new and effective treatment could alleviate this dire situation.

2.1.2 Conceptual Framework

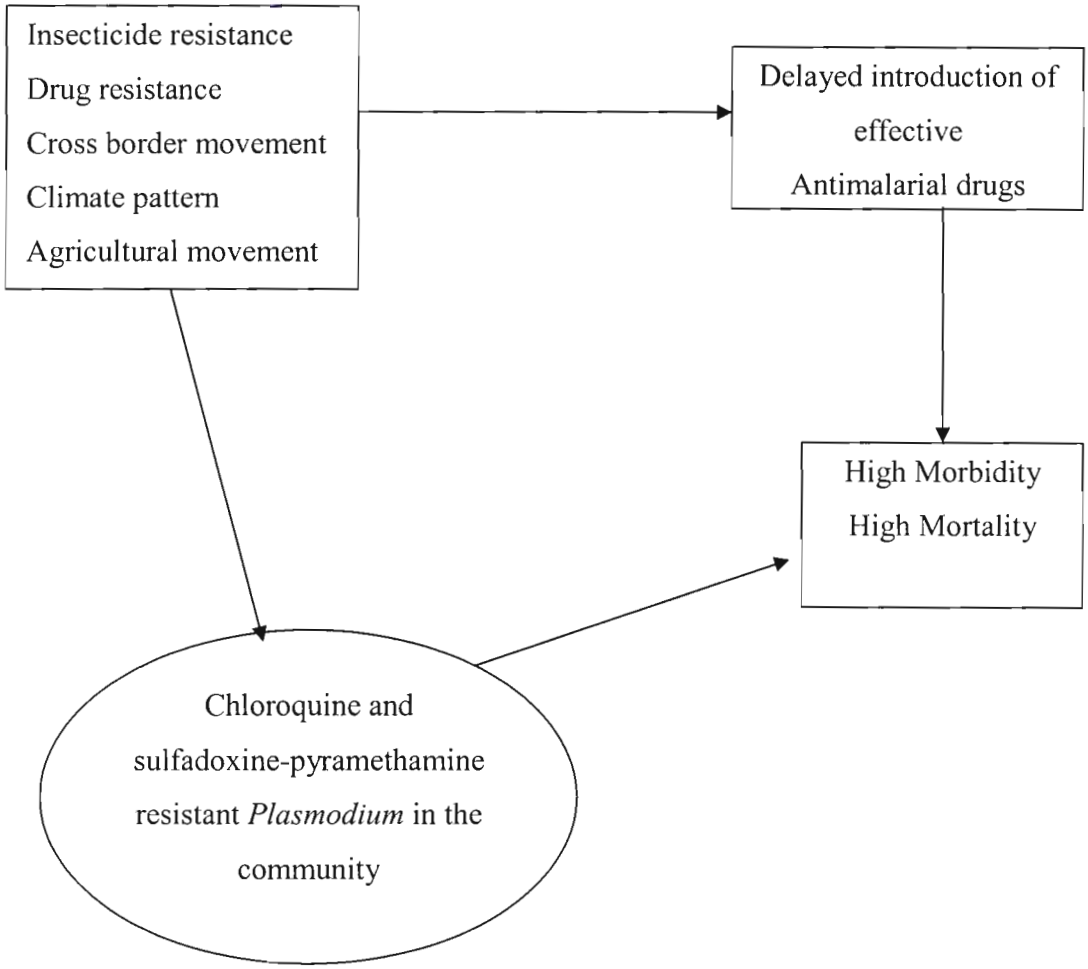

Figure 1: Conceptual framework of this study

Resistant *Plasmodium falciparum* enters the population and continues to spread through insect vectors (figure 4). The degree of such a development depends on the level of its resistance to antimalarial drugs and the availability of a population of insect vector. If people become infected and no effective drug to reduce infection exists, then infected vectors can transmit the infection to other persons in the population, thereby increasing the infected reservoirs in the population. If the mosquito vectors become resistant to insecticides and continue their activities of transmission of resistant parasites in

communities, the possibility of an increased diffusion of the parasite can be enhanced. Climatic factors and agricultural development can create a favourable breeding environment for the malaria vector. A warm, humid climate and water bodies provide the optimal environment for the multiplication of mosquitoes. As the environment (climate, agricultural factors) favours the breeding of insect vector, the insecticides formulated to reduce the vector populations fail and the mosquitoes increase transmission of the resistant *Plasmodium* in the population. Hence, any delay in the initiation of new antimalarial drugs exacerbates the extent of malaria infection in populations by increasing the resistant parasitic human reservoir, worsens the clinical condition, and may lead to the death of such patients.

2.3 LITERATURE REVIEWED

The first section describes the magnitude of malaria problems in Africa. The second section covers the change of malaria policy and time related change issues. The effect of malaria policy change is presented in the last section of the literature review.

2.3.1 Malaria Resistance

In 2003, the World Health Organisation estimated that 300-500 million cases of malaria occurred in the world. Up to 90% occur in Africa and poor African children are the most affected. Malaria is the leading cause of under-five year old deaths in Africa (WHO 2003). The malaria burden is understood to be associated with resistance of *P. falciparum* to antimalarial drugs (Trape *et al.,* 1998; 2001; Nuwaha, 2001; Kindermans *et al.,* 2002; Laxminarayan R, 2004). Interaction between drug use patterns, the characteristics of the drug itself, human host factors, parasite characteristics and vector and environmental factors are associated with development and spread of drug resistance in the population (Wongsrichanalai *et al.,* 2002). There are some suggestions that the *P. falciparum* resistance to the two most affordable antimalarial drugs, namely chloroquine and sulfadoxine-pyramethamine, may contribute to increased malaria morbidity and mortality in recent years. It has been established that insect resistance to insecticides contributed to the huge malaria burden of the late 1990s (Maharaj, 2005; Craig *et al.,* 2004).

In a study conducted in Kenya before and after the introduction of new antimalarial drugs, Zucker *et al. (*2003) demonstrated that the continued use of chloroquine in areas with resistance increased the case-fatality three fold when compared to using an effective treatment regimen. Similarly, in southern and eastern Africa the mortality due to malaria in children under five years doubled between 1990 and 1998 (Global Fund to Fight HIV/AIDS, TB and Malaria, 2005). In a prospective study, Trape *et al. (*1998) reported malaria specific mortality among three rural populations in Senegal. The risks of malaria death after emergence of chloroquine resistance among children aged (0 to 9 years of age) in the three populations were increased by 2.1, 2.5 and 5.5, respectively. Serial in vitro and in vivo tests for chloroquine sensitivity test of *Plasmodium falciparum* carried out from 1979 to 1982 by Draper *et al.* (1985), reported that chloroquine resistance in children increased markedly in 1982 in East Africa.. Chloroquine resistant parasites are more likely to be gametocyte-positive than infections of sensitive parasites (Buckling *et al.,* 1997). There is a higher probability of transmission during treatment with sub curative doses of antimalarial drugs.

2.3.2 Change in malaria treatment policy

Chloroquine resistance in Kenya began in the late 1970s (Shretta *et al.,* 2000; Nuwaha, 2001 and escalated in the 1980s. Antimalarial treatment policy change was only initiated in 1998 despite the fact that 50% of studies conducted in 1995 showed high levels of parasitological failures (Shretta *et al.,* 2000).

Similarly, in Tanzania, chloroquine resistance was first detected in 1981 (Nuwaha, 2001; Mubyazi, 2003; Williams *et al.* 2004) however, a the vital meeting where it was decided to change the malaria policy was only conducted in 1999 despite evidence of nearly 20 years of parasite resistance in East Africa.

Uganda documented its first chloroquine resistance in 1988 but only adopted a new, temporary malaria treatment policy in 2000 (Kamya *et al.,* 2002). It finally introduced

Artemisinin-based combination therapy in 2006 after documenting 12.5 million cases of malaria in 2005 (Omony, 2006).

Ethiopia first became aware of its first malaria resistance in 1986, and studies conducted between 1991 and 1996 indicated high levels of resistance to chloroquine, but a change of drug policy was only effected in 1999 (WHO, 2001).

In KwaZulu-Natal, South Africa, malaria cases began to rise in 1995 due to sulphadoxine-pyramethamine resistance but drug change to artemether-lumefantrine was officially announced in February 2001.

The inability of most scientific papers to quantify the public health cost of the late introduction of antimalarial drugs in the population seems to be a major shortcoming. In their perspective, Guerin *et al.*, (2002) noted that the inadequacy of epidemiological data was a factor preventing policy change that would result in the deployment of new and effective first line malaria treatment policy.

2.3.3 Effect of antimalarial treatment policy change

The World Health Organisation has indicated that the early and effective treatment of malaria symptoms would save many lives (WHO/UNICEF, 2003). Greenwood *et al.*, (1987) suggested that children under five years who begin treatment within 24 hours of the onset of malaria symptoms prevent the progression to severe disease or death. Studies have shown that huge gains are observable whenever new and effective antimalarial drugs are introduced in a population in terms of morbidity and mortality (Craig *et al.*, 2004; Barnes *et al.*, 2005). In Thailand, the frequency of malaria mortality declined from 200/1000 to 20/1000 persons in 1973 when it changed from chloroquine to sulphadoxine-pyramethamine treatment policy due to resistance of malaria to chloroquine (Nuwaha, 2001). Similarly, a 15% child mortality reduction was noted in Malawi in 1993 when malaria treatment policy was changed from chloroquine to sulphadoxine-pyramethamine (WHO/UNICEF, 2003). In Kenya, children receiving effective antimalarial drugs had two-thirds lower post-hospitalisation mortality than children who were treated with an

ineffective therapy (Zucker *et al.*, 2003). It is essential that change in the malaria treatment policy in this era of persistent resistance should be considered seriously in achieving the gains of applying public health solutions.

Table 1 Drug Resistance across Some Sub-Saharan African Countries

Regimen	Year	Country	Test	% Resis-tance	Reference
Chloroquine	1988 - 1995	Uganda	In vivo	25	Kamya *et al.*, 2002
Fansidar	1998	Uganda	In vivo	11	Kamya *et al.*, 2002
Chloroquine	1999	Tanzania		52	Mubyazi, 2003
Chloroquine	1997 - 1998	Ethiopia	In vivo	65	WHO, 2001
Chloroquine	1990	Malawi	In vivo	83	WHO, 2001
Fansidar	2001	Malawi	In vivo	25	WHO, 2001
Chloroquine	1986	DRC	In vitro	82	Ngunyen-Dinh *et al.*, 1985

3 CHAPTER 3: METHODS

3.1 INTRODUCTION

This chapter introduces the methodology adopted in this study on the delayed introduction of antimalarial treatments. The research population, study design, data sources, variables involved, reliability and validity of the data, bias and control, data management and ethics of the study are described.

3.2 TYPE OF RESEARCH

This is epidemiological research.

3.3 STUDY DESIGN

An observational, analytical ecological study design was used to investigate delayed introduction of antimalarial drugs in KwaZulu-Natal, South Africa. Time-trend malaria incidence data within the study area were compared to changes in malaria drug resistance patterns of *Plasmodium falciparum*. The unit of observation was the community or population.

3.4 STUDY POPULATION

The study population lives in the north-eastern part of KwaZulu-Natal South Africa, The study site stretches from Mozambique in the north to uThungulu in the south. It is bordered by the Zululand district in the west and Swaziland in the north-west. This area contributes the highest number of malaria cases in South Africa. The size of the study population was estimated from the available population data. An average population was calculated for each phase of the study. The population of the area were obtained from the KwaZulu Natal malaria control programme records and the 1996 and 2001 census conducted by the Stat SA.

3.4.1 Exposure and outcome variables

The outcome variable consisted of anonymous and non-linked malaria data, obtained from the Medical Research Council malaria database.

The exposures were divided into four groups. From the literature, it was assessed that the chloroquine baseline phase was before 1985, when *Plasmodium* resistance to chloroquine was less than 5%. The change phase between 1985 and 1988 corresponded to the time when according to the reported literature greater than 5% of *Plasmodium* was resistant to chloroquine.

Likewise, the period when sulphadoxine-pyramethamine was the drug of choice was divided into a baseline (1993 to 1997) and a change phase (1997 to 2001).

3.5 DATA SOURCES

The malaria morbidity and mortality data was sourced from the Medical Research Council Malaria Notification Database. The population of north-eastern KwaZulu-Natal was obtained from Statistics South Africa (Stats SA 1996, 2001) and the Department of Health.

3.5.1 Variables

The malaria morbidity and mortality data were reported according to the gender and age of patients.

3.5.2 Reliability and Validity of Data Source

Malaria data is based on notification of cases by healthcare workers. Compulsory notification of malaria was instituted in 1958 South Africa. Two methods are used to collect malaria data; passive methods apply when patients are notified after voluntarily

visiting either private or public hospitals, clinics or health centres and the diagnosis is confirmed malaria through either microscopy or rapid tests. Active case finding involves cases notified from house-to-house surveys, epidemiological surveillance, and special malaria surveys. Deaths were not always verified through a post-mortem. All malaria notifications at a local level are referred to the provincial and national units of the local Department of Health.

3.5.3 Bias and Limitations

Information and selection bias may have occurred, as the study could not ascertain the exact month in which the level of *Plasmodium* resistance reached 5%. Since there was no clear level of malaria resistance at which the malaria treatment policy should change, the study used available literature to decide on the probable time when the replacement of antimalarial drugs should have taken place which corresponds to when the malaria cases reported start to rise significantly. At first malaria resistant study that identified greater than 5% resistance in each regimen, there was sharp increase at the malaria cases reported at the period. This was taken as a greater than 5% level of chloroquine resistance for delayed introduction of sulphadoxine-pyramethamine and greater than 5% level of resistance to sulphadoxine-pyramethamine for delayed introduction of artemether-lumefantrine. The malaria studies identified in selecting this might not have complied with the necessary standard for assessing malaria resistance.

Mortality data for the sulphadoxine-pyramethamine baseline phase 1993 to 1995 was not available. This factor could obscure the precise effect of deaths due to malaria. The 1995/1996 malaria season data was thus employed to estimate average mortality for the sulphadoxine-pyramethamine baseline phase.

The available population figures for the 1980s may not be reliable, but extrapolations were made from the available population figures for the region.

The study could not account for confounders and interactions that might have influenced the measures of association calculated. This was an ecological study using population data non-linked to patients. Data was not verified from patients' medical records. Though every effort was made to minimise bias, the findings of the study need to be interpreted with caution as the findings may reflect the ecological fallacy.[1]

3.5.4 Statistical methods

The data were sorted and analysed using EXCEL spreadsheets and Stata 9.2 for Windows statistical analysis software package. Relative measures of association were calculated with 95% confidence interval. Statistical significance was considered when $p < 0.05$.

3.5.4.1 Confounding and Effect Modifiers

Age:

Age is associated with malaria morbidity and mortality. Several studies have shown that malaria has its greatest impact on children. Other childhood diseases might exhibit identical signs and symptoms with malaria.

Human Immunodeficiency Virus / Acquired immune deficiency Virus (HIV/AIDS):

The national HIV seroprevalence survey conducted in 1990 estimated that 0.8% of pregnant women attending antenatal clinics in KwaZulu-Natal were HIV infected. This figure rose to 36% by 2000 (Department of Health 2001). There is a strong association between HIV and malaria, especially among antenatal women and children (Grinwade *et al.*, 2004; Witworth *et al.*, 2000; Parise *et al.*, 1998). Patients with malaria/HIV co-infections exhibit high parasitaemia and severe clinical malaria. The high prevalence of HIV in the community could lower the immunity of patients, leading to an increased burden of malaria.

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[1] It is an assumption in the interpretation of the statistical data whereby the inferences on individuals are based solely on the group.

Cross Border movement:

Cross border movement is a primary risk factor of malaria spread in KwaZulu-Natal, which borders with Mozambique (Craig *et al.,* 2004; Ngxongo 1993; Hansford 1989; Herbst 1985). Malaria control across borders poses a challenge for socio economic reasons. Asymptomatic travellers might harbour parasites in their blood system, which could then be transmitted to available insect vectors. Data has revealed that 48% of malaria diagnosed in endemic regions in KwaZulu-Natal originated from Mozambique (Department of Health, 2000). This factor could result in an escalation in the incidence of reported malaria cases in the region.

Agricultural development:

The presence of water bodies in the region could modify the insect vector dynamics. Irrigation systems from dams could provide possible breeding sites for the vector. The Jozini dam in the study area is among the largest irrigation dams in the country. Ngxongo (1993) indicated that irrigation schemes in the region modified malaria epidemiology.

Insecticide resistance:

Insecticide resistance could constitute a serious factor in the control of malaria. Mosquito populations could multiply by using ineffective insecticides, which could enhance resistant parasite transmission within a community. The failure of insecticide (pyrethroid) in the late 1990s was an example of how insecticide resistance affected insect population dynamics in KwaZulu-Natal.

Again, re-introduction of the DDT-based indoor spraying could also affect the population dynamics of mosquitoes that assisted in the reduction of the insect population and consequently contributed to the reduction of malaria infection in early 2000.

Case reporting:

Data reporting and collection is pivotal in disease epidemiology. Any incomplete completion of notification forms and under-reporting of notifiable diseases could hamper the control programme and endanger human life especially during epidemics. Similarly, over reporting could alter the perception of the disease in communities.

3.5.4.2 List of association to be measured

The relative association of malaria infection comparing the chloroquine baseline and change phases and the sulphadoxine-pyramethamine baseline and change phases were calculated. This measure of association compared the rate of malaria infections between the unexposed phases (1982 to 1985 and 1993 to 1997) and the exposed phases (1985 to 1988 and 1997 to 2001). It was measured at a 95% confidence interval with statistical significance at 0.05.

3.6 ETHICS

Ethical approval was obtained from the Biomedical Research Ethics Committee of the College of Health Sciences, University of KwaZulu-Natal, South Africa (Reference number EXP 003/06)

Children (under 15 years) consistently constituted the largest number of malaria cases and accounted for 52% of the notified cases in the baseline phase of this period (Table 2). More than half (57% - 679) of the malaria cases in the 3-year baseline were females (Table 3).

During the chloroquine change phase (1985 /86 to 1987/88), 7 895 malaria cases were notified. [3] The majority of cases (78%) (6 112) were reported in the 1987/88 malaria season of the chloroquine change phase and showed a significant increase (p for trend <0.001). The overall malaria incidence risk rose from 512 to 2 824 per 100 000 in this change phase. The age and gender specific proportion of cases did not change significantly between the baseline and change phases in this period (p =0.15 and p = 0.16 respectively).

The annual incidence risk increased from 106 for 100 000 persons in 1982/83, the first malaria season of the baseline, to 2 824 for 100 000 persons in 1987/88, the last malaria season of the change phase. The average annual incidence risk for the baseline phase increased from 271 per 100 000 to 1217 per 100 000 (p <0.001) in the change phase (Table 4). The overall risk of malaria infection in the population during the chloroquine period was 4.5 times (Incidence Risk Ratio 4.5; 95% Confidence Interval: 4.1 to 5.0; p<0.001) higher in the change period than in the baseline phase (Table 3).

The overall, age and gender specific incidence risk exhibited a statistically significant increased trend over time for all these particular subcategories (p for trend <0.001) (Figure 2). The relative association between the baseline and change phase was not significantly different between females and males (Table 3).

4.2.2 Malaria mortality during the chloroquine baseline and change period

Seventy three deaths were notified to the Department of Health between 1982/83 and 1987/88 with most (56) recorded in the sixth malaria season (Table 4). During the

[3] Age was reported in 7 895 cases

chloroquine baseline period, the mortality risk was relatively constant (1 death per 100 000 population) (Figure 3). During the change period the mortality risk increased from 1 death per 100 000 populations to 26 deaths per 100 000 (p for trend <0.001). The mortality risk in the chloroquine baseline phase was 1 death per 100 000 in 1985/86 and this figure rose to 10 deaths per 100 000 persons in the 1987/88 malaria season (Incidence Risk Ratio = 10.0; 95% Confidence Interval: 1.3 to 78.1) (Table 4). The average mortality risk was 9.1 times higher between the chloroquine baseline and change phases within this period (Incidence Risk Ratio = 9.1; 95% CI: 2.1 to 38.5; p <0.001).

4.2.3 Case fatality rate during the chloroquine baseline and change phase

The case fatality risk increased from 0.3% in 1986/87 to 0.9% in the 1987/88 malaria season. The average annual case fatality risk was 0.5% and 0.7% in the baseline and change phases respectively (Table 4). The incidence risk ratio of malaria patients dying in the change phase compared to the baseline phase was 1.3 (95% CI: 1.0 to 1.7; p< 0.001).

Table 2: Age-specific number of malaria cases reported during the chloroquine baseline and change phases in north-eastern KwaZulu-Natal, South Africa (1982/83 to 1987/88 malaria seasons).

	Age Group (years)			
Malaria Season	**0 to 14**	**15 to 35**	**> 35**	**Total**
1982/83	86	78	24	188
1983/84	199	125	73	397
1984/85	447	296	84	827
Total	**732**	**499**	**181**	**1412**
Average (3 year)	244	166	60	471
p for trend	< 0.001	< 0.001	< 0.001	< 0.001
1985/86	622	391	99	1112
1986/87	343	248	80	671
1987/88	2928	2268	916	6112
Total	**3893**	**2907**	**1095**	**7895**
Average (3 year)	1298	969	365	2632
p for trend	< 0.001	< 0.001	< 0.001	< 0.001

Table 3: Gender specific number of malaria cases and incidence risk (IR) per 100 000 population reported during the chloroquine baseline and change phases in north-eastern KwaZulu-Natal, South Africa (1982/83 to 1987/88 malaria seasons)

	Gender					
	Male		Female		Total	
Year	**Cases**	**I R**	**Cases**	**I R**	**Cases**	**I R**
1982/83	88	110	101	103	189	106
1983/84	176	220	221	226	397	223
1984/85	356	439	501	511	853	479
Total	**616**	**769**	**823**	**840**	**1439**	**808**
Average (3 years)	205	256	274	280	480	269
p for trend		< 0.001		< 0.001		< 0.001
1985/86	438	450	670	563	1108	512
1986/87	249	247	426	358	675	312
1987/88	2487	2556	3620	3044	6107	2824
Total	**3174**	**3253**	**4716**	**3965**	**7890**	**3648**
Average (3 years)	1058	1084	1572	1322	2630	1216
p for trend		< 0.001		< 0.001		< 0.001
Incidence Risk Ratio (95% CI)		**4.2** (3.7 to 4.9)		**4.7** (4.2 to 5.4)		**4.5** (4.0 to 5.2)

Table 4: Annual malaria incidence risk, mortality risk (per 100 000), case-fatality risk (%), risk ratios reported during the chloroquine baseline and change phases in north-eastern KwaZulu-Natal, South Africa (1982/83 to 1987/88 malaria seasons)

Malaria Season	*Cases*	*Deaths*	*Mid-phase Population*	*Incidence Risk*	*Mortality Risk*	Case Fatality
1982/83	190	1		107	1	0.5
1983/84	397	2		228	1	0.5
1984/85	853	4		479	2	0.5
Total	**1440**	**7**		**814**	**4**	**1.5**
Average (3 years)	480	2	178155	271	1	0.5
p for trend				<0.001	<0.001	<0.001
1985/86	1112	8		514	4	0.7
1986/87	675	2		312	1	0.3
1987/88	6112	56		2826	26	0.9
Total	**7899**	**66**		**3652**	**31**	**1.5**
Average (3 years)	2633	22	216250	1217	10	0.7
p for trend				<0.001	<0.001	<0.001
Incidence Risk Ratio (95% CI)				**4.5** (3.9 to 5.1)	**10** (1.3 to 78.1)	**1.3** (1.0 to 1.7)

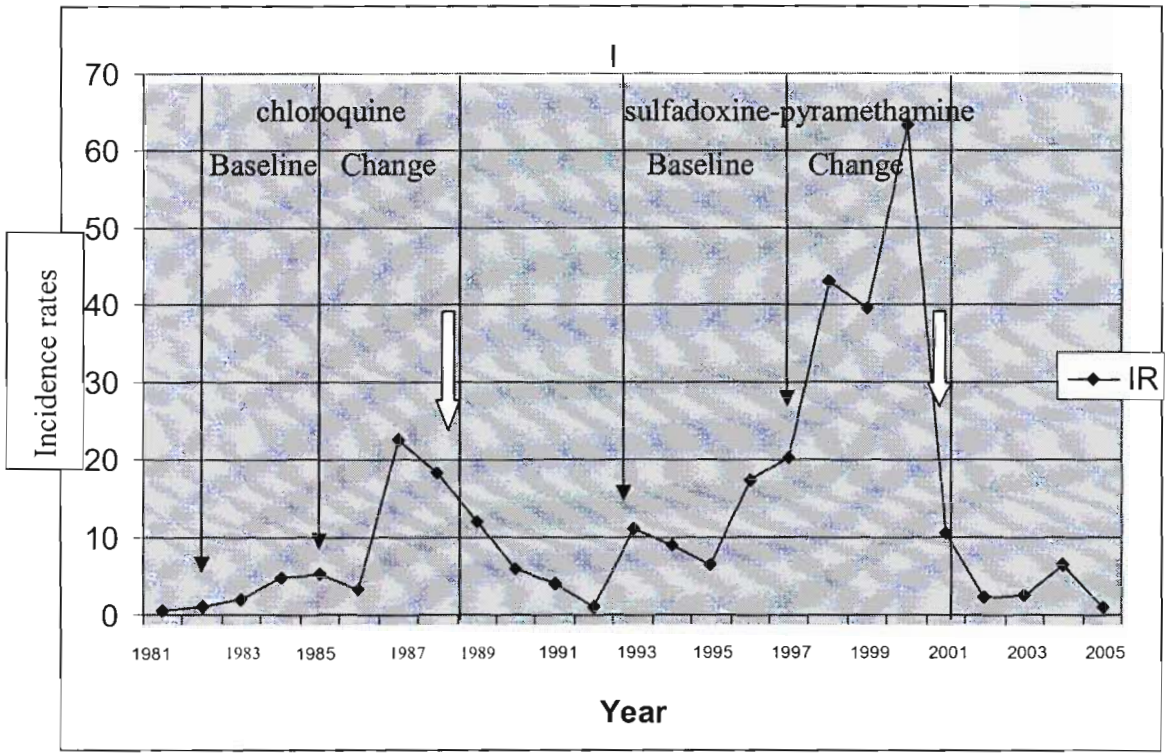

Figure 2: Annual malaria incidence risk per 100 000 during the baseline and change phases of the chloroquine and sulphadoxine-pyramethamine periods in KwaZulu-Natal from 1981/82 to 2004/5 malaria seasons.

{NOTE: The thick arrows indicate the point of new antimalarials introduction as well as the end of the change phase}:

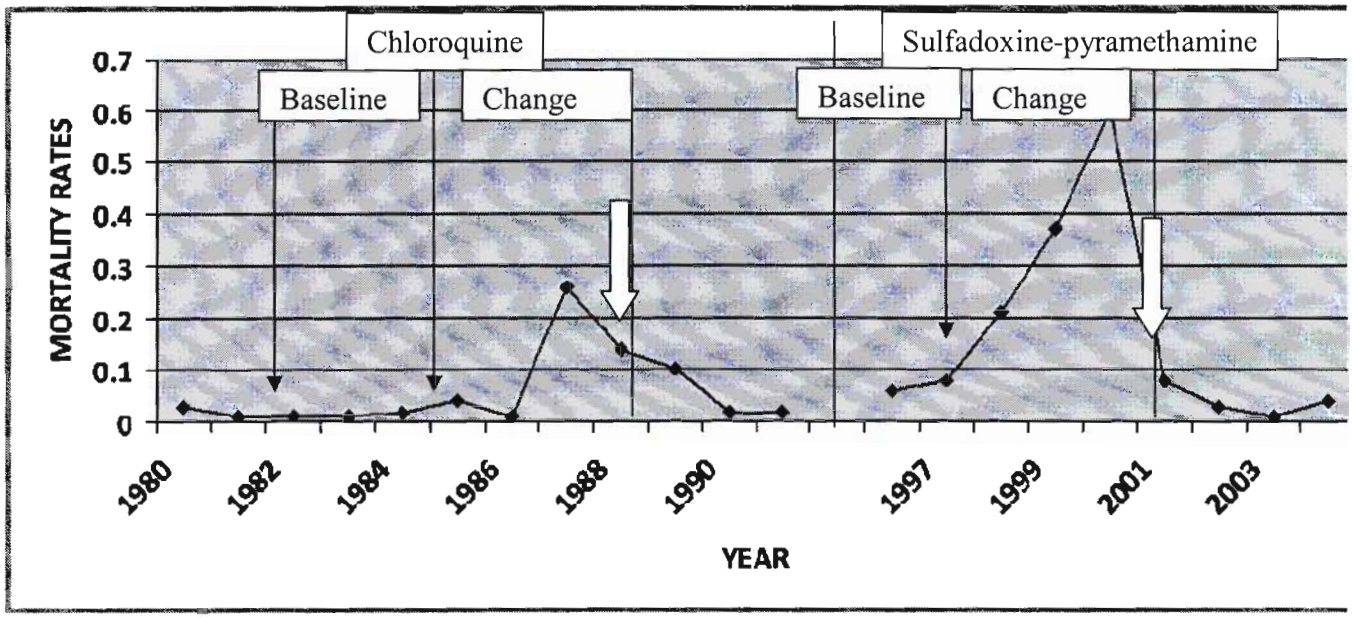

Figure 3: Annual malaria mortality risk per 100 000 people during the baseline and change phase of the chloroquine and sulphadoxine-pyramethamine periods in KwaZulu-Natal from the 1981/82 to the 2004/5 malaria season.

{NOTE: The thick arrows indicate the point of new antimalarials introduction as well as the end of the change phase}:

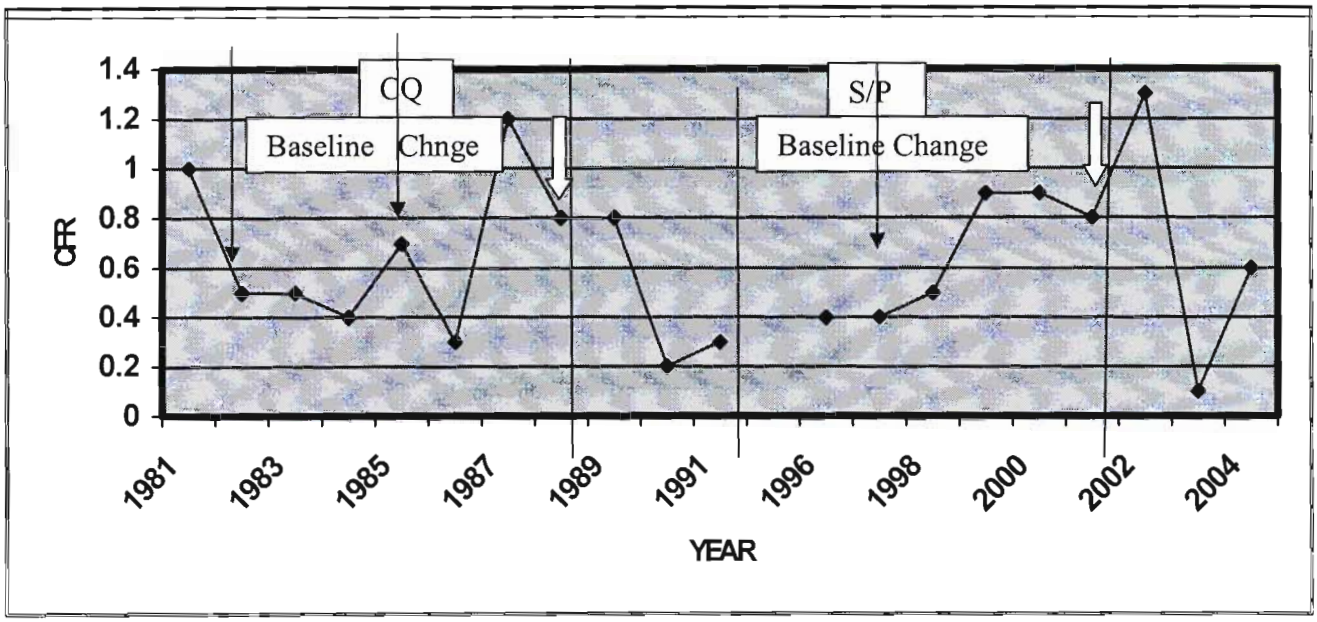

Figure 4: Annual malaria case fatality risk (%) during the baseline and change phases of chloroquine and sulphadoxine-pyramethamine period in KwaZulu-Natal from the 1981/82 to the 2004/5 malaria season.

{NOTE: The thick arrows indicate the point of new antimalarial introduction as well as the end of the change phase}:

4.3 Sulphadoxine-pyramethamine to artemether-lumefantrine treatment period (1993/94 to 2000/01 malaria seasons)

4.3.1 Reported malaria during the sulphadoxine-pyramethamine baseline and change phases.

A total of 22 764[4] malaria cases were reported to the Department of the Health in KwaZulu-Natal during the baseline phase of the sulphadoxine-pyramethamine period. During the sulphadoxine-pyramethamine baseline phase, the number of cases increased significantly from 5520 (24% of total) in 1993/94 to 9 327 (41%) in the 1996/97 malaria season (p for trend <0.001). This reflects an increased malaria incidence risk from 1112 to 1879 per 100 000 between these two malaria seasons. The average annual incidence risk rose from 1140 in the baseline phase to 4000 per 100 000 in the change phase of this period.

As in the chloroquine to sulphadoxine-pyramethamine treatment period, children constituted 46% of total malaria cases (Table 5). The average annual incidence risk in children increased from 1325 in 1993/94 to 1996/97 baseline phase to 4206 per 100 000 in the 1997/98 to 2000/01 sulphadoxine-pyramethamine treatment period.

The proportion of malaria cases among females increased from 55% in the baseline period to 58% (p<0.001) in the change phase (Table 6). The average annual incidence risk in females increased from 1190 per 100 000 in the 1993/94 to 1996/97 baseline phase to 4 245 per 100 000 females in the 1997/98 to 2000/01 malaria season. The relative risk of suffering from malaria was 3.5 times higher in the change relative to the baseline phase (Incidence Risk Ratio = 3.5; 95% CI: 3.3 to 3.8. No relative gender difference was discernible between different phases in this period.

[4] 22 762 and 22 725 were correctly reported for age and gender groups respectively

Although the average incidence risk in children was highest, the relative risk of malaria infections between the baseline and change phases in this period were highest among adults older than 35 years (Incidence Risk Ratio =4.5; 95% CI: 4.1 to 4.9; p<0.001). In children, the incidence risk ratio was 3.2 (95% CI: 3.0 to 3.4; p< 0.001). The overall age and gender specific malaria incidence risk all indicated a statistically significant increasing trend over time across both phases.

The overall average malaria infection risk in the sulphadoxine-pyramethamine period was 1145 and 4026 per 100 000 populations in the baseline and change phases respectively. The risk of the malaria infection in the population was 3.5 (95% CI: 3.3 to 3.8) times higher in the change phase than in the baseline phase. Similarly, in the general population, the risk was the same in the population 3.5 times higher (95% CI: 3.40-3.60; p<0.001). The population experienced more malaria infection in the change phase than baseline **(Figure 2).**

The high risk of infection is consistent in the sulphadoxine-pyramethamine change phase across age and gender groups. Among the age groups of 0-14 and 15-35 years, the number of cases tripled in the sulphadoxine-pyramethamine change phase (Incidence Risk Ratio = 3.2; 95% CI: 33.0 – 3.3; p < 0.001) and (Incidence Risk Ratio = 3.5; 95% CI = 3.4- 3.7; p = 0.001) respectively. The highest relative change was recorded in the adult group (≥ 36 years) (Incidence Risk Ratio = 4.5; 95% CI: 4.2 to 4.8; p < 0.001). Malaria risk was significantly higher in the change phase across gender categories (Incidence Risk Ratio = 3.4; 95% CI: 3.3-3.6; p<0.001 and Incidence Risk Ratio = 3.6; 95% CI: 3.5 to 3.7; p<0.001) in the.

4.3.2 Malaria mortality during the sulphadoxine-pyramethamine baseline and change phase

Due to lack of malaria mortality data for the years (1993 to 1995) in this study, the mortality data for the malaria season 1996/97 was assumed to be the average malaria mortality for the whole baseline phase **(Table 7).** The number of deaths reported for

1996/97 was 32 and served as the average for deaths in the baseline phase. Malaria infection or death was also assumed to be highest during the last year of each period as seen in other data. Therefore, the deaths due to delayed introduction of artemether-lumefantrine increased from 32 in the 1996/97 to 342 in the 2000/01 malaria season. Malaria mortality between 1996 and 2001 indicated a peak in 2000 (Figure 3[5]). The annual mortality risk increased from 7 per 100 000 in the first malaria season (1997/98) of the change phase to 60 per 100 000 in the last malaria season (2000/01) of the change phase. The average malaria mortality risk in the baseline phase was 6 per 100 000 compared to 31 per 100 000 deaths in the sulphadoxine-pyramethamine change phase (Incidence Risk Ratio = 5.2; 95% CI: 2.2 to 12.4).

4.3.3 Malaria case fatality during the sulphadoxine-pyramethamine baseline and change phases

The average annual case fatality risk rose from 0.1% in the baseline phase to 0.8% in the change phase when sulphadoxine-pyramethamine constituted the first-line malaria treatments in north-eastern KwaZulu-Natal (Table 7). The average case-fatality rate ratio doubled (95% CI 1.5 to 2.7; $p < 0.001$) between the baseline and change phases of the sulphadoxine-pyramethamine treatment period.

[5] Figure 3: the second part of the graph shows the trend of malaria mortality during the use of sulfadoxine-pyramethamine. The graph depicts highest mortality at the year 2000. Although there were missing data under the "BL", mortality in 1996 indicates a low rate in the baseline phase.

Table 5: Age-specific malaria incidence per 100 000 populations reported during the Period use of sulphadoxine-pyramethamine in Northern KwaZulu-Natal, South Africa (February 1993 to January 2001).

	Age Group *(years)*							
	0 to 14		15 to 35		> 35		Total	
Year	Cases	I R	Cases	I R	Cases	I R	Cases	I R
1993/94	2655	1289	2096	1231	769	640	5520	1112
1994/95	2298	1115	1660	975	649	540	4607	928
1995/96	1470	713	1255	737	448	373	3173	639
1996/97	4497	2183	3301	1938	1529	1273	9327	1879
Total (1993/94 to 1996/97)	**10920**	**5302**	**8314**	**4881**	**3395**	**2826**	**22627**	**4558**
Average (4 years)	2730	1326	2079	1220	849	707	5657	1140
p for trend		< 0.001		< 0.001		< 0.001		< 0.001
1997/98	5354	2142	3954	2016	1870	1461	11164	1947
1998/99	10787	4327	8204	4183	3894	3048	22885	3991
1999/00	10747	4311	8618	4394	4087	3194	23452	4090
2000/01 a	15068	6045	12830	6542	6343	4957	34241	5972
Total a (1997/98 to 2000/01)	**41942**	**16825**	**33606**	**17135**	**16194**	**12655**	**91742**	**16000**
Average (4 years)	10486	4206	8402	4284	4049	3164	22936	4000
p for trend		< 0.001		< 0.001		< 0.001		< 0.001
Incidence Rate Ratio (95% CI)		3.2 (3.0 to 3.4)		3.5 (3.3 to 3.7)		4.5 (4.1 to 4.9)		3.5 (3.3 to 3.7)

Table 6: Gender-specific number of malaria cases and incidence risk (IR) per 100 000 populations reported during the sulphadoxine-pyramethamine baseline and change phases in north-eastern Northern KwaZulu-Natal, South Africa (1993/94 to 2000/01 malaria seasons)

	Male		*Female*		Total	
Year	**Cases**	**I R**	**Cases**	**I R**	**Cases**	**I R**
1993/94	2457	1053	3114	1183	5571	1122
1994/95	2089	895	2534	963	4623	913
1995/96	1415	606	1770	673	3185	642
1996/97	4236	1815	5110	1942	9346	1882
Total	**10197**	**4363**	**12528**	**4761**	**22725**	**4559**
Average (4 years)	2549	1091	3132	1190	5681	1140
p for trend		< 0.001		< 0.001		< 0.001
1997/98	4947	1917	6279	1991	11226	1958
1998/99	10320	4000	12602	3996	22922	3998
1999/00	9691	3756	13773	4366	23464	4092
2000/01	13739	5325	20901	6628	34640	6042
Total	**38697**	**14998**	**52555**	**16981**	**92252**	**16090**
Average (4 years)	9674	3750	13389	4245	23063	4023
p for trend		< 0.001		< 0.001		< 0.001
Incidence Risk Ratio (95% CI)		3.4 (3.2 to 3.7)		3.6 (3.3 to 3.8)		3.5 (3.3 to 3.8)

The estimated mid- baseline phase (1993 to 1997) was 496 492 and 573 353 for the change phase (1997 to 2001)

Table 7: Annual malaria incidence risk, mortality risk, case-fatality risk and risk ratios reported during the sulphadoxine-pyramethamine baseline and change phases in north-eastern KwaZulu-Natal, South Africa (1993/94 to 2000/01 malaria seasons)

Malaria Season	*Cases*	*Deaths*	*Estimated Mid-phase Population*	Incidence Risk	Mortality Risk	Case Fatality Risk
1993/94	5587			1120		
1994/95	4626			932		
1995/96	3198			644		
1996/97	9355	32		1884	24	0.34
Total	22766	32		4580	24	1.36
Average (4 years)	5692	8	496492	1145	6	0.34
1997/98	11248	38	573353	1962	7	0.34
1998/99	22950	112	573353	4003	20	0.49
1999/00	23488	214	573353	4097	37	0.91
2000/01	34640	342	573353	6042	60	0.99
Total	92326	706		16104	124	2.73
Average (4 years)	23082	177	573353	4026	31	0.68

5 CHAPTER 5: DISCUSSION

5.1 INTRODUCTION

In this chapter, the results are discussed and the main findings compared to other malaria endemic countries. The implications of the effect modifiers and confounders that may possibly have masked the real impact of the delayed introduction of antimalarial drugs are also discussed.

5.2 FINDINGS

This study showed that malaria infections in the endemic regions of KwaZulu-Natal increased significantly between the baseline and change phase, and within the change phase when both chloroquine and sulphadoxine-pyramethamine were the first-line malaria treatment policy. This study using an ecological study design suggests that the malaria epidemic is strongly associated with increasing drug resistance and delayed introduction of new and effective antimalarial drugs. Several studies have demonstrated that delay in starting treatment in infectious disease increases the reservoir, severity, complications and, hence, increases the cost of managing the disease (WHO, 2006; Spracklen and Whittaker, 1984; Greenwood *et al.,* 1987). Therefore, the provision of prompt and effective treatment to malaria patients is important in reducing transmission and morbidity. In immune suppression due to HIV, co-infection could lead to greater parasite densities, which result in greater infectiousness to feeding vectors, thereby increasing reservoirs for transmission (Witworth *et al.,* 2000; Craig *et al.,* 2004). Migration of individuals carrying resistant gametocytes has been an important way of spreading drug resistant parasites between different regions and countries. Migration is a risk factor in malaria resistance transmission (Ngxongo, 1993; Craig *et al.,* 2004). In his review article, Nuwaha 2001 noted that the initial resistance parasite originated in Kenya in 1977. Its further spread to other countries identified migration as a major factor in the spread of resistance.

In resource- constrained-and poor-health facilities, Bjorkman and Bhattarai (2005) demonstrated that selective admission of severely ill patients could increase morbidity and mortality among the non-seriously ill patients and lead to increased transmission in the community. Use of obsolete antimalarial therapy could result in ineffective treatment being dispensed at a health facility. This discourages early treatment seeking behaviour and encourages patients to seek alternative treatment, such as from traditional healers.

Insecticide resistance in the 1990s contributed to the high malaria burden. The impact of vector resistance to synthetic pyrethroids, and the re-invasion of the highly anthropophilic *A. funestus* definitely contributed towards transmission in 1999 and 2000 (Hargreaves *et al.,* 2000).

The concurrence of agricultural practices, which encourage *Anopheles* mosquito breeding, the importation of chloroquine resistant parasites and failing antimalarial drugs, resulted in the epidemic of the late 1980s. Similarly, the late 1990s malaria epidemic was due to a co-occurrence of high sulphadoxine-pyramethamine resistant parasites and insecticide resistant vectors in the population. Subsequent introduction of sulphadoxine-pyramethamine in 1988, the co-introduction of effective insecticide for the control of the vector population, wide scale regional malaria control and artemether-lumefantrine for control of resistant parasites in 2000/2001 contributed to the epidemic being effectively managed.

5.2.1 Malaria Morbidity

This study revealed that the delayed introduction of new and effective antimalarial drugs against resistant *P. falciparum* population could be implicated in having a public health impact. A simultaneous increase was observed between the delayed introduction of sulphadoxine-pyramethamine and artemether-lumefantrine regimens and high morbidity and mortality rates ($p<0.001$) caused by the rapid increase of resistant malaria by the vectors in the population. The 4.5 and 3.5 fold increases in the two periods respectively may have been increased by late replacement of chloroquine and the late replacement of

sulphadoxine-pyramethamine compared to the baseline in each period. The use of ineffective drugs increases gametocytogenesis by 2.5 times in infected individuals (Buckling *et al.,* 1997). Similarly, the World Health Organisation confirmed that using *P. falciparum* resistant drugs in a locality inevitably leads to higher rates of transmission of resistant gametocytes in the population (WHO, 2006). Therefore, the origin of the rapid spread of the malaria resistance can be attributable to the increased parasite reservoir due to a therapeutic failure designed to eliminate resistant *P. falciparum* parasites in the population. These increased gametocytes also contribute to the exponential and rapid increase in resistant *P. falciparum* malaria and are consistent with the findings of several authors (Trape *et al.,* 1998; 2001; Wongsrichanalai *et al.,* 2002; Zucker *et al.,* 2003; Craig *et al.,* 2004;).

The number of malaria infections reported in this study greatly contributed to the national burden of malaria. In the chloroquine period, North Eastern KwaZulu-Natal had 16% of the national malaria burden (N= 2985) in 1982/85, compared to 27% of the total malaria cases (N=9741) in the 1985/88 malaria season in South Africa. In the sulphadoxine-pyramethamine use period, this area contributed 57% of the malaria burden due to late replacement of first-line medication (N=40492) in 1997/01 from 56% of the average total (N=10153) in 1993/97.

The rate of malaria increase due to late replacement of therapy was higher in the chloroquine than in the sulphadoxine-pyramethamine period.

5.2.2 Malaria Mortality

The increased mortality observed during the antimalarial drug change phase for chloroquine and sulphadoxine-pyramethamine is associated with late replacement of obsolete drugs. Various studies have demonstrated that any delay in obtaining malaria treatment, or using ineffective drugs in combating the disease aggravates the effect of malaria on patients. It also increases the potential for complications and results in further

deaths (Hansford 1989; Buckling *et al.,* 1997; White 1999; Trape *et al.,* 1998; 2001; Zucker *et al.,* 2003).

Delay in treatment was an independent risk factor of infection related mortality in nosocomial diseases (Lodise, 2003). Similarly, Heath *et al.,* (1996) discovered a significant association between delayed initiation of therapy and mortality among *Legionella pneumonia* patients. Delays of more than 24 hours in obtaining malaria treatment, especially for children under 5 years of age can lead to increased deaths.

The total number of deaths observed in this study greatly increased the burden of malaria on both South African society and the national economy. However, mortality due to malaria was very high during the two treatment regimens. The average proportion of fatalities attributable to the national malaria epidemic increased to 47 % (n=21) during the chloroquine era and 63 % (n=282) in sulphadoxine-pyramethamine era. The high mortality observed may be contributed by the late replacement of sulphadoxine-pyramethamine probably attributed to the high number of deaths observed in the country in the general population (Stat SA 2005).

5.2.3 Malaria case fatality

Malaria case fatality is a measure of the severity of malaria in causing death to patients within a defined period. The case fatality rate generally was higher in the change phases than in the baseline phases for both treatment regimens. The risk of patients dying of malaria if not treated was 1.3 and 2 times higher in the chloroquine and sulphadoxine-pyramethamine change phases respectively. The case fatality rate in the chloroquine period indicates a weaker relation between the late replacement of the chloroquine period and the baseline phase. This could be due to the limited notification data.

A case fatality rate of 1% was observed in Limpopo in 2002 because of a delay in the treatment of malaria in affected communities (Moonasar *et al.* 2004). In Kenya, the continued used of ineffective antimalarial drugs resulted in a high case fatality rate of

13% compared with 4.1% for the effective regimen (Zucker *et al.,* 2003). Unfortunately, the case fatality rates 0.7 and 0.7 respectively for chloroquine and sulphadoxine-pyramethamine were much higher than the national target of 0.5. These findings suggest that the severity of malaria is due to resistant *P. falciparum* resulting from a delay in obtaining effective treatment or the use of ineffective drugs in the treatment of malaria. Malaria is a potential threat to humanity and should be treated with caution.

5.2.4 Policy Change Phase

From this study, it can be concluded that sulphadoxine-pyramethamine replacement for chloroquine was introduced three years after it was observed that there was greater than 5% parasite resistance in the population (1985-1988). Similarly, four years (1997- 2001) after sulphadoxine-pyramethamine resistance was found to be more than in the 5% level in the population, artemether-lumefantrine was introduced.

Late replacement of antimalarial drugs was also observed in other countries with significant detection of resistant *P. falciparum* malaria and correspondingly increased morbidity and mortality. During 1984 in Malawi, parasitaemia of 41% to 65% in children was found 7 days after treatment was commenced (Khoromana *et al.,* 1986). A new treatment policy was only introduced in 1993. In Tanzania, median *in vivo* resistance of 20% among school children was observed from 1982/85, but a new treatment regimen policy was only introduced in 2001. In Kenya, by 1995, 50% of malaria resistance studies indicated and significant increase of *P. falciparum* resistance but the policy was effected in 1998 (Shretta *et al.,* 2000). The delay in the introduction of new antimalarial drugs was associated with an increased burden of malaria in those countries.

5.3 POSSIBLE CAUSES OF LATE REPLACEMENT

The findings can be generalized to other endemic countries, as the *P. falciparum* resistance and the effect of a delayed introduction of antimalarial drugs are similar. This was explained as being due to the explosive nature of the *Plasmodium* resistance (Trape *et al.,* 1998; 2001) and all the endemic countries were most probably susceptible, with

different levels of malaria resistance within the shortest possible period (Hansford 1989; Herbst *et al.,* 1985; Freese *et al.*, 1988; Craig *et al.*, 2004; Shretta *et al.,* 2000; Khoromana *et al.,* 1986; Trape *et al.,* 2001)

However, there was no clear level of malaria resistance or any criteria at which malaria policy was to be substituted (Nuwaha, 2001; Kindermans *et al.,* 2002; Williams *et al.,* 2004). Several authors suggested a range of 5% to 31% levels of resistance (Nuwaha, 2001). The study suggests that the high morbidity and mortality due to malaria could be attributable to the lack of certainty at which level of parasite resistance failing antimalarial drugs should be substituted. Many scientists expected the resistance levels to reach 25%, as suggested by the World Health Organisation before action need be taken (WHO, 2003). Other criteria to consider before changing the antimalarial treatment regimen are; defined standard method of data collection, availability of effective and affordable drugs, and the political climate and a favourable rapport among stakeholders. In KwaZulu-Natal, the delayed introduction of new antimalarial drugs on both occasions was consistently due to the lack of a standardized method of data collection. This could have been obviated by the establishment of therapeutic surveillance sites and more effective monitoring of the disease. Similar problems of the lack of standardized method were found in countries, *inter alia* Tanzania, Kenya, Ethiopia (Nuwaha 2001; Trape 2001; Kindermans *et al.,* 2002; Williams *et al.,* 2004).

5.4 BIAS AND LIMITATIONS

This study acknowledges its limitations in a number of ways.
Information and selection bias may have occurred in data collection and extraction, although much effort was made to obviate any such factor materialising. It was not possible to ascertain the exact month at which level the *Plasmodium* resistance reached the 5% level. No critical level of malaria resistance existed at which the malaria treatment policy ought to have been changed. The available literature had suggested the level when such a replacement ought to have taken place and when a corresponding increase in the number of cases and deaths was likely to occur. This was taken to be a greater than 5%

level of chloroquine resistance for delayed introduction of sulphadoxine-pyramethamine; and a greater than 5% level of resistance for delayed introduction of artemether-lumefantrine. The studies consulted for this decision might not have used a standard method in assessing malaria resistance.

Another possible limitation was the accuracy of mortality data for the entire period under study and the unavailability of any mortality data from 1993 to 1995. Therefore, 1995/96 mortality data was used as the average mortality data for the baseline phase of sulphadoxine-pyramethamine as the first line treatment.

The available population data for the 1980s may not be reliable because of the actual population figure of the region under study. The population figure might be affected by the apartheid system of government prevailing at the time and as well the figure came as a personal communication from the Dr. Maharaj, Malaria Specialist, MRC Durban. As a result, the actual incidents risks may not be that accurate, but the data still reveals that a serious epidemic of malaria had occurred.

Furthermore, the study could not account for all confounders and interactions that may have occurred at a patient care level, as the data was ecological and non-linked to patients. Despite every effort made to minimise this bias, the findings of the study should be interpreted with caution as they could be distorted by any potential ecological fallacy.

5.5 EFFECT MODIFICATIONS

5.5.1 Case reporting

The study acknowledges the limitation posed by malaria data collection. Two methods were employed routinely in the detection of malaria cases: a) passive surveillance and b) active surveillance. In this study, limitations of reporting and incomplete notification was evident as the number of reported cases across the age and sex categories did not equate with the total number of cases reported. These could constitute the peaks of the malaria epidemics in the region. Studies have noted that notifications of diseases is limited by

under-reporting and is particularly severe during epidemics where health workers prioritise patients' management over data collection and notification (Barnes *et al.,* 2005; White, 1999; Guerin *et al.,* 2002; Trape, 2001; Durrheim *et al.,* 1996). Consequently, the real impact of the delayed introduction of antimalarial drugs may be masked by the under reporting of malaria cases. The generally low number of cases and deaths, compared with the explosive nature of resistant malaria and the missing mortality data for the period of 1993 to 1996 in our study periods, may also be the effect of either under-reporting or no reporting at all.

5.5.2 HIV/AIDS

An HIV survey was first conducted in 1990 with the national prevalence estimated at 0.8%, and subsequently the disease has grown exponentially in the country, with an estimated prevalence of 36% in antenatal care, KwaZulu-Natal in 2000. Among the general population, adult aged 30-39 years were estimated to have the highest HIV prevalence of 23% (Department of health, 2005). Studies have noted the association of HIV and malaria among antenatal women (Witworth *et al.,* 2000; Parise *et al.,* 1998; Grinwade *et al.,* 2004). It was demonstrated that the following factors are particularly strongly associated with HIV infected malaria patients: high parasitaemia densities and severe clinical malaria especially in children. The study was limited in its ability to provide a further explanation as regards this factor or to adjust for HIV due to the unavailability of HIV data but noted that parasite densities and clinical malaria were associated more with adults than with children (Witworth *et al.,* 2000). It is possible that the Incidence Risk Ratio of 4.6 identified in this study indicated that more HIV positive adults are associated with clinical episodes of malaria than any other age groups during the sulphadoxine-pyramethamine change phases than during the sulphadoxine-pyramethamine baseline phase.

5.5.3 Cross border movement

Malaria in KwaZulu-Natal, South Africa is a border problem as the affected area borders with Mozambique (Craig *et al.,* 2004; Hansford, 1989; Herbst *et al.,* 1985; Ngxongo,

1993). Data has revealed that 48% of malaria diagnosed in the endemic districts originated in Mozambique (KwaZulu-Natal Department of Health, 2000). A similar event was observed between 1980 and 1991 when 15% of malaria cases in KwaZulu-Natal were imported, more than 90% from Mozambique (Ngxongo, 1993). Additionally, the proportion of malaria cases imported into the region from 1986 to 1992 was estimated at 20-40% in KwaZulu-Natal (Craig *et al.,* 2004). Hansford (1989) argued that early *P. falciparum* resistance originated from Mozambique. A study conducted in Mozambique detected 94% drug treatment failure among school children in early 1985. This study could not ascertain whether the reported epidemics were due to imported resistance malaria.

5.5.4 Agricultural development

The malaria endemic area in KwaZulu-Natal also contains one of the most extensive dams in the country and possesses much agricultural potential (Ngxongo, 1993). Dams have been shown to serve as potential breeding sites for mosquitoes (Mutero *et al.,* 2000; Ramasamy *et al.,* 1992, Hansford, 1989). During the 1980s, it was reported that water spillage from an irrigation scheme led to the development of a swamp (Balamhlanga) in the region affected by the malaria epidemic (Ngxongo, 1993; Craig *et al.,* 2004). This might have aided mosquito population dynamics thereby increasing malaria transmission. In addition, Ngxongo (1993) noted that the irrigation scheme gave rise to 750 malaria cases in 1987.

5.5.5 Insecticide resistance

The effect of replacement of the insecticide, Dichlorodiphenyltrichloroethane (DDT) might have contributed to the resistant malaria epidemic of the late 1990s. DDT was discontinued due to pressure from international bodies because of the hazardous nature of the chemical, pressure from the local community because of its residual effects, the contamination of human breast milk and the availability of the suitable alternative insecticide, deltamethrin (Maharaj *et al.,* 2005; Sharp *et al.,* 1993). Consequently, studies discovered insect resistance to pyrethroid and this observation corresponds with the

reported increased malaria incidence in the late 1990s (Maharaj *et al.,* 2005; Craig *et al.,* 2004; Barnes *et al.,* 2005). This discovery may explain the significant rise ($p<0.0001$) of malaria cases in the sulphadoxine-pyramethamine change period compared with the sulphadoxine-pyramethamine baseline phase in these findings. Such insecticide resistance was confirmed to have been a factor in contributing to increased malaria transmission but was not able to ascertain its extent to adjust for the significance of insecticide resistance.

6 CHAPTER 6: RECOMMENDATIONS AND CONCLUSIONS

6.1 INTRODUCTION

This chapter presents conclusions based on the findings and discussions made to each important issue explored in the study.

6.2 CONCLUSIONS

The study demonstrates the impact of the delayed introduction of antimalarial drugs sulphadoxine-pyramethamine and artemether-lumefantrine respectively on the epidemiology of malaria in KwaZulu-Natal, South Africa. It strongly suggests that the epidemic of malaria from 1985 to 1988 was caused by the coincidence of agricultural practices, cross border movement and parasite drug resistance. The epidemic of 1997 to 2001 was affected by a combination of factors including the high rate of HIV infections, insecticide resistance, cross border movement and drug resistance. However, it is concluded that it was exacerbated by delays in the replacement of obsolete first-line antimalarial drugs with newer effective drugs.

Three observations were made in this study: The delay replacement was noted in

1) **The standardized method of data collection**: Two studies were found to detect the rising *P. falciparum* resistance to chloroquine in KwaZulu-Natal in 1985 (Hansford, 1989 and Herbst *et al.,* 1985) but the methods of data collection were not of a World Health Organization standard. The World Health Organisation stipulated that the *in vivo* method of assessing *P. falciparum* resistance should be monitored for either sensitivity or resistance at one of three levels RI, RII & RIII. Furthermore, a follow up of the treated patients for evidence of any recurrence of parasitaemia on day 7, 14 or 28 days needs to be undertaken.
2) **Establishment of sentinel sites**: In the beginning of the second half of the 1990s, a 23.5% RI, RII, & RIII parasitological failure rate on sulphadoxine-pyramethamine was discovered, but due to the possibility of referral bias, the results were not acted upon. This evidence would have enabled a forecast of the possibility of malaria

epidemics in the near future to be established. The establishment of the sentinel sites in the province could also have tackled the problem (Durrheim *et al.,* 2001). It might have required a number of years to put the sentinel sites in place, which may have resulted in many subsequent malaria infections.

3) **The decentralization of malaria control**: this was observed to have allowed for the success of the introduction of more effective antimalarial drugs in South Africa. It was noted that KwaZulu-Natal was the first region to introduce sulphadoxine-pyramethamine in 1988 and the first to introduce artemether-lumefantrine in 2001. This success can be attributed to the decentralization of the malaria control programme to provincial level. This would not have been achieved if the malarias zones in South Africa fell under one authority. The varying resistance levels of *P. falciparum* to chloroquine differ in KwaZulu-Natal, Limpopo and Mpumalanga, which would have been an obstacle to the collation of relevant data and accepting the implementation of the new malaria treatment policy.

The findings of the study have contributed to the evidence that if malaria control continues not to adjust to new realities, then the Abuja declaration of 2005 is unlikely to meet its targets by 2010. These include maintaining the threshold level of 60% of malaria patients obtaining prompt access, affordable and appropriate treatment within 24 hours of the onset of symptoms; 60% of those at risk of malaria, particularly pregnant women and children under five years of age, benefit from the most appropriate combination of personal and community protective measures such as insecticide treated mosquito nets and other interventions. These are accessible and affordable in preventing infection and suffering and 60% of all pregnant women who are at risk of malaria, particularly those in their first pregnancies, have access to chemoprophylaxis or presumptive intermittent treatment.

6.3 *RECOMMENDATIONS*

The study noted that KwaZulu-Natal was the first region to introduce sulphadoxine-pyramethamine as a replacement for chloroquine in 1988 and artemether-lumefantrine for

sulphadoxine-pyramethamine in 2001. These were integrated with wide scale vector control and the introduction of DDT and the early success as were noted to have reduced the impact of drug resistant *P. falciparum* and the resistant insect population among those resident in the particular regions (Hansford, 1989; Craig *et al.,* 2004; Barnes *et al.,* 2005). However, it is essential that the delayed introduction of antimalarial drugs observed in this study should be countered in future by:

6.3.1 Surveillance

Establishment of sentinel sites would greatly facilitate in countering the mistakes made in the past about selection bias observed during early detection of *P. falciparum* resistance to sulphadoxine-pyramethamine. Sentinel surveillance and the effective use of sites are vital in the control of malaria in this endemic situation. Epidemiological surveillance, which is defined as a tool used in detection of epidemics, evaluation of control and prevention activities, detection of changes in health practices, quantitative estimates of the magnitude of health problems, and the monitoring of changes in infectious agents, particularly the evolution of drug resistance (Katzenellenbogen *et al.,* 1997) will assist in making the early forecasts and warnings of any impending catastrophe.

6.3.2 Drug sensitivity

Therapeutic sensitivity is very important in Africa particularly during this era of persistent *P. falciparum* resistance or drug failure. A need exists to conduct a sensitivity test annually as a minimum requirement; the establishment of a committee to monitor drug sensitivity studies would assist in early detection, thereby alerting people on the manner of undertaking, appropriate measures. *In vivo* and *in vitro* methods are recognised in assisting in the forecast or detection of resistance or drug failure. *In vivo* method is proposed as the best choice for drug sensitivity or failure. Malaria resistance such pairs as in the *in vitro* method should serve as a forecast or warning but should not be substituted for the *in vivo* method, as there are interactions of immunity in the body.

6.3.3 Behaviour change

Co-ordinated behavioural change is required by stake-holders in the malaria control programme from policy makers to the expert control team. The monthly meeting of the coordinators of various disease programmes in the district with the district manager would prevent any recurrence of the negative potential health events and loop holes. Health workers should be made to understand the implication of the late or non- reporting of malaria to the central unit.

6.3.4 Regional cooperation

Resistance malaria is primarily noted as a border problem in this study. Consequently, human migration is a risk factor in the rapid spread of *P. falciparum* resistance. Therefore, the need for the effective control of malaria, particularly at present requires substantial cooperation among countries as in the Lubombo Spatial Development Initiatives (LSDI), a cooperation involving South Africa, Mozambique and Swaziland. The control programmes should adopt integrated malaria control strategies in order to reduce any pressure on a single control strategy.

6.3.5 Insecticide control

Different classes of insecticide should be adopted and integrated with bed-nets. These insecticides require monitoring from time to time to avoid unforeseen resistance to insecticides. In addition, integrated vector control measures need adopting as well.

6.3.6 Health education

Since malaria is a public health problem, t any additional health education through information, education and communication campaigns will assist in creating an awareness of the importance of malaria and the necessity of controlling it. An awareness of visiting a suitable health care centre by patients at the onset of malaria symptoms will greatly aid in the reduction of the parasite reservoir in the population through early treatment, and provide for the monitoring of any changes in the epidemiology of malaria

parasites and vectors. Through health education, the population will be empowered to care for their health and cooperate with the particular relevance control programmes and should understand that any delay in reporting to a health centre is probably fatal.

6.4 RECOMMENDATION FOR FURTHER STUDY

This study is an ecological study of the late replacement of antimalarial drugs in a community. As indicated, the results may be disguised by the low reporting of cases and deaths due to malaria, co infection with HIV, cross border movements, agriculture and insecticide resistance or the possible existence of some ecological fallacy. Therefore, owing to these limitations observed in this study, the study suggests that in-depth studies should be conducted to ascertain the public health realities of the delayed introduction of antimalarial drugs in the presence of resistant *P. falciparum* in populations.

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