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The impact of indoor residual spraying (IRS) on malaria prevalence between 2001 and 2009 in Mpumalanga province, South Africa

By

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DECLARATION

I declare that the dissertation, which I hereby submit for the degree Master of Science (MSc) in Epidemiology at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at this or any other tertiary institution.

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ABSTRACT

Background

Malaria remains a serious epidemic threat in the Lowveld region of Mpumalanga Province. In order to appropriately target interventions to achieve substantial reductions in malaria morbidity and mortality, there is a need to assess the impact of current control interventions such as indoor residual spraying (IRS) for vector control. This study aimed to assess long-term changes in the burden of malaria in Mpumalanga Province during the past eight years (2001-2009) and whether IRS and climate variability had an effect on these changes.

Methods

All malaria cases and deaths notified to the Malaria Control Programme, Department of Health was reviewed for the period 2001 to 2009. Data were retrieved from the provincial Integrated Malaria Information System (IMIS) database. Climate and population data were obtained from the South Africa Weather Service and Statistics South Africa, respectively. Descriptive statistics were computed to determine any temporal changes in malaria morbidity and mortality. Autoregressive integrated moving average (ARIMA) models were developed to assess the effect of climatic factors on malaria.

Results

Within the eight-year period of the study, a total of 35,191 cases and 164 deaths-attributed to malaria were notified in Mpumalanga Province. There was a significant decrease in the incidence of malaria in Mpumalanga Province from 385 in 2001/02 to 50 cases per 100,000 population in 2008/09 ($P < 0.005$). The overall incidence and case fatality rates were 134 cases per 100,000 and 0.54%, respectively. Malaria incidence and case fatality rate by gender showed significant differences, higher in males than in

females (166.9 versus 106.4; *P* < 0.001; CFR 0.41% versus 0.55%). The incidence of malaria increased from age 5-14 years (70), reaching a peak at age 25-34 years (190), declining thereafter (50 in those >65 years). Mortality due to malaria was higher in those >65 years, the mean CFR reaching a 2.1% peak. Almost half (47.8%) of the notified cases originated from Mozambique and Mpumalanga Province itself constituted 50.1%. The distribution of malaria varied across the districts, highest in Ehlanzeni district (96.5%), lowest in Nkangala (<1%) and Gert Sibande (<1%). A notable decline in malaria case notification was observed following the increased IRS coverage from 2006/07 to 2008/09 malaria seasons. A distinct seasonal transmission pattern was found to be significantly related to changes in rainfall patterns (*P* = 0.007).

Conclusion

Decades of continuous IRS with insecticides have proved to be successful in reducing the burden of malaria morbidity and mortality in Mpumalanga Province between 2001 and 2009. A decline of above 50% in malaria morbidity and mortality was observed following expanded IRS coverage. These results highlight the need to continue with IRS together with other control strategies until interruption in local malaria transmission is completely achieved and alternative vector control strategies implemented. Efforts need to be directed towards the control of imported cases, interruption of local transmission and focus on research into sustainable and cost-effective combination of control interventions.

Keywords

Malaria, Prevalence, Morbidity, Mortality, Incidence rate, Case fatality rate, Vector control, Indoor residual spraying, Climate.

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ABBREVIATIONS

ACT	Artemisinin-based combination therapy
ARIMA	Autoregressive Integrated Moving Average
CI	Confidence interval
CFR	Case fatality rate
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DALYs	Disability- adjusted life years
FAO	Food and Agriculture Organization
GMEP	Global Malaria Eradication Programme
GMCS	Global Malaria Control Strategy
HIV/AIDS	Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome
HBC	Benzene hexachloride
IEC	Information, education and communication
IRS	Indoor residual spraying
IMIS	Integrated Malaria Information System
ITN	Insecticide treated-nets
IVM	Integrated Vector Management
Kdr	Knock-down resistance
Kg	Kilogram
KNP	Kruger National Park
LLIN	Long-lasting insecticidal nets
LSDI	Lubombo Spatial Development Initiative
MDGs	Millennium Development Goals
NDoH	National Department of Health
NGO	Nongovernmental Organisation

POPs	Persistent Organic Pollutants
RH	Relative humidity
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
SD	Standard deviation
SP	Sulphadoxine-pyrimethamine
UNEP	United Nations Environmental Programme
USAID	United States Agency for International Development
USEPA	United States Environmental Protection Agency
WP	Wettable powder
WG	Wettable granules
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

Indoor residual spraying (IRS) with insecticides has remained the cornerstone of vector-borne disease control for more than 50 years [1]. The rationale of residual spraying of dwellings for malaria control was based on observations of the vector's feeding and resting behaviour [2]. Large-scale malaria control operations based on house-spraying with dichlorodiphenyltrichloroethane (DDT) and dieldrin together with other early vector control measures which included the screening of houses; the use of mosquito nets; drainage or filling of swamps and other water bodies; and the application of oil the breeding sites, were successfully initiated in the 1940s leading to the elimination of malaria in most developed countries and reducing prevalence rate in some developing countries [3,4].

The effectiveness of house spraying with DDT in the 1950s, led to the adoption of the Global Malaria Eradication Programme (GMEP) in 1955-1969 [1]. Eradication was achieved in temperate regions of the world, however, this achievement eluded most African countries [2]. A combination of factors such as the emergence and spread of drug and insecticide resistance, together with challenges in the feasibility and sustainability of malaria control programmes in areas with weak infrastructure and high transmission, have conspired to make malaria a more serious problem now than it was during the first half of the twentieth century in sub-Saharan Africa [5].

The past efforts of the GMEP to eradicate malaria were abandoned when it became apparent that eradication in certain parts of the world was not a realistic goal [6]. Vector resistance to DDT and dieldrin and concerns over their environmental impact, necessitated a revised strategy for control of malaria [7]. By 1969, the World Health Organization (WHO) introduced a new Global Malaria Control Strategy (GMCS) that reflects an understanding of the importance of research, involvement of health services, improved surveillance, development of new antimalarial drugs, alternative malaria control methods, community partnership, decentralization and integration [8-10]. Over the years, several initiatives such as the Roll Back Malaria (RBM) initiative were launched to coordinate global malaria control efforts. Other initiatives for drug discovery, vaccine development and increased funding followed suit, committed to accelerate malaria control [6,11].

The main objectives of the GMCS includes the use of proven malaria control interventions like insecticide treated nets (ITNs), IRS with insecticides, preventative treatment for pregnant women and new medicines and improved diagnostics [12]. According to the Global Strategic Plan of the RBM [13], scaling up of these interventions to universal coverage for populations at risk is critical to achieve the targets of 50% mortality and morbidity reduction by 2010 and a 75% reduction in morbidity and near zero mortality by 2015. The principle of scale-up for impact has been promoted since 2005 by the RBM. This commitment has been re-affirmed by the UN Secretary-General to put a stop to malaria deaths by ensuring universal coverage of malaria control interventions by the end of 2010 through the use of vector control and case management tools and strengthening of community-level efforts [12].

A renewed effort to eliminate malaria is on the global agenda [14] and the South African government has endorsed the goal to eliminate malaria as a public health problem in the three malarious provinces by 2018 [15]. The key intervention strategies on malaria elimination for the South African setting as outlined in the Draft National Malaria Elimination Strategy encompasses: (i) prompt and effective case management (increase

definitive diagnosis and treatment with artemisinin combination therapy (ACT) to 100% coverage); (ii) integrated vector management (greater than 90% coverage of IRS); (iii) 100% coverage of long-lasting insecticidal nets (LLIN) and larviciding in targeted areas); (iv) scaling-up surveillance (passive - notified within 24 hours of diagnosis, active - 100% cases investigated within seven days of being reported); (v) epidemic preparedness and response (all outbreaks investigated within two weeks of detection); (vi) health promotion and advocacy (100% of risk groups targeted with appropriate information, education and communication (IEC) messaging) and; (vii) strengthening human resource capacity at all levels (100% of identified positions filled and appropriately capacitated).

Towards the goal to eliminate malaria, the WHO recommends the quantification of the burden of malaria using the number of malaria cases and malaria-related deaths as core indicators [12,16]. Health management information systems, including routine surveillance systems at health facilities have proved to provide evidence of the burden of diseases including malaria. Surveillance data forms a basis for planning and monitoring the impact of prevention and control activities as well as targeting interventions and advocacy [17-19].

All malaria-affected provinces in South Africa, including Mpumalanga, maintain malaria surveillance systems with valuable malaria epidemiologic data essential for monitoring and evaluating the impact of malaria control tools [20]. Within this context, this study aims to use existing malaria surveillance data to assess the impact of IRS on the prevalence of malaria and taking into account the potential effect of climatic factors which might have influenced changes in the prevalence of malaria and thus confound the relationship between IRS and the observed changes in malaria outcomes over the past eight years in Mpumalanga Province.

1.2 Aim and objectives of the study

The aim of this study is to assess the impact of IRS on the prevalence of malaria over time through the review of retrospective malaria data collected routinely by both passive and active surveillance for the eight-year period from 2001 and 2009 in Mpumalanga Province, South Africa.

The specific objectives of the study are:

- To review malaria trends in Mpumalanga Province during the past eight years (2001-2009) through retrospective analysis of routine malaria surveillance data
- To assess the effect of vector control by IRS on malaria prevalence through the review of IRS activities for the same time period
- To assess the potential effect of climatic variability on malaria transmission over time.

1.3 Justification for the study

While malaria control in South Africa has proved to be successful in terms of reducing malaria transmission in large areas [21], it remains a serious public health challenge in the northern and eastern parts of the country. The Lowveld region of Mpumalanga Province is one of the country's regions that still experience unstable malaria transmission, by contributing about 44% of the country's reported malaria cases [22]. Due to low transmission levels, malaria immunity is not thought to exist and infected individuals are therefore prone to severe disease.

South Africa is a signatory to the Abuja Declaration [23] and also committing itself to the goal of the World Health Assembly to reduce the number of malaria cases and deaths notified by 50% or more by the end of 2010 and by 75% or more by 2015 [24]. The renewed interest to control malaria and to move towards elimination is founded on the latest generation of effective tools of prevention and treatment [25]. While it is important

for malaria-endemic countries to scale-up on these intervention strategies, it is equally important to utilize malaria surveillance data for; (i) evidence-based planning; (ii) assess the level of endemicity; (iii) assess the impact of target interventions and; (iv) track progress in achieving the goals on elimination as set out in the WHO Global Malaria Action Plan [17-19,42].

In spite of several decades of malaria control in Mpumalanga Province, few studies have previously been conducted to evaluate the impact of vector control interventions on the burden of malaria using the provincial epidemiological data. The importance of analysis of data on the prevalence of disease in relation to historical levels is well documented in other malaria endemic areas. Understanding the relationship between malaria, control interventions and climate have shown to assist in providing early warning in malaria increases or potential outbreaks [26] as well as in improving the control programme [27].

This study aims to provide decision makers with vital information regarding the impact of IRS on the prevalence of malaria in the province for possible policy interventions. Moreover, to contribute to knowledge on the burden of malaria in Mpumalanga Province, with a view to stimulate further research, particularly the potential risks that IRS poses on community health and to give the status quo for malaria elimination.

1.4 Definitions of key concepts

Herewith follows the key concepts used in this study:

***Anopheles*:** genus of mosquito comprising numerous species that transmit malaria through the bite of its female.

Case fatality rate (CFR): the number of registered deaths caused by malaria, expressed as a percentage of the total number of reported cases.

Endemic: applied to malaria when there is a constant measurable incidence of cases

and mosquito-borne transmission in an area over a succession of years.

Epidemic: occurrence of cases in excess of the number expected within a specific geographical area and time period.

Endophilic: Vectors that tends to inhabit/rest in indoor areas. Examples of endophilic anopheline species include *Anopheles funestus*.

Exophilic: Vectors that tends to inhabit/rest in outdoor areas. Examples of exophilic anopheline species include *An. arabiensis*.

Indoor residual spraying: the application of chemical insecticides on the interior walls and roofs of all houses and domestic animal shelters in a given area in order to kill the adult vector mosquitoes that land and rest on these surfaces.

Intensity of transmission: rate at which people are inoculated with malaria parasites by mosquitoes (usually expressed by the annual entomological inoculation rate).

Malaria eradication: the permanent reduction to zero of the global incidence of infection caused by plasmodia as a result of deliberate efforts, so that intervention measures are no longer needed.

Malaria elimination: is defined as reducing to zero the incidence of locally acquired malaria infection caused by human malaria parasites in a defined geographic area through deliberate efforts, with continued measures in place to prevent re-establishment of transmission.

Malaria season: the period from 1 July to 30 June of the following year.

Malaria incidence rate: the number of newly diagnosed malaria cases during a specified time period in a specified population (100,000 population).

Malaria prevalence: the number of malaria cases existing at any given time in a specified population, measured by positive laboratory test results.

***Plasmodium*:** genus of the parasite that causes malaria. The genus includes four species that infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae.*

Residuals (regression models): represents unexplained variation after fitting a regression model. It is the difference between the observed value of the dependent variable and the predicted value suggested by the regression model.

Vector: an organism which transmits an infectious agent from one host to another.

CHAPTER 2

LITERATURE REVIEW

2.1 Malaria situation

2.1.1 Global malaria burden

Malaria has plagued mankind throughout history and still remains one of the major challenges to global health [28]. The disease contributes a considerable burden in endemic communities with premature deaths, disability from illness and it impedes on social and economic development [29]. According to the World Malaria Report 2010, the global prevalence of the disease was estimated at 225 million cases and 781 000 deaths in [30]. More than a third (36%) of the world's population live in malaria endemic areas and one billion people are estimated to carry parasites at any one time, while some three billion are estimated to live in areas at risk of malaria transmission in 109 countries [31,32]. In 2000, malaria was estimated to contribute to the loss of nearly 45 million disability-adjusted life years (DALYs), which represents about 13% of all infectious diseases [31,33].

Almost all these deaths are caused by *Plasmodium falciparum*, one of the four species of malaria parasites in humans. The others are *P. vivax*, *P. malariae*, and *P. ovale* [34]. Most people at risk of the disease live in areas of relatively stable transmission, infection is common and occurs with sufficient frequency that some level of immunity develops [35]. Malaria disease and deaths in other areas of the world occur mainly among individuals who lack immunity and are infected with *P. falciparum* in areas where appropriate diagnosis and treatment is not available. The total number of cases recorded outside sub-Saharan Africa is estimated at five million per year and yet the actual number is believed to be at least four times higher [36,37]. The global effects of malaria threaten public health

and productivity on a broad scale and hamper the progress of many countries toward economic development [38].

2.1.2 Malaria in sub-Saharan Africa

Assessing the burden of malaria accurately is a great challenge in sub-Saharan Africa because most deaths occurs at home, the clinical features of malaria are very similar to other infectious diseases and the lack of facilities for accurate diagnosis [39-41]. Despite these limitations it is recognized that sub-Saharan Africa bears the brunt of the disease, where at least one million deaths from malaria occurs each year (90% of all cases), mainly from *P. falciparum* [42]. The burden is estimated to be much greater, with 15% of all DALYs lost to malaria. Children under the age of 5 years are the most vulnerable to malaria infections, where the disease kills up to 20% between the ages of six months and 5 years [35,39,43]. An estimated three million suffer complications from low birth weight, including death, arising from malaria infection during pregnancy [34,44]. Other high-risk groups are pregnant women [45], non-immune travelers, refugees, displaced persons and labourers entering endemic areas [46-48]. In addition to its burden in terms of morbidity and mortality, the economic effects of malaria in Africa are tremendous [49].

Studies have shown that malaria has resurged in certain locations of Africa that had previously had effective control programs, such as Madagascar and Zanzibar. This trend is also seen in urban areas and in countries that previously eradicated the disease such as urban areas of the Amazon Basin, South and North Korea, Armenia, Azerbaijan, and Tajikistan [50]. The constancy of transmission and the resurgence of the disease in areas where eradication efforts were undertaken are largely due to subtle interactions of biologic, ecologic, social, and economic factors.

2.1.3 Malaria in South Africa

South Africa is not exempt from the threat of seasonal and unstable malaria by affecting 10% of the population living in malaria endemic areas [51]. In South Africa, malaria is limited to the north-eastern border areas, which include Mpumalanga, Limpopo and KwaZulu-Natal provinces, with over 90% of cases due to *P. falciparum* and mainly transmitted by *An. arabiensis* [52,53]. In the 1940s malaria control began in South Africa through indoor space spraying with DDT together with land drainage and the treatment of breeding sites with oil and Paris green. These interventions led to the elimination of the major malaria vector *An. funestus sensu stricto* and *An. gambiae sensu stricto* and malaria transmission from large areas of the country [54,55]. Prior to this malaria was a major cause of morbidity and mortality in many parts of the country affecting areas such as Durban and Port St Johns on the east coast, and as far as Pretoria during favourable years causing large epidemics with up to 20,000 deaths [56].

In 1999, Hargreaves and others reported the reappearance of *An. funestus* in northern KwaZulu-Natal which was eliminated many years previously [57]. Between 1996 and 2000 the incidence of malaria increased dramatically from 27,000 in 1996 to more than 60,000 cases and 423 deaths [58]. In the absence of data exploring the relationship between malaria incidence and the use of DDT during that period, several possible causes were put forward such as climate change, demographic changes, vector biology and behaviour, drug and insecticide resistance [59].

In view of the sudden upsurge in malaria cases, South Africa had to implement several interventions; a change in first-line treatment from sulphadoxine-pyrimethamine (SP) to Coarterm, the reversion to DDT as an insecticide of choice for IRS [21] and engagement in inter-country collaboration, such as the Lubombo Spatial Development Initiative (LSDI) [60]. The country has since experienced and sustained a decrease in malaria case notifications over the years, from about 13,901 cases and 85 deaths in 2006 to 6,615 and 60 deaths in 2007, a decrease of almost 50% [61]. Currently seasonal malaria is confined

in the north-eastern border areas (Mpumalanga, Limpopo and KwaZulu-Natal) with limited focal transmission in the Northwest Province.

2.1.4 Malaria in Mpumalanga Province

Unstable malaria transmission in Mpumalanga is mainly confined in the Ehlanzeni district which constitutes approximately 70% of the province's malaria cases. Seasonal transmission occurs with an annual peak from January to May, in which *P. falciparum* accounts for 90% of the cases while *P. malariae* and *P. ovale* make up the difference. *An. arabiensis* is the major malaria vector responsible for transmission [59].

A malaria control programme has been in existence in Mpumalanga Province for more than five decades and control strategies include rapid detection and treatment of confirmed malaria cases at primary health care clinics and vector control through indoor residual spraying (IRS) with insecticides and periodic larviciding. The first-line treatment for treating uncomplicated *P. falciparum* malaria is SP which replaced chloroquine in 1997, after *in vivo* studies showed high levels (48.4% RI+RII+RIII) of chloroquine resistance in *P. falciparum* parasites [62]. Chemical vector control is carried out annually using DDT, synthetic pyrethroids and carbamates. Insecticide-treated nets (ITNs) were distributed as a pilot project in Nkomazi municipality, however, their effectiveness, usage and acceptability in the community was not fully investigated.

2.2 Factors influencing malaria transmission

The prevalence and distribution of malaria in certain parts of the world that are still experiencing malaria transmission and the resurgence of the disease in areas where eradication efforts were undertaken are mainly influenced by the interplay of multiple factors [38]. Nine factors are particularly important determinants of the pattern of malaria transmission:

2.2.1 Population movement

Historically human mobility had a tremendous effect on the global malaria situation [63]. Early researchers have noted that the failure of the malaria eradication efforts in the 1950s and 60s was partly attributed to failure to consider the relationship between mobility and malaria transmission [64]. Uncontrolled and frequent inter-territorial human population movements due to political, economic or natural disasters such as floods, earthquakes and drought, are important factors in disease emergence. The presence of refugee camps can also temporarily increase malaria endemicity in areas where it is low [65]. Irrespective of the type and motivation of the movement, migrants can become active transmitters or passive carriers of certain diseases [66].

Out of 20 countries that present high risk of malaria transmission, 16 consider human mobility as the major cause for the persistence of the disease. Seasonal migration of workers has been associated with epidemics in Kenya [63]. South Africa also experience large influx of economic migrants from neighboring countries many who carry malaria parasites, resulting in a large number of imported cases and unexplained local upsurges [67].

Growing international travel in recent years has been identified as a prime factor in the global spread of both infectious and vector-borne diseases and represents a great public health concern [68,69]. Several incidences of autochthonous malaria have been reported in malaria-free countries such as the USA and Europe, resulting either from the introduction of infected mosquitoes by aircraft or from local mosquitoes that have become infected from biting infected persons returning from endemic areas [70].

2.2.2 Urbanization

The rapid increase in the world's urban population has major implications for the transmission and epidemiology of malaria and other vector-borne diseases [71]. Economic conditions are thought to encourage the mass movement of workers from rural

areas to cities and allowing infections that may once have remained obscure and localized in isolated rural areas to reach larger populations [64]. In sub-Saharan Africa, the percentage of urban population was 14.7% in 1950 and is expected to triple by the year 2050. This expansion is expected to occur primarily in urban areas and by 2025, 800 million people are expected to live in urban communities [72].

Until recently, urbanization was believed to reduce vector breeding and thus malaria transmission [65]. However, many African countries have declining economies and most cities are struggling to cope with the pace and the extent of urbanization [73]. The study conducted by Robert and others [66] to assess the impact of urbanization on malaria transmission in sub-Saharan Africa presented evidence that urbanization allows for increased rates of disease transmission, large numbers of larval development sites due to construction of new settlements, water storage practices and limited methods for disposal of wastewater and refuse. The adaptation of malaria vectors to urban areas has been well documented for the past two decades and local transmission has been demonstrated in many African cities [65,66].

Rapid urbanization is believed to alter the frequency and transmission dynamics of malaria, with significant effects on disease-associated morbidity and mortality, which in turn has important implications for control [74]. Although urban malaria transmission is substantially less intense and more focal than in rural and peri-urban settings, the danger of epidemics can be higher due to the presence of non-immune populations [18].

2.2.3 Agricultural development

The development of agricultural water resources affects the environment, which in turn affects human health. Agricultural projects can contribute to malaria transmission by creating conditions suitable for vectors. Agricultural activities, such as deforestation, irrigation, extensive farming practices or building settlements, affect the ecological conditions, which provides good breeding sites for anophelines and thus the spread of malaria [75]. Irrigation practices that use canals or pumps to periodically flood fields for

crops such as rice have a great impact on mosquito breeding [76]. In Burundi malaria prevalence was estimated to be between 24-69% in irrigated rice fields compared to 5-30% in nearby non-irrigated cotton fields [38].

Large dams, which often accompany irrigation projects, create additional opportunities for malaria to gain a foothold. Mosquitoes can breed in the reservoir itself, especially if its edges are not kept clean of vegetation. Seepage from the dam and pooling also can occur, providing new larval development sites [38]. Widespread agricultural spraying is also known as an important factor that worsens resistance of anopheline mosquitoes in the most critical cases [77]. Contamination of the mosquito breeding sites by agricultural treatments subjects all the larvae to selective pressure, which is more likely to induce resistance [78,79].

2.2.4 Changes in vector behaviour

Although malaria is transmitted exclusively by anophelines, only certain species are vectors of the disease. In sub-Saharan Africa, two species groups within this genus contain the major malaria vector species, the *An. gambiae* complex and the *An. funestus* group. Three main species are known for their important role in malaria transmission, *An. gambiae s.s.*, *An. arabiensis* and *An. funestus s.s.* [80-82]. One of the important reasons for the persistence of malaria in Africa is the presence of these most efficient vectors of malaria [41]. These mosquitoes are known as efficient vectors of malaria because of their marked preference for human environments and humans as hosts and their rapid adaptability to changes in the environment induced by human habitation and agriculture.

This plasticity is evident especially in the sibling species *An. gambiae s.s.* and *An. arabiensis* to rapidly evolve new behavioral patterns, such as the shift from indoor to outdoor blood feeding and resting in response to insecticide control programmes [83]. According to Mouchet [78], the vector biting rate is one of the principal entomological variables determining the rate of transmission, such change in mosquito behaviour can impact on the epidemiology of the disease [84].

2.2.5 Emergence of HIV/AIDS

Malaria and human immunodeficiency virus (HIV) are two of the most common infections in sub-Saharan Africa and, to a lesser extent, in other developing countries [85]. The HIV pandemic has been superimposed on the longstanding malaria pandemic, where *P. falciparum* malaria is consistently one of the major causes of infant and child mortality. The high prevalence of both HIV and malaria infection in Africa means that even small interactions between the two could have substantial effects on populations exposed to both [86,87].

Early research have failed to indicate any direct, biological association between HIV and malaria, although it was demonstrated that malaria-associated anaemia treated with unscreened blood transfusions contributed to HIV transmission [87]. However, recent studies have shown evidence of an interaction between malaria and HIV. In Malawi increased risk for malaria parasitemia and clinical malaria was reported in HIV-infected pregnant women, with the risk greatest when immune suppression is advanced [88]. In east and southern Africa, where HIV prevalence approaches 30%, it is estimated that about a quarter to a third of clinical malaria in adults (including during pregnancy) can be accounted for by HIV, leading to substantial public health implications [45,89,90].

Malaria is associated with increases in HIV viral load. The study conducted by Kublin and colleagues [91] reported that malaria, if frequent, unrecognized, inadequately treated, or untreated, might result in increased rates of HIV progression. In recent years it has been noted that malaria infection is more frequent and more severe in HIV-positive pregnant women in malaria-endemic settings and in women of all gravidity, with multigravidae most affected [92,89]. Pregnant women infected with both malaria and HIV being at higher risk of developing anaemia, delivering a low birthweight infant, and delivering prematurely [45]. Further work remains to be done on the effects and public health implications of HIV/malaria interaction.

2.2.6 Drug resistance

Drug resistance in malaria is a significant public health concern, which hinders the control of malaria [49]. The spread of drug-resistant malaria parasites has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease has been eradicated. Biological influence on drug resistance includes a weak background immunity, high parasite load in individuals and intense drug pressure [93].

Parasite resistance to chloroquine, was first discovered in South America and South-East Asia in the 1950s and has since spread throughout the world, where falciparum malaria is endemic. In sub-Saharan Africa, malaria control has been synonymous with chloroquine treatment [94]. South Africa first detected resistance of *P. falciparum* to chloroquine in 1985, after failing to provide an adequate cure rate [95].

The emergence of chloroquine resistance led to its replacement with SP as a first-line treatment for uncomplicated malaria. Similarly, strains of falciparum parasites were soon found to be resistant to SP and losing its status as a cheap alternative to chloroquine [96, 97]. Since the 1990s, the accelerating emergence and spread of resistance to SP has been documented in many areas, with parasitological failure rates of around 20% being widely reported and up to 40-80% in certain areas [98].

The introduction of each subsequent new antimalarial drug has inevitably been followed by the emergence of resistance [94]. As a result of these trends, many countries are required to change their treatment policies and use the more expensive combination drugs, artemisinin-based combination therapy (ACT), which will help reduce or delay the development of resistance [99].

2.2.7 Insecticide resistance

The use of a limited number of insecticides for both agricultural pests and vectors of human diseases on a vast and increasing scale has led to the widespread development

of insecticide resistance [100]. Levels of resistance in insect populations reflect the amount and frequency of insecticide contact as well as inherent characteristics of the target species [101]. Resistance to insecticide has now appeared in the major insect vectors from every genus. Altogether there are 150 species of arthropods of medical and veterinary importance, in which resistance to one compound or another has been detected. Resistance is not only known to organochlorines like DDT and dieldrin but also to organophosphates, carbamates, pyrethroids, including microbial drugs and insect growth regulators [102,103]. As of 1991, WHO reported that more than 55 anopheline vectors demonstrated resistance to one or more insecticides. Of these, 53 were resistant to DDT, 27 to organophosphates, 17 to carbamates, and 10 to pyrethroids [104].

Conventional detection of resistance is based on insecticide susceptibility tests, which are dose mortality experiments. This approach has been the best resistance detection technology in the field however it has many limitations [105]. Another approach is to employ biochemical techniques for detection of resistance and determination of biochemical mechanisms in single insects, which is particularly important to detect resistance at very low frequency allowing efficient monitoring of vector populations [106]. To prolong the effectiveness of the currently available insecticides and thereby prevent control failure, it is vital to detect the emergence of resistance genes at an early stage so that appropriate action can be taken [107].

The principal mechanisms of insecticide resistance that have been identified to date include: (i) enhanced metabolism of the toxicant (by means of mixed function oxidases, esterases, glutathione s-transferases and hydrolases); (ii) reduced sensitivity of the target site (nerve insensitivity and acetylcholinesterase insensitivity); and (iii) reduced penetration to the active site [108,102].

Knock-down resistance (kdr) is a separate resistance phenotype linked to a point mutation in sodium channels targeted by both pyrethroids and DDT [109, 101]. Metabolic resistance to pyrethroids in malaria vectors has been recently found in several major

vector species including *An. funestus* in South Africa [59] and *An. gambiae* in West Africa [110,111]. In other countries outside Africa, it has been detected in *An. sundaicus* from southern Viet Nam [112] and *An. culicifacies* in Sri Lanka [113].

During the last four decades insecticide resistance has been, and remains the most important technical problem facing disease control programmes in the fields of agriculture, veterinary medicine and public health in many countries [114-117] and it is expected to threaten vector control programmes [102].

Effective insecticide resistance management strategies seek to prevent or delay the development of resistance to a pesticide while at the same time maintaining an effective level of disease control [104]. Strategies to decrease insecticide resistance may include rotations, mosaics, and mixtures of agricultural and environmental insecticides guided by mathematical models [118]. Monitoring of vector resistance to pesticides should be an integral component of the planning and evaluation of vector-borne disease control programmes [119].

2.2.8 Climate and malaria

Malaria is governed by a number of environmental factors which affects its distribution, seasonality and transmission intensity [120]. It is well established that climate is an important determinant of the spatial and temporal distribution of vectors and pathogens [121]. The principal climatic factors influencing malaria transmission are temperature, rainfall and humidity.

Temperature and humidity determines the length of mosquito cycle and the sporogonic cycle of the parasite in the mosquito. Climatic conditions considered suitable for parasite development and transmission through the mosquito stage of its life cycle are temperatures within the range 25°C and 30°C while below 16°C parasite development is believed to decrease significantly. Above 32°C parasite development slows down

considerably and the survival of the mosquito is compromised. Relative humidity greater than 60% is also considered a requirement for mosquito survival [122].

In addition to the direct influence of temperature, rainfall determines the number and productivity of breeding sites and ultimately the vector density [77]. Rainfall and surface water is required for egg laying and larval stages of the mosquito life cycle and monthly rainfall of 80 mm is considered suitable. Numerous studies have demonstrated the association between *An. gambiae* complex abundance and rainfall [123].

Malaria sensitivity to climate was demonstrated in desert and highland fringe areas where rainfall and temperature were found to be critical parameters for disease transmission [124]. The effect of climate change on malaria transmission was seen in Kenya following the1997/98 El Niño, which caused devastating falciparum malaria epidemics [125]. Climate-related epidemics were also reported in southern Africa and have been attributed to heavy rainfall following a drought [67].

2.2.9 Socio-economic factors

In most malaria-endemic areas, scarce resources and socio-economic instability hinder efficient malaria control activities [126]. Factors such as health seeking practices and population growth determine the vulnerability of populations to malaria. Studies have shown that severe consequences of malaria are borne most heavily by the poorest citizens [16]. Impoverished families often reside in dwellings that offer little protection against mosquitoes and are less able to afford some form of personal protection. The lack of resources at both national and household levels, leaves these families with few options for malaria prevention and control, and limited access to appropriate health care services and are therefore at greater risk of malaria complications and death [127].

Child mortality rates are known to be higher in poorer households and malaria responsible for a substantial portion of these deaths [127]. The demographic surveillance system in rural areas of Tanzania has indicated that under 5 years mortality was 39%

higher in the poorest socio-economic group than in the richest [128]. A survey conducted in Zambia also found a substantially higher prevalence of malaria infection among the poorest population groups [129]. Poor medical practices in these areas such as misuse and under/overdosing of antimalarial treatment have been implicated in the development and spread of drug resistant malaria [63].

Malaria-related illness, in turn, has a direct impact on economic productivity. A study in the Côte d'Ivoire found that farmers diagnosed as sick from malaria for more than two days out of a growing season had 47% lower yields and 53% lower revenues than farmers who missed no more than two days of work [130]. According to van der Hoek [131], families highly affected by disease may turn from growing higher value crops to less labour intensive and yield-sensitive products, with consequences for household income and nutrition.

Malaria-endemic countries are not only poorer, they also have low rates of economic growth [2]. An analysis of economic growth over 25 years found that countries with intense malaria had 1.3% lower GDP growth rates than those in comparable countries with less intense malaria [132]. Another analysis found that countries with more than 50% of the population living at risk of infection from malaria parasites had average income levels that were one third of those in countries with less intense rates of disease, even when other confounding factors were removed [2].

2.3 Current malaria control strategies

2.3.1 Early diagnosis and effective treatment

Case management which encompasses prompt access to health care, accurate diagnosis and effective treatment is the other cornerstone of malaria control [133]. The diagnosis of malaria is based on clinical criteria, supplemented by the detection of parasites in the blood [134]. Conventional malaria diagnosis method uses the microscopic

examination of thick and thin blood films stained with Geimsa, Wright or Field stain [135]. Under optimum conditions, microscopy can detect 20-50 parasites/μL blood. Although microscopy is simple and inexpensive, to achieve high sensitivity requires training of microscopists, quality control and adequate equipment and maintenance [31]. Alternatively, several rapid diagnostic tests (RDTs) based on antigen-capture techniques have been developed that have high sensitivity and specificity for falciparum malaria and also greatly contributes to improved malaria diagnosis [136,134].

Prompt and effective treatment is probably the most cost-effective element of malaria control [137]. Effective treatment in the early stages of falciparum malaria reduces the risk of death as much as 50-fold, whereas treatment after progression to severe illness produces only a five-fold reduction in the risk of dying [99]. In areas of low transmission, prompt treatment can interrupt malaria transmission by reducing the number of gametocytes that can be transmitted to the mosquito host [138].

Resistance to earlier drugs has occurred in most countries including South Africa, necessitating changes in drug use policies. Combination therapy with drugs with different modes of action is now the preferred approach to malaria treatment to inhibit the emergence and spread of parasites resistant to one component of the combination [139]. WHO recommends the treatment of uncomplicated falciparum malaria infection with ACTs [135]. ACTs has the advantages of rapid clinical and parasitological response, improved cure rate, decreased malaria transmission and the potential to delay anti-malarial resistance. Parenteral artemisinin derivatives, notably artemether and artesunate have been successfully used for treating severe malaria in South Africa [140].

2.3.2 Vector control (IRS)

At the end of the 19th century, a number of targeted approaches for the interruption of transmission and appropriate diagnosis and treatment of malaria were discovered [141]. Early vector control measures included the screening of houses, house spraying with pyrethrum, the use of mosquito nets, drainage or filling of swamps and other water bodies used by insects for breeding and the application of oil the breeding sites [142,143]. This was aimed at breaking the chain of transmission at points, which could be combated successfully in different areas [28].

The mid 1940's represents the beginning of the modern era of organic pesticides when DDT was first used as an insecticide for vector control in many countries. Paul Muller discovered the high insecticidal properties of the synthetic compound [144]. It was originally used during World War II to control typhus and malaria vectors. Since then it has been used to control mosquito-borne diseases and was used extensively in agriculture [3]. Since its discovery, DDT was viewed as a major breakthrough in the history of vector-borne disease control. Malaria was eradicated in some developed countries, e.g. USA, Southern Europe, USSR, parts of Asia, Australia, and most Caribbean Islands, however, the same achievement were not achieved in most African countries [145]. In southern Africa, malaria vector control programmes with DDT were implemented more than 50 years ago and had a profound impact on malaria incidence in South Africa, Zimbabwe and Swaziland [53,146].

The application of IRS consistently over time in large areas has altered the vector distribution and subsequently the epidemiological pattern of malaria in sub-Saharan Africa. The major vector, *An. funestus*, has been eliminated or reduced to negligible levels. *An. gambiae s.s.* which rests and bites mostly indoors was also controlled. The vector currently responsible for low levels of transmission and seasonal increases and outbreaks, *An. arabiensis* is less affected by IRS even at high coverage levels since it does not rest indoors as much as *An. funestus* and *An. gambiae* [100].

Despite the marked success of DDT in malaria eradication, concerns related to extensive use began to appear in the 1950's [147]. Widespread public opposition to DDT began in 1962 with the publication of Silent Spring by Rachel Carson. Because of the growing environmental concerns, DDT was widely banned as an agricultural pesticide because of its potential human and wildlife health effects, their tendency to bioaccumulate and their ability to persist in the environment [148]. In view of the toxic characteristics of most organochlorine compounds, the Stockholm Convention on Persistent Organic Pollutants listed a number of them including DDT and were earmarked for elimination. Countries that continued to use DDT as an effective insecticide for vector control lobbied to have the insecticide removed from the list and succeeded in having DDT classified as a restricted pesticide for public health purposes [149,150]. Selected parts of the world where malaria remain a serious public health challenge, such as South Africa, Ethiopia, Kenya, Mozambique, Zambia, Madagascar and Zimbabwe, still use DDT as a residual insecticide to reduce malaria transmission [151,152].

2.3.2.1 Effects of IRS with insecticides

i. Human health effects

Although DDT was viewed as a major breakthrough in the history of vector-borne disease control [28,143], concerns started to emerge that residues of DDT and its metabolites were found in the environment [153]. These compounds are readily adsorbed onto sediments and soil and they can result in bioaccumulation through the food chain posing a risk to human health [154]. Trichopoulos et al. [155] reported that the bioaccumulation of DDT and dichlorodiphenyldichloroethylene (DDE) in humans occurs in adipose tissue at much higher level and to a lesser extent in the blood stream and breast milk.

There is increasing awareness and concern from new scientific evidence about indoor spraying with DDT being a significant source of human exposure to DDT and its metabolites DDE and dichlorodiphenyldichoroethane (DDD) [4]. More recently, the Pine River Statement [156] has revealed substantial evidence that suggest that DDT and DDE

pose a serious risk to human health, particularly due to IRS for vector control. Several health effects to DDT has been reported in North America and Europe and these includes, pregnancy loss, preterm birth, decreased lactation, fertility loss, leukemia, breast cancer, neuro-developmental deficits, diabetes and breast cancer [157-160].

Epidemiological studies conducted in South Africa, has revealed that inhabitants of houses sprayed with DDT has significantly higher body burdens and breast milk concentrations of DDT than residents of unsprayed houses [161]. While other studies suggests that non-occupational exposure through IRS can also be associated with impaired semen quality in men [162,163], the likelihood of sperm DNA damage in young males [164] and urogenital birth defects in neonates [165,166]. Exposure assessment studies conducted in other settings have also identified exposure of the foetus and young children through the placenta and through lactation [167]. Herrera-Portugal and others [168] reported that the exposure of children and adults to DDT is likely to occur through direct contact with DDT in the environment, indoor soil and household dust and through food chain.

ii. Environmental effects

Pesticides are included in a broad range of organic micro-pollutants that have ecological impacts. The greatest potential for unintended adverse effects of chemical compounds is through contamination of the hydrologic system, which supports aquatic life, drinking water, irrigation, and many other purposes. More than a thousand pesticides currently used in most countries in the world inadvertently reach the aquatic ecosystems. Contaminants can pollute water, sediment and aquatic biota through; surface runoff in agriculture and forestry, public health control of insect vectors or pests and from accidental spraying of water bodies and spills [153,169,4].

Most documented environmental damage is thought to be associated with agricultural use of pesticides. However, some risk of contamination can be due to accidental spillage,

washing of spray equipments or disposal of obsolete chemicals in areas of IRS [4]. Some insecticides have a persistent behaviour (i.e. DDT) and although present in trace quantities in the environment, they can result in bioaccumulation through the food chain and pose a risk of causing adverse effects to human health and the environment [151].

Traces of a number of pesticides (predominantly organochlorines) have even been detected in regions, such as the Arctic, where these chemicals were never used [170]. The likelihood and significance of pesticide occurrence in the hydrologic environment is governed by factors such as use, practices and chemical properties of pesticides [171]. Their bioaccumulation and bioconcentration in the food chain has since posed long-term risks to non-target species [172,147]. Effects at the organism or ecological level are usually considered to be an early warning indicator of potential human health impacts.

2.3 Alternative control strategies

i. Integrated Vector Management (IVM)

IVM strategies are designed to achieve the greatest disease control benefit in the most cost-effective manner, while minimizing negative impacts on ecosystems (e.g. depletion of biodiversity) and adverse side-effects on public health. The IVM approach stresses the importance of first understanding the local vector ecology and local patterns of disease transmission, and then choosing the appropriate vector control tools from the range of options available [173]. IVM takes into account the available health infrastructure and resources and integrates all available and effective measures, whether chemical, biological or environmental [174].

ii. Biological control

The best known microbial larvicides for mosquito control include *Bacillus thuringiensis israelensis* and *Bacillus sphaericus,* which are naturally occurring bacteria that synthesize potent larvicidal toxins [175]. *Bacillus thuringiensis israelensis* spores produce a toxin that is poisonous to mosquitoes and other aquatic insects but harmless to plants, animals,

and humans. *Bacillus sphaericus* is a common bacterial species found in a variety of soils and aquatic habitats is an effective mosquito larvicide. This organism multiplies in polluted waters, and produces a longer-acting toxin than *Bacillus thuringiensis israelensis*. Duration of effectiveness of these organisms depends primarily on the mosquito species, the environmental conditions, the formulation of the product and the water quality [176].
In other settings, field trials and pilot studies have shown good potential of both bacteria to manage mosquito breeding and to reduce biting rate [175]

Introduction of larvivorous fish into mosquito breeding sites may effectively reduce populations of mosquitoes. The most commonly used larvivorous fish species is *Tulapia, Poecillia* and G*ambusia*. These species have been successfully used in malaria control projects in several settings [8] as they are a safe option that can be easily introduced in defined breeding sites. To be successful certain characteristics are required of the fish species. It must be a surface feeder, as mosquito larvae are found near the water surface [177].

Genetic strategies are aimed at replacing natural vector populations of mosquitoes with populations which are unable to support complete development of the malaria parasite [34]. The oldest form of genetic control is sterile insect technology (SIT). The strategy depends on progress in three areas: the identification of parasite inhibiting genes, the development of techniques for introducing such genes into the mosquito genome, and the availability of strategies for spreading these genes through the vectors natural populations [83]. More research is in progress concerning the potential of using genetic modification to control malaria [178].

iii. Environmental management

Environmental management strategies include the reduction or elimination of vector breeding grounds altogether through improved design or operation of water resource development projects. It may entail one of two options (or both) environmental modification and environmental manipulation [174]. Environmental modification aims to

create a permanent or long-lasting effect on land, water or vegetation to reduce vector habitat. Such modifications may either sustainably control or destroy vector habitats over the long term. Environmental manipulation refers to activities that reduce larval breeding sites through temporary changes, such as the periodic removal of aquatic weeds or the removal of river vegetation to manipulate shade and sunlight conditions; altering cycles of irrigation and dry farming; or maintenance of canal-lining to prevent seepage leading to the development of vector breeding pools [173].

2.4.1 Personal protection measures

i. House siting and design

The proximity of houses or villages to a breeding site strongly influences malaria risk, especially where breeding sites are restricted [101]. In a suburb of Dakar, Senegal, malaria prevalence rose steeply from the center to the edge of town adjacent to marshy breeding sites of *An. arabiensis* [179]. In Sri Lanka, the risk of malaria was much higher among those who lived in poor quality houses within 2.5 km of a river where *An. culicifacies* bred [180].

House design and construction also influence the risk of malaria [181]. Eaves which allow interior ventilation and the escape of smoke from cooking fires are a common feature that facilitates mosquito access to sleeping areas in houses. Using mud or plaster to fill in eaves [182], or hanging eaves curtains [183] reduces human-vector contact.

ii. Insecticide Treated Nets (ITNs)

The development of pyrethroids with long lasting residual action and low mammalian toxicity suggested the possibility of treating mosquito nets as a new tool for vector control [1]. Insecticide treated nets are increasingly promoted as a relatively effective and inexpensive method for reducing human-mosquito contact. ITNs have repeatedly been shown to reduce severe disease and mortality due to malaria in endemic regions [184].

Community-wide trials on ITNs in several African settings have shown a reduction in malaria mortality by about 20% [185-189]. In a study conducted in Kenya, substantial health gains in both children and pregnant women were observed and, improved survival and health of adjacent homes to those using ITNs [190]. The prospects of ITNs as a complementary vector control measure have not been fully explored in South Africa.

Despite the proven benefits and cost-effectiveness of ITNs, achievement of widespread use has proved difficult [139]. In most sub-Saharan countries, only a small percentage of individuals who should be protected by nets use them [191-193]. Cost recovery for nets and insecticides makes them unavailable to the most vulnerable groups.

There are several debates surrounding the use and applicability of ITNs as a vector control measure, such as: (i) in high transmission areas where immunity develops over time, fewer infected bites may lead to delayed immunity and result in an increase in the number of cases of severe disease in older children; (ii) costs of nets and re-impregnation has proved difficult to sustain on a large scale, especially if householders have to pay for it [139]; (iii) ITNs usage may encourage the proliferation of anopheline mosquitoes that bite outdoors and; (iv) concerns that the emergence of pyrethroid resistance in major malaria vectors may compromise the sustainability of ITNs for malaria control [107].

iii. Zooprophylaxis

Zooprophylaxis refers to the strategic placement of domestic animals that may potentially divert vectors from humans to animal hosts. However, this diversion depends entirely on the biting habits of the local vector and varies from species to species [173]. In some cases, livestock may actually attract certain mosquitoes that would otherwise avoid human habitats, resulting in increased malaria exposure to household members [194, 195].

iv. Repellents, aerosols and fumigants

Other alternative vector control methods include the use of locally available plants or plant materials as mosquito repellents or as larvicides [196]. Products of the neem tree have been shown to exhibit a wide range of effects on mosquitoes. Neem oil extract from its seeds has repellent properties and has been successfully tested as a larvicide for anopheline mosquito control [173].

2.5 Novel prevention and control strategies

i. Insecticide wall papers

Research conducted in Benin showed that wallpapering huts with sheeting made from insecticide-treated plastic could be a new tool for malaria control. The study showed the combination of carbamate-treated plastic sheeting and pyrethroid-treated nets is a potential alternative strategy for controlling pyrethroid-resistant vectors, particularly in rural Africa [197].

ii. Fungal spray

The use of fungal spores to combat DDT and permethrin resistant mosquitoes when sprayed on indoor surfaces has shown promising results in West Africa. Trials conducted under laboratory conditions, fungal spores from *Beauveria bassiana* and *Metarhizium anisopliae* proved effective in killing both laboratory-bred and wild mosquitoes [198].

iii. Malaria vaccine

Attempts to develop a malaria vaccine began early in the 20th century, and in spite of advances in biomedical technology, no effective vaccine has been introduced for widespread use [199]. The first trials of the asexual blood stage candidate vaccine, SPf66 showed that it did not afford significant protection from *P. falciparum* malaria [200-202], despite earlier encouraging results from experimental trials in Columbia [203]. To date, efforts have been directed in the development of a pre-erythrocytic vaccine RTS,S/AS02A. This vaccine has so far demonstrated promising results by providing 30%

protection against the first clinical episode and 58% protection against severe malaria in Mozambican children [204]. A successful malaria vaccine, used in conjunction with other control interventions has the potential to greatly reduce morbidity and mortality associated with severe malaria in areas of intense transmission [205, 206].

In summary literature tells us that control of malaria presents one of the greatest public health challenges, particularly in many malarious regions of the world. It is clear that current control and prevention strategies are fraught with technical and operational issues such as the spread of drug-resistant strains of *P. falciparum*, mosquitoes becoming resistant to insecticides, limited malaria drugs and lack of resources, have conspired to make the implementation of disease control programmes difficult.

Control of malaria has relied mainly on indoor application of residual insecticides (i.e. DDT) for many decades. Evidence of the effectiveness of insecticide usage for malaria control was apparent from the elimination of malaria in some countries. However, insecticides, like most other chemicals have the potential to produce both acute and chronic injury to human health and thus becoming a major public health concern. There is a growing pressure from the Stockholm Convection on POPs to reduce the incidence of malaria around the globe while reducing reliance on DDT. Research into alternative control strategies such as the IVM strategies is desirable in order to do away with chemical vector control.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study setting

Mpumalanga Province lies in the eastern part of South Africa, bordering Mozambique in the east and Swaziland in the south. The province is divided into two regions, the Highveld and Lowveld. The Highveld is much cooler, situated at an altitude >600 m above sea level, while the Lowveld is subtropical with summer (September - April) and winter (May - August); temperature ranges from 17-30°C and 8-17°C respectively, with relative humidity of 80% in summer. The rainy season is from October to May with a mean annual rainfall of 650 mm. The two regions are administratively divided into three districts: Ehlanzeni (Lowveld), Nkangala (Highveld) and Gert Sibande (Highveld) (Figure 3.1). The districts are further sub-divided into 24 municipalities.

Current vector control interventions in Mpumalanga Province include IRS and larviciding. Regular spraying of interior walls of houses is carried out in the high risk malaria areas, a seasonal round from August to February each year. The residual insecticides of choice for indoor application are DDT for traditional structures and, carbamates and synthetic pyrethroids for western type structures. To control mosquito larvae, larviciding operation by use of Temephos (organophosphate) is carried out on identified of breeding sites.

Figure 3.1: A map of Mpumalanga Province and its neighbouring countries. [207]

3.2 Study design

This is a descriptive retrospective study based on the analysis of secondary malaria surveillance data (cases and deaths), spray data and climate data in Mpumalanga Province from 2001 to 2009.

3.3 Data collection

The following retrospective records were collected: malaria cases and deaths, spray data, mean temperature climate (mean temperature, relative humidity and monthly rainfall).

3.3.1 Malaria morbidity and mortality data

All malaria data for the period under review (2001-2009) were obtained from the provincial Integrated Malaria Information System (IMIS) under Malaria Control Programme of the Department of Health and Social Services. The information system has been in operation in the province for many years and its design is described elsewhere [208].

A confirmed malaria case was defined as patients with clinical features of malaria in whom *Plasmodium* parasites were detected on peripheral blood smears by microscopy or rapid diagnostic test at health care facilities or at community level through active surveillance. Malaria-attributed mortality, defined as patients in whom malaria was recorded as a cause of death on the death certificate.

Malaria morbidity and mortality data consisting of both passive and active cases based on definitive diagnosis reported from 2001 to 2009 were extracted from the IMIS. The data consisted of the following variables: date of diagnosis, age, gender, municipality, source country, source province and locality. Since malaria transmission in South Africa is seasonal, data were aggregated by season rather than by calendar year. A malaria

season was defined to be the period from the beginning of July to the end of June the following year. Data for Bushbuckridge municipality (former Bohlabela district in Limpopo province) (Figure 4.8) were only available from 2006, post its integration into Mpumalanga Province [209].

3.3.2 IRS data

Data for IRS activities carried out during the study period was obtained from the computerized spraying management system which is maintained in Mpumalanga Province [210]. Activities pertaining to IRS are reported on a seasonal basis, which takes place from August to February the following year. Variables recorded in this database includes: the type of insecticide used, structures targeted for spraying, number of structures sprayed, amount of insecticide used (kg) and localities sprayed.

3.3.3 Climate data

Climatic records for 2001 to 2009 were obtained from the South African Weather Service and consisted of the following variables: mean monthly temperature ($^{\circ}$C) (minimum and maximum), mean monthly relative humidity (%) and mean monthly rainfall (mm).

Climate suitability for malaria transmission is defined as a monthly rainfall greater than 80 mm, mean temperature between 18°C and 32°C and relative humidity greater than 60% [9]. These are thresholds that describe conditions that are suitable for both the development of *Plasmodium* parasite and the life cycle of the mosquito vector.

3.4 Data analysis

Data were entered and validated using Microsoft Access and Excel and checked for errors and consistency. Statistical analyses were performed using Stata version 11 software [211].

To evaluate the effect of IRS intervention on malaria prevalence, malaria trends and patterns over time were evaluated. The effect of IRS intervention was quantified by computing the total amount of insecticide used and the number of structures sprayed in relation malaria cases notified per spray season. Descriptive statistics were computed which included: mean values, standard deviations (SD), proportions and 95% confidence intervals (CI). Malaria incidence rates were estimated using the mid-year population estimates for the years 2001 to 2009 [212] as well as population counts from the 2001 national census [213]. The incidence of malaria per 100,000 population were computed for each malaria season by age, gender and administrative level (country, province, district and municipality). Malaria case fatality rates for the period under review were computed by dividing the number of malaria deaths by the total number cases. Pearson's chi square tests were used to evaluate the associations between categorical variables (gender, country, province and district) and malaria outcomes. The chi square test for trend was used to assess trends over the eight-year period. Differences at $p < 0.05$ were regarded as statistically significant.

Time series analysis was used to assess the effect of climatic factors on malaria by fitting ARIMA models on the data for 2001-2009. The models were developed using the mean monthly malaria case numbers as dependent variable and mean monthly climatic variables as independent variables. The goodness-of-fit of the models were checked for adequacy using suitable diagnostic methods (i.e. plotting the residuals of the model).

3.5 Data quality

As this study relies on surveillance data, it is likely that the quality of the data is subjected to reporting inconsistencies, incompleteness of notification forms and flawed data capturing and, therefore, presenting missing data variables. Despite these shortcomings, it is worth nothing that routinely collected data through the provincial malaria surveillance system remains the basis for measuring malaria trends over time when cautiously analyzed and interpreted. The findings of this study are therefore not expected to be substantially affected by data quality.

3.6 Ethical considerations

The study was reviewed and approved by the School of Health Systems and Public Health Academic Advisory Committee (Approved on: 16/02/2010) and the Research Ethics Committee of the University of Pretoria (Approved on: 21/04/2010, Reference no. 72/2010). Approval and permission to access malaria data was also obtained from Mpumalanga Provincial Department of Health (Approved on: 25/06/2010).

CHAPTER 4

RESULTS

4.1 Malaria trends and distribution

4.1.1 Malaria case notification and incidence rate

Table 4.1 gives the number of cases, malaria deaths and case fatality rate by malaria season. From July 2001 to June 2009, a total of 35,191 (mean 4,399; 95%CI 1,631-7,167) confirmed malaria cases were notified in Mpumalanga Province. The number of cases per malaria season ranged from 12,125 cases in 2001/02 to 1,805 cases in 2008/09, with the seasonal mean (SD) ranging from 1,010.4 (599.6) to 150.4 (94.9) cases. The number of notified malaria cases showed a decreasing trend from 2006/07 (2,288) to 2008/09 (1,805).

Table 4.1: Number of reported malaria cases and malaria-attributed deaths, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

Malaria season	No. of notified cases	Mean notified cases (SD)	95% CI	Malaria deaths	CFR (%)
2001/02	12,125	1,010 (599.6)	629 – 1,391	34	0.28
2002/03	4,050	338 (192.8)	215 – 460	14	0.35
2003/04	4,710	393 (197.6)	267 – 518	30	0.64
2004/05	3,112	259 (137.2)	172 – 345	18	0.58
2005/06	4,680	390 (361.9)	160 – 620	25	0.53
2006/07	2,288	191 (90.7)	133 – 248	16	0.71
2007/08	2,421	202 (166.5)	96 – 308	18	0.74
2008/09	1,805	150 (94.9)	90 – 211	9	0.51
Total	35,191	4,399 (3,311.1)	1,631 – 7,167	164	0.54

SD: Standard deviation; CI: Confidence interval; CFR: Case fatality rate expressed as a percentage

The incidence of malaria for 2001/02 to 2008/09 was 134 cases per 100,000 population (95% CI 44.4- 224.1), ranging from 385 cases per 100,000 in 2001/02 to 50 cases per 100,000 in 2008/09, indicating a significant decrease (x^2 = 21.3; P = 0.003). The incidence rates fluctuated over the years with peaks observed in 2003/04 (145), 2005/06 (145) and 2007/08 (68). A steep reduction of almost 70% was observed between 2001/02 and 2002/03 malaria seasons and thereafter maintained at between 145 and 50 per 100,000. Figure 4.1 shows the trends in annual incidence of malaria per 100,000 during the period 2001/02 to 2008/09.

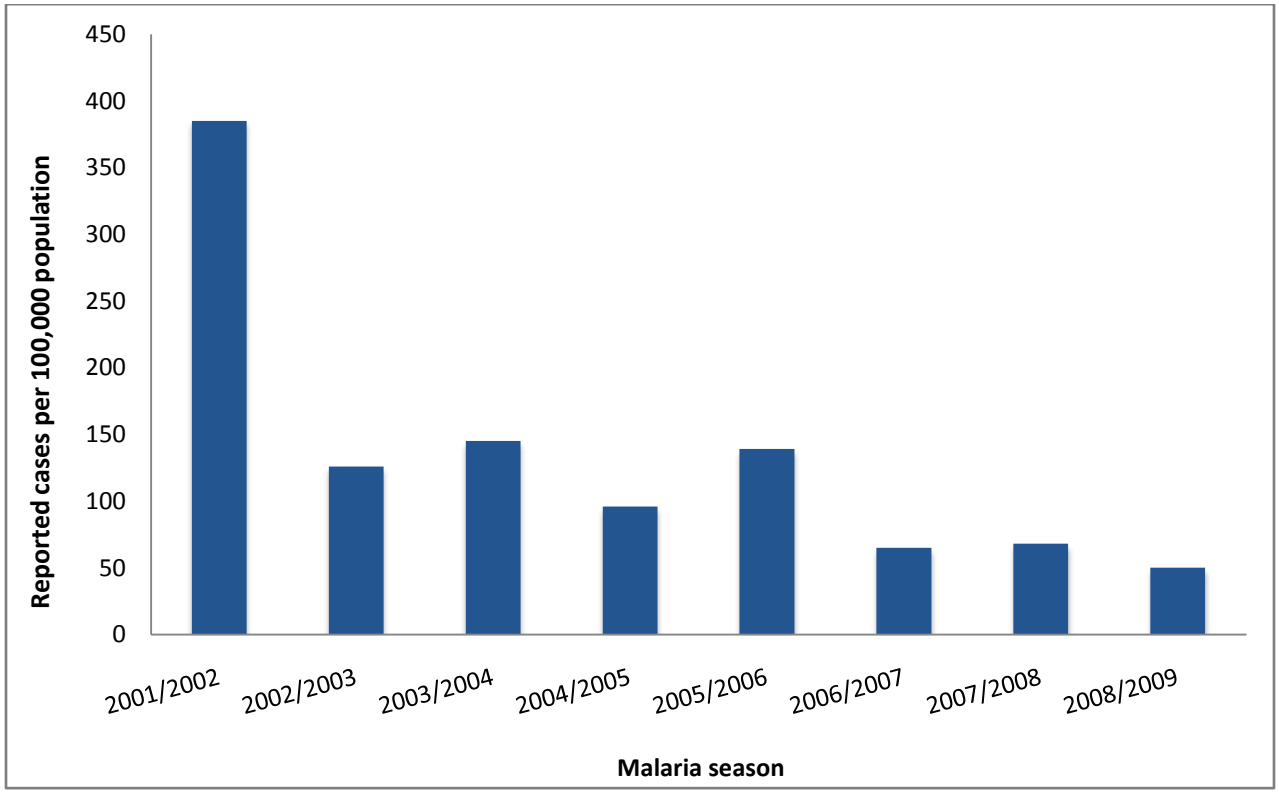

Figure 4.1: Incidence of malaria (per 100,000 population) in Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

4.1.2 Malaria according to age and gender

The incidence estimates of malaria according to age are given in Table 4.2, indicating that all age groups were affected. The mean (SD) age was 26 years (16) and range, 0 to 96 years. There were significant differences in malaria incidence among the different age groups (x^2 = 556.0; P < 0.001). Of all the cases notified, 9% (95% CI: 8.8% –9.4%) were among those under the age of 5 years, 14% (95% CI:13.8% –14.5%) among those 5-14 years, 24% (95% CI: 23.6% – 24.5%) those in the age group 15-24 years, 26% (95% CI: 25.8% – 24.5%) in the 35-44 years age group, 15% (95% CI: 14.3% –15%) among those 35-44 years and those over the age of 45 years made up the difference.

Table 4.2: Age-specific malaria incidence and case fatality rate, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

Age group (years)	Seasonal mean notified cases (SD)	Proportion (%)	CFR (%)	Malaria incidence (per 100,000 population)
0-4	401 (321.8)	9	0.28	97
5-14	622 (624.1)	14	0.14	70
15-24	1,056 (894.8)	24	0.22	128
25-34	1,157 (720.1)	26	0.39	190
35-44	645 (413.9)	15	0.7	151
45-54	307 (188.0)	7	1.22	106
55-64	134 (108.7)	3	1.31	75
>65	77 (67.4)	2	2.11	50

SD: Standard deviation

As illustrated in Figure 4.2, males had significantly higher malaria infections than females in all age groups, accounting for 59.3% (95% CI: 58.7% – 59.8%) of all confirmed cases and 40.7% (95% CI: 40.2% – 41.3%) in females; the test for trend was statistically significant (x^2 = 291.3; P < 0.001). The mean incidence rate was 166.9 cases per 100,000 in males (95% CI: 164.6 – 169.2) and 106.4 cases per 100,000 in females (95% CI: 104.7 – 108.1). In both males and females, the incidence of malaria was increasing from age 5-14 years, reaching a peak at age 25-34 years (190 cases per 100,000), declining thereafter (50 cases per 100,000 in those >65 years).

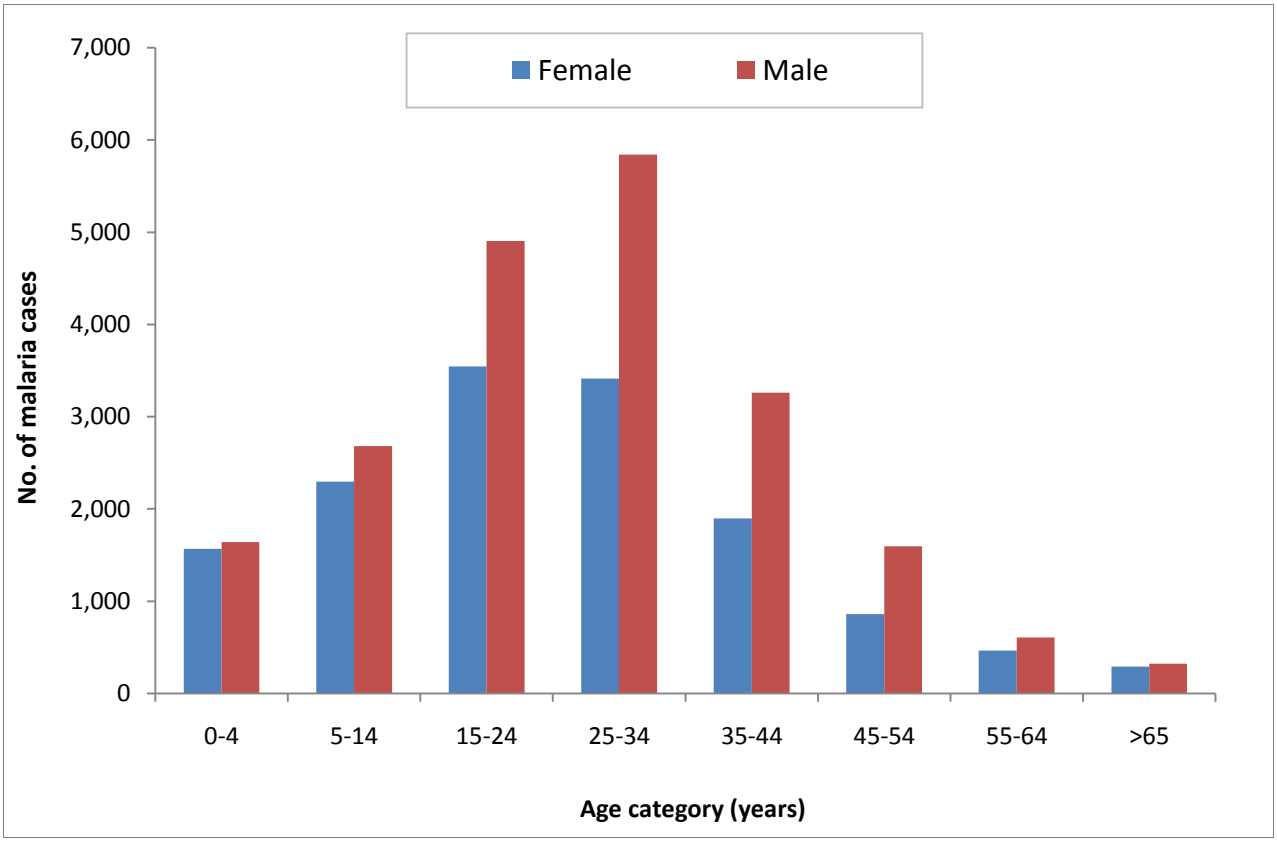

Figure 4.2: Seasonal distribution of malaria by age group and gender, 2001/02 - 2008/09 malaria seasons.

4.1.3 Malaria-attributed mortality and case fatality rate

A total of 164 deaths-attributed to malaria were recorded between 2001 and 2009 in Mpumalanga Province. The annual number of malaria deaths have significantly declined by approximately 74% from 34 in 2001/2002 to 9 in 2008/2009 (x^2 = 28.2; P < 0.001). The case fatality rate fluctuated over the years ranging from 0.28% to 0.74% (Figure 4.3). Significantly high case fatality rates were observed in 2006/2007 (0.71%) and 207/2008 (0.74%) and subsequently followed by a marked decline reaching the 0.5% in 2008/09.

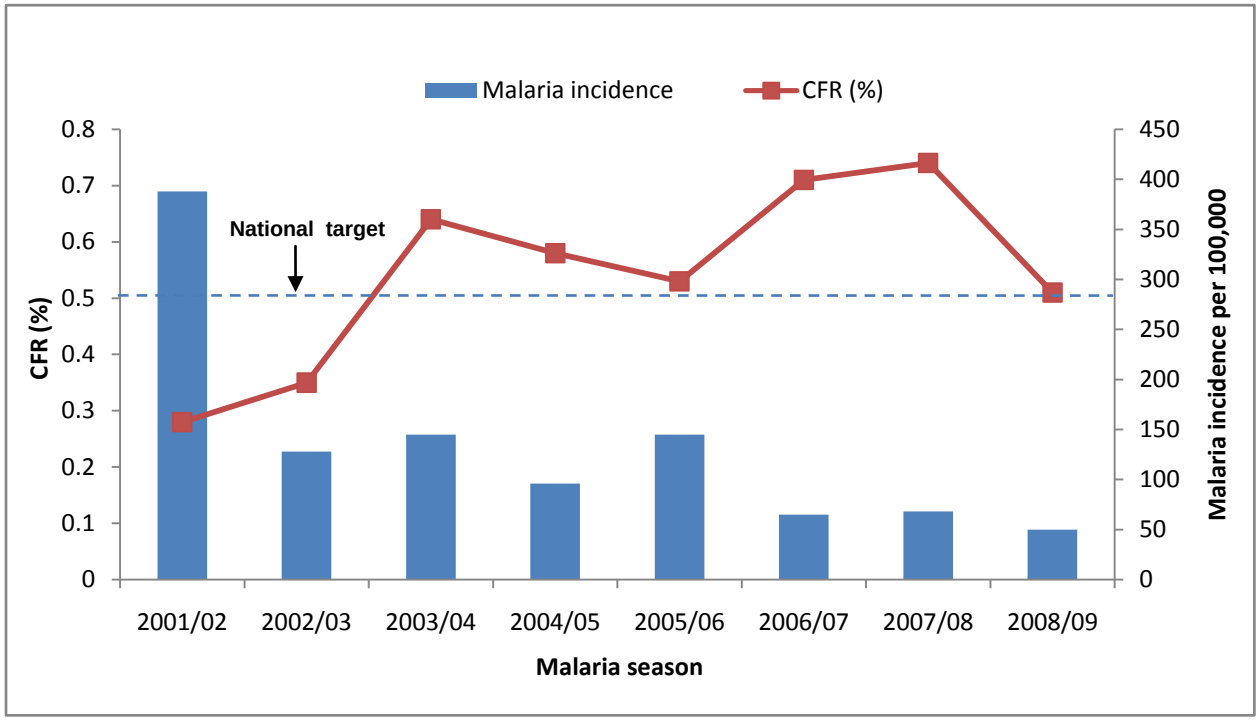

Figure 4.3: Malaria incidence rate and case fatality rate (CFR) by season, all ages, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

4.1.4 Age and gender-specific malaria mortality

Malaria-attributed mortality increased with increasing age, more pronounced in the age group 25-34 years in females and 35-44 years in males (Table 4.3). It can be seen that in Mpumalanga malaria-attributed mortality was lower in infants and children (0-14 years) accounted for only 9% of all malaria-attributed deaths, increasing from the age group 15-24 years (12%), reaching a peak at the age group 25-34 and 35-44 years (both groups comprised 22%) and the remaining age groups (>45 years) combined, constituted about 35%.

There were significant differences in the CFR among males and females (x^2 = 21.3; P < 0.001), the mean CFR was 0.41% and 0.55%, respectively. The impact of malaria is seen in the older age groups from age 45-54 years to those above the age of 65 years, the CFR ranged from 1.22% to 2.11%.

Table 4.3: Age and gender-specific malaria-attributed mortality in Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

Age group (years)	Malaria-attributed deaths (%)	Female (CFR)	Male (CFR)	CFR (%) (Female & Male)
0-4	9 (5)	5 (0.26)	4 (0.30)	0.28
5-14	7 (4)	5 (0.22)	2 (0.07)	0.14
15-24	19 (12)	13 (0.37)	6 (0.12)	0.22
25-34	36 (22)	22 (0.64)	14 (0.24)	0.39
35-44	36 (22)	11 (0.58)	25 (0.77)	0.7
45-54	30 (18)	12 (1.40)	18 (1.13)	1.22
55-64	14 (9)	6 (1.29)	8 (1.32)	1.31
>65	13 (8)	6 (2.06)	7 (2.16)	2.11

4.1.5 Seasonal malaria variation

It can be seen in Figure 4.4 that malaria transmission in Mpumalanga Province followed a distinct pattern over the eight years of the study period. Although malaria cases were prevalent throughout each year, transmission was distinctly seasonal increasing between September and May and decreasing from June to August. Distinct peaks are apparent in January and February each year. The pattern of malaria transmission in Mpumalanga Province was more pronounced in the 2001/02 season followed by a marked increase in the 2005/06 season. In general there was a downward temporal trend with some inter-annual variation throughout the eight year period.

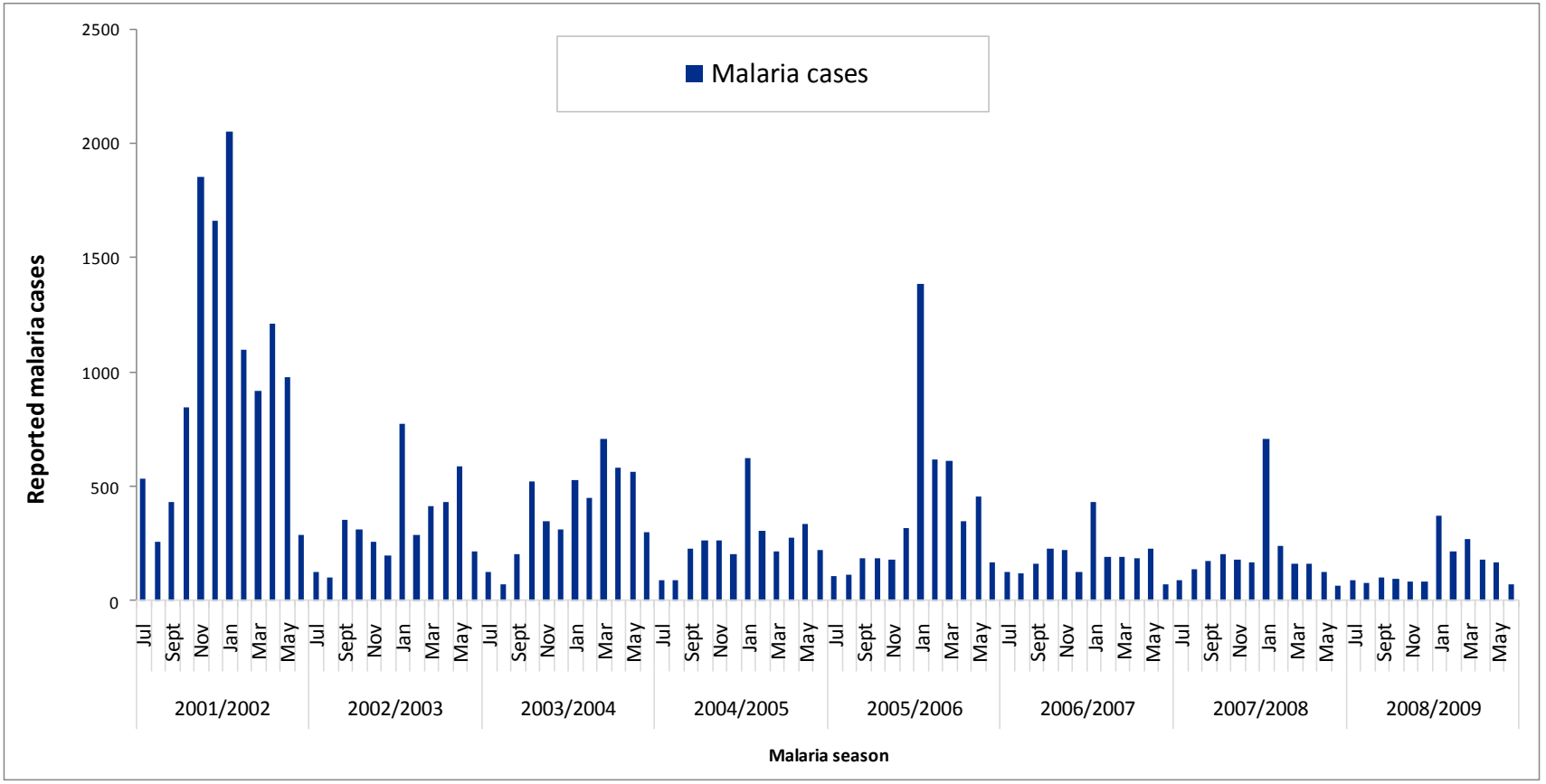

Figure 4.4: Monthly distribution of malaria cases in Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

4.1.6 Geographical sources of malaria infection

Figure 4.5 presents the geographical sources of malaria infections in Mpumalanga Province over the period of eight years (2001-2009). About half (50.1%) of the notified malaria cases were acquired in Mpumalanga Province. The remainder of the cases (49.8%) were imported from other regions, while <1% (37) of these, the source of infection was not captured. The distribution of malaria varied widely across the three districts of Mpumalanga Province ($x^2 = 43.4$; $P < 0.001$).

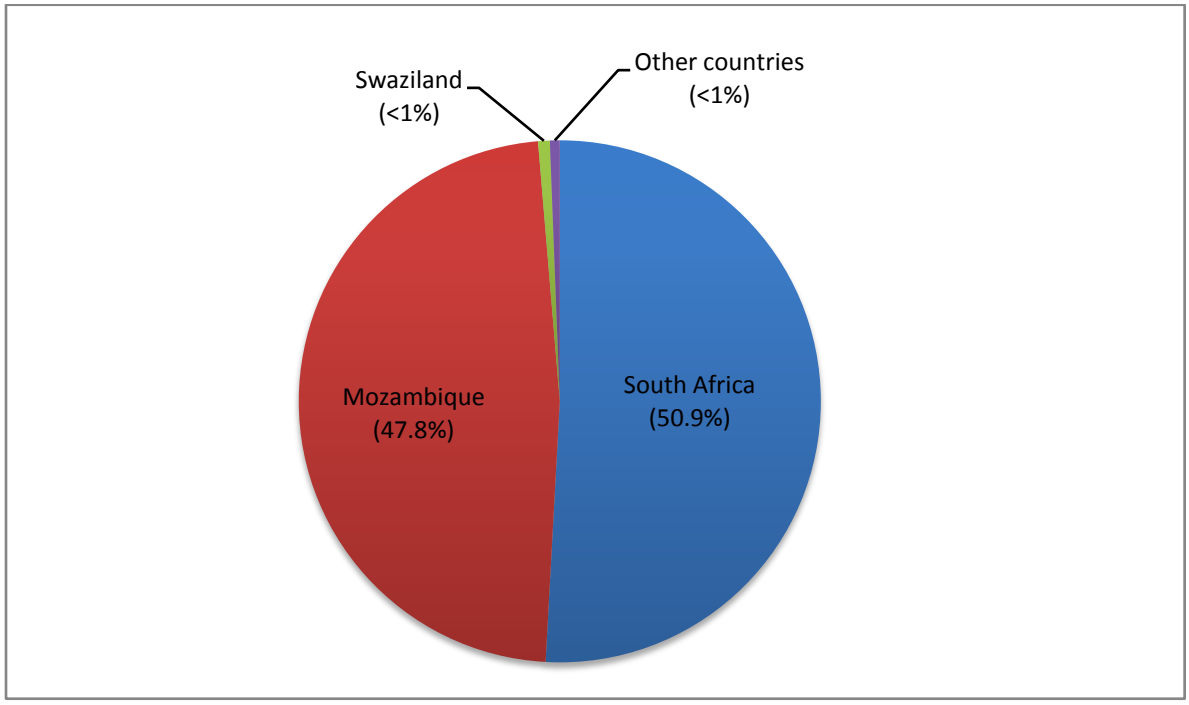

Figure 4.5: Proportion of reported malaria cases by source country, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

As can be seen in Table 4.4, half of all the notified malaria cases were cases acquired in Mpumalanga Province (50.1%; 95% CI 49.6%-50.6%) with less than 1% of these acquired in other provinces of the country.

Table 4.4: Malaria cases by source province, 2001/02 - 2008/09 malaria seasons.

Province	No. of notified cases	Proportion (%)	95% CI
Gauteng	8	0.02	0.01 – 0.04
Kwazulu-Natal	21	0.06	0.03 – 0.09
Limpopo	226	0.64	0.56 – 0.73
Mpumalanga	17,882	50.1	49.6 – 50.6
North West	1	0.003	-0.0 – 0.01

4.1.7 Malaria distribution by geographical area

Analysis of cases originating from Mpumalanga Province itself (Figure 4.6) showed a significant decreasing trend from 7,894 cases in 2001/02 to 446 cases in 2008/09. The number of deaths also decreased over the years with a marked peak in 2003/04 malaria season. The mean incidence rate was 68 cases per 100,000 population. There was a significant decreasing trend in the incidence rate over time (x^2 = 28.2; P < 0.001).

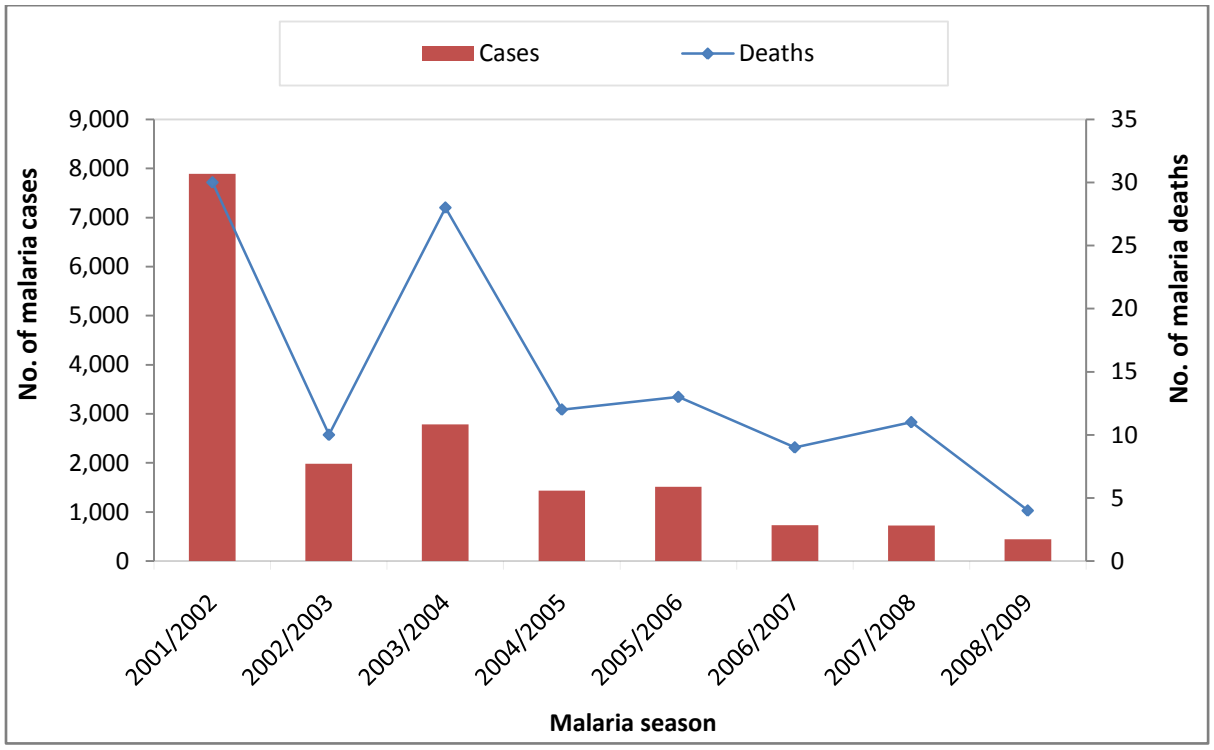

Figure 4.6: Local malaria cases and deaths in Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

According to the surveillance data, the distribution of malaria varied widely across the three districts of Mpumalanga Province (x^2 = 43.4; P < 0.001). A large proportion of the province's cases were notified in Ehlanzeni district, accounting for 96.5% (95% CI: 96.3% – 96.7%) of all notified cases (Table 4.5). The other two districts Gert Sibande and Nkangala notified the lowest number of cases during the past eight malaria seasons, contributed 0.7% (95% CI: 0.7% – 0.8%) and 0.4% (95% CI: 0.4% – 0.5%) respectively.

Table 4.5: Malaria cases, incidence and deaths by district, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

District	No. of notified cases (%)	Malaria incidence (per 100,000 population)	Malaria attributed deaths	CFR (%)
Ehlanzeni	32,096 (96.5)	2,218	158	0.49
Gert Sibande	236 (0.7)	26	1	0.42
Nkangala	140 (0.4)	14	2	1.43

The distribution of malaria in Ehlanzeni district is illustrated in Figure 4.7. The district is sub-divided into five municipal areas, Nkomazi, Mbombela, Umjindi, Bushbuckridge and Thaba Chweu. The majority of malaria cases were notified in Nkomazi municipal area accounting for 73% of the notified cases followed by Mbombela (18%), Umjindi (3%), Bushbuckridge (3%) and Thaba Chweu (1%). The Kruger National Park (KNP) and lodges were also included under Ehlanzeni district and accounted for 2% of the cases.

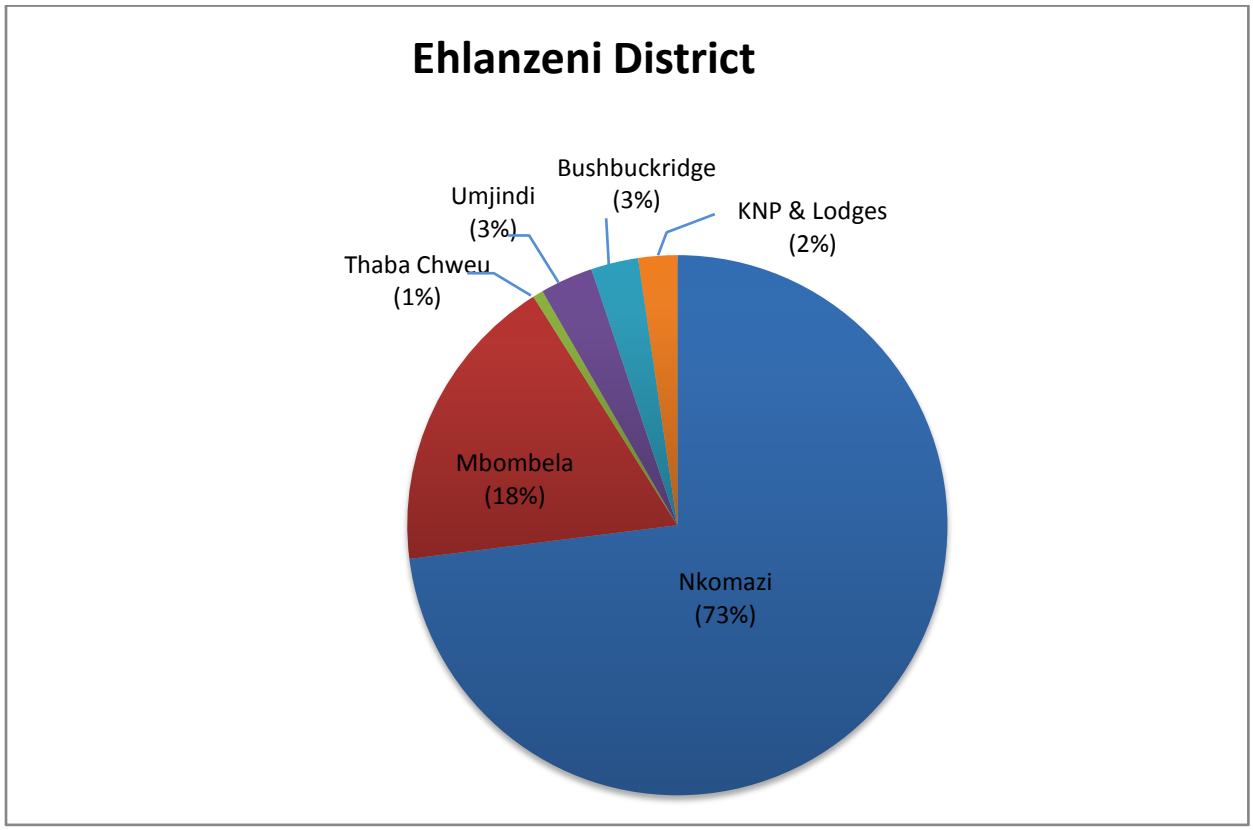

Figure 4.7: Proportion of malaria cases reported in Ehlanzeni District, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

4.1.8 Spatial distribution of malaria incidence

Figure 4.8 illustrates the spatial distribution of the incidence of malaria in the different municipalities over the eight year study period (2001-2009). The map shows that the risk of malaria lies in the Lowveld region of Mpumalanga Province, particularly in Nkomazi municipal area which is bordering Mozambique and Swaziland. The low risk areas were mainly the Highveld region of the province.

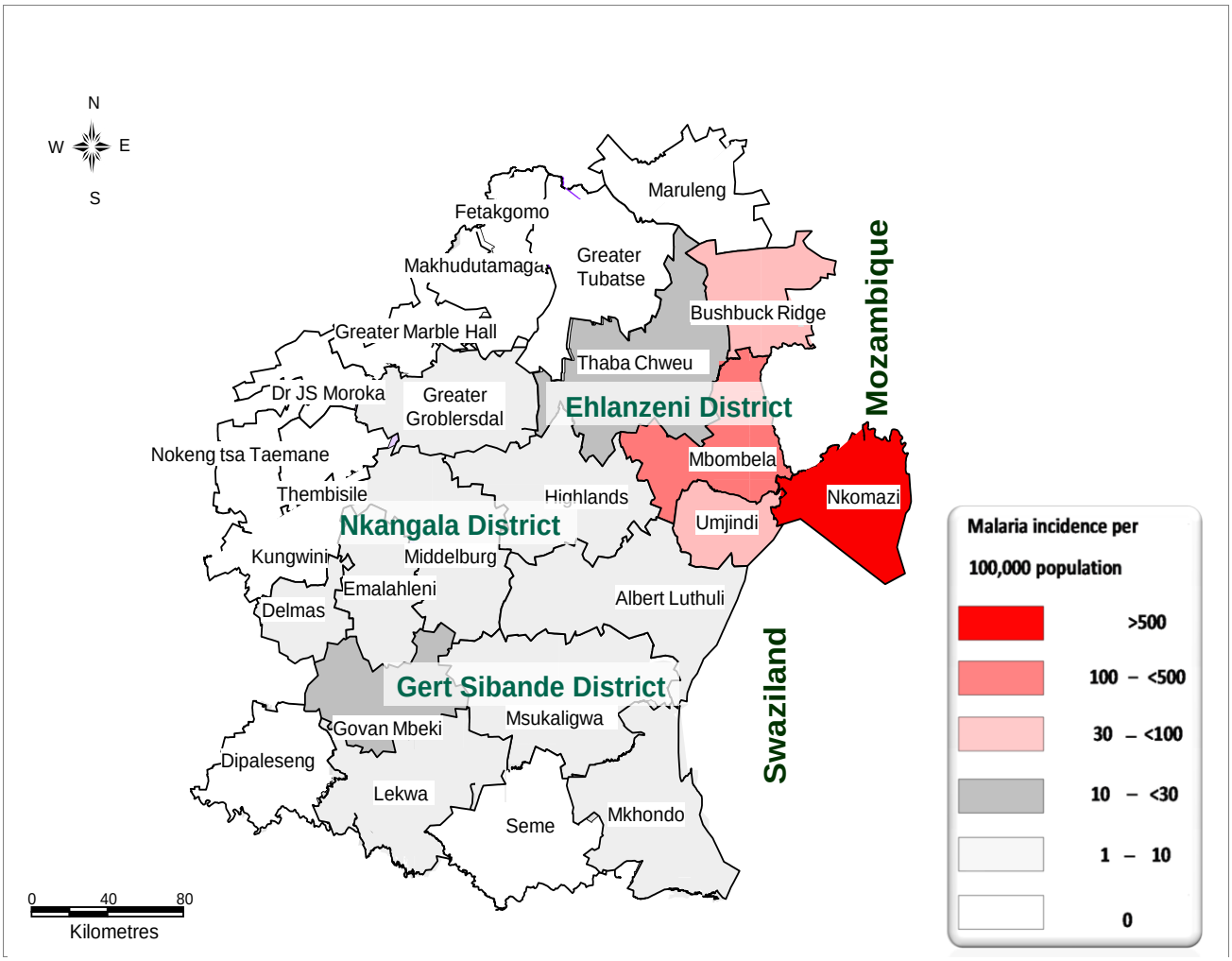

Figure 4.8: Spatial distribution of the incidence of malaria in Mpumalanga Province (2001/02 - 2008/09).

4.2 Effect of IRS intervention

Table 4.6 gives a summary of the amount of residual insecticide used, the number of structures covered with IRS and spray coverage achieved in Mpumalanga Province in the past eight (2001/02-2008/09) malaria seasons. The data shows that a total of 406,413 kg (406 tonnes) of the different residual insecticides were used to spray a total of 2,865,592 structures during the 2001/02 to 2008/09 malaria seasons.

Table 4.6: Descriptive statistics of residual insecticides applied and structures sprayed in Mpumalanga Province during 2001/02 - 2008/09 malaria seasons.

Insecticide	Amount insecticide used (kg)	Seasonal mean insecticide used (SD)	Number structures sprayed	Seasonal mean structures sprayed (SD)	Spray coverage (%)
Baythroid	75	37.3 (52.7)	7,517	3,759 (5,311.1)	83.5
DDT	176,571	5,044.9 (5,409.4)	1,588,586	45,388 (50,742.9)	81.7
Fendona	220,912	31,559 (38,817)	280,341	40,049 (49368.5)	88.4
K-Othrine WP	6,312	263 (338.1)	322,797	13,450 (17,070.1)	85.1
K-Othrine WG	2,543	106(141.6)	666,351	27,765 (38,398.1)	90.5
Total	**406,413**	**4417.5 (13304.4)**	**2865592**	**31148(41899)**	**85.8**

WP: Wettable powder; WG: Wettable granules

Figure 4.9 presents data on IRS activities in relation to malaria cases in Mpumalanga Province. IRS coverage remained stable during the first four malaria seasons (2001/02 to 2004/05), an increasing trend was observed from 2005/06 to 2008/09. Malaria cases were related to changes in IRS activities, showing a rapid decreasing trend during the same time period (2005/06 to 2008/09).

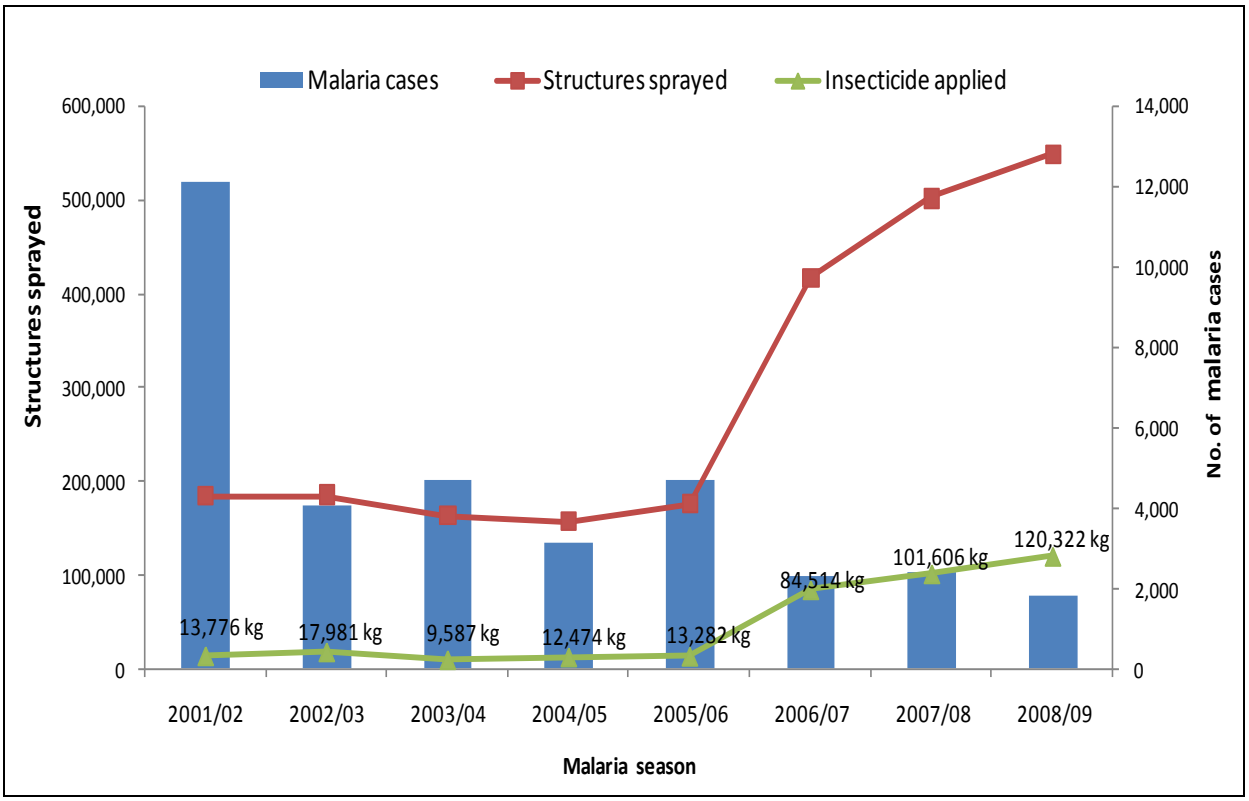

Figure 4.9: IRS activities in relation to malaria cases by season in Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

A summary of IRS activities by season is given in Table 4.7. In the table it can be seen that Baythroid was only used for one season. A large amount of Fendona was applied (54.4%), despite the fact that it has only been used in Bushbuckridge and data only became available from 2006 after the integration into Mpumalanga Province. Second most applied insecticide was DDT (43.4%), followed by K-Othrine (2.2%). However, over half of the structures were sprayed with DDT (54%) and the other insecticides made up the difference. The overall spray coverage with the different insecticides for all the eight malaria seasons ranged from 81.7% (95% CI 77.5-85.9) to 90.5% (95% CI 87.1-93.8).

Table 4.7: Summary of annual IRS activities by type of insecticide, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

Malaria season	DDT			K-Othrine			Baythroid			Fendona		
	Structures sprayed	Insecticide applied (kg)	Spray coverage (%)	Structures sprayed	Insecticide applied (kg)	Spray coverage (%)	Structures sprayed	Insecticide applied (kg)	Spray coverage (%)	Structures sprayed	Insecticide applied (kg)	Spray coverage (%)
2001/2002	115,225	14,244	85	84,917	1,706	85	7,514	74	92	–	–	–
2002/2003	137,768	17,839	91	68,309	1,340	92	–	–	–	–	–	–
2003/2004	71,464	8,984	73	111,703	2,163	80	–	–	–	–	–	–
2004/2005	107,728	12,832	81	71,858	1,302	85	–	–	–	–	–	–
2005/2006	140,926	15,727	72	78,616	635	85	–	–	–	72,270	59,877	91
2006/2007	283,472	28,315	72	113,196	442	89	–	–	–	91,562	68,646	87
2007/2008	336,119	36,536	86	129,655	487	88	–	–	–	110,662	87,827	94
2008/2009	331,135	35,386	88	172,721	647	94	–	–	–	5,847	4,562	72
TOTAL	**1,523,837**	**169,863**	**81**	**830,974**	**8,721**	**87**	**7,514**	**74**	**92**	**280,341**	**220,912**	**86**

Figure 4.10 illustrates the number of structures that were sprayed with residual insecticides (organochlorine and pyrethroids group) and coverage achieved during the period of review. An average of 163,000 structures were sprayed from 2001 to 2009 in Ehlanzeni district

As can be noted from Figure 4.10, a gradual increase in structures sprayed with insecticides was seen from 2006/07 through 2008/09 in the spray areas (Mbombela, Nkomazi, Umjindi and KNP and lodges). Annual spray coverage in the different spray areas ranged from 74%-93%; 73%-96%; 61%-99%; 75%-86%; and 81%-97% respectively.

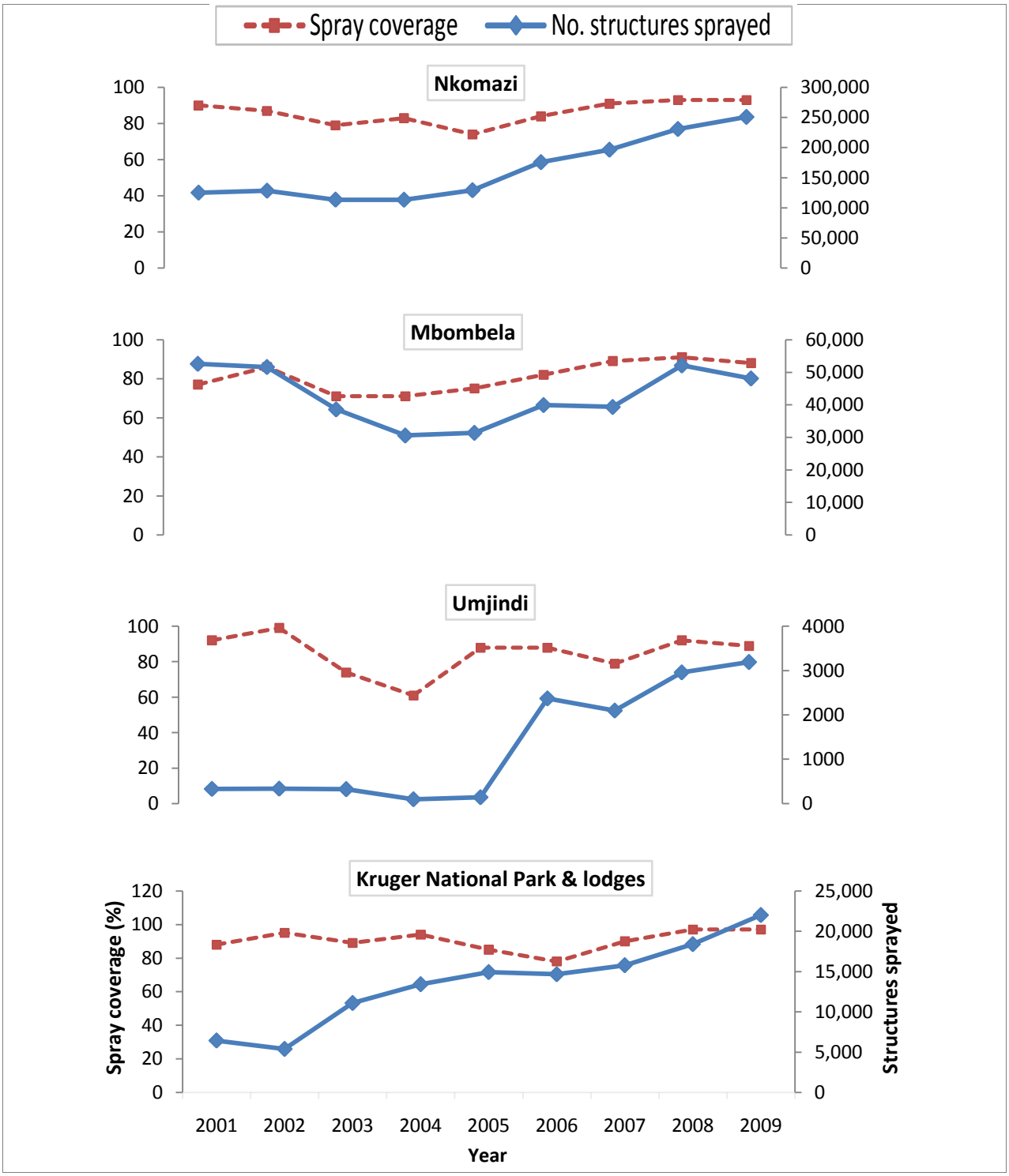

Figure 4.10: Structures sprayed by spray locality, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

The direct link between expanded IRS coverage and malaria cases is illustrated in Figure 4.11. It can be seen that malaria case notification started to decline following the increased number of structures covered with IRS beginning 2006/07 to 2008/09, particularly in Nkomazi, Mbombela and Kruger National Pak and lodges.

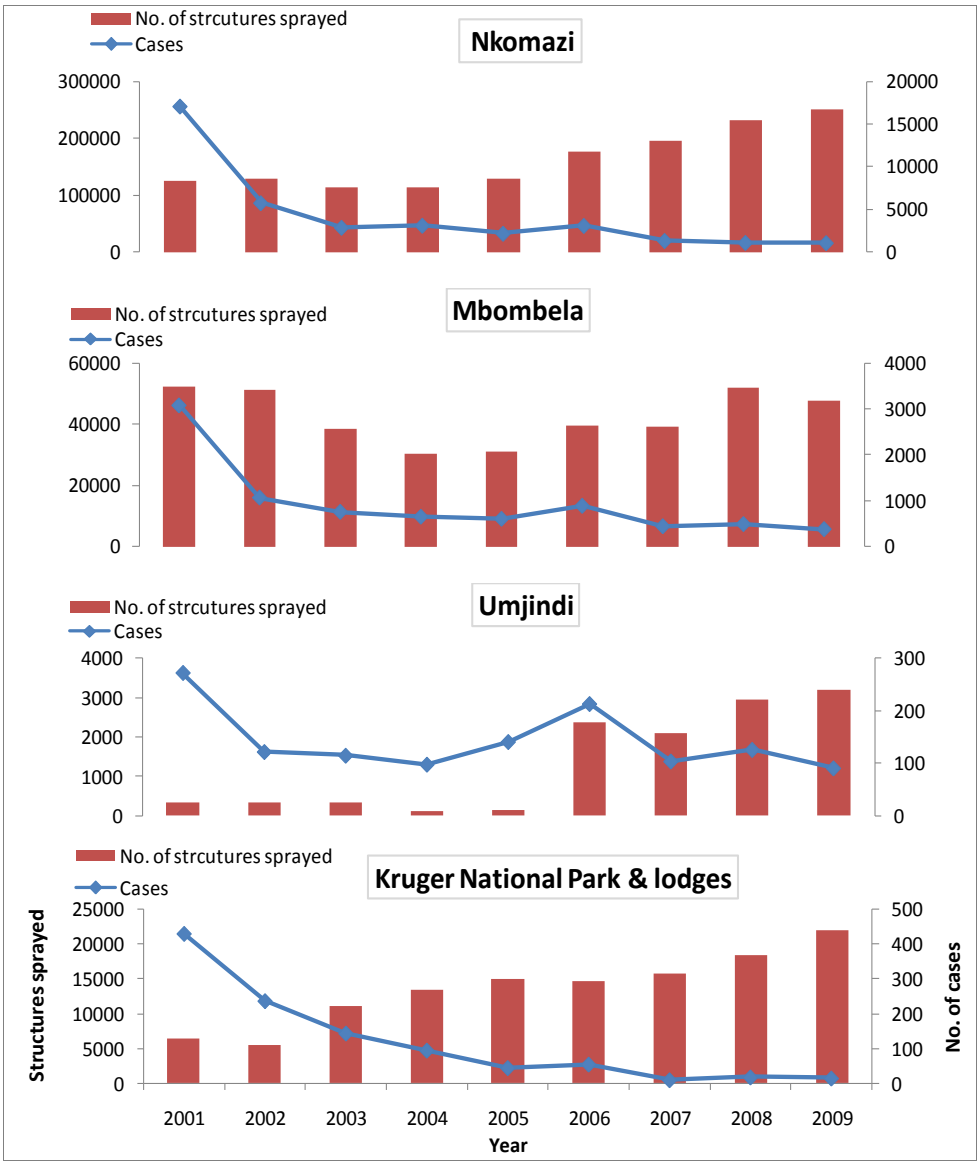

Figure 4.11: Structures sprayed in relation to reported malaria cases by spray locality, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

4.3 Effect of climate on malaria

Figure 4.12 represents the time series plot of monthly malaria cases, rainfall, temperature and relative humidity of Mpumalanga Province from 2001 to 2009. Malaria case notification peaks during spring and summer each year and lowest in the winter seasons. Climatic conditions have remained relatively stable during the eight year period, with exception for the anomaly in rainfall in 2005/06, higher than the annual average (650 mm) for Mpumalanga Province.

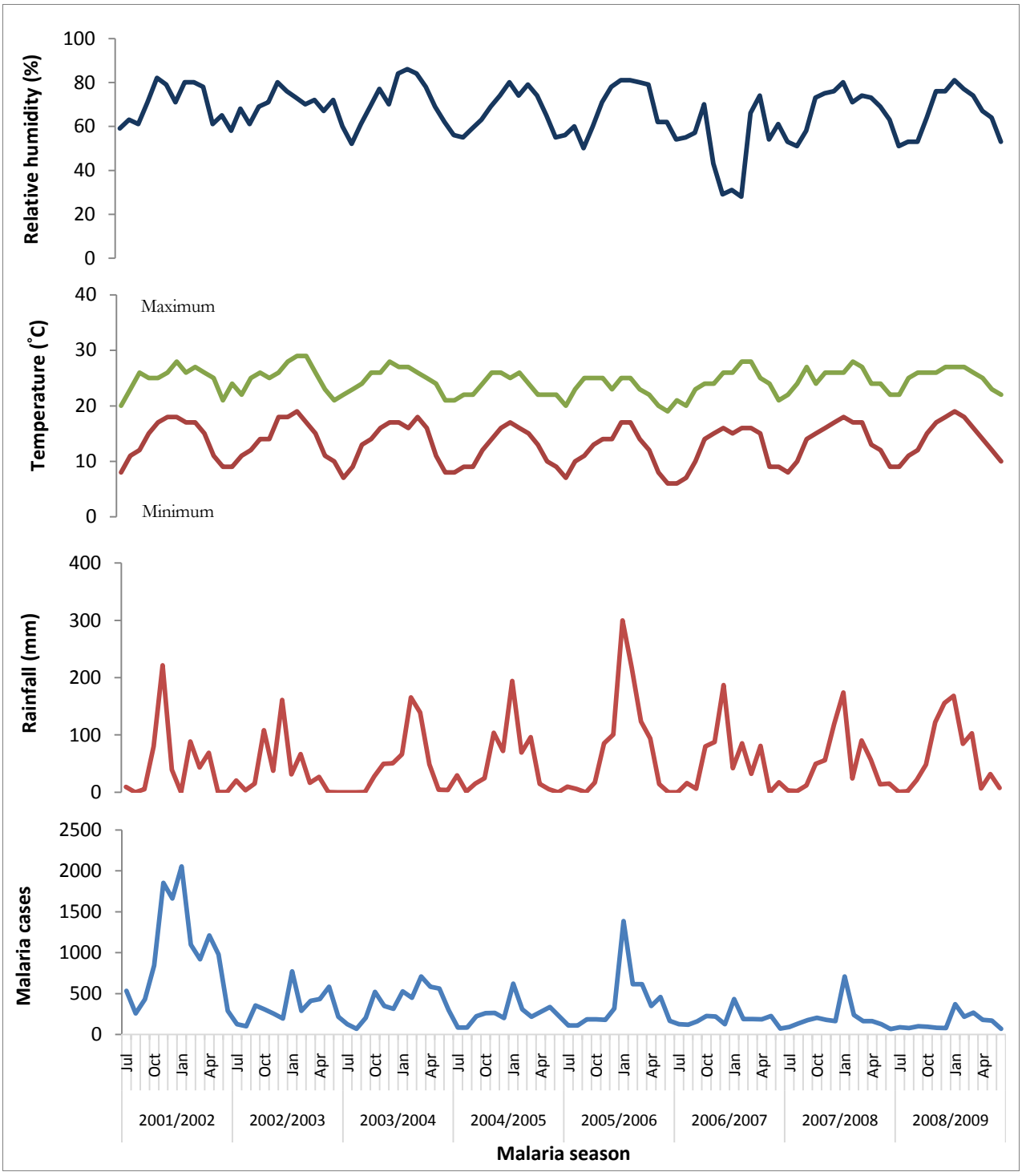

Figure 4.12: Monthly reported malaria cases in relation to mean monthly climatic factors, Mpumalanga Province, 2001/02 - 2008/09 malaria seasons.

The ARIMA models (Table 4.8) shows that rainfall was the only climatic variable significantly associated with the transmission of malaria in Mpumalanga Province (β = -0.062; *P* = 0.007). However, there was no significant association between temperature and relative humidity and monthly malaria cases (*P* > 0.05).

Table 4.8: Time series analysis (ARIMA model) of the incidence of malaria on climatic variables in Mpumalanga Province.

Variables	Coefficient	Standard error	*P*-value
Rainfall	-0.062	0.023	0.007
Tmin	0.016	0.055	0.768
Tmax	0.012	0.027	0.668
RH	0.006	0.012	0.585
Constant	-0.227	0.006	0.000

Tmin: Minimum temperature; Tmax: Maximum temperature; RH: Relative humidity

To test the fit of the model, graphic analysis of residuals over time was conducted and it shows no obvious trend in variation (Figure 4.13), suggesting that the residuals do not violate the assumption of constant location and scale and are within the range (-50, 50). Also correlation analysis of the actual versus predicted indicates that the predicted values and the actual malaria cases matched reasonably well (r = 0.83; $P < 0.05$).

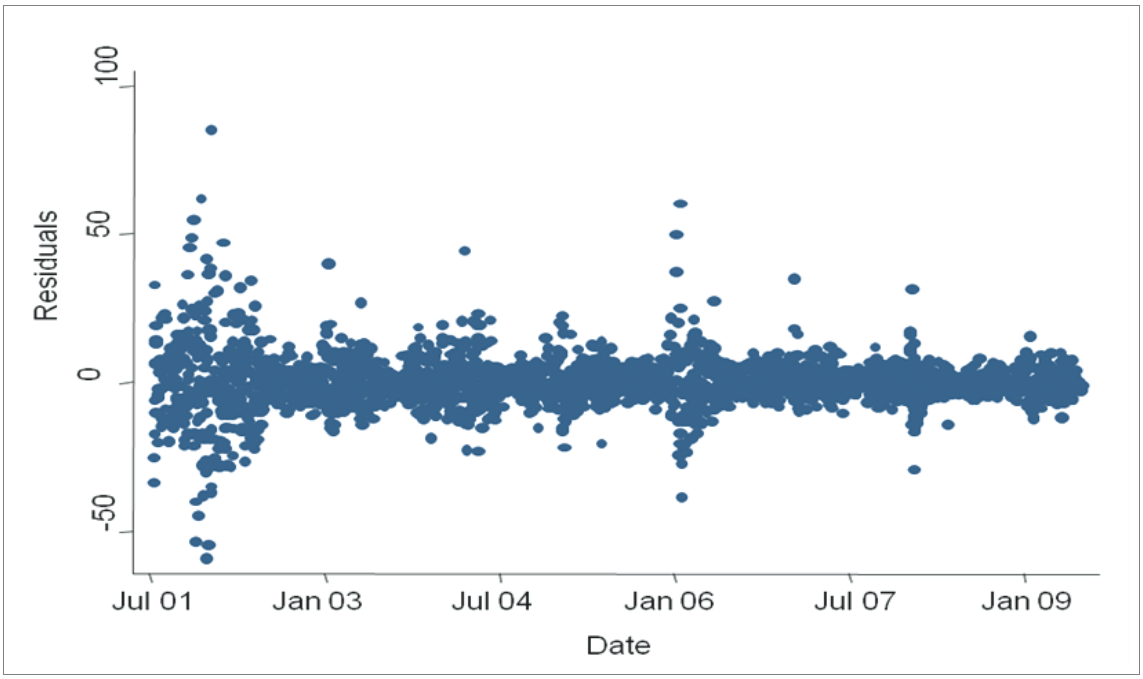

Figure 4.13: Plot of the residuals over time, Mpumalanga Province (2001/02 - 2008/09 malaria seasons).

The relationship between malaria and rainfall patterns is further illustrated in Figure 4.14, which shows monthly rainfall and monthly malaria cases in Mpumalanga Province from July 2001 to June 2009. Depending on the amount of rainfall, upsurges in malaria transmission are seen with a time lag of one to two months during the study period.

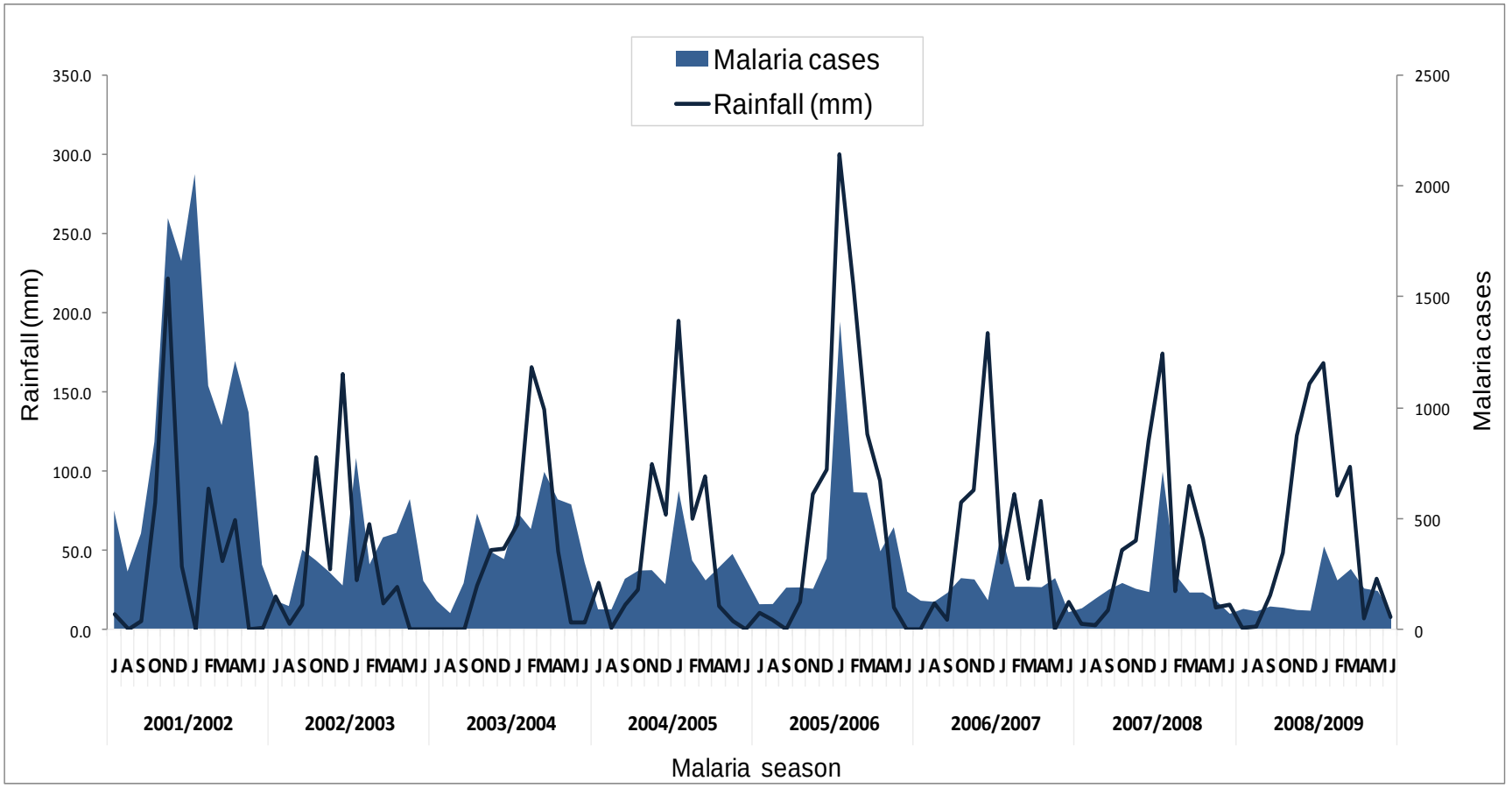

Figure 4.14: Relationship between monthly malaria cases and rainfall, Mpumalanga Province, 2001/02 -2008/09 malaria seasons.

CHAPTER 5

DISCUSSION

The time trends shows a significant decline in malaria morbidity and mortality in Mpumalanga Province over the past eight years from 2001 to 2009, representing an 85% reduction in the annual number of confirmed malaria cases and 74% in the number of deaths-attributed to malaria. A previous study estimating the burden of malaria in Mpumalanga Province in 1987 to 1999 showed fluctuating trends coupled with flood-related malaria epidemics in 1996 and 2000 [57]. After eight years of continuous malaria control, the province has achieved a marked decrease in malaria cases and deaths with no epidemics. The declining trend in malaria incidence demonstrated in this study is consistent with previously published results from other malarious provinces of South Africa; KwaZulu-Natal [214] and Limpopo [215].

Notable peaks in the number of notified cases were observed during the 2001/02, 2003/04 and 2005/06 malaria seasons. The 2001/02 peak was followed by a steep reduction of almost 70% in the subsequent season. This could be a result of the change in drug policy to combat parasite resistance to SP [140]; the re-introduction of DDT; and the Lubombo Spatial Development Initiative (LSDI), a joint development programme implemented to control malaria in Mozambique and Swaziland [60]. The introduction of ACTs for treatment of uncomplicated malaria in 2003 and 2004 [140] could partly explain the upsurge in malaria cases during the 2003/04 malaria season. However, it is possible that drug policy was not the only change that was introduced during this period. Further research is required to explain this scenario. The 2005/06 pattern may be attributed to the integration of Bushbuckridge municipality into Mpumalanga Province; the abandonment of the requirement of entry visa between South Africa and Mozambique [216] leading to large population movement between the countries thus bringing about importation of malaria cases; and rainfall anomaly.

In the present study, the finding of peak malaria incidence in the young adult age group (15-44 years) may be related to outdoor behavioural risk factors such as leisure patterns and sleeping arrangements leading to exposure to infective mosquito bites as well as the exophilic (outdoor biting) behaviour of the local mosquito vector. The low proportion of cases in infants and children also confirms the predominance of outdoor transmission since small children tend to spend more time indoor particularly during mosquito biting time [217]. In Tanzania, Russell and colleagues [218] found that high usage of intra-domiciliary vector control tools can alter vector feeding patterns from indoor to outdoor transmission, suggesting the need for additional vector control tools that target outdoor biting mosquitoes such as topical repellents [219,220], larval control [221,222] and zooprophylaxis [223].

This study found significant differences ($p < 0.001$) in malaria incidence between males and females. This was similar to previous observations in Mpumalanga Province [59], KwaZulu-Natal [217] and Limpopo [215] as well as in other countries [224-227]. According to Martens & Hall [65] men have a much greater risk of contracting malaria due to occupational reasons in particular those that work in mines, fields or forests or migrate to areas of work at peak biting time. The study conducted in Ethiopia provides evidence of the relationship between occupation and malaria risk, the authors found that highland migrant labourers were vulnerable to malaria while migrating to find agricultural work [228]. A similar scenario may exist in Mpumalanga Province.

The data shows that young adult men are at risk of contracting malaria infection in Mpumalanga Province and this may be the case in areas of low to moderate transmission intensity [217]. While in stable malaria transmission areas, non-immune pregnant women [45, 229] and children under the age of 5 years [17] are the most susceptible to malaria infection.

The burden of malaria in Mpumalanga Province is strongly connected to importation of malaria parasites by labour-related migration. As almost half (47.8%) of the cases

reported in Mpumalanga Province were acquired in Mozambique. Trend analysis of these cases reveals that 74% were among males between the age of 15 and 44 years, confirming that the majority of the imported cases were introduced by young adult males crossing the border to seek work opportunities.

The incidence of malaria in Mpumalanga Province shows inter-annual variation from 2001 to 2009 with a distinct malaria transmission season, prominent peaks in January and February. The reasons for the January/February peaks could be due to favourable climatic conditions for malaria transmission (peak summer season) or introduced parasites by human immigration from various places of origin following the December holiday season. This finding suggests important implications for the control programme in terms of timing when directing efforts in controlling malaria.

Despite the fact that a large proportion of the cases reported in Mpumalanga Province were imported, the province still accounted for half (50.1%) of the total cases notified, which indicates the recurrence of local malaria transmission. The incidence of malaria was found to be most pronounced in Ehlanzeni district (low altitude region) than in the high altitude districts (Nkangala and Gert Sibande), suggesting the effect of altitude on malaria transmission. It has long been recognized that altitude is an important determinant of malaria endemicity, whereby higher altitude levels are considered to be cold to support malaria transmission [123].

The burden of the disease in the province lies in Nkomazi municipal area by contributing 73% of the province's malaria cases. Malaria transmission recurrence in this district can be attributed to its close proximity to Mozambique as well as intensive agricultural practices. The challenge of high malaria prevalence in districts bordering Mozambique has also been reported in KwaZulu-Natal [230]. The link between malaria and agriculture has a long history, in particular irrigation, by creating suitable vector breeding sites and facilitating malaria transmission [80].

Malaria case fatality rates fluctuated over the entire study period. The overall CFR was 0.54% which is not much significantly higher than the national target. However, it is important for the province to further decrease the CFR to below 0.5% through improved case management. Unlike other African countries, where malaria is a major cause of infant and child mortality, in Mpumalanga Province malaria-attributed mortality was lower in infants and children. Severe illness due to malaria was higher among adults, with the CFR reaching 2.1% in those over the age of 65 years compared to 0.28% and 0.14% for under fives and five-14 age groups. The enquiry into all deaths-attributed to malaria in Mpumalanga Province in 1999, revealed that late presentation to health care facilities was strongly associated with increased mortality due to malaria [231]. In another study in South Africa, it was found that co-morbid diseases, especially HIV co-infection and poor management of malaria-related complications led to mortality outcomes [232]. This suggest the need to maintain sustainable training programmes for all health care workers in all levels of health facilities in both low and high risk transmission areas as well as community health promotion and education.

It is evident from this study that increased amount of insecticide used and spray coverage were directly linked to reduced malaria morbidity and mortality burden in Mpumalanga Province, particularly in the malaria high-risk areas. This trend was more apparent in the last three years of the study period. A study conducted in Uganda to assess the impact of IRS on malaria morbidity after a single round of spraying with lambda-cyhalothrin found a gradual decrease in the number of patients diagnosed with clinical malaria in the first four months after IRS [233].

To date there have been several recent reports of reductions of malaria morbidity and mortality in Africa following intensive IRS campaigns [146]. In South Africa, marked reductions in the number of confirmed cases and deaths in Mpumalanga and KwaZulu-Natal provinces were observed following the introduction of IRS campaigns in Mozambique and Swaziland through the LSDI [60]. In KwaZulu-Natal, Maharaj et al. [234]

reported a significant reduction in the number of cases in most endemic areas of the province following the re-introduction of DDT for vector control.

Although increased IRS coverage has significantly contributed to the visible decreasing trends in malaria morbidity and mortality, other factors such as the combination of preventative interventions (early diagnosis, case management and effective treatment with ACT), low numbers of mosquito vectors, improved education and awareness, and improving socio-economic indices, had played a role in the marked reduction in the burden of malaria in Mpumalanga Province.

Although IRS has had beneficial effects in the history of malaria control and prevention, there is increasing awareness and concerns from new scientific evidence regarding the safety of insecticides (i.e. DDT) on humans and the environment [98]. More recently, the Pine River Statement revealed substantial evidence that DDT and DDE pose a serious risk to human health, particularly due to IRS for malaria vector control [156]. Other studies conducted in South Africa reported several risks associated with non-occupational exposure, such as male reproductive effects [162,163]. In view of these public health concerns, efforts needs to be directed towards the development of new tools for malaria vector control in order to minimize adverse health effects and halt endemic transmission.

The present study indicates that inter-annual variability of malaria incidence in Mpumalanga Province is associated with climatic factors. In particular, rainfall has played a significant role in the transmission of malaria. The regression coefficient of rainfall was significantly associated with the incidence of malaria in the ARIMA model (P = 0.007). The transmission season of malaria in Mpumalanga showed to follow a distinct rainfall pattern and fluctuated considerably from year to year according to rainfall, with heavy rainfall associated with increased number of reported cases. This finding is not unexpected since it is well documented that rainfall is an important environmental parameter in defining the transmission of malaria with respect to the breeding and development of mosquitoes [235]. These results are consistent with previous findings

from KwaZulu-Natal where a direct and predictable relation between rainfall and malaria transmission was observed [236].

It has been suggested that anthropogenic climate change is expected to directly affect the behavior and geographical distribution of mosquitoes and the life cycle of the parasite and thus changing the future distribution of the disease [237,238]. Casman and colleagues [239] notes that since climate can correlate with transmission intensity, it can greatly affect the success or failure of control and eradication programmes. The authors, however, points out that in fringe transmission areas like South Africa, Madagascar and Zimbabwe, malaria surveillance and control maybe sufficient to mitigate any increases in transmission brought about by climate change.

Limitations

It is acknowledged that this study has several limitations given that it relies mainly on routine surveillance data. Firstly, the problem with surveillance data is that the quality might be subjected to reporting inconsistencies and incompleteness, emanating from incorrect completion of the notification forms, lack of systematic inclusion of data from other sources such as traditional healers, faith-based organizations and self-treatment cases. Secondly, over-reporting of malaria cases could have also occurred in the high-risk areas due to high awareness and advocacy regarding malaria among health care workers. Finally, it is possible that some confounding factors that may have influenced the changes in the burden of malaria were not addressed in this study, such as the effect of other preventive interventions, changes in vector population and socio-economic factors.

Conclusions and Recommendations

The data presented in this study documents a significant reduction in malaria morbidity and deaths-attributed to malaria in Mpumalanga Province in the past eight years (2001-2009). The two main conclusions that can be drawn from this study are the following: (i) although climatic conditions favourable for malaria transmission fluctuated over the years, malaria morbidity and mortality showed a gradual reduction and; (ii) there was evidence of an association and time link between increased IRS coverage and the reduction in malaria morbidity and mortality from 2006/07 to 2008/09 malaria seasons.

The findings show that Mpumalanga Province has achieved the goal to reduce malaria to low levels through expanded IRS coverage in combination with other control interventions. These results highlight the need to continue with current control strategies such as IRS until interruption in local malaria transmission is completely achieved and alternative control strategies implemented. In order to ensure continuous improvement in malaria control and subsequent elimination, a comprehensive intervention plan which encompasses a combined set of widespread interventions is required.

Based on the findings of this study, there is a need for the Malaria Control Programme to consider the following recommendations in order to achieve the goal to eliminate malaria as a public health problem in the province:

- **Address importation of malaria cases.**
  - In view of the high proportion of cases that were acquired in Mozambique, this requires the intensification of the regional cross-border collaboration efforts through the LSDI in order to lower the risk of re-importation of infections.
  - Internally, the province needs to institute initiatives addressing immigrant carriers to restrict the importation of cases such as assessing the feasibility of border screening.
  - Another approach is intersectoral collaboration involving the agricultural sector and Nongovernmental Organisations particularly in the high-risk areas to introduce

rapid response in screening and treatment of all newly employed individuals originating outside the country's borders.

- **Develop strategies to interrupt local transmission and transmission risk.**
  - Interruption of local transmission in the province will require active measures, including identification of asymptomatic infections and effectively treating all infections before transmission can occur.
- **Enhance surveillance and reporting.**
  - The province should maintain good quality surveillance system to facilitate immediate detection, notification and response to outbreaks and individual malaria cases.
  - This study identified data entries in which data was missing, this gaps needs to be addressed through vigilant monitoring of the data collection (i.e. completion of notification forms) and capturing process in order to maintain a consistent information system which is a cornerstone of a successful malaria elimination campaign.
- **Maintain strong capacity building and training levels.**
  - Training of all health care workers in all levels of health facilities and all the districts to be strengthened to effectively control transmission in both low and high risk transmission areas and during outbreaks and to reduce the case fatality rate due to misdiagnosis of cases.
- **Strengthen health promotion and awareness.**
  - While still dependent on IRS, health promotion and education needs to be strengthened to limit exposure to potentially harmful insecticides and promote the use of alternative control approaches.

- **Identify and support field applied research for improved control interventions.**
  - Research efforts should focus on the development of new tools for malaria vector control including new generation insecticides, new biological control strategies and innovative methods.

- Studies are required to explore the feasibility of introducing ITNs as a supplementary vector control strategy in Mpumalanga Province.

- **Research and development on refined tools.**
  - The provincial control programme needs to play a key role in supporting pilot projects and field trials on sustainable and cost effective combination of vector control measures that are appropriate to local conditions and relatively safe for human health and the environment.
  - Strengthening intersectoral collaboration with research institutions such as the University of Pretoria Centre for Sustainable Malaria Control is desirable in order to enhance these research efforts.

Areas for further research

The findings presented in this study raise additional areas for further research:

The emerging trend from this study is that mortality due to malaria was highest in the adult age group (>65 years) with a CFR of 2.1%, this is a concern since it is much higher than the National CFR of 0.5%, it is therefore important to establish the risk factors associated with adult mortality in Mpumalanga Province. While this study has addressed the impact of vector control by IRS in reducing malarial mortality and morbidity, it is essential to also monitor its potential harm on occupants living in the sprayed dwellings. Finally, field trials need to be initiated, implemented and evaluated to explore the feasibility of ITNs for malaria control as part of the IVM approach.

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ANNEXURE 1: Proof of Ethics Committee Approval

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

* FWA 00002567, Approved dd 22 May 2002 and Expires 13 Jan 2012.
* IRB 0000 2235 (IORG0001762 Approved dd Jun 2006 and Expires 13 Aug 2011.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee
Fakulteit Gesondheidswetenskappe Navorsingsetiekkomitee

DATE: 28/04/2010

PROTOCOL NO.	72/2010
PROTOCOL TITLE	The impact of indoor residual spraying (IRS) on malaria prevalence between 2001 and 2009 in Mpumalanga Province, South Africa.
INVESTIGATOR	**Principal Investigator:** Miss L Ngomane
SUBINVESTIGATOR	None
SUPERVISOR	Prof C. de Jager
DEPARTMENT	**Dept: Phone: E-Mail:** lindo-n@webmail.co.za **Mobile:** 072 700 1078
STUDY DEGREE	MSc Epidemiology
SPONSOR	None
MEETING DATE	21/04/2010

The Protocol was approved on 21/04/2010 by a properly constituted meeting of the Ethics Committee subject to the following conditions:

1. The approval is valid for 1 years period, and
2. The approval is conditional on the receipt of 6 monthly written Progress Reports, and
3. The approval is conditional on the research being conducted as stipulated by the details of the documents submitted to and approved by the Committee. In the event that a need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

Members of the Research Ethics Committee:

Prof M J Bester	(female)BSc (Chemistry and Biochemistry), BSc (Hons)(Biochemistry), MSc(Biochemistry), PhD (Medical Biochemistry)
Prof R Delport	(female)BA et Séan, B Curationis (Hons) (Intensive care Nursing), M Sc (Physiology), PhD (Medicine), M Ed Computer Assisted Education
Prof VOL Kamusiiet	MBChB, MFG/P(SA); MMed(Chir), FCS(SA) - Surgeon
Prof JA Ker	MBChB, MMed(Int), MD – Vice- Dean (ex officio)
Dr NK Likibi	MBBCh – Representing Gauteng Department of Health)
Prof TS Marcus	(female) BSc(LSE), PhD (University of Lodz, Poland) – Social scientist
Dr MP Mathebula	(female)Deputy CEO: Steve Biko Academic Hospital
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Mrs MC Nzeku	(female) BSc(NND), MSc(Biochem)(UCL, UK) – Community representative
Prof L M Ntlhe	MBChB(Natal), FCS(SA)
Snr Sr J Phatoli	(female) BCur(Ext.A), BTec(Oncology Nursing Science) – Nursing representative
Dr R Reynders	MBChB (Pret), FCPaed (SA)SA) MRCPCH (Lon) Cert Med. Onc (SASA)
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Dr L Schoeman	(female) B.Pharm, BA,(Hons)(Psych), PhD – Chairperson: Subcommittee for students' research
Mr Y Sikweyiya	MPH; SAREFI Fellowship in Research Ethics; SA:RETI ERC/TP; BSc(Health Promotion) Postgraduate Dip (Health Promotion) – Community representative

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Prof C W van Staden MBChB, MMed (Psych), MD, FCPsych, FTCL, UPLM - **Chairperson**

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