OPERATIONAL RESEARCH FOR ENHANCED CONTROL OF COMMUNICABLE DISEASES OF HUMANS IN MPUMALANGA PROVINCE, SOUTH AFRICA

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A Thesis submitted to the Faculty of Medicine, Health and Molecular Sciences, James Cook University, in fulfillment of the requirements for the Degree of Doctor of Public Health

Townsville, 2002

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ABSTRACT

The operational research model was utilised to enhance communicable disease policy, public health practice and patient management in Mpumalanga Province, South Africa. The value and scope of this approach for improving malaria, measles, leprosy and cholera control was investigated.

Confidential inquiries identified contributory health system related factors in deaths due to malaria and cholera in Mpumalanga Province. A multi-disciplinary medical, laboratory and public health team carefully reviewed the clinical records and special investigations of patient deaths attributed to malaria between 1 January and 30 June 1996. The record review was supplemented by interviews with next-of-kin and confidential reports by health staff to determine the presence of avoidable factors or deviations from minimum acceptable standards of case management that may have contributed to the deaths. Confidential inquiries were conducted into all suspected cholera deaths between 1998-2001. This approach resulted in corrective action to prevent future deaths.

Malahlapanga, a remote spring in the Kruger National Park, South Africa, has proven a valuable site for original research on the behaviour of *Anopheles arabiensis*, the most important malaria vector in southern Africa. An evolving operational research agenda has defined preferred feeding periods and anatomical feeding sites, biting patterns, including distance from breeding site, and the effect of mechanical barriers and application of topical N,N-diethyl-m-toluamide (DEET) to ankles and feet on *Anopheles arabiensis* feeding. Research findings have directly influenced national malaria prevention guidelines, larviciding around residential camps in nature reserves, and malaria outbreak response in a rural African village.

The Mpumalanga Malaria Control Programme traditionally relied on light microscopy of Giemsa-stained thick blood films for malaria diagnosis. A series of operational research studies documented the shortcomings of microscopic diagnosis, the appropriateness and accuracy of rapid malaria card tests and led to the first introduction of card tests for

primary diagnosis of malaria in a public health program. The Mpumalanga results highlighted the potential role of rapid tests for "Rolling Back" malaria in selected areas. A resulting national appreciation of the importance of standardised field evaluation of malaria diagnostic tests has led to Mpumalanga being requested to perform routine evaluation of new malaria diagnostic tests prior to introduction through the national purchasing system.

The first African sentinel surveillance site for routinely evaluating *in vivo* efficacy of sulfadoxine-pyrimethamine (SP) against *Plasmodium falciparum* by 42-day follow-up was established in Mpumalanga Province. This followed a successful chloroquine *in vivo* study during 1997 that led to a change in treatment policy from chloroquine to SP for first-line *P. falciparum* malaria therapy. *In vivo* SP studies in 1998 and 2000 in Mpumalanga and in KwaZulu-Natal, a neighbouring province in 2000, confirmed treatment efficacy, provided a more comprehensive understanding of drug resistance evolution, and allowed investigation of the differential resolution of clinical symptoms and peripheral parasitaemia, an initial evaluation of the adequacy of the recommended SP dosage for adults exceeding 60 kilograms, and determination of gametocyte levels at different stages following therapy. The recognised success of the Mpumalanga sentinel surveillance site for influencing treatment policy has resulted in a sentinel surveillance network for epidemiological research into malaria in South Africa.

The feasibility of measles elimination in southern Africa was studied in Mpumalanga using an operational research model. Coverage levels, obtained from a comprehensive district-based population survey in 1997, make elimination highly improbable by routine vaccination alone, and a strong negative correlation between routine and campaign coverage supported the complimentary approach of combining routine and supplementary immunisation for measles elimination. Mass immunisation campaigns have dramatically impacted on the measles disease burden, reflected by notified deaths and admissions reviewed during a Mpumalanga hospital register review in April 1999. Analysis of coverage levels achieved during recent immunisation campaigns in South

Africa supported the contention that judicious timing of campaigns is essential if high coverage is to be achieved.

A simple telephonic survey during March 2001 proved valuable for verifying the availability of appropriate patient management following potential rabies exposures. This rapid survey technique provided valuable information for correcting the official database of rabies vaccine and immunoglobulin availability and resulted in training of provincial pharmaceutical managers on rabies. Rapid telephonic surveys may be appropriate for auditing other health programs, particularly where a means for independently validating responses is readily available.

To explore positive and negative attributes of operational research that impact on its value for influencing communicable disease control policy and practice, the grounded theory approach was used with groups of experienced Masters of Public Health students in South Africa and Australia to analyse the series of operational research studies conducted between 1995 and 1999 to refine malaria diagnosis in Mpumalanga Province. A key theme was the extraordinary relevance of local operational research, which takes account of disease epidemiology, available material and human resources, and the local biological, political, socio-economic and technological environment. It emerged that where research is planned and conducted in equal partnership with control program staff, there is rapid application of research findings for control and decreased resistance from decision-makers.

The central role which operational research can play in gathering the evidence necessary for effectively planning communicable disease control programs and bridging the gap between evidence and enhanced policy and practice, is illustrated in this thesis by drawing on a wide range of operational research interventions conducted in Mpumalanga Province, South Africa, between 1995 and 2001.

PREFACE AND ACKNOWLEDGEMENTS

The nature of operational research demands multidisciplinary teams. The approach adopted by the author in Mpumalanga incorporated capacity building and equipping of control program staff to identify, define and prioritise research questions, and to develop appropriate designs to study and answer these questions. I express my appreciation to the dedicated team, which I was privileged to lead for eight years at provincial level; Professor Gboyega Ogunbanjo (part-time Expanded Programme on Immunisation coordinator), Dr. Elsa Balt (tuberculosis and leprosy coordinator), Dr. Bernice Harris (surveillance medical officer), Dr. Kelvin Billinghurst (communicable disease control medical officer), Dr. John Govere (medical natural scientist) and Nicros Mngomezulu (laboratory technologist). The Communicable Disease Control directorate enjoyed a close collaborative relationship with the Malaria Control Program, with our directorate providing technical guidance and evaluation in support of the Malaria Control Program. I would like to recognize my friends and colleagues in this Program, in particular, Kobus la Grange, Aaron Mabuza, Phillip Kruger and Marlize Booman.

My supervisor, Professor Richard Speare, provided general guidance in research design, interpretation and analysis throughout. Rick's formidable commitment to unearthing new knowledge, not for its inherent value, but to improve veterinary and human health, has been an ongoing inspiration. I am deeply grateful for his encouragement, coaching and friendship.

There were valuable contributions to the operational research agenda by many collaborators. Major collaborators are co-authors on the peer-reviewed publications that resulted from the research. Their specific contributions and additional acknowledgements are detailed below.

Chapter 1 - Introduction

I gratefully acknowledge the preparation of Figure 1.1 by Dr. Bernice Harris, my surveillance medical officer on the Mpumalanga provincial communicable disease control team.

Chapter 2 – Confidential inquiries – a useful tool for corrective public health action

Dr. Stefano Fieremans, specialist physician at Themba Hospital, assisted me with planning the research design of the original confidential inquiry into malaria deaths. He also provided invaluable assistance in refinement of the data collection tool, interpretation and analysis of data. Phillip Kruger and Aaron Mabuza, from the Mpumalanga Malaria Control Program, deserve credit for initially raising a concern about an apparent increase in malaria deaths, piloting the data collection tool and intensive data collection. They were assisted in the latter activity by Kobus la Grange and Alpheus Zitha of the Malaria Control Program. Colonel Kobus de Bruyn, Officer Commanding South African Military Health Services, Mpumalanga, Dr. Adrian Brink, specialist microbiologist Du Buisson Laboratories, Dr Boniface Wankya, specialist physician and former director of Kangwane Health Services, Nomonde Bam, Director of Primary Health Care Services and Gladness Mathebula, Director of Lowveld Health Region, were our colleagues on the confidential inquiry team. Their dedication was phenomenal.

A colleague in the provincial communicable disease control unit, Dr. Kelvin Billinghurst, assisted me in providing technical support and guidance to Mpumalanga districts for cholera outbreak response and assisted in conducting confidential inquiries into cholera deaths. He contributed to the extensive adaptation of the malaria confidential inquiry tools for investigating cholera deaths. I was ably assisted and advised in data analysis and interpretation, and report preparation by Professor Michael Reich, during a Takemi Fellowship in International Health at Harvard School of Public Health, and Professor

Rick Speare. Nerine Willers, from the South African National Department of Health, provided official malaria case and death notification data.

Chapter 3 – Targeting vector behaviour and characteristics for effective malaria control

Dr. John Govere, the entomologist in my provincial communicable disease control team, participated in all aspects of study design, field data collection and analysis. He also provided valuable inputs into the preparation of all reports emanating from the seminal research conducted at Malahlapanga. Most of the original conceptual work was my own and built on the early findings of two entomological colleagues, Anton Gericke, a former member of my team, and Dr. L.E.O. Braack, the Head of Scientific Services in the Kruger National Park. Professor Rick Speare provided exceptionally valuable advice for refining data presentation and manuscript preparation.

I was primarily responsible for conceptualizing the original approach of malaria outbreak control using limited application of insect repellent. However, Dr John Govere, Victor Gwebu, the district communicable disease control coordinator in Tonga sub-district and Aaron Mabuza from the Malaria Control Program ably assisted me in conducting community meetings. Dr. Govere provided useful input during preparation of the publication arising from this study.

Professors Richard Hunt and Maureen Coetzee, National Institute of Communicable Diseases, provided valuable comments on study design and interpretation of the data on the effect of repellent on the biting behaviour of vector mosquitoes in the Kruger National Park. As Drs Govere and Braack conducted the bulk of the demanding fieldwork during this study, it was appropriate that their contribution resulted in principal authorship.

The Mpumalanga Malaria Control Program entomological team members are thanked for volunteering to participate in night catches. I am indebted to the South African National

Parks for providing unique access to the Malahlapanga research site and for providing Figure 3.1, the location of Malahlapanga within the Kruger National Park. The Mpumalanga Department of Health provided financial support for the Malahlapanga research while Shell, South Africa donated the DEET repellent used during the Albertsnek study. Marlize Booman, of the Mpumalanga Malaria Control Program, is thanked for providing Figure 3.2, the detailed map locating Albertsnek Village.

Chapter 4 – A renaissance in malaria diagnosis

Refinement of the original research protocol on investigating the degree of laboratory concordance in malaria diagnosis, was a team effort with Dr. Kelvin Billinghurst and Dr. Adrian Brink. Dr. Piet Becker of the Medical Research Council, confirmed the validity of the statistical technique selected for analysis and assisted with construction of the final report.

I was responsible for establishing the initial sentinel site for field evaluation of rapid diagnostic tests in South Africa, and successful in transferring the skills and management of this site to Kobus la Grange and Aaron Mabuza of the Malaria Control Program over a period of three years. Their commitment to conducting high-quality relevant operational research for improving malaria control is recognized.

Members of the provincial communicable disease control team, Nicros Mngomezulu and Dr. John Govere, ably provided laboratory support and diagnostic quality assurance. Nerine Willers, National Department of Health, kindly assisted with official malaria case notifications. This research was funded by the Mpumalanga Department of Health.

Chapter 5 – Sentinel surveillance – a pre-requisite for optimal malaria drug therapy

The concept for the original sentinel surveillance research site in Mpumalanga was developed in partnership with Janet Freese from the Medical Research Council. Following the success of the original chloroquine *in vivo* study conducted at this site, I

was successful in training a team initially under the field-leadership of Dr. John Govere and more recently Aaron Mabuza of the Malaria Control Program. Dr. Barry Bredenkamp of the Medical Research Council and Nicros Mngomezulu of the communicable disease control team provided essential laboratory support, while the nurse managers at Naas and Mangweni Clinics in Mpumalanga, and Ndumu Clinic in KwaZulu-Natal deserve my gratitude for their critical role in assuring the recruitment of study subjects.

The value of the Mpumalanga research in determining malaria treatment policy resulted in the preparation of a multi-country research proposal to WHO-TDR on utilizing combination therapy for first-line treatment of *Plasmodium falciparum* malaria. This built on the foundation of successful *in vivo* studies with extended follow-up. My fellow co-principal investigators on this study (SEACAT: South-East Africa Combination Artemisinin-containing Therapy evaluation) are Dr. Karen Barnes of the University of Cape Town Medical School and Dr. Brian Sharp of the Medical Research Council.

Marlize Booman provided detailed malaria incidence maps for the Tonga sub-district, Mpumalanga, while Carryn Martin of the Medical Research Council provided the same for Ubombo-Ingwavuma District, KwaZulu-Natal. Nerine Willers, National Department of Health, provided comprehensive malaria case notification data.

Funding for the 1998 study was provided by the Mpumalanga Department of Health, while funding of the 2000 investigations was from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

Chapter 6 – Mass immunization campaigns for measles elimination: necessary and effective, but judicial timing essential

Professor Gboyega Ogunbanjo, the Provincial Expanded Programme on Immunisation coordinator on my communicable disease control team, played an integral role in the

conceptualisation, design of the studies, development of appropriate data collection tools, quality assurance and report preparation.

Elize Webb from the national Expanded Programme on Immunisation in South Africa, provided detailed campaign coverage data, measles case and death notifications, and assisted in interpretation of study findings. Dr. C.K. Lee of the National Centre for Epidemiology and Population Health at the Australian National University, provided useful advice on statistical analysis.

Dr. Bernice Harris and Dr. Amra Uzicanin, from the Centres for Disease Prevention and Control, Atlanta, Georgia, conducted the fieldwork during the detailed review of all paediatric measles admissions in Mpumalanga Hospitals.

The district Communicable Disease Control Coordinators (CDCC) in Mpumalanga proved wonderful learners and performed exceptionally in conducting the cross-sectional coverage survey data collection.

Professor Felicity Cutts of the London School of Hygiene and Tropical Medicine is acknowledged for valuable comments on study design for the coverage survey.

Chapter 7 – Optimising leprosy control after achieving the elimination target

Anita Fourie, Leprosy Mission of South Africa, Dr. Elsa Balt, the provincial leprosy coordinator on my communicable disease control team, Dr. Bernice Harris and Professor Rick Speare all contributed significantly to all aspects of study design, data analysis, interpretation and preparation of the final manuscript for publication. Martie le Roux and Moses Matebula, skilled nursing staff from the Mpumalanga Department of Health and Leprosy Mission respectively, and Mara de Villiers, the district communicable disease control coordinator from Ermelo district were principally responsible for field data collection.

Dr. Wayne Grayson of the National Institute of Communicable Diseases was kind enough to independently review all histological specimens. Dr. Bernice Harris is thanked for assisting with the preparation of Figures 7.2 and 7.3, reflecting the geographical distribution of leprosy in South Africa, and Ermelo's location within Mpumalanga Province. Nerine Willers, from the National Department of Health, assisted by providing leprosy notification data.

The Leprosy Mission International and the Mpumalanga Department of Health financed the survey.

Chapter 8 – Using a telephonic survey as a rapid operational research tool

This study was designed in partnership with Professor Rick Speare who also provided expert advice on presentation and interpretation of results. Marietjie Petzer from my provincial communicable disease control team was primarily responsible for conducting telephonic interviews and also assisted with the preparation of the study report.

Dr. Paul Kloeck, the Chairperson of the national Rabies Advisory Group is thanked for support of survey and donation of educational training videos for provincial pharmaceutical staff. The late George Bishop, honourary secretary of the South-East African Rabies Group contributed Figure 8.1.

Chapter 9 – The case for evidence-based public health policy

I am indebted to Professor Rick Speare and Tony Harries, Professor of Medicine and Advisor to the national Tuberculosis Program, Malawi for their fabulous contributions in assisting with analysis and presentation of the data, interpretation of findings and preparation of the manuscript for publication.

In addition I would like to thank the Master of Public Health students from both Thusano School of Public Health and James Cook University's School of Public Health and Tropical Medicine who willingly participated in the thematic analysis.

All study protocols included in this thesis, where human or animal subjects were involved, received approval from the Mpumalanga Research and Ethics Committee, and other Ethics Committees where appropriate.

DEDICATION

I am grateful to the Mpumalanga communicable disease control team for their unique partnership throughout an intensive eight years during which we together discovered the immense value of operational research in mapping and guiding approaches to important communicable disease control issues.

I dedicate this thesis to my remarkably tolerant and supportive wife, [redacted], and children, [redacted], who have displayed resilient solidarity during the process of thesis preparation and provided creative diversions, including countless competitive chess and other board games, hours in cricket nets and wonderful cycle rides, that have preserved my sanity.

GLOSSARY OF ABBREVIATIONS

AFB	Acid fast bacilli
AIDS	Acquired immune deficiency syndrome
An.	*Anopheles* genus of mosquitoes
CDCC	Communicable Disease Control Coordinators responsible for managing disease control programs in Mpumalanga health districts
CFR	Case fatality ratio; the proportion of diseased people who die as a result of the specific disease
CI	Confidence interval around a statistical measure
DEET	N,N-diethyl-M-toluamide
EPI	Exapnded Programme on Immunisation
GTF	Giemsa-stained thick blood films
HIV	Hhuman immunodeficiency virus
HRP-2	Histidine rich protein 2
ICD-9	International Classification of Disease version 9
MDT	Multiple drug treatment, used in treating leprosy patients
P.	*Plasmodium* genus of malaria parasites
Pf	*Plasmodium falciparum*
Pv	*Plasmodium vivax*
PCR	Polymerase chain reaction
R_0	Basic reproductive ratio, the number of new cases of infection generated by a single case into a population of fully susceptible hosts
RI	*In vivo* resistance grade I
RII	*In vivo* resistance grade II
RIII	*In vivo* resistance grade III
RAG	Rabies Advisory Group to national Ministries of Agriculture and Health
RBM	Roll Back Malaria, a World Health Organization initiative to improve malaria control in Africa
RIG	Rabies immunoglobulin

SEACAT	South-east African Combination Artemisinin-containing Therapy trial in South Africa, Mozambique, and Swaziland
SD	Standard deviation
SP	Sulfadoxine-pyrimethamine
TB	Tuberculosis
WHO	World Health Organization

TABLE OF CONTENTS

List of Figures

List of Tables

Chapter 1. Introduction

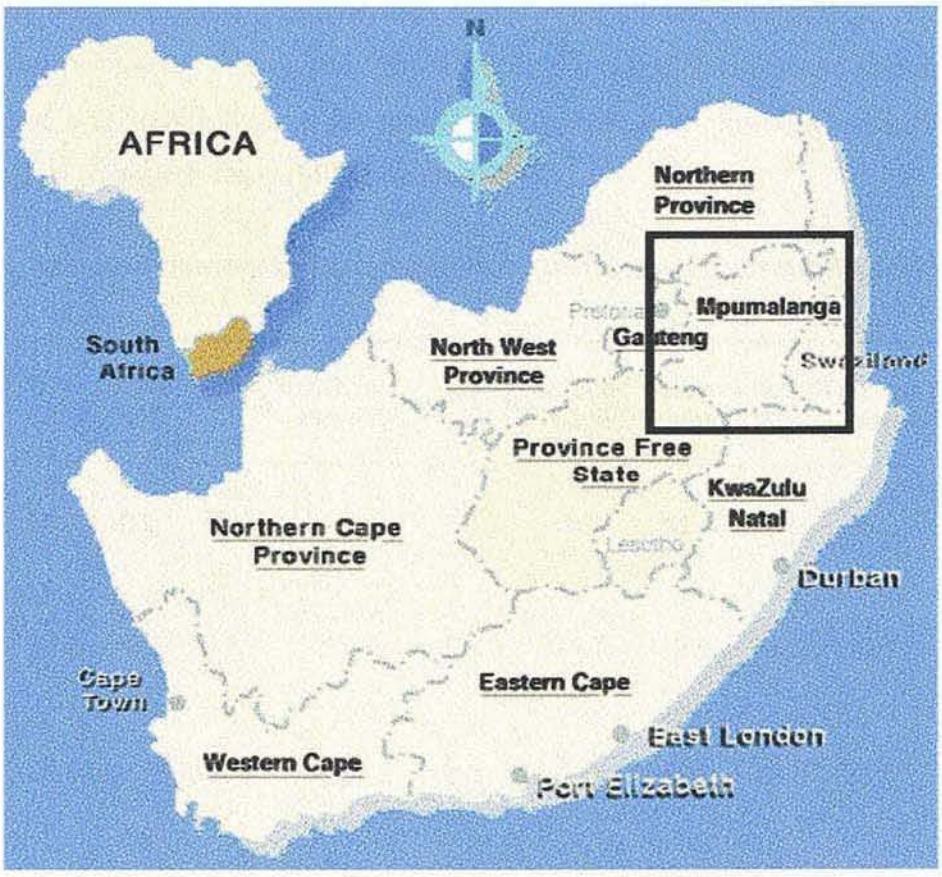
1.1. Mpumalanga Province in overview

Mpumalanga is one of nine provinces established following the first democratic elections in South Africa during 1994. The Province is situated in the northeast of the country, is flanked by Mozambique in the east and Swaziland in the south [Figure 1.1]. It was formed from the eastern portion of the former Transvaal province, and two self-governing territories, Kangwane in the east and Kwandebele in the west. Kangwane was inhabited predominantly by Swazi people but also had become home to at least 200,000 Mozambican refugees that had fled the war in that country during the 1970s. Kwandebele was populated almost exclusively of people of Ndebele origin. The vast majority of employed Ndebeles continue to commute on a daily basis to the large metropolitan areas of Pretoria and Johannesburg. The principal languages spoken in the Province are: siSwati (30.0%), isiZulu (25.4%) and isiNdebele (12.5%).

Mpumalanga means the "place where the sun rises". High plateau grasslands in the west extend eastwards for approximately 250kms before terminating in an immense Escarpment, which descends hundreds of metres down to the low-lying eastern region known as the Lowveld. The western plateau consists of two regions, the Highveld in the north and the Eastern Highveld in the south.

Nelspruit is the provincial capital, and administrative and business centre of the Lowveld. This region is dependent on agriculture, particularly sugar and citrus, forestry and tourism, boasting many nature reserves. Witbank, in the Highveld, is the centre of the local coal mining industry, while Standerton and Ermelo, in the Eastern Highveld, are established dairy farming and wool production centres, respectively. The two western regions experience a temperate climate, with maximum daily temperatures averaging 27°C in the summer months and 18°C in the winter months. The Lowveld, in contrast, is subtropical with maximum daily temperatures averaging 32°C in the summer months and 22°C in the winter months.

Figure 1.1. Mpumalanga Province, location in relation to Africa and South Africa.



1.2. Demography of Mpumalanga

The Province is predominantly rural and the population of three million people is heterogeneously settled on the 79,490 km^2 of land, with a concentration of people in peri-urban areas and on tribal land. Mpumalanga shares many of the demographic features that characterise rural areas of southern Africa, including a high fertility and population growth rate, and a relatively high infant mortality rate, being the third highest in South Africa [Table 1.1] (Chimere-Dan, 1995; Erasmus, 2000).

Table 1.1. Selected demographic indicators by province, South Africa, 2000.

	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Mpumlanga	Northern Cape	Northern Province	North West	Western Cape	South Africa
Percentage population per province	16.1	6.9	17.0	21.2	7.2	1.9	12.4	8.3	9.0	100
Area as a proportion of total area of South Africa	13.9	10.6	1.5	7.5	6.7	29.7	9.8	9.7	10.6	100
Population density (person per km^2)	38.0	21.1	365.2	92.3	37.3	2.0	42.2	28.0	28.1	33.0
Annual population growth rate	2.6	1.5	1.3	2.8	3.0	0.8	4.0	3.1	1.7	2.4
Total fertility rate	4.6	3.7	3.0	4.3	4.3	2.9	5.8	4.5	2.7	3.3
Infant mortality rate	44.7	45.8	32.3	44.9	45.1	42.9	52.9	40.1	24.4	40.2

Sources: Chimere-Dan, O. (1995) Demographic patterns in South Africa. In: Harrison, D. & Nelson, M., eds. *South African Health Review 1995.* Durban: Health Systems Trust.

Erasmus, J. (2000) *South Africa's nine provinces.* Midrand: Development Bank of South Africa.

1.3. Socio-economic status of Mpumalanga

The differential development of apartheid South Africa is reflected by the relatively poor socio-economic indicators of historically deprived rural provinces [Table 1.2] (Erasmus, 2000; Statistics South Africa, 2000). Mpumalanga certainly belongs in this category when considering the province's ranking in relation to other provinces, where 1 reflects best and 9 worst performance. Mpumalanga is ranked 8 for literacy, 6 for employment and 6 for dependency. Mpumalanga fares equally poorly when considering availability of basic amenities and services, with only 1 in every 5 African households having tap water available, a similar proportion of the population using electricity as the major source of household power supply, and 1 in 6 households not having any sanitation facilities. The gap between African and White residents within the Province is profound and exceeds the discrepancy between provinces.

1.4. Health services in Mpumalanga

Mpumalanga is a notable outlier in terms of public health service expenditure per capita, and health facility and service provision. The legacy of racial discrimination, rural impoverishment, fragmentation of services and inequitable health personnel development is particularly striking, and remains a blight on the declared national commitment to equitable health service provision in South Africa and an indictment on provincial budgetary allocation [Table 1.3] (McIntyre *et al.*, 1999).

Table 1.2. Selected socio-economic indicators by province, South Africa, 2000.

	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Mpumlanga	Northern Cape	Northern Province	North West	Western Cape	South Africa
Functional urbanization (%)	55.4	73.7	99.6	77.9	43.2	78.2	12.1	43.9	95.1	65.5
Literacy rate	59.0	60.0	69.0	58.7	54.6	67.6	52.7	55.8	71.9	61.4
Unemployment rate	45.3	24.4	28.7	32.2	36.4	32.5	47.0	36.6	17.3	32.6
Dependency ratio	3.7	1.4	0.9	2.3	2.1	1.6	4.8	1.6	1.2	1.9
Per capita income (rands)	1,358	2,419	4,992	1,910	2,164	2,865	725	1,789	4,188	2,566
Proportion of households with tap water in dwelling										
* African	16.3	19.1	57.2	25.9	20.1	20.2	12.9	21.1	39.5	27.4
* White	97.5	97.4	98.6	99.1	96.6	98.9	91.4	99.7	99.4	98.4
Proportion of households using electricity as main energy source										
* African	12.0	31.7	64.6	31.7	20.0	29.9	14.0	25.1	46.5	30.5
* White	95.8	99.8	98.4	99.4	99.1	81.9	97.9	99.7	99.4	98.2
Proportion of households without sanitation facilities										
* African	28.8	12.7	2.6	8.9	16.8	-	-	13.0	-	12.6
* White	0.1	0.0	0.0	0.0	0.0	-	-	0.0	-	0.0

Sources: Erasmus, J. (2000) *South Africa's nine provinces.* Midrand: Development Bank of South Africa.

Statistics South Africa. (2000) *October Household Survey 1998, 1999. Statistical release P0317.* Pretoria: South African Government Printer.

Table 1.3. Health expenditure and health service provision by province, South Africa, 1998.

	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Mpumlanga	Northern Cape	Northern Province	North west	Western Cape	South Africa
Expenditure										
Public health expenditure/capita (rands)	227.0	266.5	381.7	236.9	136.6	221.2	164.1	178.9	491.1	262.6
Human Resources										
Doctors/100,000 population	30.7	46.5	127.4	53.5	28.3	37.6	15.5	22.7	143.8	60.2
Nurses/100,000 population	321.3	382.3	618.4	431.9	265.8	432.3	293.2	273.5	686.3	421.5
Pharmacists/100,000 population	20.1	38.8	109.8	28.7	23.1	28.5	7.8	22.8	79.8	42.6
Facilities										
Distribution of hospital beds by type of hospital										
Academic hospitals (%)	6.8	31.0	57.6	8.2	-	-	-	-	37.5	18.5
Tertiary hospitals (%)	22.0	9.6	9.2	30.7	5.5	-	29.2	19.4	14.5	19.7
Secondary hospitals (%)	12.6	17.5	19.7	21.0	38.4	44.4	5.2	17.9	18.1	18.4
First level hospitals (%)	58.6	41.9	13.4	40.2	56.1	55.6	65.6	62.7	29.9	43.4
Hospital beds/1,000 population	3.5	4.1	6.0	3.8	2.1	4.0	2.5	3.3	5.4	4.0
Distribution of primary care facilities										
Population/clinic	10,670	10,420	14,000	22,620	13,400	5,970	13,520	7,120	7,540	12,420

Source: McIntyre, D., Thomas, S., Mbatsha, S. & Baba, L. (1999) Equity in public sector health care financing and expenditure. In: Crisp, N. & Ntuli, A., eds. *South African Health Review 1999*. Durban: Health Systems Trust.

Not only does Mpumalanga have the lowest per capita expenditure on public health services, but also displays the lowest nursing and hospital bed provision ratios in the country (Burn, 1999; Barron & Sankar, 2000).

1.5. Communicable disease burden in Mpumalanga

As would be expected, Mpumalanga with its rural sub-tropical environment and developing, predominantly African, population bears a heavy burden of communicable diseases. Indeed communicable diseases constitute approximately 70% of primary care contacts with the health services in the Province (Harrison, 1996; Harris, 1997).

Certain communicable diseases have historically differentially affected Mpumalanga within South Africa. Ranking of communicable disease notification rates, where a rank of 1 equates to highest known incidence or prevalence, reflects the particular importance of specific communicable diseases in Mpumalanga. These include malaria (ranked 1st) and measles (ranked 3rd) [Table 1.4] (Department of Health, 1994). In addition the province is second only to KwaZulu-Natal in the number of confirmed canine and human rabies cases, second again to KwaZulu-Natal in the number of cholera cases notified during large-scale epidemics during the 1980s, and is the hub of the remaining leprosy burden in South Africa (Department of Health, 1993; Durrheim *et al.*, 2001d; Durrheim *et al.*, 2001e).

Table 1.4. Notification rates* of selected important communicable diseases by province, South Africa, 1994.

	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Mpumlanga	Northern Cape	Northern Province	North West	Western Cape	South Africa
Incidence of TB	280.6	472.0	191.9	115.3	84.2	417.2	53.2	83.0	702.6	225.9
Incidence of measles	51.7	105.5	69.0	44.5	93.4	115.5	47.8	27.8	40.2	57.2
Incidence of malaria	0.1	0.5	9.0	45.1	131.0	2.9	42.7	4.4	0.5	27.5

* incident cases/100,000 population/annum

Source: Department of Health. (1994) *Health systems research and epidemiology. Notification system.* Pretoria: South African Government Printer.

1.6. Focus of thesis

The operational research model is increasingly being recognised as a valuable approach for addressing perplexing questions at public health program level. It has even been suggested that success in combating communicable diseases in Africa depends upon each country having the ability to conduct appropriate operational research (Foster *et al.*, 1990). For the purpose of this thesis, operational research is defined as the systematic search for knowledge on interventions, tools or strategies that enhance program effectiveness, with the rider that the research is planned and conducted by or in equal partnership with the local control program.

Malaria, measles, rabies and leprosy have been the particular focus of the operational research agenda of the provincial Communicable Disease Control unit over the past eight years. A collection of operational research studies relating to control of these diseases in Mpumalanga, are reported, analysed and discussed in this thesis.

1.6.1. Aim and objectives of thesis

The aim of this thesis is to use a collection of operational research studies conducted within Mpumalanga Province to demonstrate the scope and success of the operational research approach for impacting on communicable disease control practice and policy in a rural South African environment.

Specific objectives are:

* To investigate the benefit of treating deaths related to specific communicable diseases as sentinel events for initiating confidential inquiries aimed at improving patient and program management;
* To examine the usefulness of operational research for defining malaria vector behaviour and characteristics for developing innovative control strategies;
* To demonstrate, using a series of malaria diagnostic studies, the incremental and progressive nature of the operational research approach and its practical outcomes;
* To establish the value of sentinel surveillance sites for *in vivo* sensitivity testing as a key component of an operational research agenda focused on ensuring effective malaria therapy;
* To provide evidence of the value of equipping field staff to collect robust immunisation coverage and disease data for program planning;
* To employ operational research methods for establishing valid sub-national leprosy surveillance post-elimination;
* To use a simple telephone survey related to rabies management, to demonstrate that rapid techniques can provide valuable information on public health program quality;
* To use Mpumalanga data to elicit characteristics of the operational research approach that affect its ability to influence communicable disease control policy and practice; and
* To demonstrate that operational research, while improving communicable disease control policy and health outcomes, can be of high academic quality.

Chapter 2. Confidential inquiries - a useful tool for corrective public health action

2.1. Chapter Overview

Severe falciparum malaria is a medical emergency with attendant high mortality. A multi-disciplinary medical, laboratory and public health team carefully reviewed the clinical records and special investigations of the 42 patient deaths attributed to malaria in Mpumalanga Province between 1 January and 30 June 1996. The record review was supplemented by interviews with next-of-kin and confidential reports by health staff to determine the presence of avoidable factors or deviations from minimum acceptable standards of case management that may have contributed to the deaths. Delays in seeking medical attention were common, particularly among patients who had sought advice from traditional or spiritual healers. Incorrect anti-malarial prophylaxis use by travellers, unavailability of appropriate anti-malarial drugs, unacceptable delays before initiating therapy at hospitals and incomplete administration of prescribed therapy were additional avoidable factors uncovered. Inadequate assessment of malaria target-organ functioning was disconcertingly common, but cerebral affectation, renal impairment, hypoglycaemia, acidosis and multiple organ affectation were prominent findings when assessed. The success of this technique in defining remediable factors contributing to deaths of patients from malaria with implementation of resulting recommendations, subsequently led to its application for improving cholera patient management in Mpumalanga. Confidential inquiries should be used more widely in public health programmes in developing countries to highlight deficient features of programme or patient management amenable to corrective action.

2.2. Peer-reviewed publications arising from research summarised in this chapter

* Durrheim, D.N., Fieremans, S., Kruger, P., Mabuza, A. & de Bruyn, J.C. (1999) Confidential inquiry into malaria deaths. *Bulletin of the World Health Organization*, 77, 263-266.

* Durrheim, D.N. & Fieremans, S. (1999) Profile of patients dying with *Plasmodium falciparum* malaria in Mpumalanga. *Southern African Journal of Epidemiology and Infection*, 14, 24-25.
* Durrheim, D.N., Billinghurst, K.G., Speare, R. & Reich. M.R. (2002) Cholera – the role of catheters, confidential inquiries and early response. *South African Medical Journal, in press.*

2.3. Introduction

In the past decade there has been an increasing recognition of the value of auditing medical practice to assure quality of patient care (Davies & Crombie, 1995; Hayward, 1996). Mechanisms introduced to ensure optimal patient management as a result of clinical audit include: distribution of evidence-based guidelines, introduction of continuing medical education programs for health professionals and peer review (Chassin, 1996).

A recent innovation has been the establishment of independent teams of experts to review deaths associated with specific medical conditions or health service interventions. These teams view fatalities as sentinel events, possibly reflecting a failure of the health care delivery system. Examples of successful utilisation of this approach include confidential inquiries into: homicides and suicides by mentally ill people, stillbirths and deaths during infancy, peri-operative mortality, asthma deaths, and deaths due to stroke and hypertensive disease (Mersey Region Working Party on Perinatal Mortality, 1982; British Thoracic Association Research Committee, 1984; Wood *et al.*, 1984; Thomas *et al.*, 1985; Devlin & Lunn, 1986; Morgan & Priest, 1991; Clark *et al.*, 1992; Payne *et al.*, 1993; Blair *et al.*, 1996; Duxbury, 1996; Fleming *et al.*, 1996; Pillay *et al.*, 1996; Appelby *et al.*, 1997).

The Lowveld Region of Mpumalanga Province, located in the north-eastern corner of South Africa, is a predominantly rural area with 40% of the 850,000 inhabitants living in traditional dwellings and adult illiteracy exceeding 40%. This Region experiences

seasonal malaria epidemics, with *Plasmodium falciparum* infection accounting for more than 90% of cases. Intra-domicillary spraying with synthetic pyrethroid insecticides, and early diagnosis and treatment of cases at 72 public health clinics form the basis of malaria control in the area.

During an unexpectedly severe malaria epidemic in the 1995/1996 summer malaria season, the potential value of conducting a confidential inquiry into all deaths ascribed to malaria was recognised in discussion with the Mpumalanga Malaria Control Program management. The objective of the inquiry was to determine common problems and deficiencies in case management by detailed review of routine hospital and clinic records of deceased patients supplemented by interviews with close relatives and in-depth confidential statements from the responsible health professionals, where indicated. Factors investigated included the circumstances at the time of the patients' presentation, and all aspects of diagnosis, referral and treatment.

It was envisaged that the findings of the inquiry might be used to guide the design of strategies that would improve management of malaria cases in Mpumalanga Province and reduce the likelihood of future deaths.

2.4. Methods

A review team, which I led as the provincial consultant in communicable disease control, and consisting of two specialist physicians, a medical microbiologist, the head of the local military medical services and malaria control program management, reviewed all malaria-associated deaths in Mpumalanga Province which occurred between 1 January 1996 and 30 June 1996. Deaths were ascertained from three sources: routine reports to the malaria control programme, and statutory notifications to the provincial Information Office and the Registrar of Deaths at the provincial Department of Home Affairs.

A basic data collection sheet was completed for each deceased patient from hospital, clinic or private practitioners' case notes, nursing and drug records, laboratory and

radiological examinations and death certificates. Semi-structured interviews were conducted with patients' next-of-kin by malaria control programme staff and confidential statements were requested from health personnel to address particular questions or concerns of the review team.

Primary care management was judged against practices advocated in the Mpumalanga Department of Health clinic manual, "Malaria - guidelines for the diagnosis and treatment of uncomplicated malaria", that was widely available in clinics. Hospital case management was assessed against practices advocated in standard references and the hypothetical standard of the reasonable doctor or nurse working in a busy rural hospital (World Health Organization, 1990; White, 1996a). All conclusions and recommendations were a reflection of team consensus. Quantitative data were collated and analysed by means of a customised Epi Info 6 database (Dean *et al.*, 1996).

2.5. Results

A total of 42 deaths attributed to malaria occurred in Mpumalanga Province during the six-month period, January to June 1996. When related to the total of 5,726 malaria patients diagnosed by the private or public health sector during the same period, this translated into an overall malaria case fatality ratio (CFR) of 0.73% (95% confidence interval 0.53-0.99%). *P. falciparum* parasites were demonstrated on Giemsa-stained thin blood films in 41 patients and a rapid immunodiagnostic test (ICT Malaria Pf^{TM}) was positive in the remaining patient. The majority of deaths occurred during February and March (76%, 32/42) and this time period accounted for a similar proportion of the total notified malaria cases (72%). The ratio of male (n=25) to female (n=17) fatalities (1.47:1), was similar to the gender ratio of cases (1.45:1), with CFR's of 0.74% and 0.73%, for males and females respectively. The mean age of people dying was 34 years with a range from 3 to 77 years, with the majority of deaths (45%, 19/42) occurring in the 20-39 year age-group. There were two deaths, 5% of total deaths, in pregnant women, both of whom were in the age group 20-29 years. The peak CFR of 9.68% was found in the age group over 70 years [Table 2.1].

Most deaths (93%, 39/42) were among residents of the high-risk malaria area. Three fatalities had positive travel histories to malaria endemic areas; two had visited Mozambique and one Marloth Park, a small town in the heart of the high-risk area in Mpumalanga. Despite recommendations by the South African Department of Health for South Africans travelling to high-risk malaria areas, two had not used anti-malarial prophylaxis and the one visitor to Mozambique, a chloroquine-resistant malaria area, had only used chloroquine for prophylaxis (Department of Health, 1995b).

Table 2.1. Malaria case fatality ratios by age group, January-June 1996, Mpumalanga Province.

Age Group (years)	Case Fatality Ratios
0 - 9	0.74
10 - 19	0.13
20 - 29	0.88
30 - 39	1.08
40 - 49	1.47
50 - 59	2.01
60 - 69	1.80
≥ 70	9.68

2.5.1. *Delays in consulting health services*

In at least 37% (14/38) of deaths where the time of symptom onset could be determined, a delay of three or more days occurred before the patient made contact with the formal health service. Seven patients delayed for a week or longer after symptom onset. Statements in health records or made by family members which indicated that nine (21%) patients presented to health professionals on the day of illness onset may be an overestimate, for although malaria infection is unpredictable and may progress rapidly,

the advanced stage of disease at presentation in seven of these cases suggests that delays in seeking assistance from the formal health sector may well have occurred.

During interviews with relatives it was established that six patients had spent extended periods with either traditional healers (n=4) or spiritual healers (n=2) after illness onset. Resultant delays in accessing the formal health sector ranged from 2 to 22 days (mean = 11 days). Five of these six patients (83%) delayed three or more days compared to 28% (9/32) of the remaining patients that demised, and this difference was significant at the 0.01 level (95% confidence interval, 0.22-0.89).

A lack of transport contributed to the death of two people, including a young girl, who could not get to a clinic or hospital.

2.5.2. *Primary care malaria management*

Fifty-five percent (23/42) of patients were initially assessed by clinic staff (n=16) or general practitioners (n=7), while 45% (19/42) had their primary contact with a hospital. Delays in diagnosis resulting from clinic staff not considering malaria characterised three cases. Although two of these patients had a history of fever and presented with gastrointestinal upset, and jaundice, respectively, tests to exclude malaria were not performed because both patients were apyrexial at presentation. The third patient presented with fever and was initially treated with paracetamol only.

In addition malaria was not initially considered in the differential diagnosis of two patients that presented with fever to general practitioners outside the high-risk malaria area. In one case a travel history would have revealed an extended period in a high-risk malaria area and in the other, an occupational history may have provided a clue. The latter patient worked night-shifts at a railway station serving trains from the malaria area. The trains may have also provided transport for infected anopheline mosquitoes.

In two instances, the magnitude of the 1996 malaria epidemic had resulted in exhaustion of clinic anti-malarial supplies necessitating transfer to hospital with concomitant delays in initiating therapy.

One patient who presented with severe vomiting and diarrhoea was inappropriately treated with oral anti-malarial agents and only referred to hospital the following day after deterioration in clinical condition.

Chloroquine was still used as first-line anti-malarial therapy for uncomplicated malaria during 1996 in Mpumalanga. Inadequate clinical response to chloroquine therapy was found in eleven patients.

2.5.3. *Hospital malaria management*

Forty-one of the patients under review had contact with a hospital, including four public and one private hospital in the Lowveld Region, and one public and one military hospital outside the malaria area. Where the times of initial hospital contact and administration of the first dose of anti-malarial therapy were recorded (n=34), delays in initiating therapy were commonly found. Although 56% (19/34) of patients received treatment within the first two hours, 26% (9/34) waited four or more hours, with the longest delay being 98 hours after hospitalisation.

Similar delays in confirming diagnosis by hospital laboratories were also found. For the 37 cases where the times at which Giemsa blood film preparation and laboratory report reaching patient's ward could be determined, the median delay was four hours.

Anti-malarial therapy was not prescribed in six hospitalised cases despite laboratory confirmation of *P. falciparum* infection. It is notable that four of these cases were admitted over weekends. Two additional patients never received anti-malarial medication despite a doctor's written prescription in the patient notes, making a total of

eight patients (20%) who did not receive any therapy despite a laboratory diagnosis of malaria.

Five patients with complicated malaria were treated with chloroquine alone, either orally (n=4) or intramuscularly (n=1), while a further five patients were started on chloroquine but later switched to quinine, due to deteriorating clinical status. Intramuscular chloroquine was used in one patient because no quinine was available in the specific hospital. Oral quinine therapy was initiated in two patients and intravenous quinine in twenty-one. In two of the latter group, quinine was not administered in glucose. An incorrect dose of anti-malarial drugs was prescribed in 12% (4/34) of patients.

In 31 hospitalised cases, where it was possible to accurately assess the proportion of doses of anti-malarial therapy administered according to the dosage schedule prescribed, 68% (n = 21) of patients received all prescribed doses. However, in six (20%) patients who died, 50% or fewer prescribed doses were administered and recorded.

2.5.4. *Monitoring and clinical profile of hospitalised patients*

Although an assessment of consciousness was recorded for 98% (41/42) of patients, available records only allowed renal status determination in 62% (26/42) of patients, respiratory assessment in 83% (35/42) of patients, investigation for acidosis in 36% (15/42) of patients and determination of platelet counts in 69% (29/42) of patients. Fluid balance monitoring was performed in 83% (35/42) of patients.

Seventy-nine percent (33/42) of patients had regular blood pressure monitoring. Sixty-nine percent (29/42) had at least one blood glucose measurement recorded but only 48% (14/29) of these patients were monitored at the frequency recommended to allow expeditious detection and treatment of hypoglycaemia.

While taking into account the pressure on hospital beds occasioned by the epidemic, the review team nevertheless concluded that 12% (5/41) of patients had been prematurely discharged from hospital.

Complications were assessed by means of established criteria, with denominators reflecting the number of patients where completeness of records provided adequate system assessment [Table 2.2] (World Health Organization, 1990). Cerebral affectation, renal failure, acidosis and hypoglycaemia were common findings in this cohort of patients. Thrombocytopaenia with a platelet count below 100,000 was recorded in 26/29 patients, with a mean platelet count of 55,276. The six patients with spontaneous haemorrhage included one with melaena, two with haematemesis, one with spontaneous epistaxis and two with a picture of disseminated intravascular coagulation. One of these latter patients had a picture of septic shock but no causative pathogen was cultured. The mean parasite density in the 16 patients where it was accurately quantified was 19%. The semi-quantitative "plus-method" was used in 25 patients with three (+++) and five (+++) recorded.

Table 2.2. Complications in patients dying with *Plasmodium falciparum* malaria, January-June 1996, Mpumalanga Province.

Complication	Number affected / Number of patients evaluated
Disturbed consciousness	33/41 (80%)
Generalised convulsions	8/42 (19%)
Renal failure (serum creatinine > 265 µmol/liter)	18/26 (69%)
Pulmonary oedema	10/35 (29%)
Systolic hypotension (< 70 mmHg)	7/33 (21%)
Acidosis (plasma HCO3 < 15 mmol/liter)	11/15 (73%)
Hypoglycaemia (glucose < 2.2 mmol/liter)	11/29 (38%)
Severe anaemia (Hb < 5.0 g/dl)	3/30 (10%)
Hyperpyrexia (> 40°C)	8/39 (21%)
Spontaneous bleeding	6/42 (14%)
Jaundice (serum total bilirubin > 43 µmol/liter)	8/10 (80%)
Hyperparasitaemia (> 5%)	13/16 (81%)

2.6. Discussion

In Mpumalanga Province during the first six months of 1996, the number of cases in the seasonal malaria epidemic exceeded the three-year rolling average by 189%. Ninety-four percent of cases were due to *P. falciparum*. The malaria CFR is one of the key indicators of the quality of a malaria control programme and the relatively low value of 0.73% (7.3 per 1,000 cases) in Mpumalanga for the period under review, would usually be reassuring. However the results of the review show that avoidable factors were commonplace. Although gaps in clinical and laboratory detail and multiple organ pathology make it impossible to define an exact cause of death without post-mortem examination, avoidable factors appear to have contributed to many patient's demise.

Not all malaria deaths can be avoided but the majority can be prevented by a well-targeted malaria control program, a high index of suspicion amongst health care workers, the prompt diagnosis and initiation of correct therapy, coupled with a high standard of nursing care (White, 1996b).

The inquiry found that basic principles of malaria prevention and management had been violated and shortcomings included:

- the use of inappropriate anti-malarial prophylaxis or no prophylaxis by travellers to high-risk malaria areas;
- avoidable delays in diagnosis and initiation of adequate therapy due to late presentation of patients to the formal health sector, neglecting to obtain an adequate travel history from a febrile traveller, failing to correctly respond to a history of fever during the high-risk malaria period, stock-out of anti-malarial treatment and delayed confirmation of malaria diagnosis in hospitalised patients. An association between delays and poor outcome has previously been described (Durrheim *et al.*, 1996a; Luxemburger *et al.*, 1997);
- failing to administer the correct anti-malarial at the correct dosage and frequency. This included oral therapy for a patient with severe vomiting, chloroquine as first-line anti-malarial therapy without *in vivo* evidence of efficacy, incorrect dosages of anti-malarial

medication, failing to administer all prescribed doses and neglecting to administer intravenous quinine in dextrose; and

- inadequate monitoring of indicators of severity in complicated malaria cases, in particular renal and metabolic status, fluid balance and blood glucose.

At low levels of malaria transmission severe disease may occur at all ages (Luxemburger *et al.*, 1997). In this cohort of patients, CFRs were particularly high in older age groups. This may represent the play of chance due to the relatively small number of fatalities in each age group, reflect earlier presentation and treatment of young people and children, be the result of selective death registration, or indicate a greater vulnerability of the elderly for complicated disease. The expression "Domino Principle" which was coined to describe the phenomenon where malfunction of one body system leads to disruption of other organs, eloquently depicts the features of severe *P. falciparum* malaria (Jaffe & Zahger, 1996). Despite incomplete clinical and laboratory records, evidence of multiple organ affectation was present in the majority of patients.

The absence of a control group in this case-series precludes definition of predictors of fatal outcome. However poor prognostic features previously delineated in KwaZulu-Natal, a neighbouring province, including hyperparasitaemia, renal failure and cerebral affectation were also common, when sought, in the Mpumalanga patients (Soni & Gouws, 1996; Durrheim & Fieremans, 1999). Unfortunately only twelve of the 42 patients had adequate investigation of all five of these critical parameters of severe malaria. Hypoglycaemia and acidosis were also frequently present. Coma scores, urine output and renal status monitoring, blood glucose, serum bicarbonate, venous lactate and standardised parasite count have proven particularly valuable indicators of severe disease in other settings (White, 1996a). The presence of any of these features of severe disease should prompt immediate investigation for evidence of concomitant affectation of other target organs requiring urgent attention.

A detailed and comprehensive set of recommendations were formulated by the review team and fully implemented by the Department of Health in Mpumalanga. They included

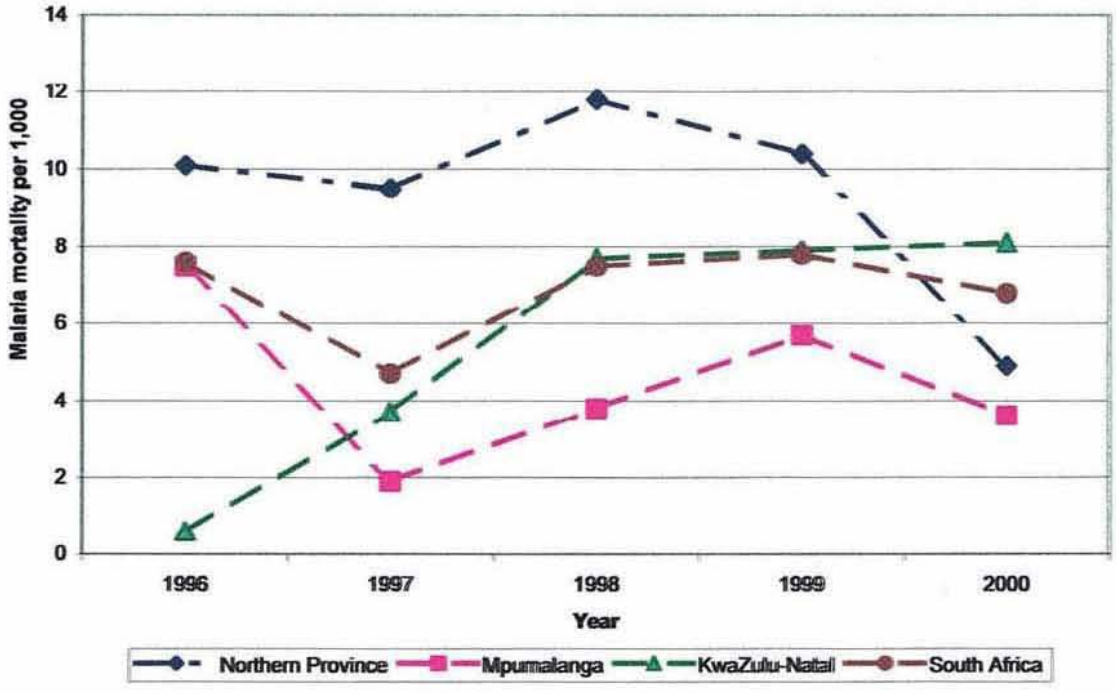
an intensive radio communication campaign to encourage patients to present at an early stage of disease, re-training of clinic staff on the guidelines in the malaria manual used by the Department of Health, ongoing monitoring of availability of anti-malarial treatment in clinics and hospitals, an *in vivo* chloroquine resistance study and the introduction of a rapid card test (ICT Malaria Pf^{TM}) for malaria diagnosis in hospital accident and emergency units. This was based on the excellent results of an earlier introduction of rapid tests at clinics (Durrheim *et al.*, 1998c).

The results of the review were communicated and debated in sessions with medical staff at each hospital. Responsibility for checking for errors in prescribing, monitoring and administering medicines was accepted by medical officers (Horton, 1997). Algorithms for diagnosis, standard treatment guidelines and a monitoring chart were developed and implemented by local medical staff, and copies of the excellent World Health Organization guidelines were distributed to hospital staff (World Health Organization, 1990). The success of this inquiry was greatly facilitated by medical staff recognising their potential for contributing to optimising patient care, with noteworthy co-operation from the responsible nursing and medical staff after reassurances that the inquiry would lead to evidence-based recommendations, rather than punitive measures.

Although a confidential inquiry is subjective and results undoubtedly vary according to the background and experience of reviewers, this assessment was less controversial, as incontestable shortcomings in aspects of routine care were found. This type of review is also vulnerable to problems common to all retrospective data collection. The quality of hospital notes, in particular, complicated the inquiry and this shortcoming has previously been discussed (Devlin & Lunn, 1986).

The value of the Mpumalanga confidential inquiry into malaria deaths in 1996 was supported by the trend in Mpumalanga's CFR when compared to neighbouring KwaZulu-Natal and Northern Province, the other South African provinces affected by seasonal malaria epidemics [Figure 2.1]. The confidential inquiry approach has subsequently been applied for investigating maternal deaths in South Africa (Theron, 2000).

Figure 2.1. Malaria case fatality ratios, South Africa, 1996-2000.



2.6.1. Confidential inquiries for improved cholera management

Recently the demonstrated utility of the confidential inquiry approach for investigating malaria deaths has lead to its application for improving cholera patient management in Mpumalanga (Durrheim *et al*, 1999a; Durrheim *et al.*, 2002a).

Vibrio cholerae O1, El Tor biotype causes epidemic, life-threatening diarrhoea. Re-emergence of this cholera biotype in rural areas of south-eastern Africa is of considerable public health consequence. The higher proportion of asymptomatic cases and carriers seen with the El Tor biotype, compared to the Classic biotype, poses a particular challenge to control (Sanchez & Taylor, 1997). Delayed detection and response to initial individual clinical cases can lead to rapid surreptitious spread in a community and environmental saturation with vibrios. Epidemic cholera is a sensitive indicator of severe under-development (Ackers *et al.*, 1998). Most large cholera outbreaks occur in environments of extreme poverty. During recent south-east African outbreaks, surface water contamination has proven an effective means for cholera transmission in rural and peri-urban environments where clean water and adequate sanitation are not readily available (Acosta *et al.*, 2001; Durrheim *et al.*, 2001e).

In Mpumalanga Province it has been mandatory that an inquiry be conducted into every suspected cholera death, since 1998. As cholera is eminently treatable, a fatality merits careful investigation to determine the cause of death, identify any health system related factors that may have contributed to the fatal outcome, and recommend remedial action necessary to prevent any future deaths (Bartlett, 1991). Hospital, clinic or private practitioners' case notes, nursing and drug records, laboratory and radiological examinations, and death certificates are carefully studied, and semi-structured interviews conducted with the health workers responsible for the patient's care by senior staff from the provincial communicable disease control unit. The health workers are assured that the results of the inquiry will remain confidential and their co-operation has been excellent (Smith, 2000). Where considered necessary, interviews are also conducted with

patients' next-of-kin. Primary care and hospital management practices are judged against existing national cholera treatment guidelines (Department of Health, 2001).

Use of this technique to investigate the five cholera deaths, which occurred during the past four years in Mpumalanga, identified several avoidable contributory factors. The death of a child and an adult female were directly attributed to delays in presenting to the health service. A further delay of four hours in transporting the moribund child between the peripheral clinic and the referral hospital occurred due to classification of diarrhoea as a non-emergency condition by ambulance staff. This was addressed through a correction of policy and an intensive education campaign targeting all emergency service staff. A second child, admitted at a regional hospital, died as a direct result of delays in receiving routine biochemistry results occasioned by a temporary suspension of laboratory services due to a failure of provincial authorities to pay accounts. The results of the confidential inquiry in this case had a profound impact on senior health management and a policy commitment to never allow delayed payment to impact on monitoring of essential biochemistry. The remaining fatalities were two hospitalised male patients. In both cases, earlier and more regular electrolyte monitoring may have altered management. Systematic in-depth retraining of clinical personnel in provincial hospitals in optimal cholera management followed these inquiries. A similar audit technique proved valuable in defining remediable factors contributing to cholera deaths in an African refugee setting (Siddique *et al.*, 1995). These included slow rate of re-hydration, inadequate use of oral re-hydration therapy, use of inappropriate intravenous fluids and inadequate experience of health workers.

2.7. Conclusions

A confidential inquiry is a thorough investigation to establish the cause of death, identify any possible contributory health system related factors, and recommend corrective action necessary to prevent any future deaths. Health workers are assured that its purpose is preventive not punitive, and confidentiality for health staff is guaranteed. While the value of reviewing deaths associated with specific medical conditions or health service

interventions has long been recognized in developed countries, confidential inquiries into health system related deaths have seldom been conducted in developing countries. Our experience demonstrates the value of the method for identifying remediable causes of death in priority public health programmes in a developing setting. The potential benefits of this approach should now be realised in other health programmes in developing countries and used to guide the design of strategies for eliminating avoidable deaths.

Chapter 3. Targeting vector behaviour and characteristics for effective malaria control

3.1. Chapter Overview

Malahlapanga, a remote spring in the Kruger National Park, South Africa, has proven a valuable site for original research on the behaviour of *Anopheles arabiensis*, the most important malaria vector in southern Africa. Research findings have been directly applied for improving malaria prevention and control. This unique oasis supports a large perennial population of *An. arabiensis* mosquitoes. Although adult *An. arabiensis* are readily collected biting humans, they are usually obliged to feed on wild mammals that are abundant in the area, as the nearest human habitation is more than 9km distant and the area is inaccessible to tourists. No other members of the *An. gambiae* complex are present and the population of *An. arabiensis* mosquitoes are free of known human pathogens, including *Plasmodium spp*. Studies conducted at Malahlapanga have found that the peak biting activity of *An. arabiensis* occurs during the predawn period and that 81% of bites on humans occur on the ankles or feet. Wearing closed shoes or application of small doses of N,N-diethyl-M-toluamide (DEET) containing insect repellent to the feet and ankles dramatically reduces vector contact. Operational research findings from Malahlapanga have influenced national guidelines, directed larviciding around residential camps in nature reserves, been employed for malaria outbreak response and offer great potential for cost-effective personal protection against *An. arabiensis* in low incidence malaria areas.

3.2. Peer-reviewed publications arising from research summarised in this chapter

* Durrheim, D.N., Govere, J.M., Braack, L.E.O., Gericke, A. & Speare, R. (2001) Malahlapanga – exploiting nature's bounty for malaria control. In: Canyon, D.V. & Speare, R. (editors). *Rural and Remote Environmental Health I.* Townsville, The Australasian College of Tropical Medicine. ISBN 0-9578717-1-6.

* Durrheim, D.N. & Govere J.M. (2002) Malaria outbreak control in an African village by community application of 'deet' mosquito repellent to ankles and feet. *Medical and Veterinary Entomology*, 16, 112-115.
* Govere, J.M., Braack, L.E.O., Durrheim, D.N., Hunt, R.H. & Coetzee, M. (2001) Repellent effects on *Anopheles arabiensis* biting humans in Kruger Park, South Africa. *Medical and Veterinary Entomology*, 15, 287-292.

3.3. Introduction

The African Continent bears the brunt of the malaria scourge, malaria being responsible for 9% of the continent's human disease burden and over one million deaths each year (World Health Organization, 2000c). The past decade has seen a global increase in malaria prevalence and malaria-specific mortality that has particularly affected Africa (Nchinda, 1998). This imminent disaster has prompted demands for novel approaches and more effective implementation of proven strategies (Marsh, 1998).

Recent malaria trends in South Africa, where *P. falciparum* infection accounts for the great majority of malaria cases, are particularly disconcerting. In South Africa the approach of combining vector control utilizing intra-domicillary spraying with a residual insecticide, and prompt diagnosis and therapy of malaria disease through an extensive clinic system, saw a massive 80% reduction in the malaria risk area (Gear *et al.*, 1981). This has been maintained since the early 1950s with malaria occurrence restricted to seasonal epidemics in the extreme north-eastern portion of the country bordering Swaziland, Mozambique and Zimbabwe. As a result, large-scale agricultural and tourism development became possible in areas previously ravaged by endemic malaria (Sharp & le Sueur, 1996). However in the past two decades the incidence of malaria has escalated from 2,343 malaria cases and 9 deaths notified to the National Health Department in 1981, to 61,934 cases and 423 deaths in 2000 (King *et al.*, 2001). Various contributory factors have been identified. Of particular note is the evolution of resistance in *P. falciparum* parasites to chloroquine in the three malaria-affected provinces, KwaZulu-Natal, Mpumalanga and Northern, and to sulfadoxine-pyrimethamine in KwaZulu-Natal

(Freese *et al.*, 1988; Freese *et al.*, 1991; Wernsdorfer, 1991; Kruger *et al.*, 1996; Govere *et al.*, 1999; Bredenkamp *et al.*, 2001; Durrheim *et al.*, 2001g).

Burgeoning travel by non-immune South Africans into malaria areas, an increased volume of cross-border migration by humans carrying malaria parasites and introduction of infected vectors from malaria endemic neighbouring countries has fuelled transmission (Durrheim, 1995; Wilson, 1997). Additional complicating factors include, the recent reappearance in KwaZulu-Natal of *An. funestus* that is resistant to synthetic pyrethroid insecticides used for house-spraying, climatic factors, particularly good rainfall that have favoured mosquito breeding and survival, changes in the biology and behaviour of *An. arabiensis* Patton (Diptera: Culicidae), the main malaria vector, towards outdoor biting (exophily), and changing community practices, including the washing and replastering of wall surfaces after insecticide spraying (White, 1974; Sharp *et al.*, 1984; Sharp & le Sueur, 1991; Bouma *et al.*, 1994; Colwell *et al.*, 1998; Mnzava *et al.*, 1998; Govere *et al.*, 2000b; Govere *et al.*, 2000d; Hargreaves *et al.*, 2000).

This altered malaria epidemiology has had a marked impact on health service utilization and perceptions of increased malaria risk appear to have detrimentally affected the tourism industry (Durrheim *et al.*, 2001a). Malaria prevention in tourists is hampered by the absence of a completely effective chemoprophylactic agent and the troubling adverse events profile of available chemoprophylaxis. For example a postal survey of Kruger National Park visitors found that 23.8% of travellers using chemoprophylaxis experienced adverse events, which they attributed to the medication, a frequency similar to that experienced by European visitors to tropical Africa (Steffen *et al.*, 1990; Durrheim *et al.*, 1999b). Adverse events were cited as a major reason for poor compliance with prescribed medication.

These evolving challenges to malaria prevention and management highlight the importance of a responsive and integrated approach to control (Durrheim & Whittaker, 1996). The need for a comprehensive operational research agenda directed at all vulnerable links in the chain of transmission cannot be over-emphasized.

3.3.1. Entomological epidemiology

The simple mathematical models constructed to capture the transmission dynamics of malaria offer an understanding of the importance of effectively targeting vectors for optimal malaria control (Anderson & May, 1992). The basic reproductive ratio (R_0), the number of new cases of malaria generated by one case introduced into a population of fully susceptible hosts during the duration of the case, may be quantified by multiplying the transmission rate factor from vector to human during the life-span of the vector (T_H) with the transmission rate factor from human to vector during the duration of infection in the human (T_V). In this model $T_H = V/H\ a\ b_H\ L_V$ while $T_V = a\ b_V\ D_H$ where: V is the density of vectors; H is the density of human hosts; a is the biting rate on the human host per vector, which includes the biting frequency (estimated as the reciprocal of the length of the gonotrophic cycle) and the proportion of blood meals taken on humans; b_H is the proportion of infectious bites on humans that produce a patent infection in humans; b_V is the proportion of bites by susceptible mosquitoes on infected people that produce a patent infection in the vector; L_V is the life expectancy of the vectors; and D_H is the duration of infectiousness in the host. Important assumptions underpinning this model include a lack of immunity in humans, which is a relatively robust assumption in the South African Mpumalanga setting where immunity is not thought to exist due to the seasonal nature of malaria, and an absence of a parasite-induced effect on vector survival or behaviour (Dye, 1986). Thus $R_0 = T_H T_V = V/H\ a^2\ b_H\ b_V\ D_H\ L_V$ (Dye, 1994). It can be seen from this equation that the biting rate (a) and life expectancy (L_V) of the vector are major determinants of the final value of R_0 (Garret-Jones & Shidrawi, 1964). Spraying programs reduce anopheline life expectancy but the potential value of effective personal protection in reducing the mosquito biting-rate is evident.

3.3.2. Personal protection and *Anopheles arabiensis*

Personal protection against mosquito bites falls within the ambit of community involvement as envisaged by the Alma Ata declaration and has proven an effective first line of defence against malaria in tourists (World Health Organization, 1978; Rifkin,

1981; Schoepke *et al.*, 1998). However this strategy has seldom been utilised for malaria control in malaria-endemic areas, except where bed-nets are common, and is under-utilised amongst travellers. A recent study of community knowledge and perceptions about *Malaleveva* (literally the sleep-and-shake illness) in Tonga, one of the highest-risk malaria sub-districts in South Africa, found that although 92% of respondents indicated that mosquito bites were the cause of malaria, only 51% reported ever using personal prevention measures against malaria (Govere *et al.*, 2000b). Only 28.4% of study participants had burnt mosquito coils, while 16.7% had used commercial repellents. Missed opportunities for personal protection commonly exist among tourists to malaria areas. A postal survey of visitors to the Kruger National Park during the seasonal high-risk period found that 13% of visitors used no personal protection measures and only 17.1% used four or more measures (Durrheim *et al.*, 1998a).

Indoor house spraying with residual insecticides is optimally effective against anthropophilic indoor feeding and resting malaria vectors, like *An. gambiae s.s.* and *An. funestus s.s.*, as proven by their elimination through the house-spraying programme from South Africa (Gillies & de Meillon, 1968). However, *An. arabiensis*, the main malaria vector in South Africa and much of southern Africa, is catholic in its feeding and resting behaviour, feeding on both humans and animals, and resting both indoors and outdoors (White, 1974; Sharp & le Sueur, 1991). This has limited the effectiveness of indoor house spraying and supplementary effective methods for controlling this vector are urgently required.

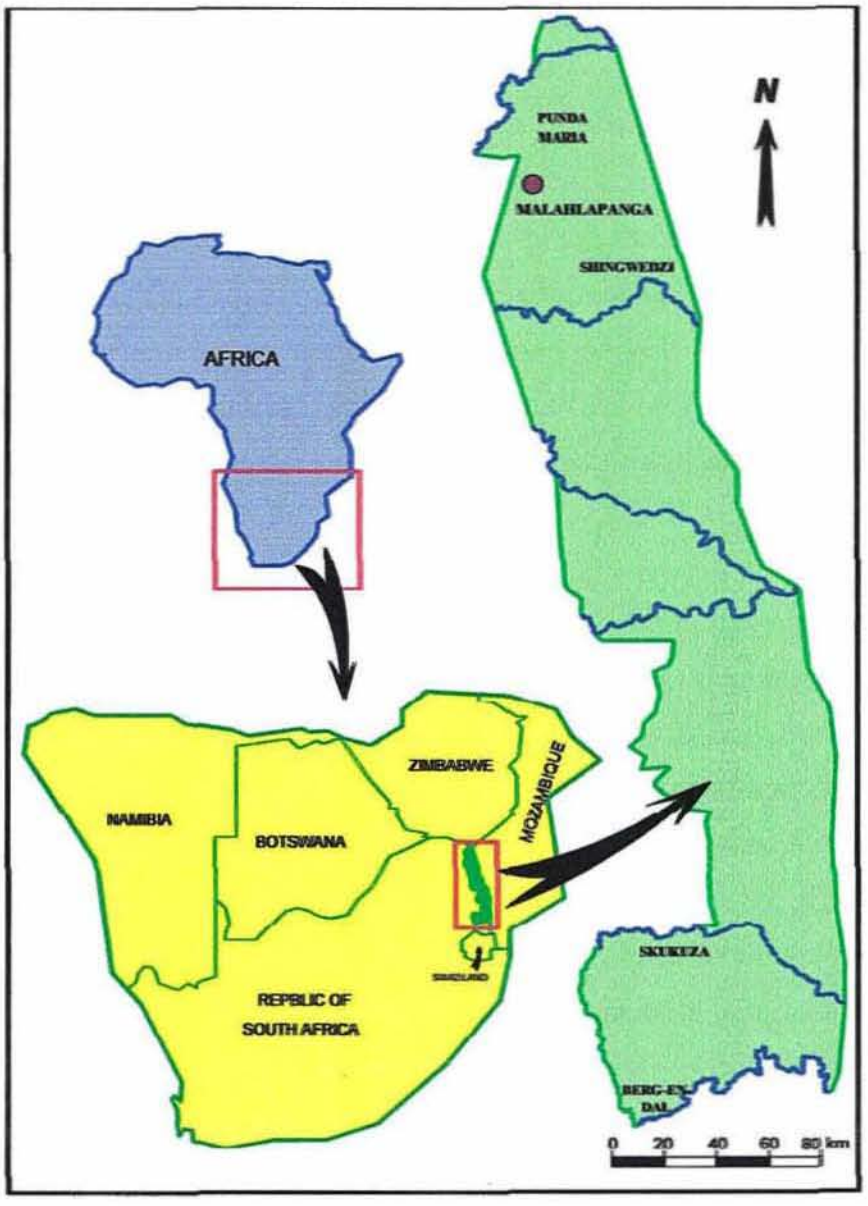
Current knowledge and understanding of *An. arabiensis* behavior in southern Africa is limited. Vector behavioural research is complicated by the relative scarcity of the vector in malaria affected areas, despite locally occurring malaria cases. The small numbers of *An. arabiensis* collected during routine vector surveillance in Mpumalanga and neighbouring provinces provide study samples of feral mosquitoes that are too small to allow meaningful field studies on mosquito behaviour (White, 1974; Sharp & le Sueur, 1991; la Grange & Coetzee, 1997). The greater relative abundance of other members of the *An. gambiae* complex, including *An. merus* and *An. quadriannulatus,* which occur

sympatrically with *An. arabiensis* in South Africa confounds field studies, as sophisticated laboratory expertise is required to reliably differentiate catches.

3.3.3. Malahlapanga ("the place of the long black dagger")

Malahlapanga ($22^0$53'S $31^0$02'E) is a fresh water geothermal spring in a pristine wilderness area in the remote north of the Kruger National Park, South Africa [Figure 3.1]. The Kruger National Park, at over 1,949 million hectares, is the largest wildlife reserve in a single African country. It is situated in the north-eastern corner of South Africa and falls within the seasonal malaria-risk area. Extensive mosquito collections made in the Kruger National Park during the early 1990s led to the discovery of this remote warm water spring with a unique breeding colony of *An. arabiensis* Patton mosquitoes (Coetzee *et al.*, 1993; Coetzee *et al.*, 2000). The spring is located in mixed *Colophospermum mopane* Kirk/*Acacia nigrescens* Oliver savannah, has a high mineral content, although not saline, and ranges in temperature between 37^0C and 38^0C where it emerges from the ground (Coetzee & Braack, 1991). The spring is located in a clearing of approximately 200 by 600m. This oasis supports a large perennial population of *An. arabiensis* mosquitoes (Braack *et al.*, 1994). Although adult *An. arabiensis* are readily collected biting humans, they are usually obliged to feed on wild mammals that are plentiful in the area, as the nearest human habitation is more than 9km distant. Mammal species include buffalo, elephant, white rhinoceros, lion, leopard, hyena, eland, kudu, impala and zebra. The area is inaccessible except by four-wheel drive vehicles and entry to this wilderness zone is prohibited to tourists.

Figure 3.1. Location of Malahlapanga in relation to the Kruger National Park, South Africa and Africa.



Polymerase chain reaction (PCR) investigation has confirmed the unsurpassed research potential of this perennial and abundant mosquito colony. Not only is it a pure colony restricted to *An. arabiensis* mosquitoes with no other members of the *An. gambiae* complex present to complicate identification, but it is also free of known human pathogens, including *Plasmodium* spp. (Coetzee & Braack, 1991; Coetzee *et al.*, 1993). This factor has allowed a number of important studies that have meaningfully enhanced the role of personal protection and malaria control in South Africa.

3.3.4. Preferred feeding period

Although there is a marked difference in human-biting catch rates between the wet and dry seasons, with wet season catches being approximately double in size, the proportional hourly nocturnal biting pattern is similar throughout the year (Braack *et al.*, 1994). *An. arabiensis* invariably commences biting after sunset but well before last light. Biting activity is relatively low in the early evening, persists throughout the night but peaks during the predawn period.

This finding has important implications for advice provided to travellers. An evaluation conducted in Mpumalanga found that DEET provides complete protection for five hours after application against *An. arabiensis* but this effect then fades (Govere *et al.*, 2000a). Results from a field evaluation of DEET in Kenya were similar and demonstrated that *An. arabiensis* is sensitive to DEET, which provided greater than 80% protection for three hours but only 60% protection after nine hours (Walker *et al.*, 1996). Where application of repellents to exposed skin is performed, as generally advocated, at dusk, the repellent effect of a single application will have greatly diminished by late evening and, in particular, the pre-dawn maximum biting frequency period. Advice provided to tourists by the only yellow fever vaccination and travel medicine centre in Mpumalanga has been tailored to include a second application prior to retiring to sleep at night with reapplication on venturing out of a screened environment prior to sunrise. This repeated application is feasible due to the excellent safety profile of DEET during 40 years of extensive use (Fradin, 1998).

3.3.5. Biting pattern and distance from breeding site

Capture stations were placed at 30m intervals up to 90m, 60m intervals up to 180m and 200m intervals up to 600m from the spring into the prevailing wind direction. Mosquito numbers were found to be relatively high in the immediate vicinity of the spring, low in the surrounding trampled area, at a maximum approximately 60m from the spring, and then rapidly declined to 600m (Braack *et al.*, 1994).

This finding was used to plan control interventions in the Kruger National Park where human dwellings are localized within tourist camps. Larvaciding with *Bacillus thuringiensis israeliensis* of anopheline breeding sites is performed within a diameter of 300m from the outer fences of residential camps and extended to a diameter of 800m during high incidence years. This protocol has been directly guided by operational research findings at Malahlapanga (Durrheim *et al.*, 2001a).

3.3.6. Preferred anatomical feeding sites

The preferential biting patterns of malaria vectors have largely been neglected when designing personal protection measures against mosquito vectors, despite evidence that selection of biting sites on humans by mosquitoes is non-random (Curtis *et al.*, 1987; Clements, 1999). *An. gambiae s.s.*, for example, prefers to bite the feet of seated humans and *An. arabiensis* mosquitoes have demonstrated a preference for biting the ankles and feet of motionless humans (De Jong & Knols, 1995; Knols *et al.*, 1996). This was postulated to be the result of odour or chemical attraction of mosquitoes but Malahlapanga research suggests otherwise for local *An. arabiensis*.

Repeated human-biting catches made with collectors seated on platforms so that their bare feet were either at 0m, 0.72-0.85m, or 1.44-1.78m above the ground, demonstrated that biting activity was significantly greater at ground level and decreased dramatically with increasing distance above ground. Random biting on the human body when lying

on the ground supported the finding that proximity to the ground is an important determinant of *An. arabiensis* biting frequency (Govere, 2000).

3.3.7. Effect of mechanical barriers on *Anopheles arabiensis* feeding

The finding of preferential feeding on humans close to the ground was the foundation of research into the role of mechanical barriers to biting. Research conducted at Malahlapanga demonstrated that the number of *An. arabiensis* biting motionless humans decreased dramatically when their feet and ankles, to 2cm above the ankle, were covered with plastic bags, without proportional shift to other parts of the legs or body (Durrheim *et al.*, 2001b). A total of 1,118 bites were recorded on 10 volunteers with alternating 45 minute collection sessions with feet covered or bare over a three-night period. Persons with feet and ankles covered received 23.8% (266) of all bites while bare-footed persons received 76.2% (852) bites.

As a consequence, particular emphasis was placed on the use of shoes and socks as a personal measure for protection against anopheline bites in the South African Department of Health malaria prevention guidelines (Department of Health, 2000). The recommendation of donning shoes and socks to prevent mosquito bites when venturing outside at night appears to have influenced practice. This measure was the second most commonly reported, after skin application of insect repellent, by a large cohort of Kruger National Park visitors responding to a postal questionnaire (Durrheim & Leggat, 1999).

3.4. The effect of topical N,N-diethyl-m-toluamide (DEET) application to ankles and feet on *Anopheles arabiensis* biting humans

A novel study was conducted at Malahlapanga to compare the biting behaviour of feral *An. arabiensis* mosquitoes on human volunteers whose ankles and feet were either treated or not treated with DEET.

3.4.1. Methods

The cream formulation of DEET (195mg/ml AI Tabard™ Shell South Africa, Pty Ltd) commercially available in South Africa was used during human night-biting catches. Eight experienced volunteers (30-41 years old) using malaria prophylaxis and dressed only in short pants were randomly paired into four teams. Two teams were randomly selected for routine application of DEET on their ankles and feet while the remaining two teams served as controls. Mosquito catches on four consecutive evenings, with each team being treated on two evenings and hourly rotation of teams through four positions, 10m apart, parallel to and about 30m from the main breeding mosquito area at the spring, compensated for positional differences in mosquito density, personal differences in catching ability and attractiveness to mosquitoes, and hour of night (Govere *et al.*, 2001a). Nightly collections were made from 18.30-22.30 with repellent applied by routine thin application on both ankles and feet of each treated subject twenty minutes before collectors commenced catching while sitting on camp chairs (seat 40cm above ground), and members of each pair collecting mosquitoes off themselves and each other, for 45 minutes per hour at each position. Fifteen minutes per hour were allowed for collating the catches, changing positions and resting. The exercise was repeated for five consecutive nights in April 1998. After each night catch period, all collectors washed thoroughly with soap before going to bed, so that DEET treatment effects would not carry over to the next day.

Using standardised procedures (Curtis *et al.*, 1987), the collectors aspirated all landing mosquitoes that attempted to bite them. Each pair of collectors transferred all mosquitoes from each hourly catch into pre-labelled paper cups with gauze tops. Cups were labelled according to biting site on the body (foot/ankle, leg, arm and body), position (A, B, C, D), hour of collection (1, 2, 3, 4), treated or untreated with repellent, and collector identity (E, F, G, H, I, J, K, L). "Body" comprised head, neck and thorax, while "leg" was defined as the limb from just above the ankle to the lower hem of the short trousers (mid-thigh). The mosquitoes of each category were held in their cup (with access to glucose solution on a pad of cotton wool) until the following day when they were killed,

counted and anophelines identified (Gillies & De Meillon, 1968). Thirty randomly selected specimens of the *An. gambiae* complex from each night collection were kept dry for polymerase chain reaction (PCR) identification of sibling species (Scott *et al.*, 1993).

Hourly collections and nightly totals of *An. arabiensis* were summed and biting rates calculated for treated and untreated collectors. Percentage protection was estimated as 100 x (control - treatment) / control, i.e. the number of *An. arabiensis* females landing on subjects treated with DEET relative to the number landing on untreated control subjects (Mehr *et al.*, 1985). Distributional requirements necessary for performing an analysis of variance were not met, nor could data be normalised by transformation, therefore nonparametric methods were used to analyse data. The Mann-Whitney U test was used to compare catches between treatment and control groups. Kruskal-Wallis non-parametric analysis of variance was used to explore positional differences between catches and personal differences in mosquito attractiveness (Norusis, 1992).

3.4.2. Results

An. arabiensis was the only member of the *An. gambiae* complex identified by PCR (n = 150). Percentage protection from bites offered by DEET was 69.2%. Most bites (76.4% [519/679]) were on untreated subjects (χ^2=43.978; P<0.001), with the biting rate reduction ranging from 36.4% to 78.2% per evening for individuals [Table 3.1]. Eighty-one percent (421/519) of mosquitoes attempting to bite untreated subjects did so on the feet and ankles, and 97.5% of all catches on untreated subjects were made on the area below the knee. No mosquitoes were caught from treated feet and ankles.

Table 3.1. Distribution of *Anopheles arabiensis* bites with ankles and feet treated or untreated with DEET repellent.

Body Part	Nights					
Untreated	1	2	3	4	5	Total (%)
Feet/ankles	48	54	145	102	72	421 (81.1)
Legs	5	8	30	31	11	85 (16.4)
Arms	1	0	1	4	1	7 (1.3)
Head/thorax	1	1	3	1	0	6 (1.2)
Total (%)	55 (10.6)	63 (12.1)	179 (34.5)	138 (26.6)	84 (16.2)	519 (100)
	Nights					
Treated	1	2	3	4	5	Total (%)
Feet/ankles	0	0	0	0	0	0 (0.0)
Legs	32	15	28	39	27	141 (88.1)
Arms	0	0	2	2	0	4 (2.5)
Head/thorax	3	0	9	1	2	15 (9.4)
Total (%)	35 (21.8)	15 (9.4)	39 (24.4)	42 (26.3)	29 (18.1)	160 (100)
% protection	36.4	76.2	78.2	69.6	65.5	69.2

There was no significant difference between catches at the four positions (χ^2=2.817; P=0.421) [Table 3.2]. There was no evidence of significant between hours variation in *An. arabiensis* captures (χ^2=5.821; P=0.121), but there were significant between night differences (χ^2=16.723; P=0.002) [Table 3.3].

Table 3.2. *Anopheles arabiensis* captures on paired untreated bait collectors at the four field positions.

Night	Position			
	A	B	C	D
1	14	11	15	15
2	13	9	22	19
3	61	52	37	29
4	31	27	31	49
5	19	21	26	18
Total (%)	138 (26.6)	120 (23.1)	131 (25.2)	130 (25.0)

Table 3.3. Hourly captures of *Anopheles arabiensis* mosquitoes on four untreated bait collectors over five nights.

Night	Hour				
	18.30–19.15	19.30–20.15	20.30–21.15	21.30–22.15	Total (%)
1	15	17	11	12	55 (10.6)
2	6	11	22	24	63 (12.1)
3	41	41	57	40	179 (34.5)
4	32	29	30	47	138 (26.6)
5	24	22	21	17	84 (16.2)
Total (%)	118 (22.8)	120 (23.1)	141 (27.2)	140 (27.0)	519 (100)

Personal variation in catches on the eight collectors was highly significant (χ^2=19.121; P=0.008) with person "I" considerably more attractive to *An. arabiensis* than the other collectors [Table 3.4].

Table 3.4. *Anopheles arabiensis* captured nightly by the eight collectors.

Night	Collector							
	E	F	G	H	I	J	K	L
1	5^T	8^T	12^U	17^U	14^T	8^T	6^U	20^U
2	3^T	1^T	20^U	19^U	6^T	3^T	10^U	16^U
3	30^U	44^U	11^T	12^T	75^U	30^U	7^T	9^T
4	16^U	39^U	8^T	16^T	59^U	24^U	10^T	12^T
Total (%)	54 (9.5)	92 (16.1)	51 (8.9)	64 (11.2)	154(27)	65(11.4)	33 (5.8)	57 (10)

^{T} = treated

^{U} = untreated

3.5. Application of N,N-diethyl-m-toluamide (DEET) to ankles and feet for malaria outbreak control in Mpumalanga Province, South Africa

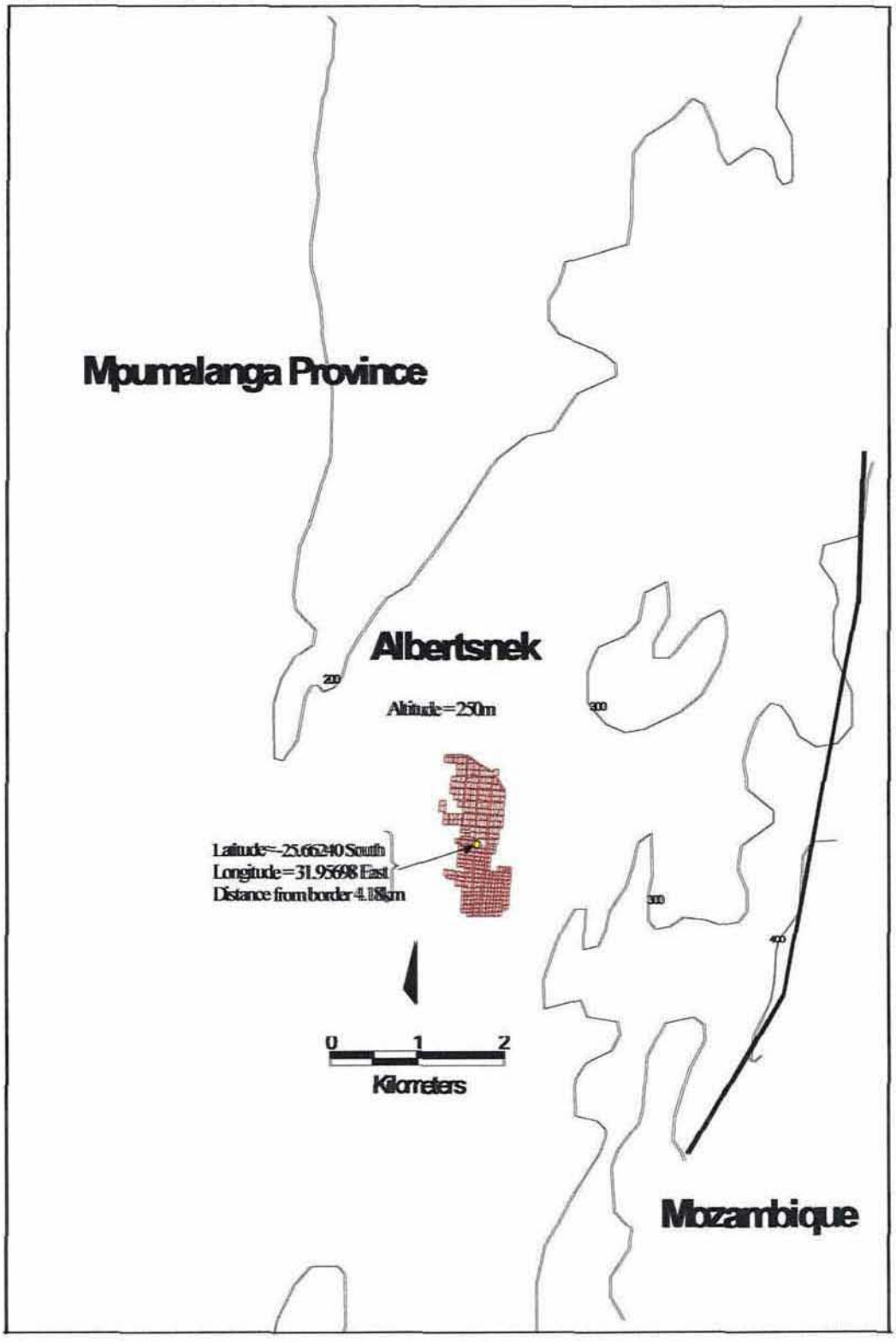
During February 2000, severe flooding in the Kruger National Park and adjoining Mpumalanga Lowveld, resulted in an outbreak of malaria in a rural village, Albertsnek. This outbreak provided an ideal opportunity for applying the results of research on the behaviour of *An. arabiensis* for outbreak containment.

The flooding resulted in numerous water collections ideal for *An. arabiensis* breeding and was followed by hot humid conditions. Albertsnek village was isolated from surrounding areas by floodwaters for a four-day period. This village has a population of 850 people and is situated approximately two kms from the Mozambican border in the east and 15kms from the Kruger National Park boundary in the north [Figure 3.2].

During the third week of February, the routine malaria surveillance system detected a marked increase in confirmed malaria cases compared to preceding weeks and similar periods in previous years. From mid-February to mid-March an average of 33 malaria cases per week were diagnosed in Albertsnek village among local residents compared to an average incidence of 18 malaria cases per week during the high-risk months, January to May during 1997-1999, and an average of 12 malaria cases per week during January and early February 2000.

All internal wall surfaces of homes in the village are sprayed annually prior to the Christmas period with deltamethrin, a residual synthetic pyrethroid insecticide. Unfortunately, many homes were flooded and although floodwaters had subsided, walls were not suitable for reapplication of insecticide. In addition, *An. funestus* mosquitoes, once eliminated from the area by indoor house spraying of DDT during the 1950s, were found inside dwellings that had not been flooded in the village. *An. funestus* from Albertsnek has been found to be resistant to synthetic pyrethroids (Govere *et al.*, unpublished data).

Figure 3.2. Location of Albertsnek village, Mpumalanga, South Africa.



Altitude contours shown (m above sea-level)

A donation of DEET (195mg/ml AI Tabard™) was made to the Mpumalanga Department of Health in the aftermath of the floods and this provided a unique opportunity for investigating topical application of DEET for malaria control.

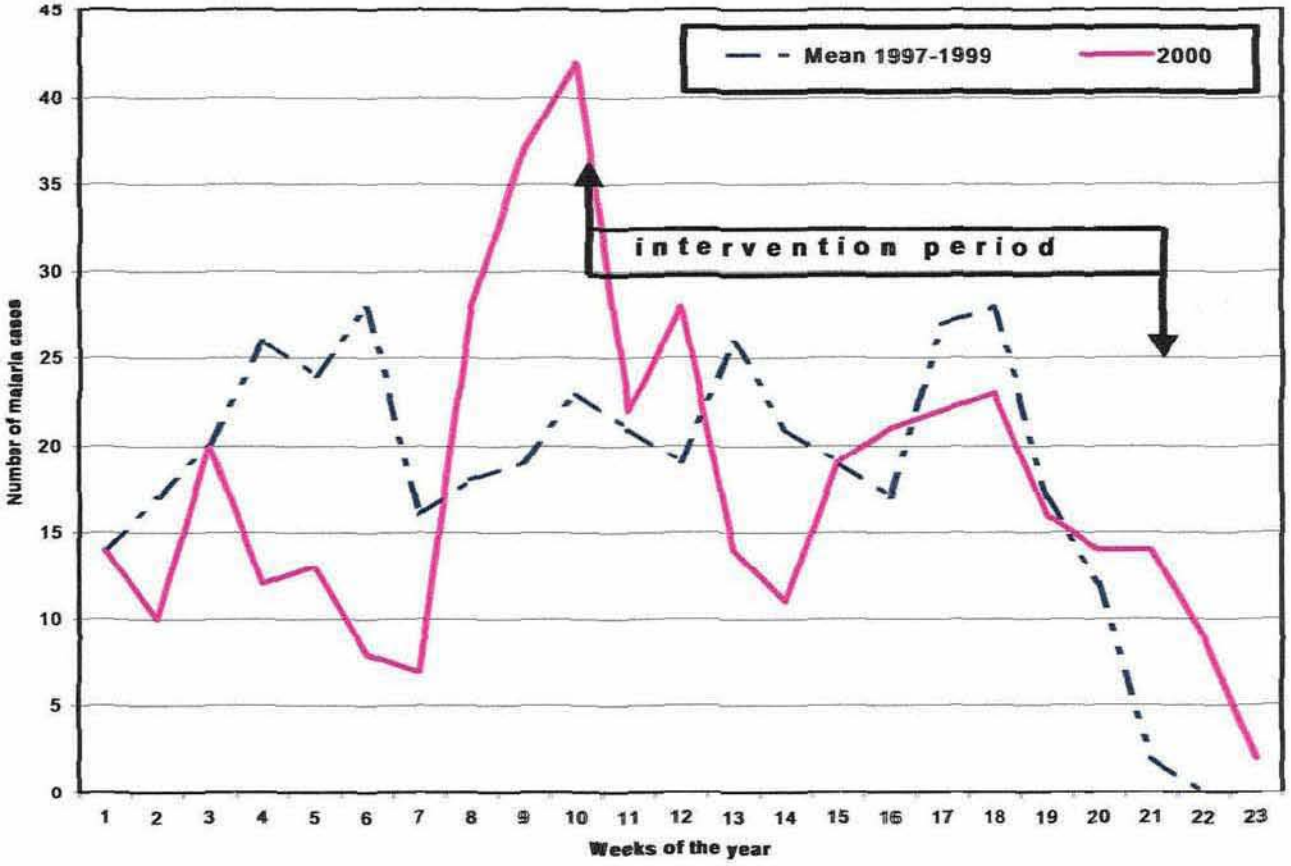
3.5.1. Methods

It was calculated that if each household received one 150ml Tabard™ bottle, there would be sufficient DEET available to allow limited application of DEET cream twice each evening to ankles and feet, initially at sunset and then just before retiring to sleep, of all non-infant members of the village for the remainder of the malaria season. After agreement was reached with local village leaders and provincial authorities, DEET cream was distributed with simultaneous careful demonstration of the application technique at public meetings in the village during the period, 6-10 March 2000.

3.5.2. Results

Malaria case numbers decreased after initiating the intervention. Although malaria incidence remained high during the week of repellent distribution (22 cases) and the following week (28 cases), in the subsequent two weeks only 14 and 11 malaria cases occurred respectively. For the remainder of the high-risk period, there were an average of 16 malaria cases per week, which compared favourably with the usual incidence in Albertsnek [Figure 3.3].

Figure 3.3. Malaria weekly incidence in Albertsnek village, January - June 2000 compared to mean incidence for the same period 1997-1999.



3.6. Discussion

Although the selection of biting sites on the human body by various mosquitoes has been documented in a number of situations, no attempts have been made to manipulate this behaviour for personal protection against mosquito bites (Haddow, 1956; Gillies, 1980; Knols & De Jong, 1996; Clements, 1999). Research at Malahlapanga confirmed that local *An. arabiensis* showed a strong predilection for biting human ankles and feet, with 97.5% of biting below the knees of untreated subjects sitting on camp chairs outdoors.

Significant interpersonal differences in attractiveness to *An. arabiensis* were found in this study, as previously reported for other mosquito species (Woke, 1962; Curtis *et al.*, 1987; Lindsay *et al.*, 1993). Mosquitoes utilise visual, thermal and olfactory stimuli to locate their hosts (Maibach *et al.*, 1966; Curtis, 1986; Bowen, 1991; Davies & Bowen, 1994; Keystone, 1996; Gibson & Torr, 1999; Takken & Knols, 1999). Carbon dioxide and lactic acid appear to act as long-range airborne attractants while skin temperature and moisture serve as short-range attractants (Snow, 1970; Gillies & Wilkes, 1972; Gillies, 1980). Variation of individual attractiveness to mosquitoes has been explained on the basis of the metabolic activity of resident skin microflora, skin pH and humidity (Tannock, 1994; Knols *et al.*, 1995). Although foot odour produced by the bacterium, *Brevibacterium linens*, was shown to positively influence the selection of biting sites on the human body by *An. gambiae*, *sensu lato*, the more general distribution of bites over the human body when lying on or near the ground indicates that proximity to the ground is a more important determinant of the biting behaviour of *An. arabiensis* and other mosquito species (De Jong & Knols, 1995; Knols & De Jong, 1996; Knols *et al.*, 1996; Clements, 1999; Durrheim *et al.*, 2001b).

The Malahlapanga study demonstrated that biting behaviour can be disrupted to reduce mosquito bites. Almost 70% suppression of *An. arabiensis* bites was provided when only the ankles and feet were treated with DEET repellent. As relatively few foraging mosquitoes transferred their attack to other parts of the same person, protection may be increased by more extensive application of repellent to other parts of the body. DEET-

repelled mosquitoes fly away, with transient disruption of their host-seeking and biting behaviour (Khan, 1965). Thus personal use of topical insect repellents, especially applied to ankles and feet, could be very beneficial in areas where transmission rates of mosquito-borne diseases are usually low, such as South Africa, but may not provide satisfactory levels of protection against malaria transmission risks in more highly endemic areas (Kondrachine & Trigg, 1997). Treatment of ankles and feet with an effective repellent may be a valuable supplement to insecticide house-spraying and use of impregnated bed-nets for malaria control, particularly where insecticide resistance problems arise or where vectors display ectophilic and ectophagic behaviour during the hours before people retire to sleep.

To our knowledge, personal application of effective insect repellents has not previously been attempted for responding to a localised malaria outbreak in Africa. The distribution of DEET containing cream for topical application to ankles and feet, combined with community education and mobilization in Albertsnek village, appeared to contain the focal malaria epidemic that followed in the wake of an environmental disaster. It is unlikely that treatment of proven malaria cases with sulfadoxine-pyrimethamine could have restricted transmission, in fact the converse may be true, as sulfadoxine-pyrimethamine promotes the appearance of *P. falciparum* gametocytes in the peripheral circulation one to three weeks after treatment (Govere *et al.*, 1999). Although meteorological variables remained highly conducive for mosquito breeding and survival throughout the month following the intervention, other poorly understood environmental and climatic factors may have contributed to the rapid decrease in malaria incidence. Unfortunately, the specific personal application technique and frequency of application were not directly monitored, and so we cannot be sure, despite affirmation by community members, that meticulous twice-evening topical application to feet and ankles was practiced for the remainder of the high-risk malaria period. A notable feature was the delay observed before this vector control measure had an impact on local malaria epidemiology. This is because villagers already infected and incubating the disease did not enjoy the protective benefit of the intervention.

Malahlapanga is also the source of the insecticide sensitive laboratory mosquito colony used for conducting regular monthly contact bioassays of walls in homes sprayed with residual insecticide by the malaria control program. This approach for ensuring the residual efficacy of applied insecticide, advocated by the World Health Organization, has proven advantageous for programme planning and quality assurance (World Health Organization, 1975; Govere *et al.*, 2001b).

The relatively high cost of commercial repellents is the main challenge to widespread community adoption of repellents, other than smoke and traditional natural products, by socio-economically deprived residents of most malarious areas. Research on development and effective use of affordable natural repellents is worthy of increased attention (Govere *et al.*, 2000c).

3.7. Conclusions

The origins of epidemiology applied to communicable disease control stem from a natural experiment dating back to the 1850s (Snow, 1885). In Malahlapanga, nature has again provided a unique epidemiological oasis for conducting operational research into mosquito vector behaviour that may be applied to malaria prevention and control.

The research agenda in Malahlapanga has been driven by the progressive failure and escalating cost of traditional malaria prevention and control strategies, and a recognition that innovative approaches, guided by operational research, are needed into all facets of malaria control (Schapira, 1989; Speare *et al.*, 1999a).

Although malaria vector characteristics, including place of feeding (exophagic or endophagic), resting behaviour (exophilic or endophilic), and host preference (opportunistic or zoophilic), have been successfully manipulated for malaria vector control, almost no research of this nature has previously been conducted on southern African *An. arabiensis*, the major and highly efficient malaria vector in this region.

Malahlapanga's unique location, unusual single disease-free species and large vector population have provided an unrivalled opportunity to address this deficiency.

Current progress is heartening with research findings already being applied in South Africa. Findings on flight and biting behaviour have resulted in refined barrier spraying strategies for vector control, particularly in nature reserves, and in cost-effective repellent application for personal protection in Mpumalanga Province.

Restricted topical application of DEET containing insect repellent provided encouraging results in containing the local malaria outbreak in rural Albertsnek Village in Mpumalanga. It is likely that insect repellent use for outbreak response will only be appropriate in settings where infectious mosquito bites are relatively infrequent. Before advocating wider application these findings require confirmation in similar settings, taking account of local vector biting preferences and malaria epidemiology.

A reality of field research sites is their vulnerability to nature's vagaries and Malahlapanga is no exception. Devastating flooding in north-eastern South Africa and Mozambique during the first quarter of 2000 destroyed all land access routes to Malahlapanga and effectively retarded efforts to further evaluate supplementary cost-effective malaria control measures by 12 months.

The malaria research agenda in Africa should be appraised by its ability to contribute to cost-effective prevention of infection or management of disease at community level (Speare *et al.*, 1999b). There is a pressing need for appropriate, cost-effective, simple personal protection and population control measures against one of humankind's greatest foes. Components of the solution may well be found at a remote spring in the African wilderness.

Chapter 4. A renaissance in malaria diagnosis

4.1. Chapter Overview

Malaria is a re-emerging disease in South and southern Africa. In response, the World Health Organization launched the Roll Back Malaria (RBM) initiative. One of six key principles adopted is the early detection of malaria cases, although in practice definitive diagnosis of malaria is the most neglected of the strategies. The Lowveld Region of Mpumalanga Province, South Africa, has approximately 850,000 inhabitants, who are at risk of seasonal *P. falciparum* malaria. Malaria treatment in this area is usually only initiated on detection of malaria parasites in the peripheral bloodstream, as many other rickettsial and viral febrile illnesses mimic malaria. The Malaria Control Programme traditionally relied on light microscopy of Giemsa-stained thick blood films for malaria diagnosis. A series of operational research studies documented the shortcomings of microscopic diagnosis and led to the introduction of rapid malaria card tests for primary diagnosis of malaria throughout the Mpumalanga malaria area. Subsequent operational research and five years of field experience since introduction of the ICT Malaria Pf™ test, confirms the local appropriateness of this diagnostic modality. A laboratory is not required and clinic staff are empowered to make a prompt definitive diagnosis, limiting delays in initiating correct therapy. The Mpumalanga results have contributed to providing an appreciation of the potential value of simple, accurate and rapid non-microscopic diagnosis as a means for Rolling Back Malaria in selected areas.

4.2. Peer-reviewed publications arising from research summarised in this chapter

* Durrheim, D.N., la Grange, J.J.P., Govere, J.M. & Mngomezulu, N.M. (1998) Accuracy of a rapid immunochromatographic test for *P. falciparum* in a malaria control programme in South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 92, 32-33.
* la Grange, J.J.P., Durrheim, D.N., Govere, J.M., Mngomezulu, N.M. & Mabusa, A. (1999) Field assessment of a combined immunochromatographic test for

malaria diagnosis in Mpumalanga Province, South Africa. *Southern African Journal of Epidemiology and Infection*, 14, 97-98.

* Durrheim, D.N., Becker, P.J., Billinghurst, K.G. & Brink, A. (1997) Diagnostic disagreement - the lessons learnt from malaria diagnosis in Mpumalanga. *South African Medical Journal*, 87, 609-611.
* Durrheim, D.N., Govere, J.M., la Grange J.J.P. & Mabuza, A. (2002c) Rapid immunochromatographic diagnosis and Rolling Back Malaria – experiences from an African control program. *African Journal of Medicine and Medical Sciences, in press*.

4.3. Introduction

Malaria accounts for approximately 2.3% of the global disease burden with the African continent disproportionately affected, malaria being responsible for 9% of African disease and over one million deaths each year (World Health Organization, 1996c). The increase in malaria prevalence and malaria specific mortality over the past decade has particularly affected Africa and this looming disaster has led to demands for fresh approaches and more effective implementation of proven strategies (Nchinda, 1998; Marsh, 1998).

The World Health Organization responded by launching the Roll Back Malaria (RBM) initiative in July 1998. The goal of RBM is to significantly reduce the disease burden associated with malaria by ensuring better access to a range of effective antimalarial interventions adapted to local needs, in order to reduce poverty (World Health Organization, 1999). One of the six key principles adopted by RBM is the early detection of malaria cases, but this important area appears to be the one that is currently most neglected. The importance of definitive diagnosis and potential value of field deployment of rapid malaria tests in RBM have been largely ignored. This was apparent at the first Multilateral Initiative on Malaria Conference held in Durban, South Africa during 1999. This meeting, destined to make an immensely valuable contribution to malaria control in Africa, had one notable omission - no data was presented on the

effectiveness of rapid and accurate diagnosis in reducing malaria morbidity and mortality, and rapid malaria antigen tests were only dealt with in trade displays (Speare *et al.*, 1999a).

Malaria treatment in Mpumalanga Province is usually only initiated on detection of malaria parasites in the peripheral bloodstream, as many other rickettsial and viral febrile illnesses mimic malaria. Traditionally, the Malaria Control Programme has relied on light microscopy of Giemsa-stained thick blood films (GTF) for malaria diagnosis. Four centralised laboratories examined most of these films, as adequate facilities and technically skilled laboratory personnel were not available in more remote areas.

Two evaluations in Mpumalanga demonstrated the inadequacy of this system. Firstly, a random sample of 40% (30/72) of Lowveld clinics found that only 20 clinics were still preparing thick blood films and of these, only three clinics received microscopy results within 24 hours (Durrheim *et al.*, 1997b). Three clinics (15%) received results only after seven days, three clinics (15%) after a two-week delay and the remaining eleven clinics (55%) never received results on the slides submitted. Nine clinics had blood slides available for scrutiny and only four clinics' slides were of acceptable quality.

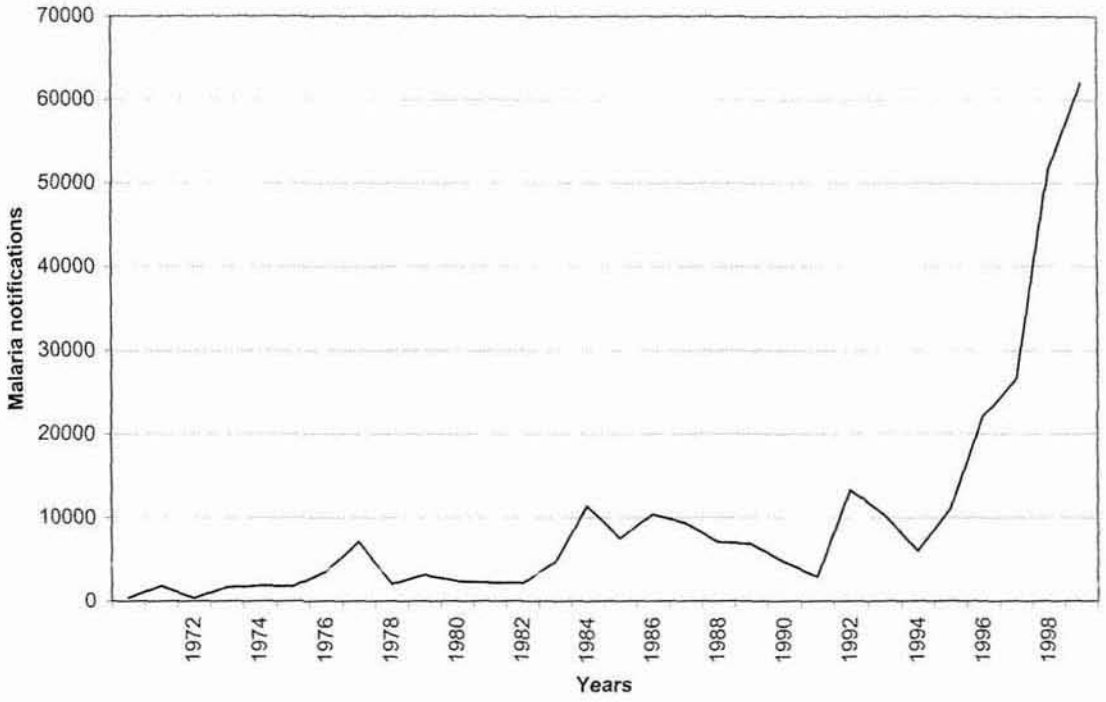
Of equal importance was the finding of disconcordant GTF results from four laboratories responsible for examining the majority of malaria blood films in the Province (Durrheim *et al.*, 1997a). The summary kappa value of 0.11 (95% confidence interval of 0.0-0.23) signified minimal agreement amongst participating laboratories, beyond chance (Landis & Koch, 1977).

The potential role of rapid diagnostic tests in "rolling back" malaria in specific geographical and epidemiological environments was investigated by an incremental operational research agenda, which saw the introduction of the ICT Malaria Pf^{TM} test throughout the Mpumalanga malaria area.

4.4. Successful introduction of a rapid immunochromatographic card test

The re-emerging nature of *P. falciparum* malaria in Mpumalanga with an increase in cases over the previous decade [Figure 4.1] demanded a novel approach for ensuring early definitive diagnosis and prompt effective therapy (Wilson, 1999). Following the disturbing findings of the investigations into traditional GTF diagnosis, two rapid malaria tests were introduced at a number of pilot clinics in the malaria area for comparison; i.e., ICT Malaria Pf™ (ICT Diagnostics, Australia) and *Para*Sight™-F (Becton Dickinson, USA). The ICT Malaria Pf™ was preferred to the *Para*Sight™-F rapid test by clinic nurses at these pilot sites (Lee *et al.*, 1996). The shorter time necessary for diagnosis and ease of using a single reagent with the ICT Malaria Pf™ test were cited as the main reasons for this preference.

Figure 4.1. Annual malaria case notifications, South Africa, 1971-2000.



4.4.1. Methods

The ICT Malaria Pf™ test had demonstrated high sensitivity and specificity in a hospital study in a malaria-endemic site in the Solomon Islands and so a decision was made to introduce it early in 1996, with concurrent training of clinic nurses, throughout the Mpumalanga malaria area (Garcia *et al.*, 1996). Following this widespread introduction we investigated the field accuracy of ICT Malaria Pf™ in Mpumalanga Province (Durrheim *et al.*, 1998c). GTF examination was still required for statutory malaria case notification because the validity and reliability of ICT Malaria Pf™ had never yet been investigated in a control programme context. This omission catalysed the present investigation.

Two hundred and sixty four consecutive patients presenting to Lowveld clinics during March 1997 with clinical signs and symptoms compatible with malaria had routine GTF and ICT Malaria Pf™ card tests prepared by clinic staff on finger prick blood.

4.4.2. Results

Using GTF as the gold standard, the card test achieved a sensitivity of 98.6% and a specificity of 97.9% [Table 4.1]. The degree of agreement between the two tests was excellent beyond chance (kappa = 0.95, 95% CI = 0.91-0.99) and all ICT Malaria Pf™ tests were correctly read and interpreted by clinic staff.

Table 4.1. **Correlation of the Immunochromatographic Test (ICT Malaria Pf^{TM}) with Giemsa Thick Film (GTF) examination for diagnosis of *Plasmodium falciparum* malaria.**

		ICT Malaria Pf^{TM}		
		Positive	**Negative**	**TOTAL**
GTF	**Positive**	68	1	69
	Negative	4	191	195
	TOTAL	72	192	264

Sensitivity = 98.6%
Specificity = 97.9%
PPV = 94.4%

4.5. Field assessment of a combined immunochromatographic test (Malaria P.f./P.v.) for malaria diagnosis

Delays in accessing GTF results, particularly after hours and during weekends, appeared to be an important contributory factor to diagnostic delays and malaria mortality (Durrheim *et al.*, 1999a; Chapter 2, this thesis). This provided the impetus for deploying ICT Malaria Pf^{TM} tests in hospital casualties in the malaria area. Shortly after introduction at a large regional hospital a number of false negative results prompted an investigation. It was discovered that these disparate results resulted from performing tests directly under industrial strength ceiling fans in the casualty unit, a situation that was simply and satisfactorily solved.

4.5.1. Methods

Field investigation in Mpumalanga of a second-generation card test (Malaria P.f./P.v., ICT Diagnostics, Australia) utilising two monoclonal bands to detect circulating histidine-rich protein-2 specific to *P. falciparum* and a pan-specific protein common to the four human malaria *Plasmodium* species, offered the possibility of diagnosing non-falciparum malaria at clinic level and thus avoiding hospital referral (la Grange *et al.*, 1999).

A total of 188 systematically presenting patients with symptoms suggestive of malaria had routine GTF, ICT Malaria Pf^{TM} and Malaria P.f./P.v. cards prepared by clinic staff based at Naas and Mangweni Health Centres, on finger prick blood specimens. Primary readers trained on the use of ICT Malaria Pf^{TM} and Malaria P.f./P.v. read and interpreted both card tests. Card tests were cross-read in a blinded fashion by experienced laboratory staff who also examined GTF. PCR was used as the reference standard due to its remarkable sensitivity and specificity, and established advantages over microscopy, particularly in cases of low parasitaemia and in mixed infections

4.5.2. Results

The field assessment in Mpumalanga found that Malaria P.f./P.v. diagnosed *P. falciparum* with comparable accuracy to ICT Malaria Pf^{TM} in the hands of experienced laboratory technologists (sensitivity = 96.2%, specificity = 98.1%, using PCR as gold standard) [Table 4.2]. However primary readers misinterpreted 2% of tests. Although there were only a limited number (n=7) of non-falciparum and mixed infections in this sample, Malaria P.f./P.v. misdiagnosed two of these.

Table 4.2. Correlation of ICT Malaria Pf™, Malaria P.f./P.v. and Giemsa Thick Film Examination (GTF) with PCR for *P. falciparum* diagnosis.

	GTF		ICT Malaria Pf™		Malaria P.f./P.v.	
	+	-	+	-	+	-
PCR +	23	3	23	3	25	1
PCR -	0	162	1	161	3	155

Sensitivity	=	88.5%	88.5%	96.2%
Specificity	=	100%	99.4%	98.1%
PPV	=	100%	95.8%	89.3%
NPV	=	98.2%	98.2%	99.4%
Kappa	=	0.93	0.91	0.91

4.6. Discussion

A cornerstone of the World Health Organization global malaria control strategy is prompt diagnosis of malaria so that effective therapy can be initiated without delay (World Health Organization, 1993). The availability of rapid assays for capturing histidine-rich protein 2 (HRP-2) synthesised by the asexual blood stages of *P. falciparum* and released from infected erythrocytes allowed production of a number of commercial immunodiagnositic tests for detecting circulating Pf HRP-2 in whole blood. Most field studies have been conducted using either ICT Malaria Pf™ or *Para*Sight™-F (Parra *et al.*, 1991; Garcia *et al.*, 1996). An antigen capture test has also been developed for detecting parasite lactate dehydrogenase produced by viable malaria parasites, OptiMAL (Flow Incorporated, South Africa). Initial investigations demonstrated the accuracy of these tests, with sensitivity and specificity similar or superior to the traditional "gold-standard", GTF (Schiff *et al.*, 1993; Garcia *et al.*, 1996; Cooke *et al.*, 1999; Tham *et al.*, 1999). Excellent field performance has been demonstrated in the hands of field staff based in rural areas, including various sites in Africa (Premji *et al.*, 1994; Van den Ende

et al., 1998; Kilian *et al.*, 1999). In contrast there is an increasing realisation of the limitations of clinical algorithms for diagnosing malaria, particularly in relatively low malaria prevalence areas (Chandramohan *et al.*, 2002). A recent study in a remote area in the Philippines obtained similar results to the Mpumalanga study, confirming the accuracy of the ICT Malaria Pf™ tests compared to traditional GTF diagnosis but also confirming that the rapid test satisfies a strong community desire for blood-based diagnosis with a potentially positive effect on treatment-seeking behaviour (Bell *et al.*, 2001).

Inherent shortcomings of these tests include: their inability to reliably establish the degree of parasitaemia which is of particular importance in the hospital management of complicated malaria cases, and prolonged positivity despite cure due to persistent antigenaemia for days and even weeks after cure (Singh *et al.*, 1997). The possibility of lower test sensitivity in adults in hyperendemic malaria areas due to age-dependent malaria immune status; and recent findings of false positive rapid tests in patients with rheumatoid factor, a phenomenon that may be twice as common with the *Para*Sight-F test compared to the ICT Malaria Pf™ test, should also be borne in mind (Fryauff *et al.*, 1997; Laferi *et al.*, 1997; Grobusch *et al.*, 1999). A positive recent development has been the production of more stable rapid tests not requiring refrigeration.

Despite the good performance of the new-generation multiple antigen test, Mpumalanga study results suggested that the comparative ease of interpreting the classic test, unavailability of therapy for non-falciparum species at clinic level and predominance of *P. falciparum* malaria in Mpumalanga made replacement with the new test inadvisable. Similar concerns regarding the relative inaccuracy of the combined test were raised by an Indonesian evaluation (Tjitra *et al.*, 1999).

A plethora of rapid tests have been developed in recent times and Mpumalanga's reputation for performing high quality field evaluation has resulted in routine evaluation of new candidate tests being conducted by the Mpumalanga communicable disease control team before incorporation in the national pharmaceutical tender. Tests are

assessed by means of a standard battery of criteria, including sensitivity, specificity, ease of use and labelling, stability of results, number of procedural steps, additional items required and average time to diagnosis.

Despite confirmation of the accuracy and utility of rapid dipstick tests compared to traditional diagnostic techniques, the unit price of rapid tests, which exceeds the cost of a blood slide and stain, is used as an argument against extensive field application in malaria-endemic areas. This perception contrasts with a preliminary consideration of the costs of malaria diagnostic alternatives including GTF, which found that rapid tests were cost-effective for malaria diagnosis (Craig & Sharp, 1997). Labour costs for performing GTF alone, exceeded the total cost of rapid test implementation. Recent African studies appear to support this view advocating that rapid tests are appropriate technology in areas where it is not possible to provide and sustain trained microscopists, as a second-line test where diagnosis is strongly suspected on clinical grounds but microscopy is negative and as an alternative for microscopy to improve case management in malaria control programmes (Lema *et al.*, 1999). A World Health Organization informal consultation concluded that rapid tests were cost-effective for malaria management in *P. falciparum* epidemics, emergencies, where there were inadequate laboratories, mobile clinics, low levels of transmission, high levels of antimalarial drug resistance and where diagnosis is suspected but blood smear is equivocal (World Health Organization, 1996a). More recently the World Health Organization has indicated that the rational use of rapid tests might result in substantial health gains by allowing earlier treatment, targeting more expensive drugs in areas of drug-resistance and possibly slowing the emergence of resistance (World Health Organization, 2000b).

Furthermore, traditional tools available to health economists may be unsuited to diseases approaching elimination levels (Dowdle, 1998). Formal economic analytical techniques are not ideally suited for handling future costs, particularly in the long-term. Application of such methods should ideally take a broad societal perspective, as benefits would also accrue outside the health sector.

Two further issues relating to the importance of definitive diagnosis are relevant in fringe areas, like Mpumalanga, that are seeking to roll back malaria; the evolution of drug resistance and effective surveillance. The most important factor in determining the development of malarial drug resistance is the prevalence of drug use (Peters, 1990). The emergence of low levels of malaria transmission as malaria is "rolled-back" with resultant waning of the population's partial malaria immunity in regions bordering holo-endemic areas, may have important implications for the evolution of malaria drug resistance (Barnes *et al.*, 1998). Treatment seeking provoked by symptoms in non-immune patients, which confers a survival advantage to resistant parasites, may result in tremendous selective pressure for resistant parasites.

Secondly, as low transmission levels are approached the importance of a sensitive surveillance system for establishing program success/elimination and allowing rapid mopping-up campaigns, is apparent (Klaucke, 1994). In sub-Saharan Africa where the differential diagnosis for acute febrile illness is extensive, definitive diagnosis is a necessary prerequisite for satisfactory surveillance. The availability of immediate definitive diagnosis has also accelerated notification of confirmed malaria cases. This allowed development of a functional malaria geographical information system, and consequently focused and timely Malaria Control Programme intervention (Booman *et al.*, 2000).

4.7. Conclusions

A critical evaluation of malaria diagnostic techniques, a key management element of malaria control, revealed deficiencies that negatively impacted on patient outcomes. These findings kindled an operational research agenda seeking the most efficient and effective tools for field diagnosis. This research saw the introduction of simple, accurate and rapid non-microscopic card tests for diagnosing *P. falciparum* malaria throughout the malaria control programme in Mpumalanga. The expertise developed in evaluating new rapid malaria tests has resulted in Mpumalanga providing an expert reference function for the national pharmaceutical tender.

The Mpumalanga experience has prompted a reconsideration of the potential role of rapid diagnostic tests in rural and remote areas for contributing towards the Roll Back Malaria initiative (Durrheim *et al.*, 2002c). Not only do rapid diagnostic tests have the major advantage of not requiring a laboratory but this technology fits neatly within the primary health care paradigm of empowering clinic staff to make a prompt definitive diagnosis that limits delays in initiating correct therapy (Chiodini, 1998). Rapid immunochromatographic tests have an important added value in constraining the selection of resistant parasites and allowing development of accurate malaria surveillance systems.

Chapter 5. Sentinel surveillance of *Plasmodium falciparum* for drug resistance - a pre-requisite for optimal malaria drug therapy

5.1. Chapter Overview

Resistance of *P. falciparum* to antimalarial drugs is a serious impediment to controlling malaria. Ineffective first-line malaria therapy appears to be a major contributor to the persistent increase in malaria cases in South Africa, particularly KwaZulu-Natal Province, during the past decade.

P. falciparum resistance to chloroquine was first reported in Africa in 1979 and emerged in South Africa during the mid 1980s. The striking increase in positive follow-up smears following chloroquine therapy in Mpumalanga Province catalysed the establishment of a sentinel site at Naas and Mangweni Health Centres in the most affected malaria sub-district, Tonga, for collecting *in vivo* resistance data. A chloroquine *in vivo* study during 1997 based on World Health Organization criteria demonstrated unacceptable levels of parasitological and clinical failure. This led to a change in treatment policy from chloroquine to sulfadoxine-pyrimethamine (SP) for first-line *P. falciparum* malaria therapy.

A baseline *in vivo* SP resistance study conducted at the sentinel site following the introduction of SP as first-line therapy in 1998, confirmed treatment efficacy. This study was unique, being the first 42-day SP *in vivo* conducted under field conditions in Africa, and thus provided a comprehensive resistance picture. It also allowed investigation of the differential resolution of clinical symptoms and peripheral parasitaemia, an initial evaluation of the adequacy of the recommended SP dosage for adults exceeding 60kgs, and determination of gametocyte levels at different stages following therapy.

Mpumalanga Malaria Control Programme management were so convinced of the value of the sentinel site that they agreed to take primary responsibility for conducting a follow up evaluation of SP efficacy two years after introduction at the same site. This second SP

study confirmed the continued efficacy of this treatment in Mpumalanga. The Mpumalanga protocol was used as the basis for conducting the first SP clinic *in vivo* study in KwaZulu-Natal after 12 years of use. Unacceptably high levels of SP treatment failure were found at Ndumo Health Centre, the KwaZulu-Natal sentinel site, which prompted a drug policy change to coartemether (artemether-lumefantrine) for first-line therapy of uncomplicated malaria. Problems with this latter study confirmed the value of a central role for control programmes, rather than research institutions, in establishing and maintaining sentinel *in vivo* drug efficacy sites.

The success of the Mpumalanga sentinel surveillance site in providing high-quality drug efficacy information for policy-making has resulted in the establishment of a fledgling sentinel surveillance network for epidemiological research and malaria policy planning in South Africa.

5.2. Peer-reviewed publications arising from research summarised in this chapter

* Durrheim, D.N., Sharp, B.L. & Barnes, K. (2001) Sentinel malaria surveillance: more than a research tool. *South African Medical Journal*, 91, 968-970.
* Mabuza, A., Govere, J.M., Durrheim, D.N., Mngomezulu, N., Bredenkamp, B.L.F., Barnes, K. & Sharp, B.L. (2001) Therapeutic efficacy of sulfadoxine-pyrimethamine in uncomplicated *Plasmodium falciparum* malaria 3 years after introduction in Mpumalanga, South Africa. *South African Medical Journal*, 91, 975-978.
* Bredenkamp, B.L.F., Sharp, B.L., Mthembu, S.D., Durrheim, D.N. & Barnes, K.I. (2001) Failure of sulfadoxine-pyrimethamine in treating *Plasmodium falciparum* malaria in KwaZulu-Natal. *South African Medical Journal*, 91, 970-972.
* Govere, J.M., la Grange, J.J.P., Durrheim, D.N., Freese, J.A., Sharp, B.L., Mabuza, A., Mngomezulu, N. & Bredenkamp, B.L.F. (1999) Sulfadoxine-pyrimethamine effectiveness against *Plasmodium falciparum* malaria in Mpumalanga Province, South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 93, 644.

5.3. Introduction

The monotonic increase in South African malaria cases with a greater than hundred-fold increase in notifications during the past three decades, from 364 notified cases in 1971 to 61,934 cases in 2000, elicited consternation throughout the South African public health sector (King *et al.*, 2001). Although this dramatic increase was clearly multifactorial, stemming from the effects of meteorological changes, human parasite-carrier migratory patterns, resistance of *An. arabiensis* to synthetic pyrethroid insecticides and an inconsistent notification system, the contribution of ineffective first-line malaria therapy should not be underestimated.

Resistance of *P. falciparum* to antimalarial drugs is a serious impediment to controlling malaria (Wernsdorfer, 1991; Marsh, 1998; Nchinda, 1998). *P. falciparum* resistance to chloroquine was first reported in Africa in 1979, while clinical evidence of *P. falciparum* resistance to chloroquine emerged in South Africa during the mid 1980s (Fogh *et al.*, 1979; Kean, 1979; Bac *et al.*, 1985; Visagie & Sieling, 1985). Despite resistance, chloroquine is still often used in areas of stable malaria because of the additive effect of host immune factors resulting in clinical but not parasitological cure. In South Africa, however, where the majority of the population resident in malaria areas are unlikely to have any immunity, the risk of rapid progression to severe disease and even death necessitates effective first-line therapy that will rapidly eliminate *P. falciparum* and effect a parasitological cure. Thus the finding of high levels of chloroquine resistance in small *in vitro* studies conducted in KwaZulu-Natal and Mpumalanga, elicited concern (Freese *et al.*, 1988; Freese *et al.*, 1991; Freese *et al.*, 1994; Deacon *et al.*, 1994). A review of positive follow-up smears following chloroquine therapy in Mpumalanga in partnership with the Malaria Control Programme Manager demonstrated a striking increase, from 1.7% in 1990 to 16.7% in 1995, a finding which demanded confirmation by a carefully conducted *in vivo* evaluation (Kruger *et al.*, 1996).

Tonga, with a population of 116,418, is the sub-district that experiences the greatest burden of malaria in Mpumalanga [Figures 5.1. & 5.2]. Malaria transmission is seasonal

with *P. falciparum* accounting for more than 90% of malaria infections notified in the sub-district. Rapid detection of malaria cases followed by prompt therapy of proven cases and residual indoor house spraying are the cornerstones of malaria control in the area.

A sentinel site for collecting *in vivo* resistance data was established at the two 24-hour Health Centres in Tonga sub-district, Naas and Mangweni, which are approximately 5kms apart and connected by a good-quality tar road. A chloroquine *in vivo* study, based on the WHO protocol with 28-day follow-up, was conducted at these Health Centres during 1997 (World Health Organization, 1996b). Unacceptable levels of RII/RIII (moderate and high level combined) parasitological failure (17.9%) and clinical failure (24%) were documented, with the total RI/RII/RIII parasitological failure rate being 48.4% (Freese & Durrheim, 1997). This formed the basis of a policy decision to change first-line treatment policy for uncomplicated *P. falciparum* malaria from chloroquine to SP.

Figure 5.1. Malaria incidence by magisterial district, Mpumalanga Province, 1991-1999.

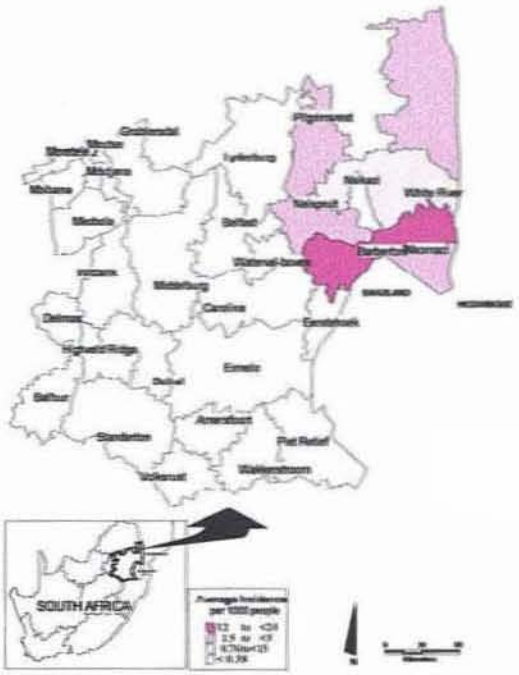
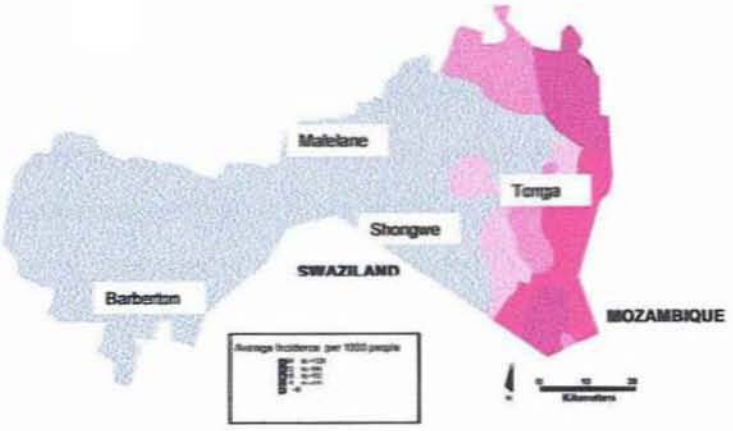


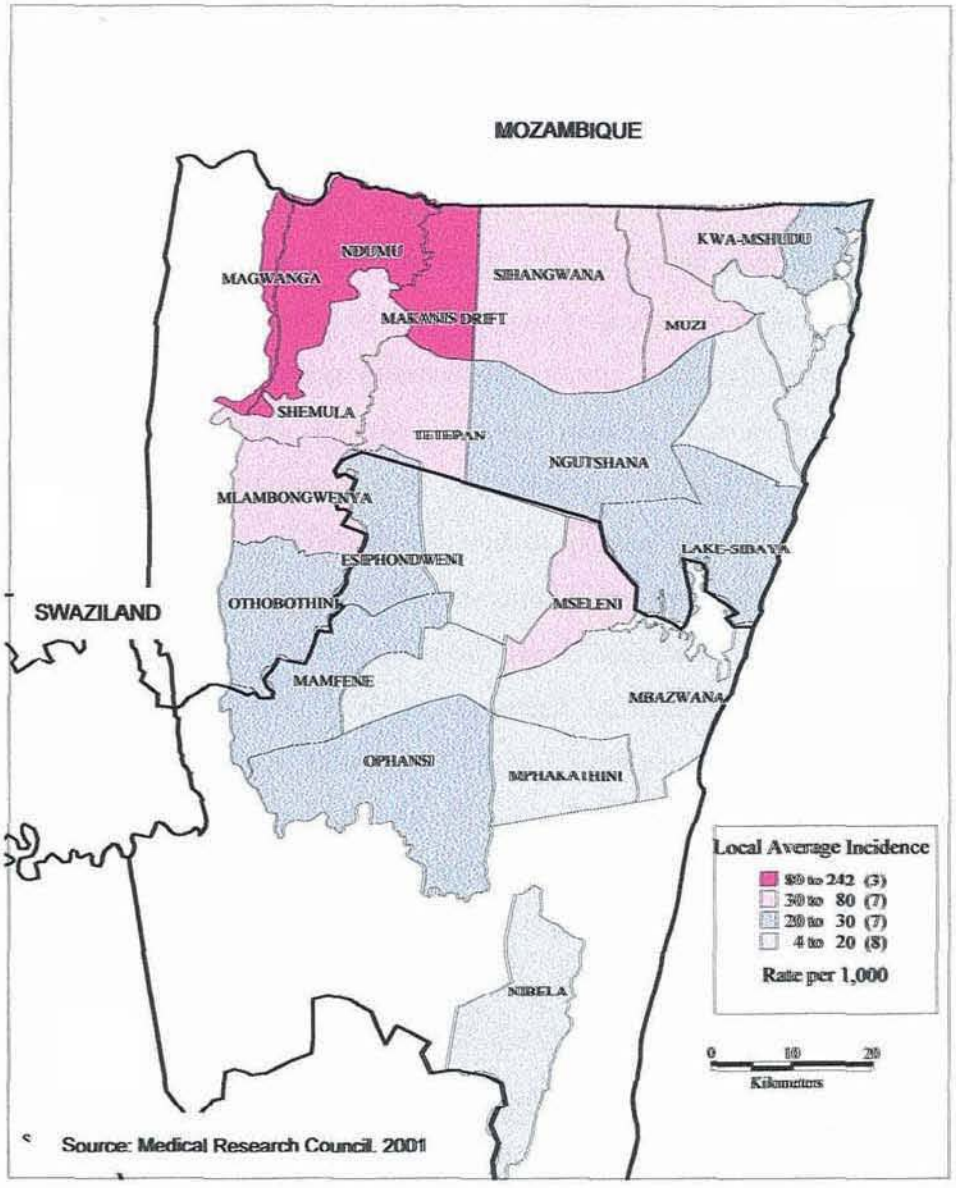
Figure 5.2. Malaria incidence rates, Barberton-Nkomasi magisterial district, Mpumalanga Province, 1995-1999.



To determine efficacy of SP at introduction and provide a baseline against which the evolution of resistance could be monitored, a 42-day follow-up *in vivo* SP treatment evaluation was conducted at the sentinel surveillance site during 1998. Two years later this was repeated to ensure ongoing efficacy. The success of this approach and anecdotal reports of clinical treatment failure prompted the Malaria Control Programme in neighbouring KwaZulu-Natal Province to request support to conduct a similar *in vivo* study in their worst affected malaria district, Ubombo-Ingwavuma [Figure 5.3].

Ndumo Clinic, in the Ubombo-Ingwavuma district of KwaZulu-Natal, is a satellite 24-hour Health Centre of Mosveld Hospital, and serves a rural population of approximately 15,000 people. Malaria transmission in this district is generally seasonal and the population is not thought to have acquired significant levels of immunity. Although the KwaZulu-Natal Malaria Control Programme initially indicated that they would provide experienced personnel to conduct the laboratory and follow-up components of the *in vivo* study, the scale of the malaria epidemic elicited a request for field support from the Medical Research Council and primary diagnostic support from laboratory personnel at Mosveld Hospital.

Figure 5.3. Malaria incidence in Ubombo-Ingwavuma District, KwaZulu-Natal, 1996-1999.



5.4. Methods

A standardised study design was applied during both Mpumalanga and KwaZulu-Natal evaluations. All patients with clinical episodes compatible with malaria presenting at the sentinel 24-hour primary Health Centres were tested for *P. falciparum* infection using an immunochromatographic card test (ICT Malaria Pf^{TM}) demonstrated to have high accuracy under field conditions in South Africa (Durrheim *et al.*, 1998c; Chapter 4, this thesis). Patients diagnosed positive for malaria were then recruited according to standardised criteria. Inclusion criteria were: age above two years, symptomatic uncomplicated *P. falciparum* mono-infection, *P. falciparum* asexual hyperparasitaemia above 1,000 parasites/µl blood, easy access to the patient's home, fully informed consent by the patient or accompanying relatives for minors, and axillary temperature above 37.5°C. Exclusion criteria included: severe malaria, concomitant disease, mixed *Plasmodium* infection, intolerance of oral therapy, refusal to provide consent or pregnancy. Criteria for withdrawal included: patient choice, clinical deterioration necessitating hospital referral, patient non-compliance, loss to follow up and protocol violation, including self-administration of other antimalarial drugs during follow-up (World Health Organization, 1996b). Baseline information collected on all study subjects included age, gender, weight and place of residence.

Patients were treated with a single oral dose of SP, corresponding to 25mg/kg of sulfadoxine and 1.25mg/kg of pyrimethamine. Thus in keeping with the Mpumalanga Department of Health guidelines, one tablet was administered to patients in the 15-20kg weight category, two tablets to patients in the 21-40 kg category and three tablets to patients weighing more than 40kg. After drug administration, patients were observed for one hour to detect vomiting. If vomiting occurred within 30 minutes of drug administration a full dose was repeated, while if vomiting occurred between 30 and 60 minutes, an additional half dose was administered. No additional treatment was administered if vomiting occurred after 60 minutes. Patients with clinical treatment failure were referred to hospital for rescue therapy with quinine.

Clinical and parasitological assessment was conducted routinely on the day of recruitment and on days 1, 2, 3, 7, 14, 21, 28 and 42 post-treatment. At each follow-up visit a thick blood smear was taken, body temperature recorded and an assessment for adverse events completed. Fever was defined as an axillary temperature exceeding 37.5°C. Parasitaemia was measured by counting the number of parasites against 300 leukocytes on a Giemsa stained, finger-prick thick blood film and multiplying the figure by 25, assuming a standard leukocyte count of 7,500/*u*l blood.

Parasitological success was defined as conversion from a positive smear at recruitment to a negative smear by day 7 and remaining negative until the end of the 42-day follow-up period. Parasitological treatment failure was defined as the presence of asexual *P. falciparum* parasites in the blood film between day 7 and 42 post-treatment. Parasite clearance time was the number of days from recruitment to the first smear with no asexual parasites. Fever duration was the number of days from recruitment to the day when axillary temperature was recorded as 37.5°C or below without a subsequent recorded increase in temperature. Recrudescence (RI) was defined as absence of asexual parasites for two consecutive days by at least day 7 and re-appearance of parasites during the remaining follow-up period. RII was defined as a reduction of asexual parasitaemia to less than 25% of the day 0 count within 48 hours of treatment initiation but no subsequent disappearance of asexual parasites (World Health Organization, 1996b). RIII was defined as a parasitaemia that remained above 25% of the initial count within 48 hours of initiating treatment.

Recrudescence was determined by comparing polymerase chain reactions (PCR) performed on filter paper blood-spots prepared on the day of recruitment for all study patients with those repeated on patients demonstrating reappearance of asexual parasites on a thick blood smear between day 21 and 42 of follow-up. PCR amplifications of the genetic markers MSP1, MSP2, GLURP 1 and GLURP 2 differentiated between true recrudescence of the original infection and possible new infections (Ranford-Cartwright *et al.*, 1997)

To explore clinical and parasitological response in relation to mg/kg drug dose, exact doses administered were determined for each subject during the baseline SP evaluation in Mpumalanga. Cases were classified into three categories: patients who received doses within one standard deviation of the recommended dose and patients who received more than one standard deviation greater or less than the recommended dose. Proportions were compared using Pearson's Chi-square and Mann-Whitney U tests.

5.5. Results

5.5.1. Mpumalanga *in vivo* study, 1998

One hundred and thirty two patients were recruited between January and April 1998. One hundred and nine (82.6%) patients completed follow-up to day 42, or until parasitological or clinical evidence of treatment failure. Of these 109 patients, 103 (94.5%) were cured and recrudescence occurred in four (3.7% RI) on days 21 (n=1), 28 (n=1) and 42 (n=2). One case (0.9% RII) had persistent parasitaemia to day 7 and one case had early treatment failure (0.9% RII) on day 3 [Table 5.1].

Table 5.1. Malaria patient parasitological outcomes with sulfadoxine-pyrimethamine, *in vivo* studies, Mpumalanga 1998 & 2000, and KwaZulu-Natal 2000.

Response to therapy	Mpumalanga *in vivo* 1998	Mpumalanga *in vivo* 2000	KwaZulu-Natal *in vivo* 2000
Parasitological success (S)	94.5% (103/109)	93.6% (103/110)	12.2% (11/90)[1]
Resistant grade I (RI)	3.7% (4/109)	4.5% (5/110)	35.6% (32/90)
Resistant grade II (RII)	1.8% (2/109)	1.8% (2/110)	40.0% (36/90)
Resistant grade III (RIII)	0% (0/109)	0% (0/110)	12.2% (11/90)

[1] Four of the 90 patients (4.4%) were judged by PCR to have acquired new infections at Day 42, and therefore considered cured of their original infection.

By day 3, asexual parasitaemia had cleared in 91.4% of patients and 99.1% had cleared by day 7. Follow-up revealed that 74.1% of patients were apyrexial by day 3 and 92.9% by day 7. Resolution of clinical symptoms was significantly slower than parasite clearance (p=0.037) [Figure 5.4]. The gametocyte count increased during follow up and peaked on days 7 and 14 [Figure 5.5].

Patients receiving a treatment dose exceeding one standard deviation less than the recommended mg/kg dosage experienced delayed parasite and fever clearance, with only 66.7% (8/12) clearing parasites within two days compared to 94.1% (16/17) of the remaining patients (p=0.045) while 38.5% (5/13) were afebrile within two days, compared to 81.3% (13/16) of remaining patients (p=0.016).

5.5.2. Mpumalanga *in vivo* study, 2000

Between January and May 2000, 119 patients were recruited and follow up was completed for 108 patients (90.8%, 108/119) to days 7, 14 and 21, 105 (88.2%) to day 28 and 103 (86.6%) to day 42. One hundred and ten (92.4%, 110/119) patients completed follow-up to day 42 or until parasitological or clinical evidence of treatment failure.

By day 2, fever had cleared in 47.8% (54/113) of patients while 79.1% (87/110) had cleared by day 3 and 95.5% (105/110) by day 7. By day 2, asexual parasites were absent in 49.6% (56/113) of patients, while 84.6% (93/110) and 100% (108/108) were cleared of parasites by days 3 and 7 respectively. Of the 108 patients who were followed-up until day 7, all (100%, S/RI) were cleared of asexual parasites. Of 110 patients who had complete follow-up until day 42 or until parasitological or clinical evidence of treatment failure, 103 (93.6%, 103/110) were radically cured, recrudescence occurred in five (4.6%, RI) on day 28 (n = 3) and day 42 (n = 2), and two cases (1.8%, RII) were early treatment failures on day 3 [Table 5.1]. Gametocytes were counted and they peaked between days 7 and 28 [Figure 5.5].

5.5.3. KwaZulu-Natal *in vivo* study, 2000

At least 79 of the 129 (61.2%) patients enrolled failed, but this may have been as high as 79/90 (87.8%) if the patients lost to follow-up are excluded from the analysis. High-level resistance (RII and RIII) was common in the 90 patients followed-up to day 42 or failure [Table 5.1]. Gametocytes were found in the blood of patients for an extended period during follow-up. The proportion of patients with gametocytes peaked on day 14 when 73.7% had gametocytes on blood smear [Figure 5.5].

Patients enrolled in the study were predominantly young, with 68.8% between 3 and 15 years of age.

Figure 5.4. Resolution of fever and parasitaemia, Mpumalanga sulfadoxine-pyrimethamine *in vivo* study, 1998.

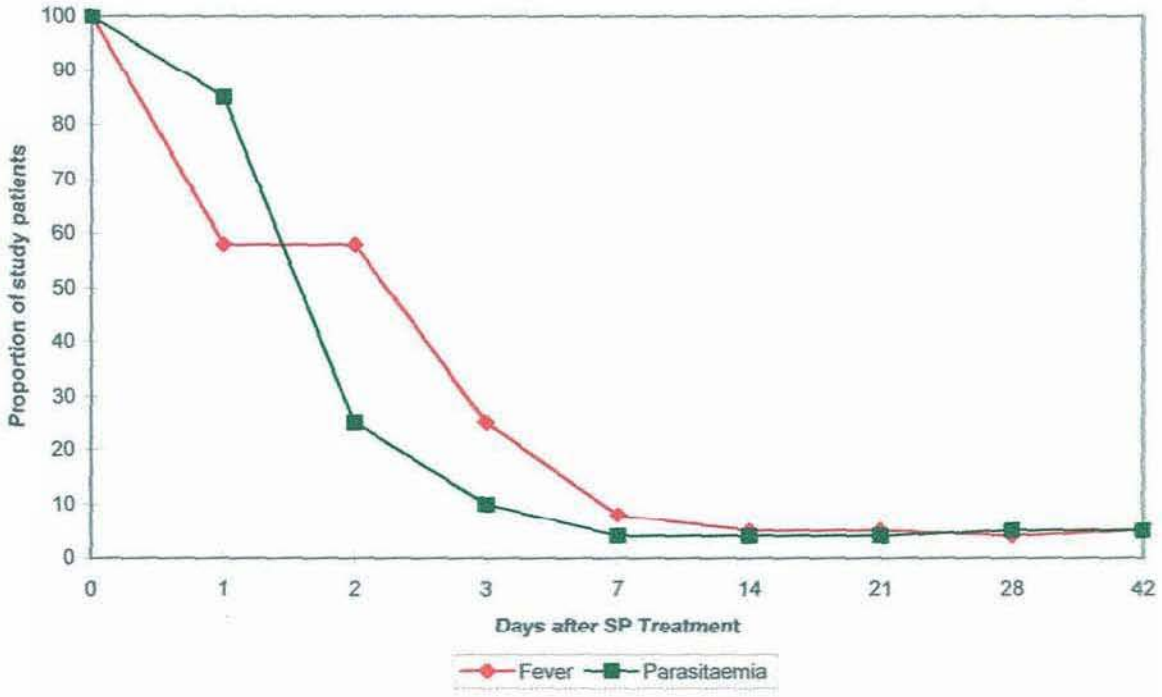
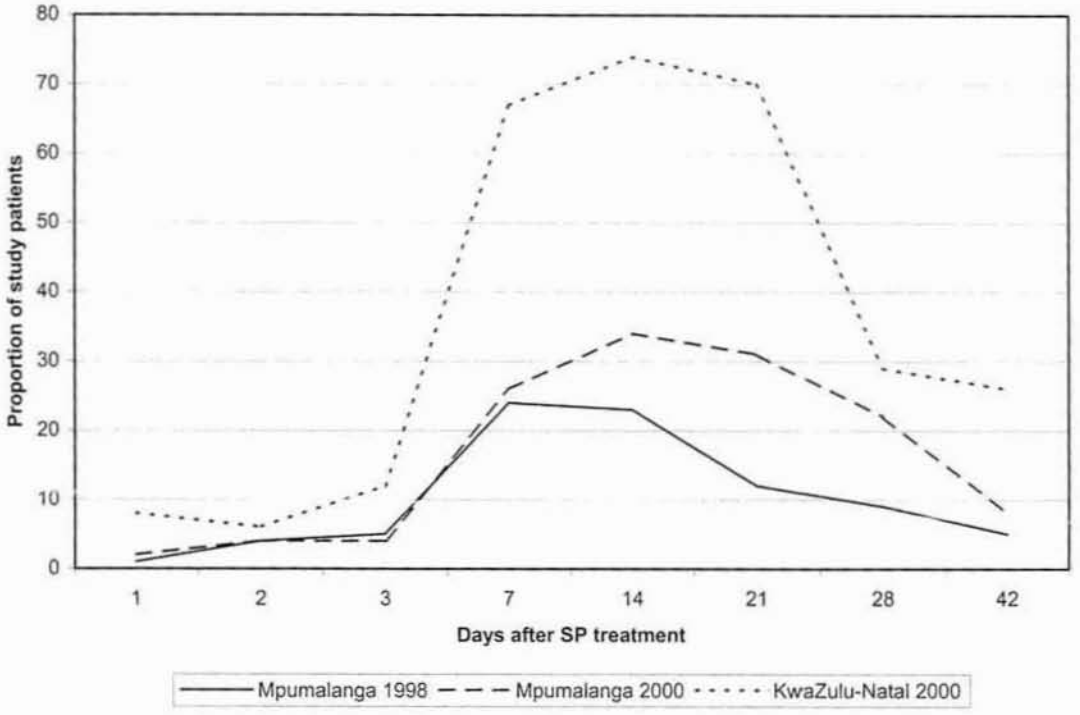


Figure 5.5. **Gametocyte rates (proportion of patients with gametocytes) following sulfadoxine-pyrimethamine therapy, KwaZulu-Natal 2000, and Mpumalanga 1998 and 2000 *in vivo* studies.**

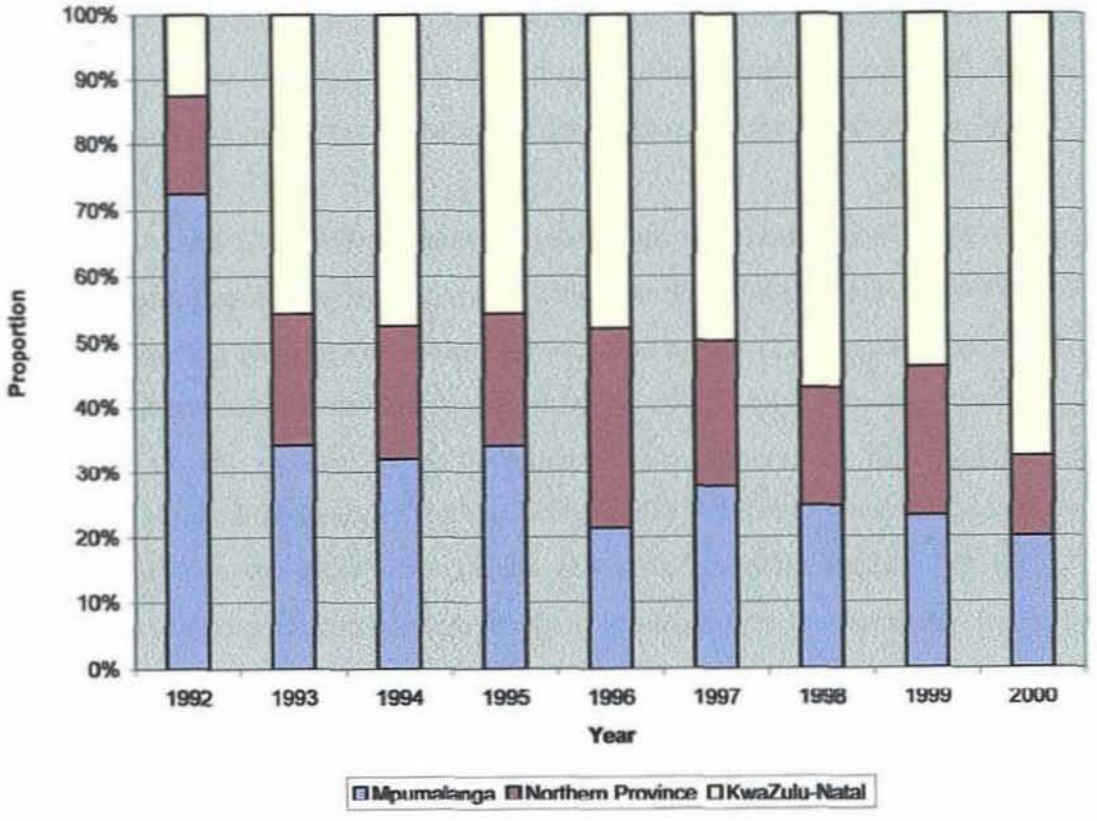


5.6. Discussion

Resistance has developed rapidly to SP in other world regions. The evolution of resistance is exacerbated by SP's long half-life, with parasites exposed to sub-therapeutic drug concentrations for relatively long periods (White & Olliaro, 1996). Single dose SP therapy provided a satisfactory parasitological cure rate in patients with uncomplicated *P. falciparum* malaria in Mpumalanga at introduction and over two years *P. falciparum* remained sensitive to SP, with no significant difference between cure rates, being 94.5% in 1998 and 93.6% in 2000 (Govere *et al.*, 1999; Mabuza *et al.*, 2001). This finding raises the possibility that SP usefulness may be extended through combination with a rapid acting and preferably gametocydocidal antimalarial, for example artesunate, thus sustaining affordable therapy (White & Olliaro, 1996).

The increasing proportional contribution of KwaZulu-Natal to the national malaria burden with a dramatic increase in case numbers, is clearly related to evolving SP resistance in KwaZulu-Natal [Figure 5.6]. The discovery of high-level failure of SP for treating uncomplicated malaria in KwaZulu-Natal by the standardised *in vivo* study meant that SP could no longer be effectively utilised for treatment and formed the basis for a change in policy to using coartemether (artemether-lumefantrine) for treating uncomplicated malaria (Bredenkamp *et al.*, 2001).

Figure 5.6. Proportional provincial contribution to malaria notifications, Mpumalanga, KwaZulu-Natal and Northern Province, South Africa, 1992-2000.



Remarkably, a small 1996 hospital-based study in northern KwaZulu-Natal found a 23.5% RI/RII/RIII parasitological failure rate on SP therapy (Medical Research Council, unpublished data). Although this finding was inconclusive because of the possibility of referral selection bias, this should have prompted an urgent thorough evaluation of the effectiveness of SP therapy. The establishment of a sentinel surveillance site in KwaZulu-Natal at that time could have circumvented unnecessary malaria morbidity and mortality, although the precise contribution of drug resistance cannot be calculated.

Mpumalanga Malaria Control Programme management were convinced of the value of the sentinel surveillance site by the initial chloroquine *in vivo* study in 1997. The investment in training Control Programme personnel to conduct high-quality regular drug efficacy evaluations has clearly been worthwhile, as evidenced by the completeness of recent *in vivo* studies and the results of routine quality assurance. The value of the Control Programme taking primary responsibility is also reflected by the differential loss to follow up between the 2000 Mpumalanga and KwaZulu-Natal studies. Of the nine patients (7.6%) who did not complete the study in Mpumalanga, four were lost to follow-up, two took other antimalarial drugs during follow-up, two were referred to hospital due to persistent clinical symptoms and one moved from the study area. The four subjects lost to follow up were all as a result of inaccessibility due to severe flooding. In KwaZulu-Natal, 39 patients (30.2%) were lost to follow-up. Follow-up was complicated by staff not being familiar with the area, as Medical Research Council personnel from Durban conducted fieldwork. In addition, the high levels of failure led to a conservative threshold for rescue therapy by the clinic microscopist provided by the hospital, resulting in 30 patients being classed as treatment failures and prematurely excluded. The assessment that these exclusions were premature was based on quality control re-examination of all blood slides at the Medical Research Council's Durban laboratories, which confirmed that they were negative. Ownership of the process due to an appreciation of the value of routine efficacy monitoring has resulted in these studies becoming a routine aspect of programme management in Mpumalanga and there is now a commitment from KwaZulu-Natal's Malaria Control Programme to be primarily responsible for conducting future *in vivo* studies. The value of *in vivo* studies for

establishing and monitoring malaria therapy policy has recently been appreciated by the remaining malaria affected South Africa Province, Northern. In 2001 Mpumalanga staff assisted this neighbouring Province's programme to establish a sentinel surveillance site.

Delayed resolution of symptoms with SP has also been reported from Gambia (Onyiorah *et al.*, 1996) and may result in unnecessary early referral, inappropriate use of second-line drugs and increased pressure on the health system. In addition, patients with delayed symptom resolution may lose faith in the public health system and delay seeking treatment in future. A disparity in fever and parasite clearance patterns, with symptoms persisting despite reduction in parasite load was observed in the present study confirming the findings of the previous study and a report from Gambia in which patients treated with SP returned to clinics within the first few days after treatment with persistent symptoms (Muller *et al.*, 1996; Onyiorah *et al.*, 1996; Govere *et al.*, 1999). In a Gambian study, routine administration of paracetamol to control symptoms failed to prevent children treated with SP returning to the health service with symptoms (Bojang *et al.*, 1998). Combination therapy with antimalarial drugs may be necessary for cure and adequate alleviation of fever.

The impact of increased gametocyte production following SP therapy on malaria transmission deserves further study. In the three studies gametocytes peaked between days 7 and 28. This finding is similar to that of a Gambian study, which found that 28.9% of patients treated with SP carried gametocytes at two-week follow-up (Von Seidlein *et al.*, 1998). SP has no known gametocytocidal properties, and gametocyte generation and development appears to persist despite SP treatment (Sinden, 1983). A laboratory-based study in Mozambique demonstrated that SP treatment may suppress gametocyte infectivity and possibly decrease *An. arabiensis* infectivity after ingestion of viable gametocytes (Hogh *et al.*, 1998). The impact of increased gametocyte production after SP treatment on malaria transmission deserves further study.

A study to monitor the efficacy of a single dose of SP in Kenyan children with symptomatic malaria (Ter Kuile, *personal communication,* 2001) found a marked

difference in failure rate between 3 and 4 year old children, which was attributed to differences in mg/kg treatment doses administered. This is consistent with the results in Mpumalanga patients weighing more than 60kg who received less drug per kg with resultant delayed clearance of parasites and fever. Higher drug levels are needed to ensure satisfactory therapy and to protect against drug resistance.

Of interest was the finding that the patients systematically enrolled in the KwaZulu-Natal study were predominantly young, with 68.8% between 3 and 15 years of age, compared to 39.9% of Mpumalanga patients enrolled in the same year and KwaZulu-Natal census data for the area that showed this patient age group over-represented (68.8% versus 43.2% in the population). In addition, a prevalence survey conducted in 1999 revealed that 40% of the asymptomatic population were malaria positive by immunochromatographic test (Sharp *et al.*, 2001). This high prevalence and the preponderance of young patients in this study raises the possibility that the KwaZulu-Natal population now has significant immunity to malaria.

Public health surveillance has many uses, the most well known being detection of epidemics, evaluation of control and prevention activities, detection of changes in health practice, quantitative estimates of the magnitude of health problems, and monitoring of changes in infectious agents, particularly the evolution of drug resistance (Teutsch & Thacker, 1995). Although the term surveillance was initially restricted to the collection, analysis and dissemination of data and did not encompass direct responsibility for responding to findings, more recently the quality of surveillance has been judged by its capacity to provide "data for action" (Langmuir, 1963; Thacker *et al.*, 1983; Giesecke, 1999).

Sentinel surveillance encompasses those activities focused on monitoring key health indicators in the general population or specific population sub-groups. The term sentinel is applied to health events, including cholera, malaria or maternal deaths, which provide a warning signal that the quality of preventative or therapeutic health services merits investigation (Rutstein *et al.*, 1983; Durrheim *et al.*, 2002a). Sentinel surveillance may

also refer to specifically chosen sites, whether health facilities or health providers, where data that is not routinely available is collected (Woodall, 1988). Careful selection of sites allows for adequate resources, and allocation of experienced and dedicated personnel for collecting detailed information on each case and providing careful follow-up. As the collection of data is the most costly and difficult component of any surveillance system, it is essential that all elements to assure quality, reliability and uniformity of data are in place (Declich & Carter, 1994). These include the ease of data collection facilitated by clarity, simplicity and lack of ambiguity of standardised forms and flow-charts, well-defined case definitions, timeliness, mechanisms for preventing loss to follow-up and measures to motivate data collectors, including feedback, participation in planning and review, recognition and other incentives.

In selecting a sentinel surveillance site, consideration must be given to a number of issues. These include the particular purpose of surveillance, frequency of the health event (accuracy of sample estimate), available resources, feasibility, the need to generalise findings (external validity), duration (trends) and likely quality of data (internal validity). Use of hospitals or other sophisticated facilities may pose problems because of the selection bias that usually operates (Otten, 1994). However, hospitals are particularly valuable sites for tracking mortality trends or for detecting severe diseases that are almost inevitably admitted (Trape *et al.*, 1998; Durrheim *et al.*, 2001c).

South Africa has been tardy in recognising the potential value of sentinel sites. A number of malaria control programs in other African and South East Asian countries have an established tradition of assessing the efficacy of their first-line malaria therapeutic regimens at sentinel surveillance sites to guide public health policy. In recent years both Zambia and Malawi have altered their national malaria treatment policies on the basis of results from standardised *in vivo* studies conducted at sentinel clinics (Barat *et al.*, 1998; World Health Organization, 1994a).

Malaria sentinel sites may serve additional valuable functions. In particular their utility as an epidemiological early warning system for malaria epidemics is being increasingly

realised. The alarm is triggered when monthly morbidity thresholds set for particular clinics are exceeded (Albonico *et al.*, 1999; Connor *et al.*, 1999; Carrasquilla *et al.*, 2000). Mpumalanga has also harnessed the capacity developed at its sentinel site to field-test the accuracy and utility of rapid malaria diagnostic tests (Durrheim *et al.*, 1998c; la Grange *et al.*, 1999). The seasonal nature of malaria transmission in South Africa creates the opportunity for using the capacity developed at these sites to the benefit of other public health programmes.

5.7. Conclusions

The need for a sentinel surveillance network as a prerequisite for epidemiological research and health planning in South Africa was mooted more than 60 years ago (Gear, 1937). This plea appears vindicated by major policy changes made possible by the availability of high-quality drug efficacy information and data on the accuracy of diagnostic tests collected at the malaria sentinel sites in Mpumalanga.

Although the true impact of persistent use of failed SP first-line therapy during the recent past in KwaZulu-Natal on morbidity, mortality, economic losses, malaria transmission and resultant public health expenditure cannot be accurately determined, the resulting crisis could have been circumvented had regular clinic-level sentinel surveillance been conducted.

The proposed plan to establish sites in KwaZulu-Natal, Northern Province, Swaziland and Mozambique for regular routine drug efficacy monitoring by control programmes should be vigorously pursued. However, the true value of the sentinel sites will not be measured by the volume of information they generate but rather by the ongoing public health action they trigger.