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Challenges and Prospects for Malaria Elimination in the Southern Africa Region

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Abstract

The burden of malaria has decreased dramatically within the past several years in parts of sub-Saharan Africa, including regions of Southern Africa. Important to effective regional malaria control in Southern Africa is the appreciation that the reductions in malaria have not been achieved uniformly, with some countries experiencing resurgence. Understanding the reasons for sustained low-level malaria transmission in the face of control efforts, why malaria control efforts have not been successful in particular epidemiological settings and the epidemiological and transmission patterns following resurgence are critical to improving further malaria control and possible elimination. The overall goal of the International Center of Excellence for Malaria Research in Southern Africa is to contribute to regional malaria control efforts that can be sustained beyond the duration of the project. This goal will be achieved through a combination of: 1) state-of-the-art research on malaria epidemiology, vector biology and the genetics of the malaria parasite in three different epidemiological settings; 2) collaborations with national malaria control programs to develop locally-adapted and sustainable control strategies; and 3) training, career development and capacity building at research institutions throughout the region.

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Keywords

malaria; Zambia; Zimbabwe; epidemiology; vector control; parasite genomics

1. 1 Introduction

Dramatic reductions in the burden of malaria have been achieved in parts of Southern Africa, particularly Zambia (Chizema-Kawesha E, Miller JM 2010). If further reductions in the burden of malaria are to be achieved in Southern Africa, and the goal of malaria elimination seriously considered, the reasons for these reductions must be understood. Of equal importance to regional malaria control in Southern Africa is that the reductions in malaria have not been achieved uniformly and in some countries, such as Zimbabwe, there has been a resurgence of malaria after more than 50 years of successful control (O'Meara WP, Mangeni JN 2010). Understanding the reasons for sustained low-level malaria transmission despite high coverage with current control efforts, why interventions have not been successful in some epidemiological settings and the epidemiological patterns following resurgence are critical to extending malaria control efforts, developing new control strategies and achieving malaria elimination in Southern Africa. We describe challenges and prospects for malaria elimination in three epidemiological settings in Southern Africa, field sites for the Southern Africa International Center of Excellence for Malaria Research (ICEMR).

1.2 Challenges for Malaria Control in Southern Africa

Declines in the burden of malaria have been observed in Zambia, coincident with the widespread implementation of malaria control strategies, including the use of artemisinin combination therapy (ACT) as the first-line treatment regimen, the distribution of long-lasting insecticidal nets (LLINs), and targeted indoor residual spraying (IRS) (Steketee RW, Sipilanyambe N 2008). The overall prevalence of malaria parasitemia in children younger than five years of age decreased 53% from a baseline prevalence of 22% between 2006 and 2008 (Chizema-Kawesha E, Miller JM, Steketee RW, Mukonka VM, Mukuka C, Mohamed AD, Miti SK, and Campbell CC 2010). In Choma District, Southern Zambia, pediatric hospitalizations at Macha Hospital for malaria decreased from approximately 1400 admissions per malaria season in 2000–2001 to 41 in 2008. This decline began in 2004, shortly after the introduction of ACT but before widespread distribution of LLINs, and followed a severe drought that reduced vector populations and may have temporarily facilitated the reduction in malaria transmission. In fact, *An. funestus* mosquitoes could not be found for several years following the drought (Kent RJ, Thuma PE 2007). Thus, Choma District, one Southern Africa ICEMR site, represents successful malaria control in southern Zambia. Challenges to progress in malaria control in this setting of reduced transmission include:

- Sustaining gains in malaria control in the face of a declining burden of malaria, to avert the potential loss of political, donor and community support
- Sustaining gains in malaria control to address the potential development of insecticide-resistance in anopheline vectors and drug resistance in *Plasmodium falciparum*
- Sustaining gains in malaria control to address the potential changes in selection for vector behavior, including exophagy and increased biting during crepuscular periods (Fornadel CM, Norris LC 2010a), limiting the effectiveness of LLINs and IRS

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- Sustaining gains in malaria control to address competing public health problems, including HIV/AIDS, tuberculosis and vaccine-preventable diseases
- Achieving further progress toward malaria elimination in regions with sustained, low level transmission and the potential for importation of malaria infections.

Despite progress in scaling-up malaria control in Zambia, malaria transmission remains high is some regions of the country. Nchelenge District in northern Zambia, the second Southern Africa ICEMR site, represents a region with ineffective malaria control despite implementation of currently available interventions. This district lies to the northeast of Ndola in the marshlands around the Luapula River and the environs of Lake Mweru. The area borders the Democratic Republic of the Congo and population movement across the border is common. The ecology in the vicinity of Lake Mweru and local agricultural practices contribute to typical habitats for *Anopheles funestus* as well as *An. gambiae* and *An. arabiensis*. The prevalence of parasitemia in children younger than five years of age residing in Luapula Province was 32.9% according to the 2006 National Malaria Indicator Survey and decreased to only 21.8% by the time of the 2008 National Malaria Indicator Survey (Ministry of Health and Government of the Republic of Zambia 2009), making Luapula Province the province with the highest parasite prevalence in Zambia ahead of North-Western (15.2%) and Northern Provinces (12%). Challenges to malaria control in this setting of ineffective control include:

- Understanding why malaria control has been less effective in this region, including assessment of coverage levels of LLINs and IRS, the potential role of insecticide resistance, changes in vector behavior, health-related beliefs and practices, and human population movement
- Development of more effective and sustainable control strategies to achieve malaria control at the community level
- Challenges to malaria control programs on national borders where importation of *P. falciparum* is common

Some regions of Southern Africa have witnessed a resurgence of malaria following successful control. Mutasa District, on the eastern border of Zimbabwe and Mozambique, the third Southern Africa ICEMR site, represents a region with resurgent malaria and currently has one of the highest malaria incidence rates in Zimbabwe. Mutasa District is an area of farm land in the Eastern District of Zimbabwe with an altitude that ranges from 700 to 1100 meters and a landscape that abuts the Pungwe River and the eastern border of Mozambique. The area had effective malaria control as part of the Ministry of Health integrated malaria control program that commenced in the early 1950's. This program ceased to be functional in the 1990s, resulting in a resurgence of malaria. According to the Roll Back Malaria Country Needs Assessment Zimbabwe Report of 2008, the national malaria incidence was 126 cases per 1000 persons per year in 2007. The highest incidence of malaria was in Mutasa District, with an incidence of 682 cases per 1000 persons. Between 1995 and 2005 the annual number of reported malaria cases seen at health centers in Mutasa District ranged from a low of 19,883 in 2002 to a high of 67,978 in 1998. However, the number of reported cases rose to 75,510 in 2006 and peaked at 75,844 in 2007. These clinical cases of malaria in Mutasa District demonstrate the dramatic resurgence of malaria in this region of Zimbabwe. The lack of recent progress in malaria control contrasts with the highly successful malaria control program prior to the 1990s. Challenges to malaria control in this setting of resurgent malaria include:

- Understanding the epidemiology of resurgent malaria, particularly changes in vector biology, insecticide resistance and parasite genomics
- Regaining malaria control following resurgence

- Development of sustainable and effective malaria control interventions to prevent another round of resurgence once control is again achieved

1.3 The International Center of Excellence for Malaria Research in Southern Africa

The overall goal of the Southern Africa ICEMR is to contribute to regional malaria control that can be sustained beyond the duration of the project. This goal will be achieved by combining: 1) state-of-the-art research on malaria epidemiology, vector biology and the genetics of the malaria parasite in three different epidemiological settings in Southern Africa; 2) collaborations with national malaria control programs to develop locally-adapted and sustainable control strategies; and 3) training, career development and capacity building at research institutions in the region. The different epidemiological settings of the Southern Africa ICEMR reflect different stages of malaria control (successful, ineffective and resurgent) that are present throughout the malaria endemic regions of the world. The long-term goal is to develop risk-based strategies for malaria control and elimination. The specific aims address malaria epidemiology, vector biology and parasite genomics.

1.3.1 Epidemiology

Building upon existing epidemiological studies based at the Macha Research Trust and Johns Hopkins Malaria Research Institute field site in rural southern Zambia, we will investigate the epidemiology of malaria in three distinct transmission settings in Southern Africa. Understanding the epidemiology of malaria first requires knowledge of how parasite prevalence varies across time and place. We will measure changes in spatio-temporal patterns of malaria parasitemia in three epidemiological settings in Southern Africa and identify individual, household and ecological risk factors for symptomatic and asymptomatic parasitemia. We expect risk factors for parasitemia will vary by epidemiological setting and level of malaria control, and will change over time in response to changing ecological factors and control efforts. Our objective is to identify multi-level risk factors for malaria parasitemia in different epidemiological settings to guide the development of malaria control strategies in Southern Africa.

Gametocytes are essential to continued malaria transmission and understanding their age-specific temporal and spatial distribution will be important for malaria elimination (Drakeley C, Sutherland C 2006). We will identify individual, household and ecological risk factors for gametocyte carriage during high and low transmission seasons in the three epidemiological settings using a reverse-transcriptase polymerase chain reaction (RT-PCR) assay to detect sexual stage transcripts (Mlambo G, Vasquez Y 2008). RT-PCR has greater sensitivity than microscopy in detecting gametocytes, as shown in prior studies in Macha, Zambia (Stresman GH, Kamanga A 2010). We expect risk factors for gametocytemia will differ by epidemiological setting, level of malaria control and transmission season. Our objective is to identify these factors t o guide strategies to eliminate the gametocyte reservoir during low transmission seasons and interrupt transmission.

Measures of antibodies to *P. falciparum* asexual stage antigens have been used to quantify transmission intensity in settings with different levels of malaria endemicity (Drakeley CJ, Corran PH 2005). We will measure spatio-temporal changes in age-specific antibody responses to *P. falciparum* antigens in three epidemiological settings. Spatio-temporal patterns in age-specific seroprevalence to *P. falciparum* antigens are expected to be associated with different levels of malaria transmission intensity and stages of control. Our objective is to use these surveys to measure medium and long-term changes in malaria transmission intensity in different epidemiological settings and identify populations with waning immunity that could be at risk for malaria resurgence (Corran P, Coleman P 2007).

The above studies are intended to provide the detailed epidemiological data necessary to develop locally-adapted malaria control strategies that are cost-effective and acceptable in three transmission settings in Southern Africa. Models will be used to develop risk-based combinations of malaria control strategies based on locally available measures of key malaria indices (Smith DL, Guerra CA. 2007;Smith DL, McKenzie FE 2007;Smith DL, Hay SI 2009). Our overall objective is to achieve high levels of community participation and support for locally-adapted, cost-effective malaria control strategies to further malaria control and elimination in Southern Africa.

1.3.2 Vector Biology

Building on several years of entomological studies conducted at the Macha Research Trust and Johns Hopkins Malaria Research Institute field site in rural Southern Zambia (Kent RJ, Coetzee M 2006;Kent RJ, Mharakurwa S 2007;Kent RJ, Thuma PE, Mharakurwa S, and Norris DE 2007;Fornadel CM and Norris DE 2008;Fornadel CM, Norris LC 2010a;Norris LC, Fornadel CM 2010;Fornadel CM, Norris LC 2010b), we will investigate malaria transmission by examining the biology of anopheline vectors in the three different epidemiological settings. These studies will provide a detailed understanding of the dynamics of vector populations in response to ecological changes and vector control interventions, will guide development of locally-adapted vector control strategies and will address challenges to malaria elimination in Southern Africa.

We will measure the composition of vector populations, human biting rates, sporozoite infection rates, and seasonal entomological inoculation rates (EIR) in the three Southern Africa ICEMR epidemiological settings. We expect these parameters will vary over space and time throughout the transmission season, and may vary dramatically depending on local vector species. At each of the three sites, we will characterize the feeding and resting behavior of *An. arabiensis*, a prevalent vector that can be difficult to control due to its tendency to forage and rest outdoors. This knowledge is important to assess the potential impact of vector control strategies such as distribution of LLINs and IRS. Our objective is to identify the vector species and their relative contributions to malaria transmission in each of the three settings to inform locally-adapted vector control strategies. As vector species may change characteristics or behavior in response to preventive interventions such as LLINs and IRS, including, for example, increased exophagy (Fornadel CM, Norris LC, Glass GE, and Norris DE 2010a), malaria transmission may be sustained in the face of high coverage with these interventions. Documenting these changes in vector behavior will be critical to developing new strategies to sustain malaria control.

The most widely implemented vector control intervention in Southern Africa has been the distribution of LLINs and this is at least in part responsible for the declines in malaria burden in some regions of sub-Saharan Africa. However, the emergence and spread of insecticide resistance in southern Africa, particularly pyrethroid resistance in *An. funestus* (Hargreaves K, Koekemoer LL 2000;Brooke BD, Kloke G 2001;Casimiro S, Coleman M 2006;Hunt RH, Edwardes M 2010), could hinder further progress in malaria control as pyrethroid-based insecticides are the only class of insecticides used to impregnate LLINs. We will measure the susceptibility of vector populations to insecticides in each of the three sites using bioassays. Associations between the prevalence of insecticide resistance and the use of LLINs, IRS and insecticide use in agricultural practices will be evaluated. We will attempt to identify the mechanisms of insecticide resistance by screening mosquitoes for target site mutations and metabolic pathways responsible for insecticide resistance. Our objective is to determine which insecticides are effective for vector control and to provide national malaria control programs with evidence to make informed choices.

Understanding how readily insecticide resistance genes spread through a mosquito population requires detailed knowledge of vector population genetics. We will conduct genetic analyses of *An. arabiensis* population structure using single-nucleotide polymorphism (SNP) markers. Using these markers, we will quantify genetic variation, migration and effective population size of *An. arabiensis* in the three epidemiological settings. The long-term goal is to provide the evidence-base and training to devise sustainable strategies to reduce malaria transmission, manage insecticide resistance, and assess the feasibility of malaria elimination in Southern Africa.

1.3.4 Parasite Genomics

The abundant genetic diversity exhibited by *P. falciparum* is critical to parasite persistence. This genetic diversity is presumably shaped by pressures exerted on the parasite to adapt to human and mosquito immune responses, chemotherapy and environmental changes. The product of this dynamic interplay between *P. falciparum* and its environment is not a single clonal population but a constellation of evolved genotypes. Understanding the nature, extent and distribution of this genetic diversity, and how it changes over time, will be important to devising long-term, effective malaria control strategies. To date, only sparse data are available on the population genetics of *P. falciparum* in Southern Africa.

We will establish profiles of the genetic diversity of *P. falciparum* in the three epidemiological settings through high- and low-resolution profiling. For high resolution profiles, genotyping will be conducted using a whole genome approach with a GeneChip that interrogates more than 75% of the *P. falciparum* genome for SNPs, insertions, deletions and amplifications (Dharia NV, Sidhu AB 2009). In addition to covering known mutations associated with drug resistance and virulence, this array-based genome-wide survey of diversity may identify additional polymorphisms associated with drug resistance, transmission, virulence, and environmental and climatic pressures. For lower resolution profiling, we will use the recently introduced “barcode” profiling (Daniels R, Volkman SK 2008). This relatively simple and cost-effective PCR-based assay of polymorphisms in 24 loci will allow us to genotype a greater diversity of isolates from each site and thus gain a broad profile of parasite diversity. Importantly, barcoding can be adapted for use in laboratories in Southern Africa to serve as a tool in the design and monitoring of control efforts. In addition, studies will examine the scope and dynamics of parasite genetic diversity within individuals, with emphasis on persons with asymptomatic infection.

We expect the ability to compare and contrast the population genetics of *P. falciparum* from the three epidemiological settings will provide insights into how the parasite responds to environmental changes and the selective pressures exerted by control strategies. Information on parasite genetic diversity, including drug resistance and virulence, will be used to inform the next generation of mathematical models of malaria transmission and the impact of control efforts.

1.4 Role of the ICEMR in Malaria Control in Southern Africa

The scale-up of malaria control interventions in much of Zambia, and the past success of malaria control in Zimbabwe, provide evidence that the burden of malaria in Southern Africa can be reduced using currently available tools. However, this progress has not been uniform and further progress is needed to improve and develop sustained malaria control efforts in the region. The expectation is that the Southern Africa ICEMR will:

- Provide the evidence base for locally-adapted and sustainable malaria control strategies
- Provide insight as to why current strategies are not uniformly effective

- Provide insight into resurgence of malaria in some areas

Increasing the number of qualified scientific and technical personnel in Southern Africa with the training and expertise to conduct independent malaria research is critical to the success and long-term sustainability of the ICEMR program. In addition to training and capacity building through the research activities, the ICEMR will support two career development positions for junior or established investigators who wish to focus or refocus their careers on malaria research. Based on the expressed needs of the region, we are particularly interested in building local capacity in biostatistics, modeling and spatial analyses. Each candidate will receive training both in-country and at the Johns Hopkins Malaria Research Institute. The ICEMR in Southern Africa will provide the research experience and career development paths for these scientists to become independent researchers and public health practitioners.

1.5 Success of the ICEMR Program and the Move toward Malaria Elimination in Southern Africa

The success of the ICEMR in Southern Africa will be achieved by contributing to a regional malaria control strategy that can be sustained beyond the duration of the project. In regions of effective malaria control, the Southern Africa ICEMR will be successful by contributing to the development of strategies for risk-based interventions leading toward malaria elimination. In regions where malaria control has been unsuccessful, the Southern Africa ICEMR will succeed by defining the reasons for the failure to manage transmission and by the development of successful approaches. And in regions of resurgent malaria, the Southern Africa ICEMR will succeed by contributing to the understanding of the epidemiology of resurgent malaria and development of sustainable control strategies. Importantly, the ICEMR can facilitate coordinated regional control strategies across Zambia, Zimbabwe and other countries within Southern Africa.

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Non-Standard Abbreviations

ICEMR	International Centers of Excellence for Malaria Research

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Research Highlights

- The Southern Africa ICEMR goal is to contribute to regional malaria control
- Based at three diverse epidemiological settings in Zambia and Zimbabwe
- Conduct research on malaria epidemiology, vector biology and parasite genetics
- Develop locally-adapted, targeted and sustainable malaria control strategies
- Provide training, career development and capacity building within the region