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MALARIA – PATIENT PROFILE AND COMPLICATIONS AT HELEN JOSEPH HOSPITAL

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Masters in Medicine

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 2016

DECLARATION

I, Marilyn Reddy declare that this dissertation is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……..

Dr Marilyn Reddy, MBBCH (WITS), FCP (SA).

……..day of ……., 2016

DEDICATION

To my best friend, my husband, Yugen, and my beautiful girls, Arabella-Dior and Amariah-Milan, for all the days you have had to spend without me.

To my late dad, Patrick Reddy (1949-2013). You have instilled in me the importance of knowledge and education. I know that you will forever be in my heart and I will always treasure the memories we had.

ABSTRACT

Background

Malaria, an important parasitic disease, carries a huge burden locally and globally specifically imported malaria in non endemic industrialized regions like Gauteng. We evaluated the profile of patients treated for *P. falciparum* malaria at the Helen Joseph Hospital (HJH).

Methods

A retrospective review of 171 patient's files was undertaken at HJH between January 2009 and December 2010.

Results

Imported malaria contributed to an over-whelming 96% of the population, with males accounting for 85%. Pyrexia and thrombocytopenia were the most common features. Quinine and doxycycline combination was most frequent used treatment. The number of patients with complicated and uncomplicated malaria was almost equal. Mortality rate was 5.8% (10/171). Mortality in the HIV positive and negative groups was not found to be different. Females had a higher risk of severe malaria and its complications ($p < 0.005$). Admission to ICU predicted an even higher mortality rate. There were four predictors of mortality in ICU patients; severe hypotension, respiratory distress and/or ARDS and lastly the need for mechanical ventilation.

Conclusion

Considerable progress has been made in malaria prevention and management however there are still significant prevention gaps that exist. The immense burden of imported malaria and male patient predominance was illustrated in this study. The demand for employment may have been the driving force here. The mortality rate was above national target of 0.5%. This places undue stress on the health system despite malaria being a preventable disease.

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ABBREVIATIONS

AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
ACT	Artemisinin Combination Therapy
AIDS	Acquired Immune Deficiency Syndrome
DDT	Dichlorodiphenyltrichloroethane
DOH	Department Of Health
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HJH	Helen Joseph Hospital
ICU	Intensive Care Unit
RAT	Rapid Antigen Test
RRT	Renal Replacement Therapy
SA	South Africa
SP	Sulphadoxine-Pyrimethamine
WHO	World Health Organization

CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Malaria is the most important and prevalent parasitic disease in humans, posing an enormous global public health burden (Suh *et al*, 2004). It is a disease that has entrenched disproportionately in poverty stricken areas of the world. The social and economic burden created by this devastating disease in these developing countries is immense. Over 40% of the world's population is said to live in malaria endemic areas (Suh *et al*, 2004). Almost a million people around the globe die each and every year from this dreadful infection (Marks *et al*, 2014).

1.2 EPIDEMIOLOGY

1.2.1 Global

According to the World Malaria Report in 2010, the global prevalence of the disease was estimated at 225 million cases in 2009. Further, there were 781 000 deaths reported in that year (World Health Organization [WHO] 2010). Sub-Saharan Africa hosts the vast majority (80%) of these malaria cases, predominantly saturating remote rural areas with poor access to health services (Ngomane *et al*, 2012). Despite a constantly evolving field of knowledge, the morbidity and mortality caused by this devastating disease globally is tremendous (Suh *et al*, 2004). This has direct impact and negative consequences on the economic growth of the area. Most of the *falciparum* malaria across the USA and Europe is acquired from Sub-Saharan Africa (Marks *et al*, 2014).

1.2.2 South Africa

In South Africa transmission of malaria is low and seasonal (Weber *et al*, 2010). Infection rates have been reported to be reduced and is now limited to a small area in the North-

Eastern part of the country (Kwa-Zulu Natal, Mpumalanga and Limpopo provinces) (National Department of Health [DOH], 2009). Almost all South Africans are non-immune to malaria thereby escalating their risk of severe malaria (DOH, 2010). Due to malaria being a nationally notifiable disease, reduced infection rates has been confirmed with a decrease in the number of malaria notifications reported in the country. In 2000 there were just over 60 000 notifications, however in 2010 there was a substantial decrease to approximately 8000 (Moonasar *et al*, 2011). Mpumalanga province however, is one of the country's provinces that still experiences relatively high volumes of unstable malaria transmission, by contributing to 44% of the country's notified malaria cases (National DOH 2007). While malaria is now limited to the smaller areas in the country (Weber *et al*, 2010), migrants and mobile populations still represent a significantly high percentage of the total number of cases (Opie *et al*, 2014).

1.3 IMPORTED MALARIA

The most common cause of imported infection in non endemic areas is actually malaria, mostly *falciparum* (Marks *et al*, 2014). This is a direct consequence of the escalated travel between endemic and non endemic areas (Marks *et al*, 2014). Gauteng is an area non-endemic to malaria due to its altitude and also its climate (Frean *et al*, 2014). Being an economic hub of the country, the province has seen an alarmingly high incidence of the disease. Around 20% of the country's malaria burden is actually generated here in Gauteng through imported malaria (Frean *et al*, 2014). This may be related to travelers entering the city of gold from endemic areas outside South Africa (Weber *et al*, 2010. Perovic *et al*, 2000. Frean *et al*, 2014). Many foreigners working in the Sub-Saharan areas are also flown into Gauteng during periods of illness. Imported malaria is exclusively a disease of the young to middle-aged adult, contrary to endemic areas where it mainly affects children (Marks *et al*,

2014). The escalation of immigrant workers travelling through endemic regions into Gauteng in the face of employment has been a critical point (Weber *et al*, 2010). According to the report compiled by the United Nations Refugee Agency, South Africa was the main overall destination country of thousands of new asylum seekers between 2006 and 2011. These numbers are probably underestimated though, as not many migrants are registered asylum seekers (Opie *et al*, 2014). Presentation to a health institute frequently follows recent travel of foreign migrants. This places strain and a huge burden on the health system of the country. Very few study reports however actually focus on the impact of imported malaria specifically in non-endemic industrialized areas (Weber *et al*, 2010; Bruneel *et al*, 2003).

1.4 ODYSSEAN MALARIA

Malaria acquisition in non-endemic areas can occur (Frean *et al*, 2014). The entity of airport / suitcase malaria was first recognized in Europe in the 1970's (Frean *et al*, 2014). Odyssean malaria is a rare form of malaria transmitted by mosquitoes that have been translocated (Frean *et al*, 2014). Travel history is typically non- existent in these patients and the possibility of transfusion related malaria is also excluded. The probable source of translocated mosquitoes remains with all vehicles of transport including air, road and rail traffic from within and outside South Africa (Frean *et al*, 2014). Road transport is probably more important than air transport as a source of translocated mosquitoes from endemic regions (Frean *et al*, 2014). In Gauteng, possible sources of translocated malaria- infective mosquitoes are from neighboring countries, mainly Mozambique as well as Zimbabwe (Frean *et al*, 2014). Translocation within endemic areas of the country is also possible. In view of the negative travel history in this group of patients, malaria is not always initially considered. Hence the diagnosis is almost always delayed thereby promoting cases of complicated malaria and increased mortality (Frean *et al*, 2014). Although *falciparum* malaria is a

significant cause of morbidity and mortality across the world, it is also a preventable one too (Suh *et al*, 2004).

1.5 PREVENTION AND CONTROL

Vector control has been the most effective method of reducing malaria transmission. Dichlorodiphenyltrichloroethane (DDT) is one of the most effective pesticides used to control malaria. In the 1940's house-spraying with DDT was done as large scale prevention programme in South Africa. This prompted a decrease in the level of malaria transmission in large parts of the country. Major malaria vectors *Anopheles funestus* and *Anopheles gambiae,* were also eliminated (Ngomane *et al*, 2012). Use of insecticide has raised many concerns as the chemical fumes may be hazardous (Ngomame *et al*, 2012).

Malaria transmission occurs mainly between dusk and dawn as the Anopheles mosquitoes feed at night (Moonasar *et al*, 2013). Therefore reduced contact with the mosquitoes especially during these hours is important. Insect repellants containing diethyl-meta-toluamide (DEET) can be applied to exposed skin (Moonasar *et al*, 2013). Bed nets provide a physical barrier to mosquitoes. Further, the effectiveness is greatly improved if treated with insecticides like permethrin (Suh *et al*, 2004). This generates a chemical halo that extends beyond the net as a repellent.

Malaria is preventable in travelers (Suh *et al*, 2004). Data consistently illustrates that travelers do not adhere to malaria prophylaxis appropriately (Marks *et al*, 2014). One may either assume that their risk is low, particularly those that grew up in an endemic area or there may be concern about anti-malarial side effects. Prophylactic anti-malarial drugs include mefloquine, doxycycline and malarone (atovaquone-proguanil) (Moonasar *et al*, 2013). No prophylaxis is a 100% effective. Even if there is failure of the prophylactic drug it may confer some degree of protection against complicated malaria (Seringe *et al*, 2011). Travelers must

be educated about the importance of these preventive measures and immediate presentation to a health institute should they experience a fever (Suh *et al*, 2004).

1.6 TRANSMISSION

Tropical and subtropical areas promote breeding and enhance transmission due to the warm humid climates with heavy rainfall (Marks *et al*, 2014).

There are approximately 3500 species of mosquitoes grouped into 41 genera. A bite from an infected female of the genus *Anopheles* transmits human malaria. Infection can also be transmitted through blood transfusion and congenital transmission (Trampuz *et al*, 2003). Malaria in humans is caused by one of five species including *Plasmodium falciparum; P. ovale; P. malariae; P. vivax and P.knowlesi.* The likelihood of the non *falciparum* malaria causing severe malaria is of low probability (Cohen *et al*, 2005). Infection with *P. falciparum* has been shown to cause the most clinically severe and complicated form of malaria. Over 90% of all malaria in Africa is from *P. falciparum* (Suh *et al*, 2004. Perovic *et al*, 2000).

1.7 DIAGNOSIS

Early diagnosis and prompt access to treatment remains the cornerstone. Microscopy is the gold standard for diagnosis and has the advantage that it can be used for speciation, quantification of parasites and hence response to malaria treatment (Singh *et al*, 2010. Marks *et al*, 2015). It may also identify other causes of fever if not malaria. The peripheral smear stained with Giemsa demonstrates the parasite on a thick film. Thin films assist with determination of parasitemia densities and species identification (Trampuz *et al*, 2003). The presence of schizonts on blood smear can be a marker of severity (Marks *et al*, 2014). Microscopy may however be a serious obstacle to therapeutic delays since it is labor intensive and requires skilled staff. Additionally, laboratory errors may occur even in the

hands of the skilled as it can take many years of experience and skill to accurately interpret malaria slides (Singh *et al*, 2010). A smear should be repeated if there is a high index of suspicion for malaria with an initial negative smear. Parasitemia quantification is a predictor of severe malaria and prognosis. However due to it being technician dependant there may be much variability especially in a semi-immune patient.

Malaria remains a diagnostic challenge more especially in resource limited settings (Singh *et al*, 2010). The introduction of the Rapid Diagnostic Tests (RDT's) is fast and simple to use in malaria diagnosis allowing for rapid institution of anti-malarial treatment (Singh *et al*, 2010). It is used for the qualitative detection of *P falciparum* on blood. RDT's detects parasite associated proteins and enzymes like the histidine rich protein II (HRPII) antigen (Perovic *et al*, 2000. Trampuz *et al*, 2003. Marks *et al*, 2014). Due to the high sensitivity of RDT's for *falciparum* malaria, there is a reduced risk of missing a patient infected with malaria (Singh *et al*, 2010). Important shortcomings however is that these tests are expensive, vulnerable to high temperatures and humidity, suboptimal with low parasitemia levels and can neither quantitate parasitemia nor differentiate between species (Singh *et al*, 2010). The RDT although enhances the speed of diagnosis, smear microscopy is still mandatory (Trampuz *et al*, 2003). It should be considered as an adjunct the diagnostic arm. The role for PCR as a diagnostic tool for malaria remains more for research purposes (Marks *et al*, 2014).

1.8 SUSCEPTIBLE PATIENT GROUPS

South African residents including those from malaria areas are generally non immune and therefore are at high risk of complicated malaria (DOH 2010). Any age group can be susceptible to malaria infection however mortality rates escalates in children, elderly, splenectomised individuals, pregnant or postpartum females and HIV groups with malaria complications (DOH, 2010).

1.8.1 Malaria in pregnancy

An increased risk of parasitic infections especially *falciparum* malaria has been well described in pregnant females (McLean *et al*, 2015). It appears that there may be an increased risk of *P. vivax* as well in pregnancy. However data is somewhat conflicting (McLean *et al*, 2015). Apart from pregnant women having a higher susceptibility to *falciparum* malaria than non pregnant, the risk of infection is remarkably higher in primigravid females (McLean *et al*, 2015). The underlying pathological process involves changes in hormonal and immunological systems in pregnancy. Malaria in pregnancy can have a negative impact on both mother and fetus (McLean *et al*, 2015). In the mother it has been associated with an increased risk of hypoglycemia, anemia, severe complicated malaria, pulmonary edema and death. Malaria in the post partum period is also documented as is the risk of post-partum hemorrhage. The effect on the fetus may include miscarriage, intrauterine growth retardation, premature birth, congenital infection and perinatal death (WHO 2000).

1.8.2 Malaria and HIV co-infection

Due to geographical distribution, malaria endemic areas are found to have a distinctly high prevalence of HIV infection as well (Pereira *et al*, 2015). This overlap of infections augments the possibility that travelers coming from endemic areas may well present with co-infection (Pereira *et al*, 2015). The consequence of this co-infection may be detrimental as the severity of malaria is escalated with HIV co-infection. These patients seem to have a higher parasite burden and the risk of severe malaria and its complications is escalated (Pereira *et al*, 2015). Parasite density is said to directly correlate with the degree of immune-suppression. HIV co-infection particularly in non immune patients has higher risk of severe malaria, its associated morbidity and mortality (Cohen *et al*, 2005. DOH, 2010). The risk of severe malaria is associated with a low CD4 count (Cohen *et al*, 2005). Additionally, malaria can accelerate

the progression of HIV disease itself (Pereira *et al*, 2015). An immunological interaction occurs between both diseases, favoring the spread and viral replication of HIV (Pereira *et al*, 2015). In patients with co-infection opportunistic infections may be easily confused with features of malaria infection (Mehta *et al*, 2007). Patients can be incorrectly diagnosed as tuberculosis meningitis or cryptococcal meningitis when in actual fact the diagnosis is cerebral malaria and vice versa (Mehta *et al*, 2007). Fever may be the cardinal feature to all these infections hence lending itself to a major diagnostic dilemma (Pereira *et al*, 2015). The interaction of malaria and HIV is well established and acknowledged in endemic areas, however it may be lacking in non endemic areas (Pereira *et al*, 2015). The clinician should therefore have a high index of suspicion for malaria in a febrile patient with HIV, more especially in a malaria endemic region (Mehta *et al*, 2007). Screening for both malaria and HIV infections are advocated in any patient with travel history (Pereira *et al*, 2015).

1.9 CLINICAL DIAGNOSIS

1.9.1 Non specific symptoms and delays in diagnosis

The times between an infective mosquito bite and the start of illness is usually 7 to 21 days (average of 10 days) in *P. falciparum*. The vast majority of patients classically experience fever, chills, headache and diaphoresis (Trampuz *et al*, 2003. DOH, 2010). Other symptoms include malaise, myalgia abdominal pain, nausea and vomiting. These are however non-specific symptoms and frequently lead to mis-diagnosis of malaria. The clinical diagnosis of malaria can therefore be challenging and requires a high index of suspicion as the symptoms can mimic many other diseases more especially influenza (DOH, 2010). Health care workers in non malaria areas may have a low index of suspicion for malaria or to even recognize the clinical features thereof. This directly contributes to a delay in diagnosis and directed

management (Weber *et al*, 2010). Failure to diagnose *falciparum* malaria promptly and hence subsequent delay in targeted management results in progression to complicated malaria and morbidity and mortality heightens (Perovic *et al*, 2000. Trampuz *et al*, 2003). Malaria is one of the most common causes of febrile illness in a returning traveler (Marks *et al*, 2015). Any patient that presents with non specific symptoms like fever and has a travel history to a malaria endemic area must be screened for malaria. Further, the differential diagnosis must include malaria when there is concern for pyrexia of unknown origin. Poor patient insight and awareness also has direct impact on presentation to a health care facility. It has been singled out as a definite problem requiring attention (Perovic *et al*, 2000).

1.9.2 Clinical signs

Examination of a patient may be completely unremarkable or may include tachycardia, fever, jaundice, pallor, hypotension (Trampuz *et al*, 2003). Signs of specific organ involvement may also be present. Severe *falciparum* malaria can manifest as a complex multi-system disease involving respiratory, renal and hematological or the central nervous systems. Metabolic complications including hypoglycemia or metabolic acidosis may also occur (Trampuz *et al*, 2003).

1.9.3 WHO severe malaria criteria

In 1990 the WHO established the criteria for severe *falciparum* malaria (WHO, 1990). In 2000 these criteria were revised, providing additional information and highlighting the specific risk factors of severe complicated malaria. These criteria include clinical manifestations and laboratory values. Major complications of severe *falciparum* malaria include circulatory collapse; bleeding; pulmonary edema; cerebral malaria; hypoglycemia; anemia; acute renal failure and/or metabolic acidosis (WHO, 2000). These complications

may coexist or evolve within hours of presentation (Trampuz *et al*, 2003). The Department of Health guidelines of South Africa closely follows and is based on the WHO guidelines (DOH, 2013). Severe malaria is a medical emergency requiring rapid and appropriate therapy and neglect thereof results in rapid progression of disease and its complications (DOH, 2013). Currently the WHO criteria are used in most countries to diagnose patients with malaria. However these criteria have been based on studies done in endemic areas (Bruneel *et al*, 2003). Further the prognostic value of these criteria in adult patients with severe imported malaria is poor. There are few studies done on the presentation and complications of patients seen with imported malaria in non-endemic areas (Bruneel *et al*, 2003). In addition, definitions and criteria exist to assist clinicians on a clinical level and also for research basis. However in clinical practice it is important to emphasize that one should not defer treatment due to lack of fulfillment of these criteria (WHO, 2000). Every patient can present differently. Moreover these criteria may actually be present in many other diseases as well. Due to the high associated mortality and morbidity, if there is a suspicion for the disease, the benefit should be given to treat while awaiting further laboratory test results (WHO, 2010).

1.9.4 Cerebral malaria

Cerebral malaria is one of the most feared and most fatal complications of severe *falciparum* malaria. Patients may present with neck stiffness, abnormal posturing, depressed level of consciousness, convulsions or coma. Eye abnormalities like retinal hemorrhages or disorders of conjugate gaze may also occur (WHO 2000). Clinicians should be aware that convulsions may also indicate hypoglycemia. Other causes of a decreased level of consciousness should be excluded like hypoglycemia, meningitis or encephalitis (Trampuz *et al*, 2003). The strict definition of cerebral malaria requires a Glasgow Coma Scale score of below 6 together with the presence of a parasitemia. However, for practical purposes any alteration in level of

consciousness should be considered and treated as cerebral malaria (Trampuz *et al*, 2003). The pathophysiology of cerebral malaria is poorly understood and the mortality can escalate to even 50% with treatment (Trampuz *et al*, 2003). A well recognized complication within this category also includes cerebral edema (Marks *et al*, 2014). The use of dexamethasone and mannitol has been associated with prolonged coma states (Marks *et al*, 2014).

1.9.5 Circulatory collapse

Circulatory collapse defined as a systolic blood pressure ≤ 80mmHg may be associated with dehydration and hypovolemia. Bacterial sepsis, pulmonary edema, hemorrhage and acidosis are also important and possible contributors (WHO, 2000).

1.9.6. Respiratory distress and Acute Respiratory Distress Syndrome (ARDS)

Respiratory distress in these patients may be related to firstly a primary lung involvement that being acute lung injury, ARDS or even pneumonia. Secondly, it may be an expression of the underlying metabolic acidosis, anemia or fever (Marks *et al*, 2014). Acute lung injury can occur early in the course of disease. It can occur rapidly and sometimes despite an initial response to therapy and a decrease in parasitemia (Trampuz *et al*, 2003. Suh *et al*, 2004). Pulmonary edema is non cardiogenic and can manifest as tachypnoea and dyspnoea, followed with hypoxemia and respiratory failure (Trampuz *et al*, 2003). Pulmonary edema may progress to Acute Respiratory Distress Syndrome (ARDS) which can be defined as an acute lung injury and an arterial oxygen tension/fractional inspired oxygen ratio of ≤ 200mmHg (Trampuz *et al*, 2003). The underlying pathology lies with there being an immune mediated complication (Suh *et al*, 2004), causing increased permeability at the level of the pulmonary capillaries. Interestingly, evidence is now pointing to the free parasite antigens that can persist after malaria therapy, resulting in a potential consistent stimulus for inflammatory

response (Marks *et al*, 2014). Hypoalbuminemia and volume overload may aggravate capillary leakage (Trampuz *et al*, 2003). The aim therefore is to avoid aggressive fluid resuscitation. The maintenance of intravascular volume at a level providing adequate systemic perfusion is the cornerstone to fluid resuscitation (Trampuz *et al*, 2003). Both respiratory distress and ARDS are markers of poor prognostic features in imported and endemic cases (Marks *et al*, 2014). The mortality associated with pulmonary edema can be as high as 80% (WHO, 2000).

1.10 LABORATORY FEATURES

1.10.1 Anemia and Thrombocytopenia

There have been many hematological changes noted in malaria. Severe anemia forms one of the WHO criteria of severity and has been associated with increased morbidity and mortality. Various degrees of anemia can be found ranging from slightly below normal; moderate (Hemoglobin [Hb] 5.1 to 10g/dl) and then severe life-threatening (Hb < 5g/dl). The mechanisms of the anemia in malaria may be multifactorial. Hemolysis and inappropriate marrow response largely contributes to anemia (DOH, 2010). Drug related causes may also play a role like artemesinin-induced haemolysis of parasitized red blood cells. Thrombocytopenia is not a criterion of severe malaria. It is however one of the most common laboratory findings. It is likely due to splenic sequestration and consumption (Marks *et al*, 2014). With regard to the entity of Odyssean malaria explained above, a patient with unexplained fever and thrombocytopenia must be tested for malaria even in the absence of a travel history (Frean *et al*, 2014). Usually thrombocytopenia on its own is not associated with bleeding (DOH, 2010). Additional factors like disseminated intravascular coagulopathy (DIC) causes an increased risk of significant bleeding.

1.10.2 Renal failure

Falciparum malaria is the most common species causing an acute kidney injury (AKI) (Marks *et al*, 2014). Many patients presenting with malaria have a history of vomiting and decreased appetite hence contributing to a state of dehydration. Often this pre-renal dysfunction is restored to normal with rehydration. Other mechanisms of renal injury documented in malaria include an immune mediated glomerulonephritis and an acute tubular necrosis (Marks *et al*, 2014). The risk of AKI is estimated to be as high as 25-50% in imported cases of malaria (Marks *et al*, 2014). While quinine doses require dose adjustment in AKI, artemisinin derivatives do not need adjustment (Marks *et al*, 2014). The outcome of renal dysfunction has been showed to be positive and full recovery ultimately (Marks *et al*, 2014).

1.10.3 Acidosis

Metabolic acidosis may be multi-factorial in severe malaria. Hypovolaemia, anemia and obstruction of microvascular circulation by sequestered parasites all contribute to reduced tissue perfusion. The clinical picture of respiratory distress is exacerbated by severe metabolic acidosis. The presence of metabolic acidosis is a severe malaria feature and heralds an associated increased mortality risk (WHO, 2000). Lactic acidosis can occur due to tissue anoxia and anaerobic glycolysis (WHO, 2000). The degree of hyperlactatemia is said to directly correlate with the degree of parasite microvascular sequestration rather than hypovolemia (Marks *et al*, 2014).

1.10.4 Hypoglycemia and hyperbilirubinemia

Hypoglycemia is commonly seen in pregnant patients and those with severe *falciparum* malaria. The pathophysiology may be related to impaired gluconeogenesis or increased glucose consumption by both parasite and host (Marks *et al*, 2014). Drug related hypoglycemia is also well documented especially with quinine.

The combination of thrombocytopenia and hyperbilirubinemia in a traveler has a positive predictive value of 95% (Trampuz *et al*, 2003).

1.10.5 Parasitemia

Quantitative parasitemia can be technician dependant and thereby lend itself to much variability. It can however indicate severity to an extent and its trend can also be used to monitor therapeutic response to anti-malarial therapy (Frean *et al*, 2014). Parasite density greater than 2% in non endemic areas is associated with severe malaria more often than not, however lower counts cannot exclude it (Marks *et al*, 2014). Peripheral smears may not accurately capture the actual parasite burden (DOH, 2010). Due to the sequestration of parasitized erythrocytes, the parasite density on peripheral smear may not be a true reflection of actual parasite burden (Marks *et al*, 2014). Therefore for these reasons, hyperparasitemia may not be a consistent finding with severe malaria. Both a higher total body parasite burden and sequestered parasites contribute to disease severity (Marks *et al*, 2014).

1.11 CRITICAL CARE MANAGEMENT OF SEVERE MALARIA

Patients with malaria may have rapid deterioration and turn for the worse (Marks *et al*, 2014). Severe malaria is a medical emergency and should be managed in an Intensive Care Unit (Santos *et al*, 2012). The admission of a patient to ICU is usually associated with a greater mortality (Marks *et al*, 2014). The most frequent factors validating ICU support are acute kidney injury (AKI), ARDS and cerebral malaria whether on its own or in combination

(Marks *et al*, 2014). Despite institution of appropriate therapy, the patient's clinical condition can rapidly deteriorate due to the systemic inflammatory response and multi-organ failure (Santos *et al*, 2012)). Continuous and close monitoring is essential to reduce the associated risk of mortality (Santos *et al*, 2012). Cardiac dysfunction although not well researched, has evidently been found to play a role in severe malaria as well (Marks *et al*, 2014). There have been studies documenting detectable levels of cardiac enzymes and pro-BNP in patients with severe malaria (Marks *et al*, 2014). It would appear that additional research is required in this territory to fill the gaps and understand its clinical relevance in these patients (Marks *et al*, 2014).

Fluid balance in malaria patients is of critical importance. The argument against rapid and liberal fluid expansion is that it may consequently follow with capillary leak and pulmonary and cerebral edema (Marks *et al*, 2014). Mortality rate has been shown to escalate in patients receiving fluid boluses as opposed to those on maintenance fluids only (Marks *et al*, 2014). Studies have pointed to a phenomenal increase in the risk of pulmonary edema in patients who were aggressively fluid resuscitated despite being euvolemic or even hypovolemic (Marks *et al*, 2014). Positive fluid balances meant worse outcomes. The bottom line is that one should exercise caution with fluid administration in these critically ill patients. Early inotropic support may be required for haemo-dynamic support rather than the risk of over-hydration and that of acute lung injury (Trampuz *et al*, 2003). Further, prompt institution of haemodialysis may reduce the risk of acute lung injury and probably even death (Trampuz *et al*, 2003). Mechanical ventilation may be required in patients with depressed level of consciousness or acute lung injury (Trampuz *et al*, 2003). The mortality rate can actually be elevated even with high standards and experienced ICU (Bruneel *et al*, 2010).

1.12 MORTALITY

Despite effective preventative and curative measures, sadly patients still die from malaria (Mehta *et al*, 2007). Advances in patient management have been ongoing however the mortality rate estimated for patients with severe malaria remains around 10% (Marks *et al*, 2014). A lack of clinical experience and recognition of severe malaria contributes to the increased mortality (Mehta *et al*, 2007). Data from studies done in the UK emphasize that this outcome is probably worse in areas with poor experience in managing severe malaria (Marks *et al*, 2014). Almost all severe malaria cases and associated mortality is due to *P falciparum* infection (Trampuz *et al*, 2003. Suh *et al*, 2004. Perovic *et al*, 2000. Marks *et al*, 2014). Mortality rate is estimated at 1 million deaths every year (Marks *et al*, 2014)). Sub-Saharan Africa hosts 90% of these deaths, unfortunately children bearing the major brunt (Suh *et al*, 2004). Most life threatening complications have been described in non-immune travelers returning from endemic areas (Trampuz *et al*, 2003). The mortality rate of severe imported malaria is estimated to be 10-15% (Bruneel *et al*, 2010). Risk factors for mortality should be identified promptly facilitating optimal treatment care. However there have been various studies that have identified different factors as contributing risks for severe malaria and death. The national target case fatality rate is 0.5%. A confidential study done identified many problems contributing to increased mortality rate at health care institutes in three provinces in South Africa (Mehta *et al*, 2007). The causes that were highlighted included delay in prompt access to health care, delayed admission of outpatients with severe malaria, inadequate inpatient care, inappropriate drug treatment and non- response or adverse drug effects to the anti-malarials (Mehta *et al*, 2007). Early institution of the appropriate therapy certainly reduces mortality and correlates with improved outcome.

1.13 TREATMENT OPTIONS

There are different anti-malarial drugs with differing modes of action against different species of the malaria parasite as well as targeting different stages of development in the life cycle of the disease. The treatment of *falciparum* malaria is a medical emergency requiring prompt institution of anti-malarial therapy (Suh *et al*, 2004). The emergence of resistant strains poses a problem on the management of infected patients. The development of initially chloroquine resistance and subsequently sulphadoxine-pyrimethamine (SP) prompted changes in South African treatment policies (DOH, 2010).

Combination therapy is advocated over monotherapy in an attempt to combat the issue of resistance (DOH, 2010). The improved treatment outcomes of artemisinin- based combination therapy (ACT) have most definitely been proved by its cost effectiveness (DOH, 2010).

Artemether-lumefantrine (Coartem) which is basically an artemisinin plus another anti-malarial agent is recommended by the WHO as first line therapy for uncomplicated malaria. Alternatively if this cannot be used then quinine with either doxycycline or clindamycin can be used. If the patient cannot tolerate oral therapy then intravenous treatment is indicated (Suh *et al*, 2004).

Severe malaria requires in-patient care in hospital. Intravenous quinine has been the mainstay of therapy (Marks *et al*, 2014). However in the recent years, artemisinin's have become more popular. Intravenous artesunate is now advocated over quinine and should be used as the preferred agent for treatment of severe malaria (Marks *et al*, 2014). WHO has endorsed intravenous artesunate as the standard of care over quinine specifically in severe malaria patients (WHO 2006). Firstly, it has a superior safety profile and secondly, it has mortality benefits (Visser Kift *et al*, 2011). Severe malaria carrying the high mortality rate that it does (10 – 50%) requires prompt and effective therapy to prevent death (Visser Kift *et al*, 2011).

Artesunate has shown to have a rapid parasite clearance and broad stage specificity (Visser Kift *et al*, 2011). Two major trials, the SEAQUAMAT and the AQUAMAT studies illustrated significant decrease in mortality rates with artesunate (Marks *et al*, 2014). Additionally, artesunate can also be safely administered and with better tolerability. Its effectiveness in the treatment of patients with complicated malaria has favored its use. Artesunate was approved for use by the Medicines Control Council (MCC) in June 2009. It was then launched in South Africa in January 2010 and was only available for use under Section 21 of the Medicines and Related Substances Act (Visser Kift *et al*, 2011). Of importance and concern is that partial resistance against artemisinin has also been documented in certain areas like Cambodia and Thailand (Marks *et al*, 2014).

If artesunate is unavailable, then intravenous quinine with either doxycycline or clindamycin is recommended. The cardiotoxic and hypoglycemic side effects of quinine however, demands strict monitoring thereof and administration through drug infusion pump (Trampuz *et al*, 2003).

Although the ACT's forms part of national policy in malaria-risk areas in the country, this therapy is not accessible in other areas (Weber *et al*, 2010). Hence this makes quinine the drug of choice. There should be no delay in using quinine while trying to access artesunate (Marks *et al*, 2014).

There may be a rise in parasitemia counts in the first 12 to 24 hours after commencing anti-malarial treatment. However a rise in parasitemia beyond 48 hours of starting anti-malarials may indicate treatment failure (Trampuz *et al*, 2003).

Severe malaria is a multisystem disorder and each organ complication requires specific management thereof. This makes the treatment approach of severe malaria a multi-faceted one. Apart from the anti-malarial drug therapy, fluid status, anemia and bleeding must be addressed. Seizures should be treated with anticonvulsants. Secondary bacterial infections are

not uncommon and may be masked by the malaria infection itself. These infections must be treated appropriately and promptly (Trampuz *et al*, 2003).

Some patients may require mechanical ventilation, hemodynamic or haemodialysis support. Exchange transfusion has been a treatment option in some patients with severe parasite infestation and severe malaria, however its benefit is a controversial one and there are very few trials supporting its effectiveness (Trampuz *et al*, 2003. Bruneel *et al*, 2010). There should be a low threshold for early advice from an expert or Infectious disease unit (Marks *et al*, 2014).

1.14 RATIONALE, AIMS AND OBJECTIVES FOR RESEARCH

1.14.1 Rationale for Research

This study aims to identify the profile of the patients treated for *P. falciparum* malaria and their clinical spectrum of disease at a university hospital in the heart of Gauteng, Helen Joseph Hospital (HJH).

It is hoped that the data results obtained from the study would provide insight to the burden of malaria faced by a public tertiary institute. It would also serve to improve our understanding of the presentation and complications of *P. falciparum* malaria in a non endemic area of South Africa.

1.14.2 Aims

To assess the profile of patients with *P. falciparum* malaria at Helen Joseph Hospital between January 2009 and December 2010.

1.14.3 Specific Objectives

1. To describe patient demographics (age, sex, and travel history).

2. To describe clinical spectrum, laboratory findings and outcome of patients with *P. falciparum* malaria.

3. Estimate the prevalence of HIV co-infection in those patients that are tested for HIV infection.

4. To identify predictors of mortality in these patients admitted to ICU.

CHAPTER 2 MATERIALS AND METHODS

2.1. Site of Study

The study was conducted at a tertiary academic institution, HJH, located in Gauteng. HJH provides healthcare to a large drainage area including mainly Randburg, Mayfair, Hilbrow and Florida. It is also a referral hospital for patients from two other secondary hospitals - Yusuf Dadoo and Leratong.

2.2. Study Design and Sampling

This is a retrospective study conducted on patients diagnosed with malaria at HJH over a 2 year period between January 2009 and December 2010.

The study sample consisted of 290 patients, both males and females over 14 years of age with smear and/or antigen positive for malaria. The diagnosis of malaria was confirmed with blood smears stained with Giemsa (thick and thin smears) and with the Rapid Antigen Test (RAT). A review was conducted of the malaria database processed at the National Health Laboratory Service (NHLS). All requested malaria tests including microscopy smear and RATs during the 2 year period were extracted. All results were printed with the patient name and hospital number. Those patients that were smear and/ or antigen positive results were included in the study. Patient files were subsequently retrieved from the records department in the hospital. Tests that were repeated on the same patient during that admission were not included. However, new separate admissions were included. The patient files which included an outpatient, casualty and inpatient notes were fully reviewed. Some files were unable to be traced possibly due to spelling errors of patient names and or incorrect hospital numbers. Outstanding blood results that were not found in the patients file were traced through the laboratory computer system at the hospital.

2.3. Data collection and diagnostic criteria for severe malaria

Each patient was allocated a patient code. A standardized data sheet (Appendix A) was used. Information was obtained on:

- Patient demographics: age; gender; place of citizenship; travel history and place.
- Admission date.

The clinical criteria were defined as per WHO criteria for *falciparum* malaria (WHO, 2000). Based on available clinical and laboratory parameters present during the admission, *P. falciparum* malaria was classified as complicated (severe) malaria or uncomplicated malaria. Severe *falciparum* malaria was diagnosed based on the presence of one or more criteria. HIV positivity and pregnant states are also considered high risk factors for complicated malaria and were therefore included as part of the criteria of severity.

Clinical parameters assessed for severe malaria included the presence of:

- Neurological features: this included firstly the presence of any impairment in the level of consciousness and secondly evidence of 2 or more seizures.
- Pyrexia: temperature $\geq 40\ ^{o}C$.
- Circulatory collapse: systolic blood pressure < 80mmHg or clinical features of hypovolaemic shock.
- Respiratory distress: included dyspnoea; respiratory rate >32/min.
- Pulmonary edema and ARDS (based on the assessment of the attending clinician).
- Spontaneous bleeding: included epistaxis; haemoptysis; hematemesis; melena and macroscopic haematuria.
- Splenomegaly: presence of a clinically palpable spleen was noted but this was not included in severity criteria.
- Pregnancy; estimated gestational age.

Laboratory parameters included:

- Bicarbonate level and blood pH; presence of acidosis if bicarbonate level < 15mmol/l and blood pH < 7.35.
- Glucose level; presence of hypoglycemia if glucose < 2.2mmol/l.
- Hemoglobin level; presence of severe anemia if Hb ≤ 5.0g/dl; a category of moderate anemia included Hb between 5.1 to 10g/dl.
- Platelets level; presence of thrombocytopenia if platelets < 137×10^9/l.
- Creatinine level; presence of severe renal failure if creatinine > 265µmol/l; a category of moderate renal failure included a creatinine level of 100 to 264.9 µmol/l.
- Smear microscopy indicating *Plasmodium* species; level of parasitemia; hyperparasitemia indicated by a parasitemia level of ≥4%.
- Rapid diagnostic antigen test
- Bilirubin level; presence of jaundice if bilirubin > 50µmol/l
- Lactate level; hyperlactatemia if lactate > 5mmol/l
- HIV testing

Final aspects that were assessed included:

- Presence of severe malaria; number of criteria.
- Management plan including inpatient or outpatient care; ICU admissions; treatment options; requirement of haemodialysis or mechanical ventilation.
- Outcome: patient discharged or demised.

Patient information was transferred from the data collection sheets onto an Excel spreadsheet.

2.4. Ethics approval and other considerations

Written permission to analyze patient files and blood results was granted by the CEO of the hospital. Consent was also granted by the NHLS based at the hospital.

The study was approved by the Postgraduate Committee, University of the Witwatersrand and the Committee for Research on Human Subjects (Appendix B) (medical) - Ethics approval number M110975.

2.5. Statistical Analysis

Data were entered into Microsoft Excel and Access which was then imported into Stata® (version 12.5, series 0414) for statistical analysis. Descriptive statistics were calculated. Description of categorical variables was illustrated with numbers and percentages and continuous variables with means and standard deviations (SD). Medians with inter-quartile range (IQR) were also used for variables with non parametric distribution. Associations between categorical values and patient outcomes were assessed with the Pearson's chi square tests. The Students t- test was used for continuous variables and comparison of independent groups. A P value < 0.05 was considered as statistically significant.

CHAPTER 3 RESULTS

In 2009 there were 87 patients reported to have had malaria and this increased to 203 cases in 2010. Of the total 290 patients who tested positive for malaria by RATs or smear tests over the 2 years, 171 files (study population) were retrieved from the records department at the hospital.

3.1. Demographic Information

3.1.1. Age and Gender Distribution

Figure 1 illustrates the age distribution of the study population. The median age was 28.5 years (IQR 23-36).

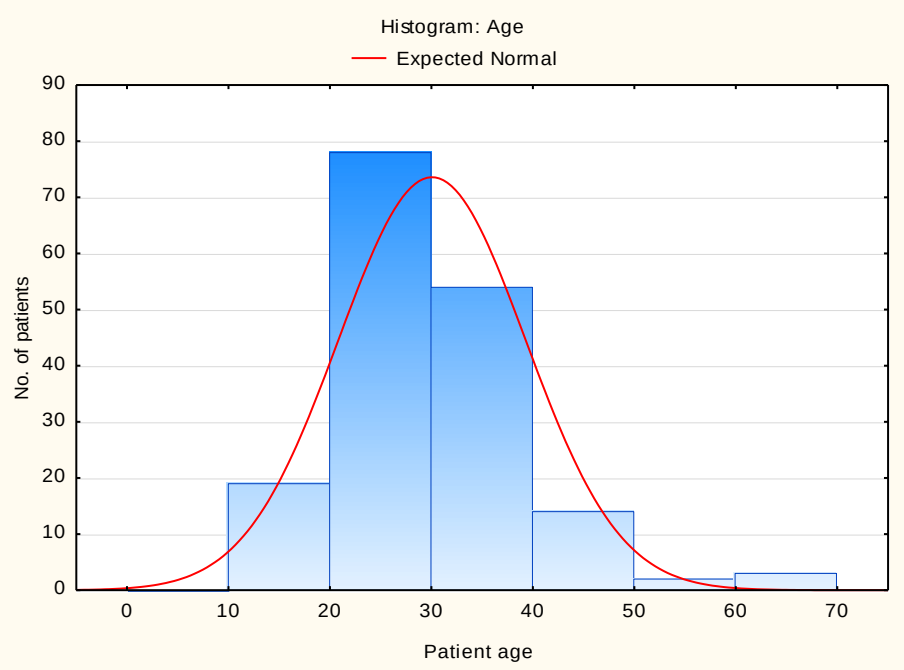


Figure 1 Age distribution of the study group

The gender distribution as demonstrated in Figure 2 showed that males had a higher risk of malaria infection than females. Males accounted for 85% (146/171) of the confirmed cases compared to 15% (25/171) in females over the 2 year period.

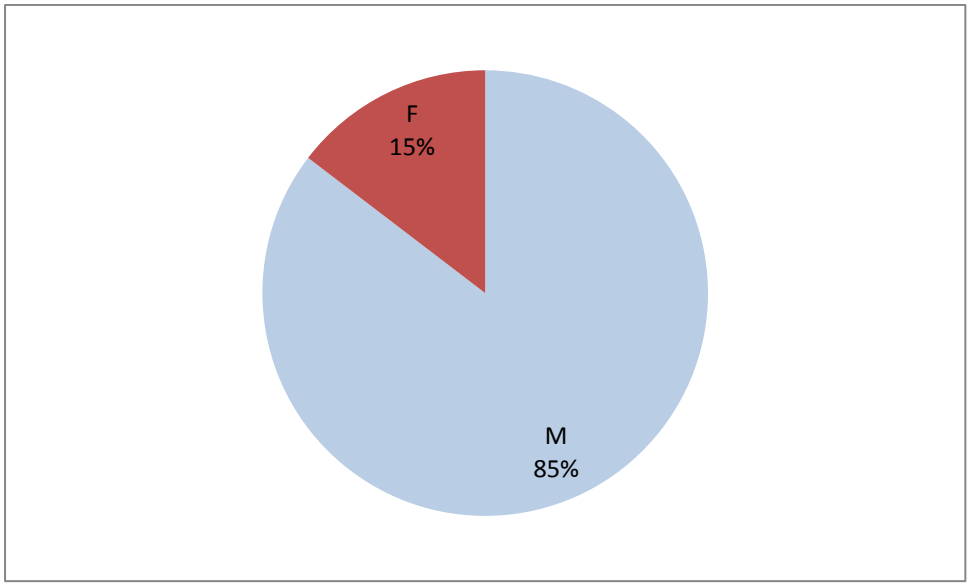


Figure 2 Gender distribution of the study population

3.1.2. Travel history and Place of Citizenship

3.1.2.1. Travel History

Of the 171 patients reviewed, 164 (96%) had a positive travel history documented. Of these patients who travelled, the exact place of travel was noted in 97% (159/164) patients. However in the remaining 5 (3%) patients among those that had travelled, the travel place information was unobtainable either due to language barrier or the patient having a decreased level of consciousness and not being able to answer questions appropriately.

The majority of malaria infections contracted was from outside South Africa (159/164 [96%]). Locally acquired infections were 6/164 (4%) of which travel to Limpopo contributed 3%.

The 4 main areas where malaria was acquired outside South Africa were Mozambique, Somalia, Zimbabwe, and Malawi.

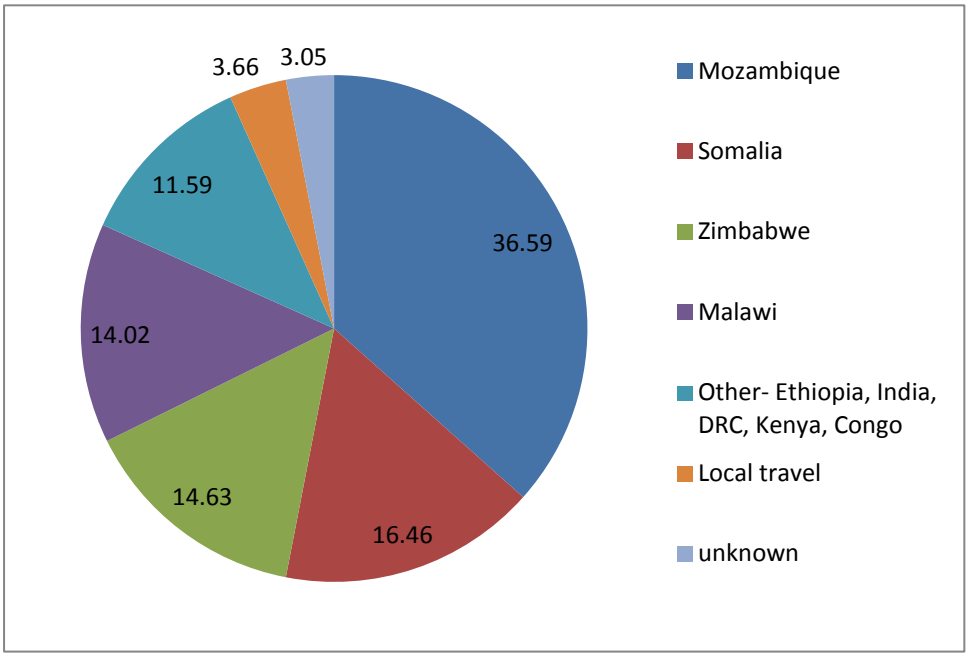


Figure 3 Percentage distribution of Travel Place

3.1.2.2. Place of citizenship

Approximately 55% (94/170) of the patients were non South African residents according to the demographic records charted in the file. The vast majority were Somali nationals 37/170 (22%), followed by Mozambique nationals with 16/170 (9%), Malawi citizens 16/170 (9%) and Zimbabwe citizens 11/170 (6%).

3.2. Seasonal Variation

Although malaria cases were detected every month of the year, transmission was distinctly seasonal. There was a range of 17 to 28 malaria cases diagnosed each month between December to May (summer and autumn seasons) in both years. There were decreased malaria infections rates between June to November.

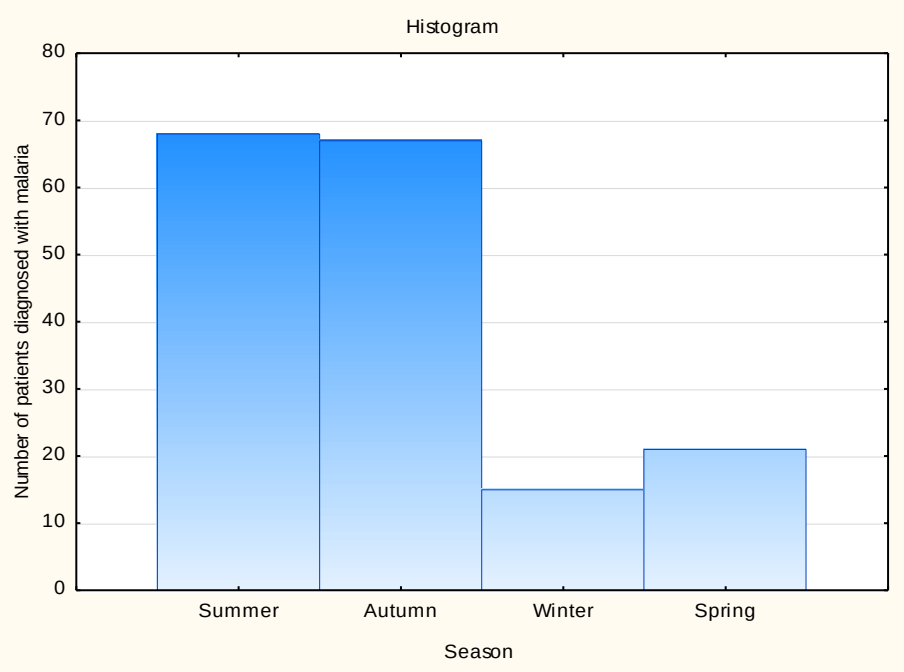


Figure 4 Seasonal Variation of patients with malaria

3.3. Clinical Spectrum of Disease

Table 1 presents the percentage distribution of patients diagnosed with malaria according to the clinical features. Pyrexia was the most common documented clinical feature found in 43% of patients. Impaired consciousness was the second most predominant clinical feature, found in 12% of patients. Less so common was seizures in 2%.

The presence of splenomegaly was sought for in 168 patients of whom 12% were found to have a clinically palpable spleen. This may be under estimated clinical finding as it is dependent on clinician clinical skill.

Respiratory distress occurred with lesser frequency (6%), of which ARDS was diagnosed in 50% of these patients.

Circulatory collapse was evident in 5% patients.

Table 1: Clinical features of patients admitted with malaria at HJH

Clinical features, n, %	**Yes**
Impaired Consciousness (restlessness, disorientation, confusion, coma)	21 (12%)
Seizures	3 (2%)
Pyrexia (Temperature ≥40^{0}C)	74 (43%)
Circulatory Collapse (Systolic Blood Pressure < 70mmHg)	9 (5%)
Respiratory Distress (tachypnoea, nasal flaring, dyspnoea)	10 (6%)
Acute Respiratory Distress Syndrome (ARDS)	5 (3%)
Spontaneous Bleeding	6 (4%)
Splenomegaly (by palpation)*	20 (12%)

n = 171 except * n = 168

3.4. Laboratory Features

3.4.1. Hematological and biochemical tests

Laboratory data is presented in Table 2. Thrombocytopenia was the most common laboratory finding, documented in almost 80% patients. In addition, anemia (Hb ≤ 10g/dl) was found in 22%. The vast majority of patients with anemia (almost 90%)) were categorized into an intermediate group of moderate anemia (Hb 5.1 to 10). Severe anemia (Hb ≤ 5g/dl) was identified in 10% of anemia group (2% of total population).

Renal failure according to WHO classification of severe malaria (creatinine > 265µmol/l), was present in almost 10%. However a quarter of the study population (26%) also had renal dysfunction with a creatinine values between 100 to 264.9µmol/l.

Acidosis was evident in 21% of the patients. Acidosis with associated renal failure was found in a third of these patients whilst two thirds were acidotic with no associated renal failure. Almost a third of the study population had biochemical jaundice. Hypoglycemia being increasingly recognized as a manifestation of severe malaria was found in only 2%.

3.4.2. Malaria Tests

Thick and thin smears were done on all 171 patients studied. Smear results revealed that 97% (165/171) had a positive smear for *P. falciparum*. Only one patient was found to have *P. ovale*. In 5 patients (3%) there were no parasites observed on smear microscopy.

The RAT was positive in 170 patients (99%). It was negative in the one patient found to have *P. ovale.*

Hyperparasitemia was evident in 22%. Parasite densities ranged from < 1% to 39%.

Table 2: Laboratory findings of patients admitted with malaria at HJH 2009/2010

Laboratory findings	Yes
Thrombocytopenia (Platelets < 137 x 10^9/L)	135/170 (79%)
Anemia **Hemoglobin > 10g/dl** **Hemoglobin < 10g/dl** **Hemoglobin 5.1-10g/dl (moderate anemia)** **Hemoglobin < 5.0g/dl (severe anemia)**	 132/170 (78%) 38/170 (22%) 34/170 (20%) 4/170 (2%)
Acidosis (pH < 7.35 / Bicarbonate < 15 mmol/l)	33/160 (21%)
Renal Failure (Creatinine > 265 µmol/l) **Creatinine < 100** **Creatinine 100 to 264.9** **Creatinine > 265**	 106/165 (62%) 44/165 (26%) 16/165 (10%)
Jaundice (Serum Bilirubin > 43umol/l)	37/134 (28%)
Hypoglycemia (Glucose < 2.2 mmol/l)	3/146 (2.06%)
Hyperlactatemia (Lactate > 5 mmol/l)	3/7 (43%)
Rapid Antigen Test (RAT)	170/171 (99%)
Hyperparasitemia (Parasitemia ≥ 4%)	38/170 (22%)
Pregnant	4/14 (29%)
HIV reactive	27/49 (55%)

3.5. Management

3.5.1. Inpatient versus outpatient management

A total of 11% (19/171) patients were managed as outpatients. Among the 152/171 (89%) inpatients, 12 patients (8%) required management in ICU.

3.5.2. Treatment options

Of the 171 files assessed, seven patients were found to have either inadequate or no treatment for malaria due to lack of follow up of outpatient results. There were three patients that had absconded from the hospital.

Among the remaining 161 patients, the most frequent treatment option was a combination of quinine and doxycycline given in 100 patients (62%). Quinine was used as monotherapy in 38/161 (24%). The combination of quinine and clindamycin was used in 14/161 (9%). Coartem was the drug of choice in 8/161 (5%). Only one patient had received artesunate therapy.

Data regarding loading dose of quinine was assessed in patients admitted to ICU. Of the 11 patients for whom data was available, 8 were given an intravenous loading dose of quinine. There were no patients that had exchange transfusion.

3.5.3. Outcome

3.5.3.1. Mechanical Ventilation

A total of 8 out of the 171 patients (5%) required mechanical ventilation.

3.5.3.2. Haemodialysis

There were 12 patients that required haemodialysis of which 11 had severe renal failure and one patient had moderate renal failure but had multiple other severe malaria criteria including ARDS.

3.5.3.3. Discharge versus death

Among the 152 inpatients, 137 (90%) were discharged from the hospital. There was 1 patient transferred to a down- referral hospital and 1 patient had refused further treatment. There were 3 patients that had absconded from the hospital.

The mortality rate during the study period was 5.8% (10/171).

3.5.3.4. Malaria deaths

There were 10 patients that demised during the study period due to malaria and its complications. All 10 patients had severe malaria fulfilling 3 or more criteria of severity. Females were found to have a higher mortality rate than males (12% and 5% respectively) however not statistically significant. There was one pregnant female that demised. There were no differences in age noted between those that demised and survivors.

Clinical features that were strongly associated amongst these fatalities included impaired consciousness, respiratory distress and ARDS. Impaired consciousness was found in 7 of the patients. Respiratory distress occurred in 8 patients, of which 5 were found to have ARDS. Half of these patients had pyrexia. Three patients were found to have had seizures. There were nine patients with circulatory collapse and six with spontaneous bleeding.

Laboratory tests in the demised group showed acidosis to be present in all 10 patients ($p < 0.005$). Mean bicarbonate levels were as low as 12 mmol/l in the demised group (19 mmol/l in the survival group).

Only one patient from the demised group had a creatinine level < 100 µmol/l. Severe renal failure was evident in 5 patients and moderate renal failure in 4. The mean creatinine was higher in the demised compared to the survivor group (309µmol/l and 112µmol/l respectively). Majority of the patients that demised had moderate anemia (70%). Only 1 patient had severe anemia. The mean Hb was lower amongst the patients in the demised group (8g/dl) compared to survivors (12g/dl).

All 10 patients had a hyper-parasitemia. The mean parasitemia among demised group was comparably higher at 23%. However the average amongst those discharged was 3%.

Jaundice was found in 70% (7/10) of demised group and also with a higher level of bilirubin than survivors (average bilirubin was 173µmol/l and 43µmol/l respectively). Hyperlactatemia was found in 50% (5/10). Only 1 patient was found to have hypoglycemia.

Among the 10 patients that died, 7 were admitted in ICU and all 7 required mechanical ventilation. Haemodialysis was initiated in 5 patients. Data on quinine loading which was available for 6 of the 10 patients that demised showed that 4 had received the loading dose. Due to the small number of the demised group, many of the comparisons above were not found to be statistically significant.

3.6. Gender differences and outcome

The data analysis illustrated that females with *falciparum* malaria had a higher risk of severe malaria and its complications. There was one female that was infected with *P ovale* species.

Table 3: Differences in gender and outcome

	Females	Males
Total malaria cases	25/171 (15%)	146/171 (85%)
Severe malaria	19/25 (76%)	66/146 (45%) $p < 0.005$
≥3 Severe malaria criteria	11/19 (58%)	22/66 (33%)
ICU admission	5/25 (20%)	7/146 (5%) $p < 0.05$
Impaired consciousness	6/25 (24%)	15/146 (10%)
Hyper-parasitemia	11/24 (46%)	27/146 (19%) $p < 0.005$
Anemia	15/25 (60%)	23/145 (16%) $p < 0.0005$
Acidosis	9/22 (41%)	24/138 (17%) $p < 0.05$
Renal failure	5/24 (21%)	11/141 (8%) $p < 0.05$
Haemodialysis required	4/25 (16%)	8/141 (6%)
Case fatalities	3/25 (12%)	7/141 (5%)

3.7. Malaria and pregnancy

Among the 25 females of child bearing age, only 14 females were tested for pregnancy. Of the 14 females tested, 4 were found to be pregnant. Data on whether they were primigravidae was unavailable. All of them were in their first trimester. One pregnant female was found to have a glucose level of 2.5mmol/l, however this did not fulfill WHO criteria of hypoglycemia (glucose < 2.2mmol/l). Three of the four pregnant patients had moderate anemia but none fulfilling a diagnosis of severe anemia. The mean parasitemia among the pregnant women was higher than non-pregnant (10% and 5% respectively). Two of the four patients had severe malaria with 3 or more WHO criteria identified. There was one pregnant female who demised. She had fulfilled 4 severe malaria criteria. She was found to be HIV reactive and also required ventilation in ICU.

3.8. Malaria and HIV

Of the 49 patients tested for HIV, more than half (55%) tested positive. A comparison between the HIV reactive and non reactive group showed that impaired consciousness was doubled in the HIV group. Acidosis was more prevalent in the HIV positive group (40% and 25% respectively) however statistically this was not significant. Anemia was also more common in the co-infected group (15/27 [56%] versus 6/22 [27%] in the HIV negative group [$p < 0.005$]). Among the HIV positive group, 27% (7/26) had severe renal failure comparing with 9% (2/22) of the negative group (statistically not significant). Hence a larger proportion of patients who were co-infected were dialyzed (22% versus 14%). Hyper-parasitemia however was higher among the HIV negative than positive patients (32% [7/22] versus 22% [6/27]).

Patients fulfilling ≥ 3 criteria was slightly higher in the HIV group (44%) compared to the negative group (38%). The death rate in the HIV positive and negative groups were similar (11% versus 9%).

3.9. Complicated versus uncomplicated malaria

The number of patients found with complicated and uncomplicated malaria was almost equal. There were 85/171 with complicated malaria and 86 with uncomplicated. There were no significant differences in age and gender among patients with complicated and uncomplicated malaria.

3.10. ICU Admissions

3.10.1. Clinical findings

There were 12 patients admitted to the ICU. There were 7 males and 5 females (one pregnant). Of the twelve patients, eight had pyrexia. Six of the twelve patients had respiratory distress ($p<0.005$), with four of them complicating with ARDS. An impaired level of consciousness was more prevalent in ICU group (9/12) than non ICU patients ($p<0.005$). Less than two patients were found to have either circulatory collapse; seizures; abnormal bleeding or hypoglycemia. There were seven patients that had moderate anemia, however none were found to have severe anemia.

The presence of acidosis was a strong risk factor for ICU admission. Acidosis was present in 11 of the 12 patients ($p<0.005$).

Among the 12 patients there were 9 patients that had renal failure and 6 of which were severe. Only 5 patients were tested for hyperlactatemia, 2 of which were high.

Hyperparasitemia was found in 11 of the 12 patients. The mean parasitemia density was 16%.

All 12 patients were infected with *P falciparum* species. Almost 80% of these patients had jaundice. Only 7 patients were tested for HIV of which 5 were found to be positive.

All 12 patients had severe malaria with a range of 4 to 10 criteria in each patient.

With regard to administration of quinine loading dose the data for 1 patient was missing. However of the remaining 11 patients, 8 were given a loading dose of quinine.

There were 8 patients that required mechanical ventilation and 7 patients that had been haemodialysed.

Among the twelve patients admitted to ICU, seven demised (almost a 60% mortality rate).

3.10.2. Predictors of mortality in ICU

Table 4: Comparison of patients discharged and those that demised in ICU

	Discharged n, %	**Demised n, %**
Impaired LOC	5/5 (100)	4/7 (57)
Seizures	1/5 (20)	1/7 (14)
Pyrexia	4/5 (80)	4/7 (57)
Circulatory collapse	0/5	2/7 (29)
Respiratory distress	1/5 (20)	5/7 (71)
ARDS	0/5	4/7 (57)
Abnormal bleeding	1/7 (14)	1/7 (14)
Acidosis	4/5 (80)	7/7 (100)
Anemia	2/5 (40)	5/7 (71)
Severe renal failure	2/5 (40)	3/7 (43)
Hyperparasitemia	4/5 (80)	7/7 (100)
Jaundice	5/5 (100)	4/6 (67)
Hyperlactatemia	0/2	2/3 (67)
HIV	2/2 (100)	3/5 (60)
Quinine loading dose	4/5 (80)	4/6 (67)
Haemodialysed	3/5 (60)	4/7 (57)
Ventilated	1/5 (20)	7/7 (100)

Analysis of patients that demised and those that were discharged from ICU showed that age did not affect the outcome. The demised group had a higher risk of circulatory collapse. The mean systolic blood pressure was lower among the group that demised compared to ICU survivors (80mmHg and 99mmHg respectively). There was also a strong association of the demised patients having features of respiratory distress and ARDS. Further, all the patients from the demised group required mechanical ventilation.

The demised group of patients had a higher risk of anemia, jaundice and acidosis. The mean creatinine was also found to be higher in the demised group (295µmol/l versus 250µmol/l). The mean parasitemia level was substantially higher in patients who demised than those discharged (25% and 7% respectively).

The loading dose of quinine was given in 4/5 ICU survivor group and 4/7 ICU demised group.

Due to the small numbers assessed in this group, the results were not found to be statistically significant except for the need for mechanical ventilation in the demised group ($p < 0.005$).

CHAPTER 4 DISCUSSION

Summary of the Main Findings

The escalation in the number of malaria cases reported at HJH from 2009 to 2010 showed a steep annual increase in the incidence of infection. Malaria notifications in the country have been shown to decrease substantially between 2000 and 2010 (Moonasar *et al*, 2011). This however may be controversial. A large study conducted in Gauteng province from 2005 to 2006 illustrated that the malaria incidence was actually higher than what was reported to the DOH (Weber *et al*, 2010). This increase may be related to improved reporting (Weber *et al*, 2010). More likely, it may probably be explained by the escalation of imported malaria and poor malaria chemoprophylaxis. Studies conducted in Soweto and Cape Town, showed significant numbers of imported malaria despite the area being non endemic (Cohen *et al*, 2005. Opie *et al*, 2014).

The median age of the study population was 28.5 years which were consistent with other studies done in SA (Opie *et al*, 2014. Ngomane *et al*, 2012. Weber *et al*, 2010). An alarming 85% of patients were males compatible with the findings of other studies across our country (Opie *et al*, 2014. Ngomane *et al*, 2012). This is probably due to them searching for employment.

A positive travel history was documented in 96% of the population. Interestingly, more than 90% of malaria infections contracted was from neighboring countries outside South Africa. The 4 most popular areas of acquisition were Mozambique, Somalia, Zimbabwe, and Malawi. This was similar to a large study done across Gauteng's public and private hospitals, where almost 83% of malaria was likely to be acquired from Mozambique (Weber *et al*, 2010). The study done on malaria at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto

also showed the majority of infections were acquired from neighboring countries, mostly Mozambique (Perovic *et al*, 2000).

More than half of the patients were non South African residents according to the demographic records charted in the file. Some patients were reported to be SA citizens on their demographic form, however it was found that there were language barriers and they spoke a foreign language. Hence this is probably an under estimated number of foreign residents. The vast majority of non South Africans were Somali nationals, followed by Mozambique, Malawi and Zimbabwe nationals. A study conducted in Cape Town found >90% of their study population to be foreign nationals, 48% being from Somalia (Opie *et al*, 2014). One could extrapolate that given the dominant profile in our patients which encased a young male foreigner, employment is likely is driving force in this regard. It emphasizes the burden of imported malaria faced by the healthcare system both in Gauteng and South Africa as a whole. Gauteng, a non-endemic malaria area and the economic hub of the country, bears almost 20% of the country's malaria burden specifically as imported malaria (Frean *et al*, 2014).

There was no history of any travel in 4% of the patients. They were diagnosed with malaria without having travelled outside Johannesburg. Neither was there any history of mechanical transmission like blood transfusion. This may have been cases of odyssean malaria. A study done in Gauteng identified a total number of forty six patients with odyssean malaria over an eight year period (Frean *et al*, 2014). Most of these patients were initially mis-diagnosed as influenza, viral hepatitis and septicemia. Malaria transmission rates were clearly seasonal with summer and autumn being the peak seasons. These peaks are probably related to both favorable climatic conditions and increased number of people travelling during these periods. January and February had the highest patient numbers and one may assume that this may have been related to more people travelling through endemic areas outside the country and

returning back after the festive period. Research studies have shown a correlation with people traveling to endemic areas to visit family having a higher risk of malaria than those traveling for 'other' reasons (Marks *et al*, 2014). This illustrates that intensive efforts from a prevention point is probably lacking.

A delay in the diagnosis of malaria exponentially impacts disease severity and predicts outcome (Frean *et al*, 2014). The study conducted at the CHBAH revealed an average delay of 1 week in patients seeking help (Perovic *et al*, 2000). Further, there may be a low index of suspicion for the diagnosis of malaria infection in areas where malaria is non-endemic and not frequently seen. This may directly contribute to patient morbidity and mortality (Frean *et al*, 2014).

Thrombocytopenia being the most common laboratory and hematological finding documented here has also been shown in other studies (Perovic *et al*, 2000). Malaria therefore remains an important differential diagnosis in a patient with thrombocytopenia irrespective of an existent travel history or not (Frean *et al*, 2014).

An important cause of morbidity and mortality in patients with *falciparum* malaria is anemia. Of note the WHO guidelines emphasizes severe anemia with an Hb less than 5g/dl. This however was only illustrated in a menial 2% of the total amount of study group. The vast majority (20%) of patients were actually classified with moderate anemia. Further, repeated seizures and hypoglycemia although included in the study as part of the WHO guidelines was actually quite infrequently seen. This finding was also demonstrated in other studies outside Africa as well, thereby questioning the prognostic value of those specific criteria which may be more relevant in pediatric population (Bruneel *et al*, 2010. Sagaki *et al*, 2013).

Almost 10% of patients had severe acute renal failure. This degree of renal failure was reflected in other studies done in South Africa (Opie *et al*, 2014). Again, a substantial number of patients (25%), although could not be classified as having severe renal failure according

WHO criteria, had moderate renal failure. The vast majority of patients with renal dysfunction improved with rehydration and anti-malarial therapy. There were 12 patients that required renal replacement therapy (RRT) and more than a third of them were in ICU. High levels of creatinine may be associated with increased mortality. Mortality in these patients may be as high as 75% without dialysis and reduced to 26% with it (Bruneel *et al*, 2003). Other studies done in South Africa have also found *P. falciparum* malaria to be the most common malaria parasite (Cohen *et al*, 2005. Perovic *et al*, 2000). Further, the symptoms caused by the other species like *P. vivax*, *P. malariae* and *P. ovale* are usually milder than that of *P. falciparum* (Cohen *et al*, 2005. Suh *et al*, 2004).

Females had a higher risk of severe malaria and its complications ($p < 0.005$).

Pregnant females are more susceptible to *falciparum* malaria than non pregnant females (McLean *et al*, 2015). Malaria infection in pregnant women and post partum period is well described. In this study pregnant females had twice the average parasitemia when compared to the non pregnant group. Higher parasite densities in pregnant women infected with the *falciparum* species has been documented (McLean *et al*, 2015). One of the four pregnant women in the study demised.

Malaria and HIV has been reported to interact synergistically with each other (Pereira *et al*, 2015). More than half of our patients tested for HIV were actually co-infected with malaria and HIV. This co-infection rate was found higher than the study done at the CHBAH where 33% of patients were co-infected with HIV (Cohen *et al*, 2005). Patients from our cohort co-infected with HIV had a higher risk of impaired consciousness, anemia, acidosis and renal failure. HIV positive patients had a slightly higher risk of severe malaria criteria. The mortality risk however was found to be similar in the positive and negative groups. The study done in Soweto illustrated that HIV positive patients had a tripled risk of severe malaria. There was an increased prevalence of severe malaria in patients with CD4 counts less than

200 x 10^6 cells/l. Secondly they also showed that HIV positive patients had a higher risk of anemia, acidosis and renal failure (Cohen *et al*, 2005). Unfortunately patients co-infected have been shown to have a greater delay in malaria diagnosis compared to that of HIV negative patients (Cohen *et al*, 2005). The management of a co-infected patient requires vigilance, close monitoring and a low threshold for escalation into a high-care or ICU. Similar to other studies outside Africa, there were no significant differences in age among patients with complicated and uncomplicated malaria (Sagaki *et al*, 2013). The study done in Thailand found that the presence of clinical jaundice with any other vital organ dysfunction was the most common complication noted (Sagaki *et al*, 2013).

Patients with severe *falciparum* malaria should be managed in a high care or ICU. In studies conducted outside Africa, patients with both severe and less severe malaria were admitted into ICU (Bruneel *et al*, 2003). Due to limited resources in our country however, this is unfortunately not feasible. Even patients with severe *falciparum* malaria may sadly not reach ICU due to resource constraints and will remain in a general medical ward. ICU bed availability was the predominant determining factor for ICU admission. Consequently, only 14% of patients with severe malaria had the benefit of ICU care. There were certain parameters that one could associate as predictors for requiring more intensive care and monitoring. These included the presence of impaired level of consciousness, respiratory distress, ARDS, moderate anemia, acidosis, renal failure, jaundice and hyper-parasitemia ($p<0.005$). All 12 patients that were admitted to ICU had a minimum of 4 criteria. A previous study outside Africa showed that patients with severe *falciparum* malaria having ≥ 3 criteria had almost an 80% sensitivity and specificity for requiring ICU admission (Sagaki *et al*, 2013).

In our study admission into ICU inadvertently escalated ones mortality risk due to their critical state at that point. We found four predictors of mortality in the ICU category of

patients. These included severe hypotension, respiratory distress and/or ARDS and lastly those patients requiring mechanical ventilation. The presence of shock, acidosis, coma and pulmonary edema were the main associated features with mortality that was found in the study in France (Bruneel *et al*, 2003).

The patients that were admitted to ICU were in a profoundly critical state. Consequently and naturally their risk of mortality as expected accelerated.

The vast majority of patients (85%) were treated with quinine either as monotherapy or in combination with another agent. A quarter of the patients were treated inadequately with quinine as monotherapy. The loading dose of quinine failed to change the outcome in the demised group when compared to survivors.

Only 5% of patients were treated with coartem despite its convenient dosing and better side effect profile. This may have been related to drug availability.

The availability of artesunate has been restricted in numerous countries including the UK and South Africa (Marks *et al*, 2014). During the study period only one patient was treated with intravenous artesunate. The reason for this is likely that artesunate was only approved for use by the Medicines Control Council (MCC) in June 2009. Further, due to the nature of the approval process, informed consent was necessary. This may have posed a potential challenge bearing in mind that the majority of patients were foreign nationals in the study and were unable to comprehend or communicate in English.

Amongst the ten patients that succumbed to death a minimum of 3 or more criteria of severity were present. The clinical features that were strongly associated with these fatalities were impaired consciousness, respiratory distress, and ARDS. Laboratory complications associated with death included metabolic acidosis, renal failure, hyper-lactatemia and jaundice. Despite the technician based variability identified with parasite counts across different institutes,

hyperparasitemia was undoubtedly elevated in every single patient that succumbed to death from malaria.

Severe imported malaria even in the hands of the highly skilled and expert institute nonetheless carries a significant mortality rate (Bruneel *et al*, 2010). The case fatality rate in returning travelers with severe *falciparum* malaria may exceed 20%, despite being managed in an ICU (Trampuz *et al*, 2003). The case fatality rate during the study period was 5.8%. This is however higher than the national target of 0.5%. It may be attributed to the fact that the study was conducted at a tertiary and referral institute and hence the burden of complicated malaria was higher. Time to presentation to health care facility may have played a role too. Studies have demonstrated that referral centers were more likely to see severe complicated malaria secondary to delayed diagnosis and ineffective therapy (Sagaki *et al*, 2013). A study done outside South Africa evidently found that if the first presentation was to a general practitioner rather than a hospital, the risks of severe malaria escalated immediately by 40% (Seringe *et al*, 2011). Finally, it must also be emphasized that not all patients with severe complicated malaria that are deserving of ICU management, actually succeed to getting to ICU. Living in a country with resource constraints and managing these critically ill patients in a general ward creates a battle against the odds of survival.

LIMITATIONS

Due to it being a retrospective study, retrieving patient files from records department actually was a difficult task. One has to rely on the doctor's interpretation and diagnostic skills. Definitions become difficult to apply. Further, accurate interpretation of handwriting was sometimes a problem to decipher.

CONCLUSION

A striking correlation exists between malaria and poor socio-economic areas. Malaria carries with it a huge burden both globally and locally. Unprecedented achievement has been attained in malaria control globally and also in our country. Imported malaria however remains a huge challenge especially in non endemic industrialized regions like Gauteng. The escalation of immigrant workers travelling through endemic regions into Gauteng in the face of employment has been a critical point (Weber *et al*, 2010). South Africa was the main overall destination country of thousands of new asylum seekers between 2006 and 2011 (Opie *et al*, 2014). Presentation to a health institute frequently follows recent travel of foreign migrants. This places an undue pressure on the financial burden of the health system of the country. Imported malaria contributed to an over-whelming 96% of the population studied. The predominance of young male foreigners probably reflects desperate individuals likely in search of employment or even a place of refuge. The crucial point is the fact that many of these patients have failed to take the appropriate chemoprophylaxis (Bruneel *et al*, 2003). Despite these patients travelling so frequently to endemic areas and back, there is a lack of insight on malaria and its complications. Malaria is preventable and curable. There should certainly be room for improvement from a prevention point. This may entail pre-travel assessments and education (Suh *et al*, 2004). The non specific nature of the disease can result in diversion of clinicians from the diagnosis. A diagnosis of malaria must be entertained as a differential diagnosis in any patient with imported fever (Marks *et al*, 2014). A negative travel history however should never negate the possibility of the diagnosis. The entity of odyssean malaria should be considered.

The ultimate goal is aimed at a reduction in morbidity and mortality. Failure to recognize and initiate prompt treatment directly impacts on morbidity and mortality (Trampuz *et al*, 2003. Perovic et al, 2000).

According to a previous study, patients with severe malaria who meet ≥ 5 WHO criteria may have a mortality rate of 50% (Sagaki *et al*, 2013). Not all the WHO criteria may be relevant when assessing an adult patient with imported malaria (Bruneel *et al*, 2003). The identification of clinical predictors of severity for *falciparum* malaria through various studies across the world has illustrated much disparity (Sagaki *et al*, 2013). Major complications associated with severe malaria can develop rapidly. Once again, this highlights that early diagnosis and institution of appropriate therapy may well improve patient outcome (Sagaki *et al*, 2013). The critical care management in patients with severe malaria is an important aspect demanding meticulous and multi-disciplinary care (Marks *et al*, 2014). Understanding the concepts of fluid balance and requirements for mechanical ventilation and hemo-dialysis should be well known to the attending clinician. Over the decades the mortality rate associated with malaria has clearly delineated the strengths and weakness that exists between the health care system and the patient (Mehta *et al*, 2007).

The importance of exercising pharmaco-vigilance cannot be over-emphasized.

Screening for HIV and malaria co-infection is crucial. The interaction between malaria and HIV infections can constitute a challenge. The association between low CD4 T cell counts and severe malaria is well described (Cohen *et al*, 2005). Further, progression of HIV infection to Acquired Immune Deficiency Syndrome (AIDS) can occur with co-infected patients (Pereira *et al*, 2015). All patients returning from malaria endemic area should be screened for malaria and HIV (Pereira *et al*, 2015).

Considerable progress has been made in malaria prevention and management however there are still significant gaps that exist specifically in resources. More emphasis on resource

allocation is fundamental in the strategy of prevention, control and treatment. Exceptional surveillance measures are vital for swift detection and therapy. We need to be collaborating with health care workers across all levels to strengthen our health system. Every effort should be made to pursue streamlined training for health care providers, starting at a community level and filtering up to tertiary hospitals and Intensive Care Units. There should be improved awareness and education. The magnitude of the burden of imported malaria both locally and abroad is a crucial problem at hand. There should be more focus on intensifying regional cross borders movements with the vision of reducing imported malaria infection. One needs to embrace solutions that emulate the actual mobility of population presently. Going forward, research specifically in non endemic countries is lacking. There should be proposed research studies aimed and focusing on anti-malarial drug resistance, new anti-malarial agents and malaria vaccines. Medicine is always evolving and improved data on all these factors will be a platform for addressing gaps and solutions thereof.

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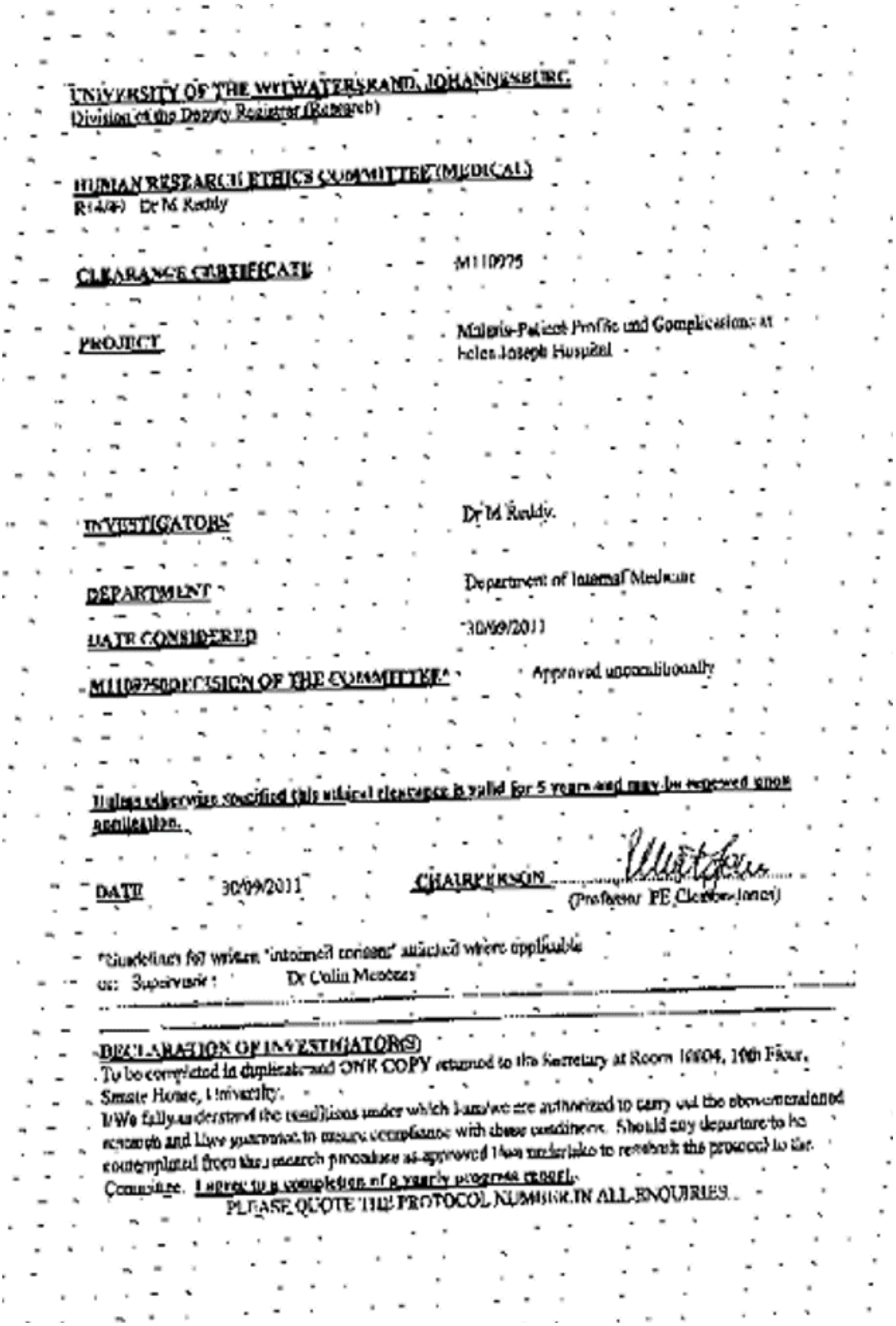
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APPENDIX 1



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/96 Dr M Reddy

CLEARANCE CERTIFICATE — M110975

PROJECT — Malaria-Patient Profile and Complications at Helen Joseph Hospital

INVESTIGATORS — Dr M Reddy

DEPARTMENT — Department of Internal Medicine

DATE CONSIDERED — 30/09/2011

M110975 DECISION OF THE COMMITTEE* — Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/09/2011 CHAIRPERSON (Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor: Dr Colin Menezes

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the proposal to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2

Data Collection Form:

Malaria - Profile of Patients and Complications at Helen Joseph Hospital

Patient Demographics:

1. Patient code …….
2. Age: ……years
3. Sex: Male…… Female……

Travel history (last 12 months)

Yes ……..Where (……..) No……..

Place of Residence: ……

Admission month:

Clinical:

1. Impaired Consciousness: Yes ……. No……..
2. Seizures: Yes …… No …….
3. Pyrexia: Yes …… No …….
4. Circulatory collapse: Yes ….. No ……Systolic BP ……...
5. Respiratory distress: Yes …… No ……
6. Pulmonary edema: Yes ….. No ……
7. Abnormal bleeding: Yes …… No……
8. Pregnant: Yes …… (Gestation ….) No……
9. Splenomegaly: Yes ……No……

Laboratory

Indicators	Normal Values	Criteria	Yes (Actual Values)	No (Actual Values)	Not found
Acidosis	7.33 – 7.44	PH < 7.35			
	18 – 29mmol/L	Bicarbonate < 15			
Hypoglycemia	4.2 – 7.1	Glucose < 2.2			
Severe Anemia	14.3 – 18.3g/dl	HB < 5.0			
Thrombocytopenia	137 – 373x10^9/l	Platelets < 137			
Renal Failure	Creatinine 64- 104 ml/min/1.73m^2	Creatinine > 265			
Plasmodium species					
Parasitemia	N/A	< 4%			
		>/= 4%			
Rapid Diagnostic Antigen Test	N/A	N/A			
Jaundice	0 – 21 umol/l	Total bilirubin > 50			
Lactate	0.5 2.2 mmol/l	Lactate > 5			

VCT offered: Yes …..(Positive…. Negative …..) Not tested …..

Severe Malaria: Yes ……. (Number of criteria …….) No ……

Management Plan:

Outpatient ……. Ward patient ……. ICU …….

Treatment:

1. Co-artem …….

2. Quinine ……..
3. Quinine + Doxycycline …….
4. Quinine + Clindamycin ……..
5. Artesunate ……

Outcome: Discharged …… Demised ……..