CLINICAL ASPECTS AND OUTCOMES OF PATIENTS WITH MALARIA AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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DECLARATION

I, Darren Joshua Fox declare that this Dissertation is my own, unaided work. It is being submitted for the degree of Master of Medicine (in the submissible format with my protocol and extended literature review) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Dr Darren Joshua Fox (Electronic signature)

21st Day of April, 2020 in Johannesburg

Dedication

To my parents, Barry and Debbie and my sisters, Tamaryn and Lauren, who have always been there to support me.

Abstract

***Background*.** South Africa (SA) is currently experiencing a significant increase in malaria cases despite having shifted focus from malaria control towards malaria elimination. The clinical features of malaria are non-specific, but the relative frequency on presentation are not well described. There are important interactions between human immunodeficiency virus (HIV) infection and malaria, including a high mortality associated with both diseases in Sub-Saharan Africa.

***Aim*.** To describe the population characteristics, clinical and biochemical features of severity, the proportion of participants with HIV infection and the management and outcomes of participants with malaria at Chris Hani Baragwanath Academic Hospital (CHBAH).

***Methods*.** A prospective observational study was conducted whereby patients with a confirmed laboratory diagnosis of malaria were identified, approached and consented for study inclusion over the time period from January 2017 to January 2018. Clinical and biochemical data were collected at the time of consent and later analysed.

***Results*.** The mean age was 35.7 years of age (±SD=12.98) and 72 (70.6%) of the 102 participants were male. Peak admissions for malaria were in January where 58 (56.9%) participants were admitted during January 2017/2018. All malaria cases were imported with 75% associated with travel to Mozambique. The majority of participants (62%) were expatriates living in SA. The most common presenting symptoms were chills (95%), weakness (94%,), fever (91%), headache (90%) and lethargy (88%). The most common clinical signs were dehydration (31%), prostration (20%) and jaundice (14%). The number of participants with severe malaria was 40

(39.2%), with prostration as the most common feature of severity (20%). ICU admission occurred in 8 participants (7.8%) and 6 participants (5.9%) required haemodialysis. The median duration of stay was 5 days (IQR=3). HIV status was known in 83 (81.4%) participants, of these 32 (38.6%) were found to be HIV positive. Malaria prophylaxis was taken by only 8 participants. The all-cause mortality rate was 4.9%, and mortality attributable to malaria was 3.9% .

***Conclusion*.** This study showed a high proportion of complicated malaria cases, particularly in January. The majority of participants were young expatriate males with a travel history to southern Mozambique or Limpopo with very few taking malaria prophylaxis. Most clinical signs and symptoms were constitutional and non-specific. A large number of participants were found to be HIV positive and most were newly diagnosed. The mortality was high at around five times the national average, and was possibly an underestimate.

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ABBREVIATIONS

AOR	Adjusted odds ratio
ART	Anti-retroviral treatment
CD4	Cluster of differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
HRP2	Histidine-rich protein 2
ICU	Intensive care unit
IQR	Interquartile range
LSDI	Lubombo Spatial Development Initiative
MIS	Malaria Information System
MOSWASA	Mozambique Swaziland South Africa Agreement
NHLS	National Health Laboratory Services
NICD	National Institute for Communicable Diseases
OR	Odds ratio
RDTs	Rapid diagnostic tests
RNA	Ribonucleic acid
SA	South Africa
SD	Standard deviation
VCT	Voluntary testing and counselling
VFRs	Visiting friends and relatives
WHO	World Health Organisation

CHAPTER 1: Protocol with extended literature review

1.1 Introduction/Background

1.1.1 Global perspective

Malaria continues to impose a significant burden of disease throughout the world with Sub-Saharan Africa being disproportionately affected (1). According to the 2017 World Health Organisation (WHO) report on malaria, there were 216 million cases identified in 2016 (95% confidence interval (CI): 196–263 million) (1). The majority (80%) of these cases occurred in Sub-Saharan Africa (1). Malaria is associated with a significant number of deaths worldwide, with 445 000 deaths reported by the WHO in 2016 (1). The majority of these deaths (80%) occurred in Sub-Saharan Africa (1).

1.1.2 Malaria epidemiology in South Africa

South Africa (SA) is currently listed as one of the 21 countries identified by the WHO in 2016 for potential malaria elimination by the year 2020 (1). The number of malaria cases in SA has been on the rise in recent years (2). There were 22 517 malaria cases reported in 2018, an increase from the 4 323 cases reported in 2017 (2). This increase is large enough to constitute an epidemic (2). More than a third of these malaria cases were imported from neighbouring countries (2). South Africa has thus been labelled as 'Off Track' by the WHO due to current regional epidemics (3).

Malaria is considered endemic in three provinces in SA, namely Limpopo, Mpumalanga and north-eastern areas of KwaZulu-Natal (4,5). Approximately ten percent of the South African population are living in areas that are high risk for malaria transmission (6). Multifaceted malaria control policies and practices put in place during the early 2000's led to a marked reduction in the number of malaria cases and deaths during that period (4,5). These interventions included a tri-pronged approach of vector control strategies (indoor residual spraying), improving diagnostic modalities and artemisinin-based combination therapy (4,5). Data obtained from the Malaria Information System (MIS) and reported by Maharaj *et al* (4) showed a marked decrease in the number of malaria cases and malaria mortality from 2000 to 2010. Over this ten year period, malaria cases decreased from 64 622 to 8066 (4). Mortality attributable to malaria also decreased from 459 to 87 deaths (4).

1.1.3 Malaria Epidemiology in Gauteng province

South Africa, and in particular Gauteng province, remains an important economic hub in Southern Africa (7). Gauteng draws many migrants, both internal and international, in search of opportunity (7). The migrant population in 2007 comprised just over a third of Gauteng's total population (35.4%) (7). The international migrant community accounts for about 13% of the total migrant population in Gauteng (7). In 2011 64% of malaria cases in SA were imported (contracted outside of SA) (4). In Gauteng province 85% of malaria cases were imported in 2011 (4). The majority of these imported malaria cases were contracted in southern Mozambican provinces (4).

The decline in malaria seen during the 2000's appears to have been related to cross border collaborations between SA, Mozambique and Swaziland. During this time period, malaria in southern Mozambique was down from a prevalence of 60% to 15% (4). The Lubombo Spatial Development Initiative (LSDI), an example of such a cross border collaborative project resulted in a 90% reduction in the incidence of malaria in northern KwaZulu-Natal, Swaziland and Maputo provinces (4). These control programs led to marked reductions in malaria cases within SA, with only 555 cases in 2005 (4). Thus, because the majority of malaria cases in Gauteng are imported, the frequency of malaria within the province is directly related to malaria transmission in north-eastern border areas of SA (4).

Unfortunately, in areas such as Limpopo where incidence of malaria is closely linked to incidence in bordering areas of Zimbabwe and with a high degree of socio-political instability, infection rates have remained high (4). Although extremely successful, there was a limited time frame of the Lubombo collaborative effort which ended in 2011 (4). Since then, malaria in SA and in Gauteng has been on the rise (4). The new 'MOSWASA' initiative was launched in 2015, which aims to rejuvenate the cross-border collaborative effort between Mozambique, Swaziland and SA (8).

1.1.4 Seasonal variation of malaria in South Africa and more specifically Gauteng province

Malaria transmission in SA is considered as meso-endemic occurring between September and May; and peaking in August (9). In a study conducted in Mpumalanga the temporal malaria peaks are described as triphasic (9). The three phases described

occur in August where climatic changes are primarily thought to be responsible for increased malaria transmission (9). August marks the beginning of the rainy season and thus correlates with a rise in vector reproduction (9). The association between peak rains and peak malaria transmission has been widely demonstrated and was shown occur in Mpumalanga by Silal *et al* (9). The other two time periods where malaria incidence appears to peak are associated with the holiday periods around Easter and Christmas (9). These time periods are associated with population movement from areas of low transmission to areas of high transmission (9). Despite incidence data showing local weather-related peaks, endemic regions are still prone to sporadic outbreaks due to unpredictable local transmission as well as importation from neighbouring regions (9). Gauteng province demonstrates similar peaks that mirror the peaks in endemic areas that are associated with cross-border travel during Easter and Christmas periods (10). Low to no cases are expected from June to August where the weather patterns are cold and dry being unfavourable for vector replication (9,10).

Small isolated outbreaks of local malaria transmission do occur in non-endemic areas within SA but are exceedingly uncommon when compared to the number of imported cases in these regions (11,12). The best documented outbreaks in non-endemic areas are in Gauteng. Dubbed ‘odyssean malaria’, a call to the underlying nature of transmission where infected *anopheles* mosquitos from endemic areas are thought to have survived perilous travels in cars, trucks or any other means and result in small pockets of malaria cases in areas where they come to rest (11,12). These small but significant outbreaks have been well described by Frean *et al* (11,12). These outbreaks pose a particularly high risk for morbidity and mortality owing to delayed

diagnosis (median 6 days, range 1-11 days) and institution of appropriate therapy (11,12). From 1996 to 2004, 46 cases were reported in Gauteng with a case fatality rate of 13% (11) . Over a time period from 2007 to 2013 a case series reported 21 spread over eight separate outbreaks over that time period. Of these 21 cases, 14 were confirmed cases and seven were presumed (11). There was a case fatality rate of 9.5%, this being ten times the national average of 0.5-1.0%. This indicates that delay in diagnosis, due to a lack of clinical suspicion and absence of travel history, is a major factor in the high number of severe complicated cases (11). Even though only 21 cases are reported, Frean *et al* conclude that many more cases are likely to go missed. More recently the National Institute for Communicable Diseases (NICD) Communicable Diseases communique reported on a further 4 cases over the time period 2017-2018, one of which was a mortality (12).

1.1.5 Malaria in Gauteng province

Gauteng province treats a large number of imported and occasional odyssean malaria cases (6). Gauteng is a major economic centre and is a focal point for travel in the African Sub-continent. More than a million African travellers entered SA in 2005, the majority of which were from malaria endemic regions (13). Although Gauteng is not considered an endemic malaria area within SA, it has been reported that 18% of all malaria cases in SA are treated within Gauteng (6). This is higher than any other non-endemic province within SA (6).

Over the time period November 2005 to December of 2016, there were 1,701 cases of malaria reported in Gauteng (10). Public sector hospitals within Gauteng province

managed 91% of these cases (10). Chris Hani Baragwanath Academic Hospital (CHBAH) managed 17% of these cases (10). Other Gauteng hospitals that had a high case load were Leratong Hospital (14%), Edenvale Hospital (12%) and Natalspruit Hospital (10%).

1.1.5.1 *Population characteristics.*

In Weber *et al* (10), a study over the time period December 2005 to November 2006, The majority of patients treated for malaria in Gauteng were young (median age: 27 years; range 1 - 89 years) males (68%). In a study by Cohen *et al* (14), conducted at CHBAH, the majority of patients seen during the time periods January 2001 – May 2001 and January 2002 – April 2002 were young (median age: 30 years; range: 15 – 49 years) males (64%) (14). In Dube *et al* (15), who described malaria from 2003 to 2006 in Pretoria, the majority or patients were adult males (data presented graphically without descriptive statistics).

Most patients with malaria in Gauteng appear to present in warmer months with a large peak in January followed by lesser numbers in February (10,14). In Weber *et al* (10) 47.2% of all malaria cases were seen in January and 17% of cases seen in February. In Cohen *et al* (14) data collection was only done during expected peak malaria months (January - May).

Most patients treated for malaria in Gauteng present with a travel history to Mozambique (10,15). In Weber *et al* (10), a travel history to or from Mozambique was present in 84% of malaria infections and a travel history to one of the three endemic regions in SA was present in 10%; eight patients reported no travel history.

In Dube *et al* (15), a travel history to Mozambique was present in 71% of cases and to other endemic countries in 10% of cases. Furthermore, in the same study only 1 patient was reported to have travelled to an endemic area within SA (15). In Cohen *et al* (14), the vast majority of patients that were semi-immune reported prior residence in Mozambique (97%, n=219).

1.1.5.2 *Proportion of patients with HIV infection*

In Cohen *et al* (14), the proportion of patients with malaria that had co-morbid HIV infection was 33% (n=336). Other studies done in Gauteng reported they did not have access to information on HIV status (10,15). There is a paucity of local data on the concurrence of malaria and HIV infection in Gauteng and other non-endemic areas in SA.

1.1.5.3 *Clinical features and biochemistry*

Malaria infection exists on a continuum that can be asymptomatic, uncomplicated, severe/complicated and can result in death (16). The clinical features of acute malaria infection are non-specific and result in a flu-like illness (16). The WHO describes the illness as beginning with malaise, then patients may experience a posterior headache which may be severe and associated arthralgias and myalgias, dizziness, loss of appetite, abdominal discomfort, nausea, vomiting and occasionally mild diarrhoea (16). Fever as a feature of malaria can be erratic and associated chills or rigors may or may not be present (16). Cyclical fevers are more typical of *P.vivax* and *P.ovale*, however can be present in *Falciparum* malaria (16). Physical signs that may be seen include: clinical features of anaemia, jaundice, dehydration, confusion, hepato-splenomegaly, isolated splenomegaly - usually a few days after infection (16).

Specific clinical and biochemical features define severe/complicated malaria infection and are supposed to guide clinicians on how to manage different patient populations (16). Severe/complicated malaria usually occurs in the setting of *falciparum* malaria infection, although *P.vivax*, *P.ovale* and *P.malariae* may also result in severe/complicated malaria (16). Features of severity usually appear after 3-7 days of non-specific flu-like symptoms, although in some patients progression to severe illness and death can occur in under 24 hours (16).

The WHO makes use of specific defining characteristics for severe malaria for research purposes, see Table A below (16). Local data on the frequency of presenting clinical features is lacking. In Cohen *et al* (14), the frequency of certain features of severity were described but the WHO definitions have been updated since that publication. In Cohen *et al* (14), 9.5% of patients were classified as having severe malaria. The most common features of severity were: renal impairment in 23 (6.8%) patients, acidosis in 14 (4.2%) patients and hepatic dysfunction in 14 (4.2%) patients. Patients with HIV infection were more likely to present with acidosis (11 Vs 3) when compared to HIV negative patients ($p < 0.01$) (14). In Weber *et al* (10), where data on severity was available (n=1374), 23% were classified as having severe malaria. Patients that were born in SA were more likely to have severe malaria (OR=1.43 (1.08 - 1.91)) and patients who had a delay of greater than 48 hours from onset of symptoms/diagnosis to institution of therapy (OR=1.98(1.48 - 2.65)) (10). In Dube *et al* (15), 8.6% (n=198) of patients had cerebral malaria (although the case definition for cerebral malaria was not clear) and 1% of patients had renal failure (although the definition of renal failure was not given).

Cohen *et al* (14) also described two distinct population groups that presented with malaria to CHBAH. One group were considered semi-immune and the other non-immune. Semi-immunity was defined as being born and growing up in a malaria-endemic area for at least 5 years (14). Patients were otherwise considered non-immune (14). The majority of patients recruited into the study during that time period were semi-immune (68%). Those patients whom were classified as non-immune with co-morbid HIV infection had significantly higher risk of developing severe malaria (22 Vs 10) ($p < 0.01$) (14).

Table 1: Adapted from WHO epidemiological and research definition of severe *Falciparum* malaria (16).

Severe malaria is defined as one or more of the following features without an alternative cause and with asexual *P.falciparum* parasitaemia:	
Impaired Consciousness	Glasgow Coma Score <11
Acidosis	Base deficit >8mmol/l, if unavailable then a plasma bicarbonate <15mmol/l or venous plasma lactate >5mmol/l. Manifests as Kussmaul breathing.
Hypoglycaemia	Blood or plasma glucose <2.2 mmol/l
Severe Anaemia	Haemoglobin <7g/dl or Haematocrit <20% with parasite count >10 000/ul
Acute Kidney Injury	Plasma or serum creatinine >265umol/l or blood urea >20mmol/l
Jaundice	Plasma or serum bilirubin >50umol/l with parasite count >100 000/ul
Pulmonary Oedema	Radiologically confirmed, or oxygen saturation<92% on room air with a respiratory rate >30/min, often with clinical features of respiratory distress and crepitations on auscultation.
Significant bleeding	Recurrent or prolonged bleeding from nose, gums or venepuncture sites; haematemesis or melaena.
Shock	Compensated: Capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb) without hypotension. Decompensated: Systolic blood pressure <80 mm Hg with evidence of poor perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitaemia	*P.falciparum* parasitaemia >10%, in the absence of other features of severity.

The diagnosis of malaria in the laboratory can either be made by identifying malaria parasites on thick or thin peripheral blood smear using the Giemsa stain or by the use of rapid diagnostic tests (RDTs) which utilise antigen testing. RDTs detect the presence of histidine-rich protein-2 (HRP2) which may clear more slowly than parasites from peripheral blood after treatment (16). Thus RDTs may be falsely positive for current malaria infection in those patients recently treated for malaria infection. Interestingly, RDTs can be falsely negative in the setting of HRP2 gene deletions as the protein is no longer produced (1). Other causes of false positive RDTs include various auto-immune conditions (17) . Weber *et al* (10) reported that a blood smear was used to make a diagnosis of malaria in 98% of cases, whilst RDTs were used to make the diagnosis in <1% of cases and a clinical diagnosis was made in around 1% of cases. The *Plasmodium* speciation in this study showed that the majority (96%) were caused by *P. falciparum*, and the other three species accounted for the remaining 4% (*P. malaria*e: 2*%; P. vivax and P. ovale* < 1%) (10).

1.1.5.4 ***Management and outcomes***

Management of patients with severe malaria often requires admission to high care and intensive care units (ICU) as the patient's condition can rapidly change (16). Patients with severe malaria may require mechanical ventilation, be haemodynamically unstable and require inotropic support and require haemodialysis due to acute kidney injury (16). Patients with severe malaria frequently have anaemia and the WHO recommends transfusion of packed red cells when the haemoglobin concentration falls below 7 g/dl (16). ICU admission, haemodialysis and blood product transfusion are particularly costly. In Cohen *et al* (14), 6% of patients required admission to ICU and 6.3% of patients required haemodialysis. The frequency of blood product

transfusion, dialysis and ICU/HC admission has not been well described in SA (10,15,18).

The median duration of hospital stay in Cohen *et al* (14) was 3 days (range: 1-21 days). In a study by Opie *et al* (18), although not conducted in Gauteng this study was conducted at Groote Schuur hospital in Cape Town - a tertiary facility in a non-endemic area in SA, the median length of stay was also 3 day (range: 1 - 32).

The case fatality rate reported specifically for severe malaria, in the 2018 SA guidelines on malaria treatment, can be as high as up to 10-40%, although no reference was provided (19). Frean *et al* (11) reported a national case fatality rate of 0.6 - 1.0 % from 1999 to 2005. Malaria mortality was shown to increase from 1992 to 2013 in North-eastern SA, related to this was easier travel to Mozambique, labour migration and employment (20). Of the 13 251 registered deaths 1.2% were attributable to malaria. Cohen *et al* (14) reported a case fatality rate of <1% at CHBAH in 2001/2002. The case fatality rate reported by Weber *et al* (10) was 4% over 2005/2006 (10). Importantly Weber *et al* (10) suggest that the case fatality rate reported in their study was probably an underestimate, as the number of positive smears assessed within Gauteng laboratories was almost three times higher than the numbers reported in the study. Dube *et al* (15) reported a case fatality rate of 2% in Pretoria from 2003-2006.

1.1.6 Malaria and HIV

There is a high burden of HIV infection in Sub-Saharan Africa (21). South Africa has the highest affliction of HIV in the world (21). Given this and the high incidence of malaria in the sub-continent, it is not surprising that much interest and research has been aimed at assessing the interactions between these two conditions. With at least 2.7 million people eligible for antiretroviral therapy in 2012 and 80% of these patients receiving antiretroviral treatment, there has been an exponential increase in the number of South Africans receiving antiretroviral therapy (21).

The interaction between malaria and HIV infection is an important one. There remains high morbidity and mortality associated with both diseases in Sub-Saharan Africa, where both these disease states are prevalent and often overlap. Studies from Sub-Saharan Africa have demonstrated an increased risk of clinical malaria in endemic areas associated with a reduction in host immunity as represented by a decline in CD4 count (22–24).

There have been some conflicting reports on whether HIV infection is a risk factor for the development of severe malaria with some studies finding a significant association and others finding no association (14,21,25,26). One of the studies showing a positive association with severe malaria was conducted at CHBAH (14). In this study 336 patients were collected over a two-year period. The proportion of patients in this study with severe malaria was 10%. Patients that were HIV infected and non-immune to malaria were shown have an increased risk of severe malaria with an odds ratio of 4.15 (95% CI, 1.57-10.97). In a subgroup of patients that were resident in endemic

areas (n=75), there was no association demonstrated between HIV infection and the risk of severe malaria. Thus, there appears to be an increased risk of severe malaria in patients who are not resident in endemic areas, are HIV positive and develop malaria infection (14). In the same study, univariate analysis revealed a low CD4 count to be associated with severe malaria and non-immune patients had a significantly lower CD4 count (14). The majority of HIV positive patients in the same study were clinically asymptomatic for HIV, with only 9% of the 110 HIV positive patients being classified as WHO stage 2/3, and none of the patients having WHO stage 4 disease (14).

A significant reduction in morbidity and mortality has been shown with the use of co-trimoxazole prophylaxis in patients with HIV infection, which has some activity against malaria parasites (27–29). In malaria endemic areas, it has been suggested that some of this mortality reduction may be attributed to the lower rates of malaria associated with the use of co-trimoxazole prophylaxis (27,28). In studies from Uganda, it was demonstrated that the risk of developing malaria in an endemic setting was significantly reduced whilst on co-trimoxazole prophylaxis from a baseline incidence of 50.8 per 100 person years down to an incidence in their cohort (n=989) of 9.0 per 100 person years (27,28).

These various interactions between malaria and HIV occur as a result of complex host response and the interactions between HIV infection and malaria infection (30-32). *Falciparum* infection has been demonstrated to result in up to a seven-fold increase in HIV-1 RNA blood concentrations (30). In the same study treatment with anti-malarial drugs resulted in a decline in HIV-1 RNA blood concentrations. The inflammatory

response to malaria results in robust CD4 response that may provide an environment that promotes progression of HIV disease (31). The effect of malaria infection on HIV viral load appears to be maintained until about four to eight weeks after which the HIV virus detectable in the blood of patients with both infections begins to decline (32,33). This is theoretically long enough to have an impact in HIV transmission in endemic areas. The degree to which the HIV RNA increases in blood during and after malaria infection also appears to be related to the patients baseline CD4 count (33). Those patients with a higher CD4 count (>300) appeared to have a greater increase in Viral RNA than those with lower CD4 counts (33). The CD4 count also seems to show a significant reduction (median of 66 cells per microlitre) during and after malaria infection but has been demonstrated to return to baseline post infection (33).

1.1.7 Pharmacotherapy of malaria: treatment and prophylaxis

Artemether-lumefantrine remains the first choice treatment for uncomplicated malaria in SA (34). Artemisinin-based therapies are considered safe and unlikely to be affected by resistance in our setting (34–36). A weeks course of oral quinine and doxycycline is an alternative therapy for uncomplicated malaria (34). For severe malaria intravenous artesunate is the preferred drug therapy as it has proven mortality benefit (34,37–39). Where access to artesunate is limited, the use of intravenous quinine followed by a course of artemether-lumefantrine is currently recommended (34).

The use various pharmacological strategies has been partially described in two studies conducted in Gauteng (10,15). Dube *et al* (15) reported in their cohort the majority of

patients received quinine and doxycycline 79% (n=198) and 6% were treated only with quinine. Despite proven mortality benefit , no patients received artesunate as the drug was not available from the pharmacy at the time of the study (15). In Weber *et al* (10), treatment data was available for 97% of patients (n=1645), of these, 95% received quinine. Of the patients who received quinine in this study, 53% received quinine alone, 36% received a combination of quinine and doxycycline and 11% received a combination of quinine and clindamycin (10). In those patients with severe malaria, only 9% received the recommended loading dose of quinine (10).

The SA 2018 malaria treatment and prevention guidelines recommends malaria prophylaxis for people travelling to malaria endemic areas (19). This is despite the fact that the public sector does not currently offer malaria prophylaxis. Leggat *et al* (40) reported on malaria prophylaxis use in SA from 1994 - 2000, but the prophylaxis regimens used are now outdated and they could not include doxycycline in their analysis. They did however demonstrate that the higher use of prophylaxis correlated with reduced notifications of malaria in presumably more affluent travellers (40). In Dube *et al* only 4/198 patients (2%) reported taking chemoprophylaxis prior to travel (15). There have been no other studies in SA assessing the use of malaria prophylaxis.

Thus, whilst malaria appeared to have been on the decline in the late 2000's there has been a sharp increase in malaria cases and mortality in recent years. It can be expected that as malaria increases in endemic regions a larger number of severe malaria cases can be expected to be seen predominantly in public sector healthcare facilities within Gauteng including CHBAH. It would be of use to assess the population characteristics, clinical features and outcomes of those patients presenting

to CHBAH as there are notable gaps in the literature and to assess for possible changing trends over time as similar research has not been conducted in the Gauteng for more than a decade.

1.2 AIM

Therefore, it is the aim of this study to assess clinical features and outcomes of patients presenting to Chris Hani Baragwanath Academic Hospital treated for malaria from the time period January 2017 to January 2018.

1.3 STUDY OBJECTIVES

1. Define the population characteristics of patients presenting to Chris Hani Baragwanath Academic hospital with the diagnosis of malaria infection.
2. Define the clinical characteristics of patients who present with malaria to Chris Hani Baragwanath Academic Hospital over the study period. This includes presenting complaints, examination findings, proportion diagnosed as severe and certain biochemical characteristics.
3. Ascertain the proportion of patients presenting with malaria who have human immunodeficiency virus (HIV) infection.
4. Define the clinical outcomes and management of the study group. These include primary outcomes such as mortality (all-cause and malaria attributable) and discharge, and secondary outcomes such as length of stay, time spent in high care and ICU.

1.4 Methods:

Site of study: Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg, Gauteng, SA.

Study Design: Prospective Observational Study.

Study Participants: Participants that will be eligible to be included the study are those patients diagnosed with malaria infection defined as having evidence of parasitaemia and a consistent clinical picture (smear or RDT positive with clinical signs and symptoms consistent with malaria infection whom have not received treatment for malaria in the preceding month) who present to CHBAH during the data collection period or before 140 participants have been recruited into the study (see information on sample size calculation below), whichever comes first (this will be considered the endpoint of the study). Only patients more than 18 years of age for whom informed consent to participation can be acquired will be considered eligible and included in the study. It is possible that the target of 140 patients as a significant sample size may not be achieved given reported decreased incidence of malaria, but based on previous data published on the number treated at CHBAH this target should be attainable within the time frame.

The sample size required for a p=0.05 will be calculated to be 140. This number is derived from previous studies at CHBAH that have assessed malaria at that facility with a rate of severity of 10% (14).

Process of patient identification and inclusion: Once a potential study participant (positive malaria test and more than 18 years of age) has been identified; either by identification by the treating clinicians or other ward staff or from laboratory staff, they will notify us about the potential participant and the patient will be approached by a designated person(s) involved in the study. That person(s) will explain the nature of the study and present the details of the predefined information sheet in a manner and language that the patient understands. This information sheet can be found in appendix A of this proposal. If this patient has given adequate informed consent (understood the information sheet and agrees to participate by signing the informed consent document that can be found in appendix A) to participate in the study, they will be allocated a study number so as to maintain adequate confidentiality and will be considered a study participant for the duration of their hospital stay at CHBAH.

Inclusion criteria:

- >18 years of age.
- Diagnosis of malaria – Positive malaria smear or RDT with clinical features in keeping with malaria infection and not having received treatment for malaria in the past month.
- Only those patients for whom informed consent either from the patient or an appropriate guardian can be obtained.

Exclusion Criteria:

- <18 years of age or where the age of the patient is unknown and may be <18yrs of age by morphological characteristics.

- Questionable diagnosis of malaria where either laboratory staff or experienced clinicians are not convinced of the diagnosis despite positive RDT/reported positive smear or where the patient has been treated for malaria in the preceding month.
- Those patients discharged prior to being identified with malaria by the clinical or laboratory staff.
- Those patients whom decline consent.

Due to the nature of RDTs there can be a false positive result in the setting of auto-immune conditions and where the patient has already been treated for malaria due to the persistence of histidine-rich protein 2 (HRP2). In patients identified by the laboratory with a positive rapid test only, the patient's clinical records will be reviewed and a discussion with the treating clinicians will be made in order to ascertain whether or not the patient's clinical status is in keeping with acute malaria. If the diagnosis is not clear or where questionable based on expert clinical opinion and other laboratory tests, these patients will be excluded from study participation.

Data Collection: Once a study participant is identified and enrolled into the study, a set data collection sheet will be used by a person(s) involved in this study to collect and record both clinical and biochemical information relevant to this study (see Appendix B). The majority of this information is expected to be located via the patient's clinical records and biochemical results as accessed via the "Trakcare" program (National Health Laboratory Service) where biochemical results are registered. Data collection may include a short interview and/or a brief clinical examination to ascertain information and clinical characteristics that may be lacking

from clinical documents. Patients will be made aware of this prior to participation as part of the informed consent process.

Data to be collected includes basic parameters such as demographics and travel history in order to define the population being studied and identify areas from which patients are being infected with malaria. Information regarding presenting complaints and findings on examination will also be recorded to identify common presenting features of malaria in our setting.

Where available, information regarding HIV-status and details about diagnosis, treatment as well as biochemical features such as CD4 count and viral load and WHO staging will also be collected so as to define the study group in terms of this important co-morbidity. Through this, a sub-population within the study, participants co-infected with HIV can be compared to those non-infected with HIV in terms of outcomes (mortality) and other features such as severity and length of stay. HIV unknown patients will be included in the study but will be excluded from statistics/analysis where this knowledge is required.

Severity will be defined according to the WHO epidemiological and research definition of severe malaria and WHO clinical definitions (see table 1) (16) . This will be done so as to define the proportion of patients in our setting who present with severe malaria and ascertain whether certain co-morbidities such as HIV co-infection are more prevalent in the severe malaria group. The WHO classification is a well-established classification system used throughout Southern Africa in both clinical and research settings.

An important aspect of malaria is the costs involved with its management. As such, defining the economic burden in our setting is important. For this reason, information on malaria treatment protocols used (including information on drugs prescribed), length of stay, blood transfusions and admissions to areas of higher care such as ICU or high care will be collected.

In order to define the anti-malarial drug use in our setting an extensive drug history will be sought and recorded from the relevant clinical charts.

Various biochemical results that are expected to be of relevance in the management and definition of severity will be collected so as to compare between subgroups and define the study population (See Appendix B).

Primary outcomes to be assessed are discharge and mortality. Mortality will be defined as either 'all cause' mortality, which is defined at the discretion of an experienced clinician, or mortality directly attributable to malaria itself also at the discretion of an experienced clinician. Each individual case will be assessed on its merits and where the cause of mortality remains unclear, a discussion between senior clinicians will be sought so as to get a general consensus opinion of clinicians experienced in the treatment of malaria and other medical conditions.

Where few data are missing, analysis will be conducted only using those participants where relevant data are available. Where a large amount of data is missing, those participants are to be excluded. Where variables are unavailable only those with

available information will be included in the relevant reporting of data and statistical analysis

Interventions: No specific interventions are included in the design of this study, although it is possible that the situation may arise where a patient is receiving the incorrect treatment or suboptimal care because of misdiagnosis or misclassification of severity or dosage errors. If of the opinion that this will negatively affect the outcome of the patient it is the authors belief that it would be ethically appropriate to make recommendations to the treating clinicians. No direct intervention will be undertaken, with the exception of emergency medical care where the investigator(s) is appropriately experienced or trained.

Consent for possible inclusion in a broader study on malaria at CHBAH was also included, reference number: M160549. Thus, consent should be inclusive not only of the details of this project but also inclusive of the aforementioned study. It is for this reason that all patient will be offered to participate in both studies and if amenable to the larger study, a separate consent form is included for further analysis of blood samples – see Appendix A. It is foreseeable that some patients may not want further testing done on their blood samples but are not opposed to participation within the definition of the Master of Medicine Study. As such, those patients will be allowed to consent to participation in the Master of Medicine Study only and will not be included as part of the data analysis of the other study.

Data Analysis:

Sample Size: target = 140 (rounded up from 138)

Formula used: $n=Z^2P(1-P)/e^2$

Z=1,96

P=0.05

$e^2=0.05^2$

P=0.01 (10% severe malaria)

$n=Z^2P(1-P)/e^2$

$= (1.96)^2 0.10(1-0.10)/(0.05)^2$

$= 3.8416X0.10(0.9)/0.0025$

$= (3.8416)X(0.09)/0.0025$

$= 0.345744/0.0025$

$= 138.2976$

n = 140

The required sample size has been calculated using the proportion formula with help from the statistics division of postgraduate studies and is based on previous data from CHBAH that showed a 10% proportion with severe malaria (14). Categorical data and epidemiological information will be presented in tabular/graph form. Clinical characteristics and outcomes of the study group will be analysed as a whole. The clinical characteristics, treatment and outcomes of those patients in whom HIV-status is known will also be analysed by comparing HIV-infected and HIV non-infected patients with malaria where possible.

The outcomes and relative risk of those patients whom are HIV infected and on treatment versus those that are not on treatment will also be calculated using Chi^2 data analysis. The relative risk for mortality and adverse outcomes will be calculated for HIV negative and HIV positive patients. Using regression analysis, risk factors for severe malaria and mortality will be assessed.

1.5 Ethics

Participation in this study deals with a potentially sensitive topic, in that one of the aspects of this study is to assess the impact of HIV and its treatment on the clinical course and outcome of patients infected with malaria. It is therefore imperative to make every effort to maintain confidentiality. As explained in the information sheet (see Appendix A) no identifying personal information will made available to the public and every effort will be made to ensure confidentiality although no absolute guarantee can be made in this regard. It is foreseeable that some patients affected by malaria may be very ill and unable to consent to participate in the study at the time of identification as a potential study participant.

It is expected that a proportion of the potential study participants will not be of mental state to give adequate informed consent to participate in the study. These patients may be confused due to the severity of their malaria infection (cerebral malaria) or may have other non-related medical conditions (psychosis, dementia, intellectual disability etc.) that make obtaining informed consent directly from these patients impossible. It would be unfortunate not to include this portion of patients with malaria from the study as they would represent a significant proportion of those patients with severe

malaria. Due to this, we have included a separate consent procedure whereby the closest guardian available could give consent (see Appendix C). Where the specified participant is recruited into the sample through this process and that participant later becomes of sound mind to consent due to improved clinical condition, that participant will be re-approached and will be consented according to the normal protocol. If after being presented with the information sheet the participant wishes to not participate in the study, they will be allowed to do so without prejudice and will from that point on no longer be considered a study participant and any data and or blood samples previously collected will be discarded and no used as part of the final data analysis. A record of all patients who decline participation will be kept with reasons when patients wish to give them are available. This information will be presented in the final write-up of the project so as to determine the percentage of those patients with clinical malaria that were not included in the study data.

Ethics approval has already been submitted as part of the aforementioned larger study. See reference number: M160549 (The Ethics committee has requested this be included in the protocol submission). A separate Ethics approval has been submitted and approved for the conduction of this study ref: M1611137 (see Appendix D).

1.6 Timing:

	Aug 16	Sept 16	Jan 2017 – Jan 2018	2018	2019
LITERATURE REV/ETHICS	X				
PROTOCOL	X				
PROTOCOL ASSESSMENT		X			
DATA COLLECTION			X		
DATA ANALYSIS				X	
WRITE UP PAPER					X

1.7 Funding:

Funding will mainly entail paper and print supplies for data collection sheets, Information documents and informed consent forms. A personal budget of approximately a thousand rand expected to be utilized as needed.

1.8 Limitations:

As the study is prospective in nature and patients and information need to be collected on premises at CHBAH, time spent travelling to and from the hospital will have to be taken into consideration when allocated to rotations not within the hospital. Every effort will be made to ensure rotations are done at CHBAH hospital during expected

peaks of malaria. As this project forms part of a larger study, other permanent staff have kindly offered to assist with some aspects of data collection when travel to and from the hospital are impractical or impossible so as not to miss potential participants and avoid problems with sample size. However, it is my preference to collect the data myself wherever possible. Not all patients seen in ward 20 or casualty with malaria will be admitted to the wards as some patients referred have uncomplicated malaria that can be managed as outpatients; thus, the study is likely to be more representative of those patients with severe malaria that are managed as inpatients.

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CHAPTER 2: Article for submission (SAMJ formatting)

Title: Clinical Aspects and Outcomes of Patients with Malaria at Chris Hani Baragwanath Academic Hospital

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Conflict of Interest: Nil

Keywords: Malaria, HIV, South Africa

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Abstract

***Background*.** South Africa (SA) is currently experiencing a significant increase in malaria cases despite having shifted focus from malaria control towards malaria elimination. The clinical features of malaria are non-specific, but the relative frequency on presentation are not well described. There are important interactions between human immunodeficiency virus (HIV) infection and malaria, including a high mortality associated with both diseases in Sub-Saharan Africa.

***Aim*.** To describe the population characteristics, clinical and biochemical features of severity, the proportion of participants with HIV infection and the management and outcomes of participants with malaria at Chris Hani Baragwanath Academic Hospital (CHBAH).

***Methods*.** A prospective observational study was conducted whereby patients with a confirmed laboratory diagnosis of malaria were identified, approached and consented for study inclusion over the time period from January 2017 to January 2018. Clinical and biochemical data were collected at the time of consent and later analysed.

***Results*.** The mean age was 35.7 years of age (±SD=12.98) and 72 (70.6%) of the 102 participants were male. Peak admissions for malaria were in January where 58 (56.9%) participants were admitted during January 2017/2018. All malaria cases were imported with 75% associated with travel to Mozambique. The majority of participants (62%) were expatriates living in SA. The most common presenting symptoms were chills (95%), weakness (94%,), fever (91%), headache (90%) and lethargy (88%). The most common clinical signs were dehydration (31%), prostration (20%) and jaundice (14%). The number of participants with severe malaria was 40

(39.2%), with prostration as the most common feature of severity (20%). ICU admission occurred in 8 participants (7.8%) and 6 participants (5.9%) required haemodialysis. The median duration of stay was 5 days (IQR=3). HIV status was known in 83 (81.4%) participants, of these 32 (38.6%) were found to be HIV positive. Malaria prophylaxis was taken by only 8 participants. The all-cause mortality rate was 4.9%, and mortality attributable to malaria was 3.9% .

***Conclusion*.** This study showed a high proportion of complicated malaria cases, particularly in January. The majority of participants were young expatriate males with a travel history to southern Mozambique or Limpopo with very few taking malaria prophylaxis. Most clinical signs and symptoms were constitutional and non-specific. A large number of participants were found to be HIV positive and most were newly diagnosed. The mortality was high at around five times the national average, and was possibly an underestimate.

Introduction

Malaria still imposes a significant burden of disease throughout the world. Approximately 216 million cases were reported by the World Health Organisation (WHO) in 2016, together with approximately 445,000 deaths (1). Sub-Saharan Africa continues to be disproportionately affected with an estimated 80% of the disease burden and mortality (1). In South Africa (SA), malaria is endemic in low altitude regions of Limpopo, Mpumalanga and northern KwaZulu-Natal provinces with an estimated 10% of the national population at risk (2,3). Gauteng is not an endemic malaria area but treats approximately 18% of the national disease burden (4). Public health-care facilities manage the majority of malaria cases in Gauteng (4). There has been a large increase in the number of malaria cases since 2016 (5).

The vast majority of malaria cases managed in Gauteng province are imported, with 71-97% of these cases associated with travel to or from Mozambique (2–4). In Gauteng, the patient population with malaria has typically been young adult males (4,6,7). Economic factors have been shown to drive population movement between Gauteng and malaria endemic areas (2,8). Small amounts of local malaria transmission in Gauteng do occasionally occur and results in sporadic outbreaks (9). These cases of odyssean malaria are exceedingly rare, but are well reported by Frean *et al* (9,10), and carry a very high case mortality rate at around 13%.

The majority of malaria cases in Gauteng are caused by *P. falciparum* (99%) with 10-30% of these cases being classified as severe (4,6,7). Seasonality of malaria in Gauteng differs somewhat from the tri-phasic peaks described in endemic areas such

as Mpumalanga (11). The peaks of malaria in Gauteng somewhat mirror endemic areas but data from local tertiary facilities demonstrates a large peak in January related to travel during the December festive season (4,6,7).

For the management of malaria, the median duration of hospital stay in tertiary facilities in SA has been reported to be around 3 days but ranges broadly (1 - 32 days) (6,12). Local data on mortality show a national case fatality average of between 0.6-1% and case fatality rate in Gauteng of 1-4% (4,6,7,9). Malaria mortality in north-eastern SA has been reported to be on the increase (13).

Clinical features of acute *falciparum* malaria are described by the WHO but are non-specific (14). Acute malaria begins with malaise and is then followed by headache, myalgias, dizziness, anorexia, abdominal pains, nausea and vomiting, and occasionally diarrhoea (14). This is accompanied by fevers, chills and occasionally rigors (14). The physical signs that may be found include: pallor, jaundice, and splenomegaly (14). When present certain signs and symptoms are said to indicate clinically severe/complicated malaria infection and imply a higher risk of morbidity and mortality and inform on treatment strategies (14). The features of severity are listed in *table 1*. (14). The WHO uses these definitions of severe malaria to guide decision making at the bedside with regards to management. The WHO uses a similar but somewhat different definition of features of severity for the purposes of epidemiological research which can be seen in table 1 (14). The two features of severity used in clinical practice that are notably absent from the research definition are repeated convulsions and prostration (14).

There is a paucity of local and international data on the relative frequency of presenting clinical symptoms and signs of patients with malaria at hospitals in non-endemic regions. In Cohen *et al* (6), the most common features of severity at CHBAH were renal impairment in 23 (6.8%) patients, acidosis in 14 (4.2%) and hepatic dysfunction in 14 (4.2%). In a retrospective study by Francis *et al* (15), the most common symptoms reported in association with imported malaria cases seen at three east London hospitals were fever (93.6%), vomiting (36.8%), diarrhoea (23.3%) and haemoglobinuria (1.5%). However, this data set included children which may affect relative frequency of presenting symptoms (14). In another retrospective study of 100 patients with imported malaria, conducted in the United States of America by Akselrod *et al* (16), the commonest presenting symptoms were fever (92.0%), chills (78%), headache (64%), myalgias/arthralgias (53%), nausea/vomiting (35%), diarrhoea (26%), fatigue/malaise/weakness (25%), abdominal pain (18%) and altered mentation (9%). Neither of these studies reported on the frequency of clinical features such as splenomegaly.

Management of severe malaria ideally requires admission to the intensive care unit or the highest level of care when facilities are available. Management of severe malaria may include mechanical ventilation, haemodialysis and blood transfusions (14). The cost of these interventions can be immense and the local demands on limited resources should be monitored. Previous work at CHBAH showed 6% of 336 patients being admitted to ICU and 6.3% receiving haemodialysis (6). Admission to other higher levels of care and the use of blood products have not been well described in local publications.

Artesunate has begun to replace quinine as first line treatment for severe malaria due to proven mortality benefit and a superior safety profile (17,18). Historically, the most commonly used anti-malarial regimens for the treatment of malaria in Gauteng were quinine-based (79 - 97%). No local data has been published on the frequency of artesunate use at tertiary facilities. Malaria prophylaxis is recommended in national guidelines for South Africans travelling to malaria endemic areas, although the public health-care system does not currently offer this service (19,20).

South Africa has one of the highest rates of human immunodeficiency virus (HIV) infection in the world (21). There are a number of interactions between HIV and malaria that have been described. A decline in CD4 count has been associated with an increased risk for clinical malaria in endemic countries (22–24). There is conflicting data on whether HIV is a risk factor for severe malaria, but HIV appears to be a risk factor for severe malaria in patients who are non-immune (6). Furthermore, a lower CD4 count appears to be associated with an increased risk for severe malaria (6). Malaria also has an effect on HIV viral load with up to a seven-fold increase that can be maintained for eight weeks post infection (25–28). The CD4 count also appears to decline post malaria infection but returns to baseline (27). It has also been suggested that some of the reduction in morbidity and mortality with the use of co-trimoxazole can be attributed to reduced rates of malaria in endemic countries (29,30). In a previous study at CHBAH the proportion of patients with malaria that had HIV infection was 33% (6).

South Africa is currently facing a malaria epidemic and increasing mortality due to malaria in endemic areas. Despite not being a malaria endemic area, Gauteng

province has also seen an increase in malaria numbers and mortality. Therefore, the aim of this study was to define population, clinical and laboratory characteristics, ascertain the proportion of patients with HIV and define the clinical management and outcomes of patients with malaria at CHBAH during this epidemic.

Methods

Study design and setting. The study was conducted as a prospective observational study at CHBAH over the time period January 2017 to January 2018. CHBAH is a large tertiary public referral hospital situated in the south of Johannesburg in Gauteng province that provides healthcare services to the peoples of Soweto and the surrounding areas. Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) prior to commencement of the study (M1611137).

Study Participants. All patients ≥18 years of age presenting to CHBAH with a laboratory confirmed diagnosis and clinically compatible features of malaria over the defined time period were considered eligible to enter into the study and were approached for possible inclusion with the use of an information sheet. Patients were only included in the study if adequate informed consent could be obtained from the patient or next of kin. Patients who had been discharged or who had died prior to being identified for possible inclusion were excluded from the study.

Definitions. Similar case definitions were used as in a previous study conducted at CHBAH so as to allow for comparison (3). A diagnosis of malaria was defined as a

positive rapid diagnostic test (RDT) for malaria and/or positive Giemsa stain on thick or thin blood smear together with a clinical picture in keeping with acute malaria infection. The RDT used at the time of study recruitment was the ICT (immunochromatographic test) Malaria *P.falciparum* antigen kit from ICT Diagnostics. In cases where RDT was positive and blood smear was negative patients were included if they had not received treatment for malaria in the preceding month. Semi-immunity was defined as the participant having lived in an endemic malaria area for at least 5 years during childhood (3). The WHO criteria for both clinical and research purposes were used to define severe malaria and were included on the data collection sheet and can be seen in tables 1 and 4 (9).

Patient identification and consent. Patients were identified via positive specimen results recorded by the CHBAH National Health Laboratory Services (NHLS) or via clinical staff working at the hospital. Once identified patients were approached and informed consent was obtained, with the assistance of translators when necessary. Where patients were unable to consent due to delirium or altered level of consciousness consent was obtained on a separate form from the participant's next of kin. All patients that survived to discharge gave informed consent themselves.

Data Collection. Data was collected from January 2017 to the end of January 2018. Once participants were entered into the study, participant data was collected on standardised data collection sheets. Participant and family interviews were used to ascertain travel history and other relevant history. Clinical records, limited clinical examination, review of laboratory records and follow-up over the course of hospital stay were used to ascertain clinical and laboratory characteristics and inform on

supportive and specific treatments. Data collected included: demographics, travel history, details of residence, hospital stay, symptoms and clinical features of malaria, presence of severe malaria, HIV status and treatment, laboratory results, management and outcome data. Data once recorded were then entered and stored onto an excel database for later analysis.

Sample size. Based on previous research done at CHBAH in order to obtain a representative sample with at least 10% of participants meeting criteria for severe malaria so as to be adequately powered to make comparisons between groups with severe and non-severe malaria, target sample size was n=140 based on the formula: $n=Z^2P(1-P)/e^2$ (3).

Data analysis. Categorical variables were described using frequencies and percentages. Differences in normally distributed continuous variables between patients by HIV status and immune status were assessed using Student's *t*-tests. Wilcoxon's rank sum test was used to compare medians for non-normally distributed variables. For categorical variables chi-squared analysis was used, however, where $n<5$ in any of the cells, Fisher's exact test was used. Binary logistic regression analysis was used to assess risk factors for severe malaria. All analyses were conducted in Stata version 15. Significance was set at 5%.

Results

A total of 122 potential participants were approached for possible inclusion during the prescribed recruitment period. Fourteen patients were excluded: four due to early

discharge and seven due to being <18 years of age. Two patients were excluded because informed consent could not be obtained due to language barriers and one patient refused consent. Of the 108 participants enrolled five were excluded because of incomplete data collection sheets and one was excluded because he had received treatment for malaria two weeks prior to his current admission. This left a final sample size of 102 participants. The percentage of participants with severe malaria greatly exceeded 10% despite the target of 140 participants not being reached due to time constraints imposed by the study design.

Population characteristics. The mean age of the study participants was 35.7 years of age (±SD=12.98). All but one participant was of African descent and 72 (70.6%) were male. None of the 30 female participants were pregnant. Of the 102 participants, 64 (62.7%) were born outside SA. The most common country of birth was Mozambique (84.4%), followed by Ethiopia, Malawi and Zimbabwe (each 4,7%) and Paraguay (one participant). Fifty-nine (57.8%) participants spent at least 5 years growing up in malaria endemic areas and were considered to be semi-immune. Of those participants that were semi-immune, the median duration of residency in SA was 10.5 years (IQR =19).

All participants had travelled to an endemic malaria area (96%) or were visitors from one (4%). There were no cases of odyssean malaria. Malaria infection was most frequently acquired whilst in Mozambique (75%), Limpopo province in SA (18%), Zimbabwe (3.9%), Malawi (3.9%), Tanzania (2.0%), Ghana (1.0%) and Kenya (1.0%). Three participants reported having travelled through more than one endemic malaria country during their travels. The first travelled to Zimbabwe, Mozambique and Malawi, the second to Tanzania, Kenya and Mozambique and the third to

Limpopo in SA and Mozambique. Sixty-three percent of participants reported travelling to an endemic malaria area on more than four previous occasions and of these 66% were born outside of SA.

Peak malaria period. The number of participants admitted with malaria infection was highest in January 2017 and January 2018 (29 each) and February 2017 (14). (see Figure 1). There was a low number of baseline cases seen throughout the rest of the year except in the winter months (June - August) and early spring (September) where no participants were recruited into the study. *P.falciparum* was identified in 101 participants (99%) and *P.ovale* in one participant. Of the 102 participants, 100 had RDTs and 99/100 (99%) tested positive. The only negative RDT with a positive smear, as expected, was seen in the participant with *P.ovale* infection. Twelve participants (12%) were RDT positive but smear negative. In two participants the diagnosis of malaria was made on smear without a RDT.

Clinical and laboratory features. The mean time from return from traveling to presentation at a healthcare facility was 11.39 days (±SD=7.33). The mean time from symptom onset to presentation at CHBAH was 5.08 days (±SD=3). The frequency of clinical signs and symptoms are presented in table 2. The most common presenting symptoms were: chills (95.1%), weakness (94.1%), fever (91.2%), headache (92.1%), lethargy (88.2%), loss of appetite (86.3%), night sweats (80.4%), dizziness (67.6%), nausea (66.7%), arthralgia (63.7%), myalgia (57.8%), and vomiting (54.9%). The most common clinical features on examination were dehydration (31.4%), prostration (19.6%), jaundice (13.7%), and confusion (11.8%). The finding of clinical splenomegaly was uncommon (4,9%).

From admission laboratory results, the median white cell count was 5.6 $x10^9$/L (IQR= 2.8 $X10^9$/L), the mean haemoglobin concentration was 12.4 g/dl (±SD=2.4) and the median platelet count was 64.5 $X10^9$/L (IQR=56.25). The platelet count was below 150 $X10^9$/L in 92 (90.2%) of participants on admission. On presentation, the median blood urea was 6.6 mmol/L (IQR=5.10), the median serum creatinine was 96 µmol/L (IQR=41) and the median total serum bilirubin was 28 µmol/L (IQR=29). Of the 46 participants that had a follow up platelet count done on day 3 of admission 39 (84.8%) had counts below 150 $X10^9$/L. There were 4 participants who underwent lumbar punctures, one of whom had cerebral malaria, all of which were normal. In the 12 participants who had blood cultures on admission, all were negative.

Forty participants (39.2%) were assessed to have severe malaria based on at least one feature of severity. The most common features of severity were prostration/severe weakness in 20 (19.6%) participants, jaundice in 15 (14.7%) participants, renal impairment in 11 (10.8%) participants and acidosis in 11 (10.8%) participants (Figure 3). Prostration was the only feature of severity in 6 participants. Parasitaemia >4% was the only feature of severity in 2 participants. A single feature of severity was present in 22 (21.6%) of participants, 2-4 features of severity in 14 (13.7) and $\geq$5 features of severity in 4 (3.9%) of participants. Cerebral malaria was present in 4/5 (80%) of participants that demised. In those participants with renal impairment, 4/11 (36.4%) had acidosis as a feature of severity as well. There were no significant differences in the features of severity between immune and semi-immune participants (Table 3).

Proportion with HIV. HIV infection was the commonest co-morbidity, followed by asthma in 3 participants and heart failure in 2 participants. Of the 83 (81.3%) participants where HIV status was known 32 (31.4% of the total cohort) were HIV positive. Of the 12 with previously known status, 11 were on anti-retroviral treatment, of whom 7/8 (87.5%), where HIV viral load was known, were virologically suppressed (viral load <400 c/ml) and none were taking co-trimoxazole prophylaxis. The other 20 participants were newly diagnosed with HIV during their current admission. The majority of participants with HIV infection were asymptomatic for HIV. The WHO classification was used to categorize the 20 newly diagnosed HIV positive participants. Thirteen (65%) HIV newly diagnosed participants were WHO clinical stage 1, 5 (25%) were clinical stage 2, 1 (5%) participant was clinical stage 3 based on unexplained weight loss >10% and persistent oral candidiasis and 1 (5%) participant was clinical stage 4 based on the diagnosis of pneumocystis pneumonia. The CD4 count was known in 19/32 (59%) participants with HIV infection. The mean CD4 count was 261.3 x 10^6cells/L (±SD = 144). In secondary analysis, there were a few significant differences between HIV positive and negative groups (Table 4). The HIV positive participants were more likely to have acidosis as a feature of severity, 7 versus 3 (p=0.042), to have a longer duration of stay, 5 versus 4 days (p=0.03) and were more likely to receive haemodialysis, 6 versus 0 participants (p=0.007). There was no significant difference in severe malaria between the two groups.

Management. The median length of hospital stay was 5 days (IQR=3 days). Nineteen participants were admitted to a higher level of care, 17 of which had severe malaria. Eight participants (7.8%) were admitted to ICU with a mean length of stay of five days (±SD=2.42). Five participants were admitted to high care with a mean length of

stay of three days (±SD=1.83) and 6 participants were admitted to short stay ward (2 of whom did not have features of severe malaria) with a mean length of stay of 2 days (±SD=0.75).

Thirty-eight participants with malaria received parenteral therapy, 19 (50%) intravenous quinine and 19 (50%) intravenous artesunate (Table 5). Of those participants that received intravenous quinine, 13 (68%) received the correct loading dose. Two participants with uncomplicated malaria received artesunate for 1 day after which treatment was de-escalated. Of the 102 participants, 95 (93%) received artemether-lumefantrine combination therapy, with 91.6% of them having taken the correct dosing schedule. Eight participants received artemether-lumefantrine therapy for more than 72 hrs. Doxycycline was administered to 7 participants, always in combination with quinine. Clindamycin was administered in 2 participants after treatment with artesunate. Of the 12 participants that received artesunate at a higher level of care (high care/ICU), 4 required mechanical ventilation, 6 required dialysis and 6 received blood transfusions.

Eight participants (7.8%) reported having taken some form of malaria chemoprophylaxis. The most commonly used drug for chemoprophylaxis was mefloquine in 4 participants, 1 participant had taken doxycycline and in 3 participants the chemoprophylactic agent could not be reliably identified. Of the 102 participants, 23 (22.5%) reported previously being treated for one or more episodes of malaria infection after travelling to malaria endemic areas. Of these 23 participants only 3 reported taking malaria prophylaxis during their most recent travels.

Outcomes. The all-cause mortality during the study period was 5/102 (4.9%), 4 (3.9%) participants died due malaria and one participant successfully treated for malaria died later due to nosocomial sepsis. In the two participants that died where date of symptom onset was available, they presented at 6 and 9 days after symptoms began. Of the participants that demised, 3 had 5 features of severity and 2 had 3 features of severity. All participants that demised received artesunate as first-line therapy and were managed in the ICU.

Table 1: Adapted from WHO epidemiological and research definition of severe malaria for clinical and epidemiological research purposes (14).

Severe malaria is defined as one or more of the following features without an alternative cause and with asexual *P.falciparum* parasitaemia:	
Impaired consciousness	Glasgow Coma Score <11
Acidosis	Base deficit >8mmol/L, if unavailable then a plasma bicarbonate <15mmol/L or venous plasma lactate >5mmol/L. Manifests as acidotic breathing.
Hypoglycaemia	Blood or plasma glucose <2.2 mmol/L
Severe anaemia	Haemoglobin <7g/dl or Haematocrit <20% with parasite count >10 000/ul
Acute kidney injury	Plasma or serum creatinine >265µmol/L or blood urea >20mmol/L
Jaundice	Plasma or serum bilirubin >50µmol/L with parasite count >100 000/µL
Pulmonary oedema	Radiologically confirmed, or oxygen saturation<92% on room air with a respiratory rate >30/min, often with clinical features of respiratory distress and crepitations on auscultation.
Significant bleeding	Recurrent or prolonged bleeding from nose, gums or venepuncture sites; haematemesis or melaena.
Shock	Compensated: capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb) without hypotension. Decompensated: systolic blood pressure <80 mm Hg with evidence of poor perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitaemia	*P.falciparum* parasitaemia >10%, in the absence of other features of severity.

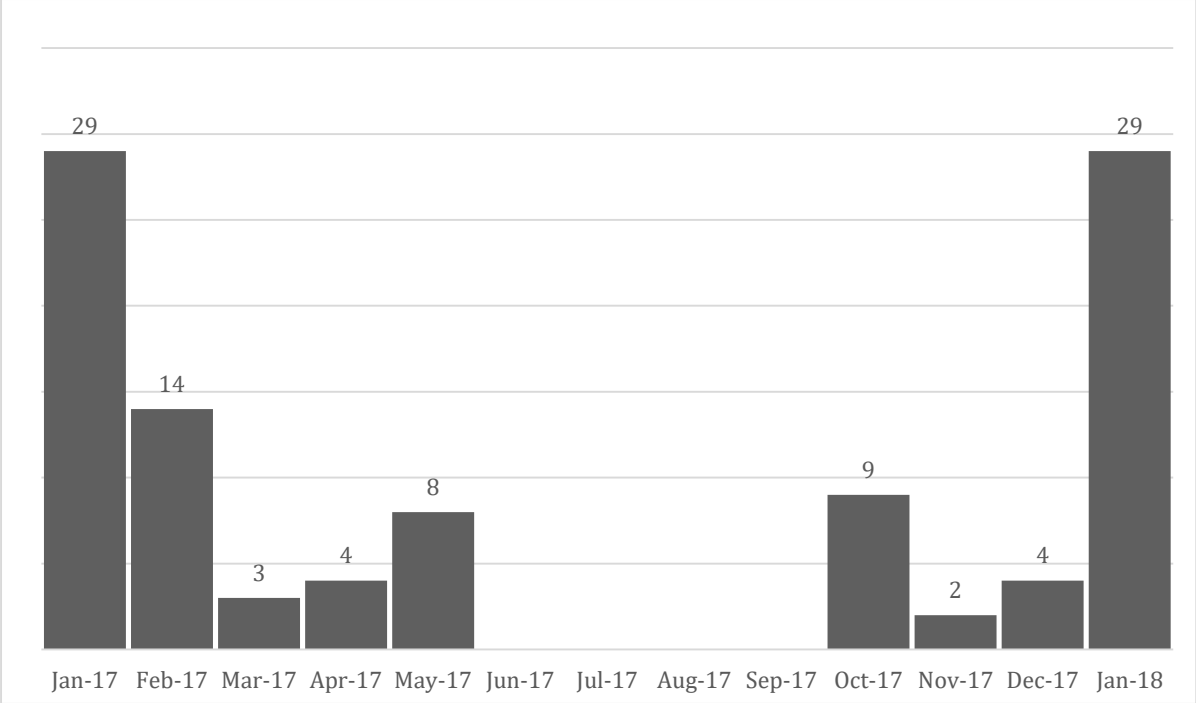

Figure 1. Number of malaria cases seen by month from January 2017 to January 2018

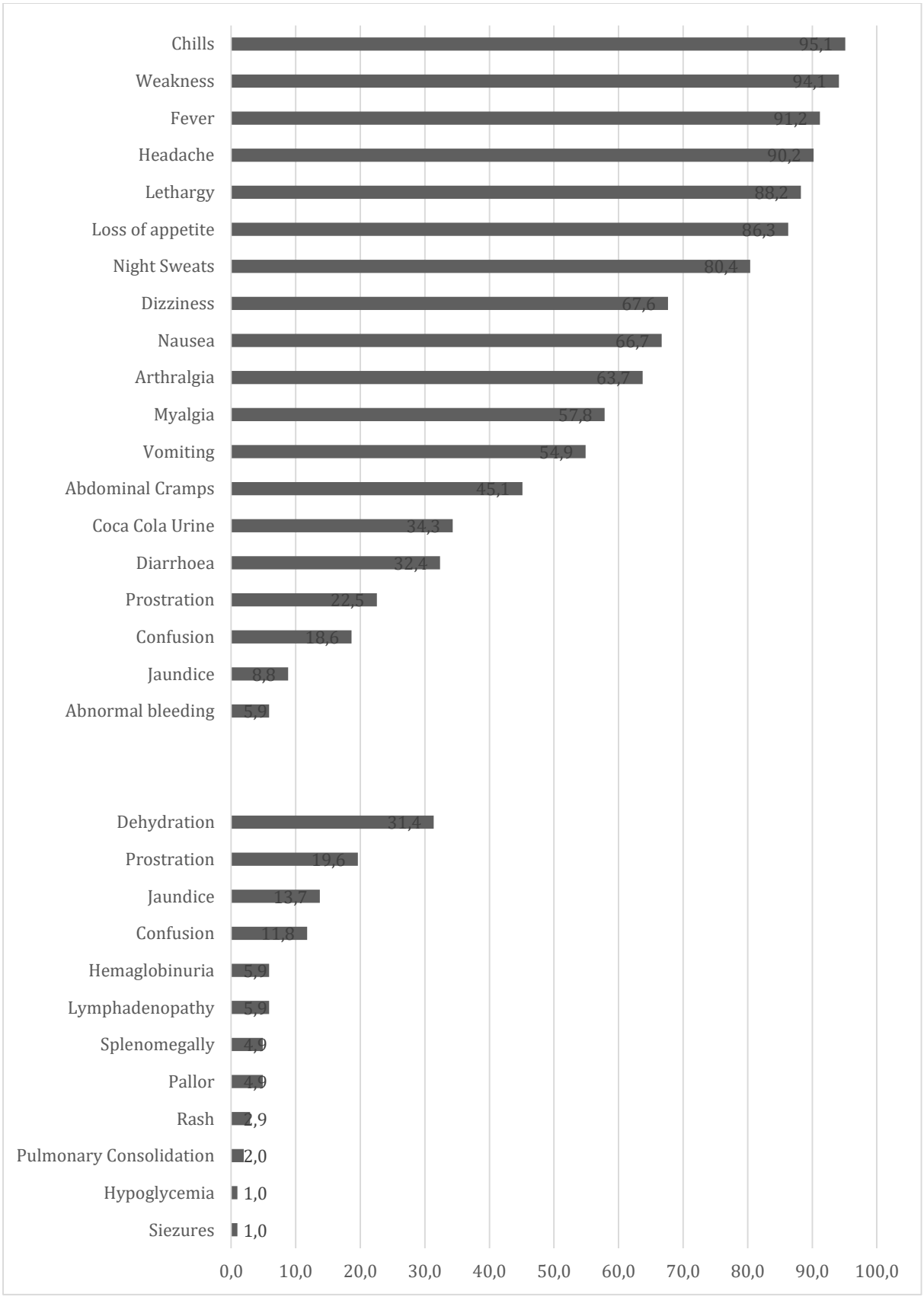

Figure 2. Percentage of participants presenting with specific symptoms (top) and signs (bottom) attributable to malaria (n=102).

Table 2: Risk factors for severe malaria on multivariable analysis.

	Participants with malaria (N=102)			
Risk factor	Severe (n=40)	Non-severe (n=62)	Crude OR (95% CI)	Adjusted OR (95% CI)
Non-immune	21	22	2.01 (0.89 – 4.51)	1.57 (0.51 – 4.79)
HIV infection	14	18	1.43 (0.58 – 3.52)	1.40 (0.43 – 4.52)
Parasite level, median % (range)	2.1 (0 – 18)	0.9 (0 – 3.8)	**1.59 (1.21 – 2.10)**	**1.41 (1.07 – 1.86)**
WBC count, median cells X 10^9/L	6.8 (2.5 – 36.0)	5.4 (2.4 – 14.6)	**1.31 (1.08 – 1.59)**	1.21 (0.94 – 1.54)
Platelets	52.5 (11 – 388)	76.5 (13 – 291)	0.99 (0.98 – 1.00)	1.00 (0.99 – 1.01)
CD4 count	180 (44 – 460)	299 (153 – 667)	0.99 (0.98 – 1.00)	-

Table 3: Comparison of demographic characteristics, complications of malaria, parasitaemia, and CD4+ T cell count for nonimmune and semi-immune adults with malaria.

	Non-immune (*n*=43)	**Semi-immune (*n*=59)**	**P**
Demographic Characteristics			
Age, median years (range)	30 (18 – 72)	34 (18 – 68)	0.135
Male sex (%)	29 (67.4)	43 (72.9)	0.552
Features of severity (%)			
Hyperparasitaemia WHO (>4%) WHO (>10%)	 7 (16.3) 2 (4.7)	 4 (6.8) 2 (3.4)	P 0.104 0.638
Severe anaemia	0 (0.0)	2 (3.4)	0.225
Renal impairment	5 (11.6)	7 (11.9)	0.661
Shock	1 (2.3)	0 (0.0)	0.241
Significant bleeding	0 (0.0)	0 (0.0)	-
Prostration/severe weakness	14 (32.6)	4 (6.8)	**0.005**
Acidosis/acidaemia	4 (9.3)	4 (6.8)	0.397
Hypoglycaemia	0 (0.0)	1 (1.7)	0.393
Cerebral malaria (GCS<15)	5 (11.6)	3 (5.1)	0.128
Impaired consciousness (GCS<11)	3 (7.0)	1 (1.7)	0.177
Jaundice	8 (18.6)	7 (11.9)	0.345
Pulmonary oedema/ARDS	1 (2.3)	0 (0.0)	0.241
Repeated convulsions	0 (0.0)	1 (1.7)	0.393
Complication of malaria			
Severe malaria (%) (prostration excluded)	21 (48.8) 17 (39.5)	19 (32.2) 17 (28.8)	0.089 0.257
Death (%)	3 (7.0)	2 (3.4)	0.648
Admission into ICU (%)	5 (11.6)	3 (5.1)	0.225
Duration of hospitalization, median days (range)	5 (2 – 35)	5 (2 – 18)	0.708
WBC count, median cells X 10^9/L (range)	6.0 (3.9 – 36.0)	5.2 (2.4 – 14.6)	**0.006**
Parasite level, median % (range)	2.0 (0 – 18)	0.9 (0 – 17.5)	**0.020**
HIV Infection (%)	8 (18.6)	12 (20.3%)	0.054
CD4+ T cell count, median cells X 10^6/L (range)	362 (264 – 460)	222 (44 – 667)	0.232

Table 4. Demographic data and characteristics of HIV-infected and non-HIV-infected adults with malaria.

Variable, by class	**All Participants (*n*=102)**	**Non-HIV infected participants (*n*=51) ***	**HIV-infected participants (*n*=32)**	**P****
Demographic Characteristics				
Age, median years (range)	34 (18 – 72)	35 (20 – 72)	31 (18 – 59)	0.757
Male sex	72 (70.6)	38 (74.5)	19 (59.4)	0.148
Nonimmune	43 (42.2)	27 (52.9)	10 (31.2)	0.053
Time from return to current presentation (days), Median(range)	10 (0 – 42)	10.5 (0 – 42)	10 (2 – 22)	0.530
Malaria Prophylaxis taken	8 (7.8)	5 (9.8)	1 (3.1)	0.398
Severe Malaria, by feature				
All	40 (39.2)	18 (35.3)	14 (43.8)	0.441
WHO research definition	34 (33.3)	13 (25.5)	13 (40.6)	0.148
Prostration as only feature	6 (5.9)	5 (9.8)	1 (3.1)	0.398
Cerebral Malaria (GCS<15)	8 (7.8)	2 (3.9)	4 (12.5)	0.728
Hyper-parasitaemia				
WHO (10%)	6 (5.9)	2 (3.9)	3 (9.4)	0.376
WHO (4%)	13 (12.7)	5 (9.8)	6 (18.8)	0.262
CDC (5%)	12 (11.8)	4 (7.8)	6 (18.8)	0.179
Severe anaemia	2 (2.0)	0 (0.0)	1 (3.1)	0.386
Renal impairment	11 (10.8)	2 (3.9)	6 (18.8)	0.051
Shock	1 (1.0)	0 (0.0)	1 (3.1)	0.386
Significant Bleeding	0	0	0	-
Prostration/severe weakness	20 (19.6)	10 (19.6)	8 (25.0)	0.562
Acidosis/Acidaemia	11 (10.8)	3 (5.9)	7 (21.9)	**0.042**
Hypoglycaemia (<2.2mmol/L)	1 (1.0)	0 (0.0)	1 (3.1)	386
Impaired Consciousness (GCS<11)	4 (3.9)	0 (0.0)	3 (9.4)	0.054
Jaundice	15 (14.7)	7 (13.7)	4 (12.5)	1.000
Pulmonary Oedema/ARDS	1 (1.0)	1 (2.0)	0 (0.0)	1.000
Repeated Convulsions/seizures	1 (1.0)	0 (0.0)	1 (3.1)	0.386
Outcome				
All deaths	5 (4.9)	2 (3.9)	1 (3.1)	1.000
Malaria deaths	4 (3.9)	2 (3.9)	0 (0.0)	0.520
Duration of hospitalization, median days (range)	5 (2 – 35)	4 (2 – 18)	6 (3 – 35)	**0.003**
Therapeutic intervention				
Admission into ICU	8 (7.8)	3 (5.9)	3 (9.4)	0.672
Dialysis	6 (5.9)	0 (0.0)	5 (15.6)	**0.007**
Laboratory finding				
Parasite level, median % (range)	1.3 (0 – 18)	1.0 (0 – 18)	1.5 (0 – 15)	0.205
WBC count, median cells X 10^9/L	5.6 (2.4 – 36.0)	5.6 (2.5 – 18.0)	6.0 (3.1 – 36.0)	0.929
Platelets	64.5 (13 – 388)	76 (11 – 214)	64.5 (13 – 388)	0.925

*19 participants had unknown HIV status

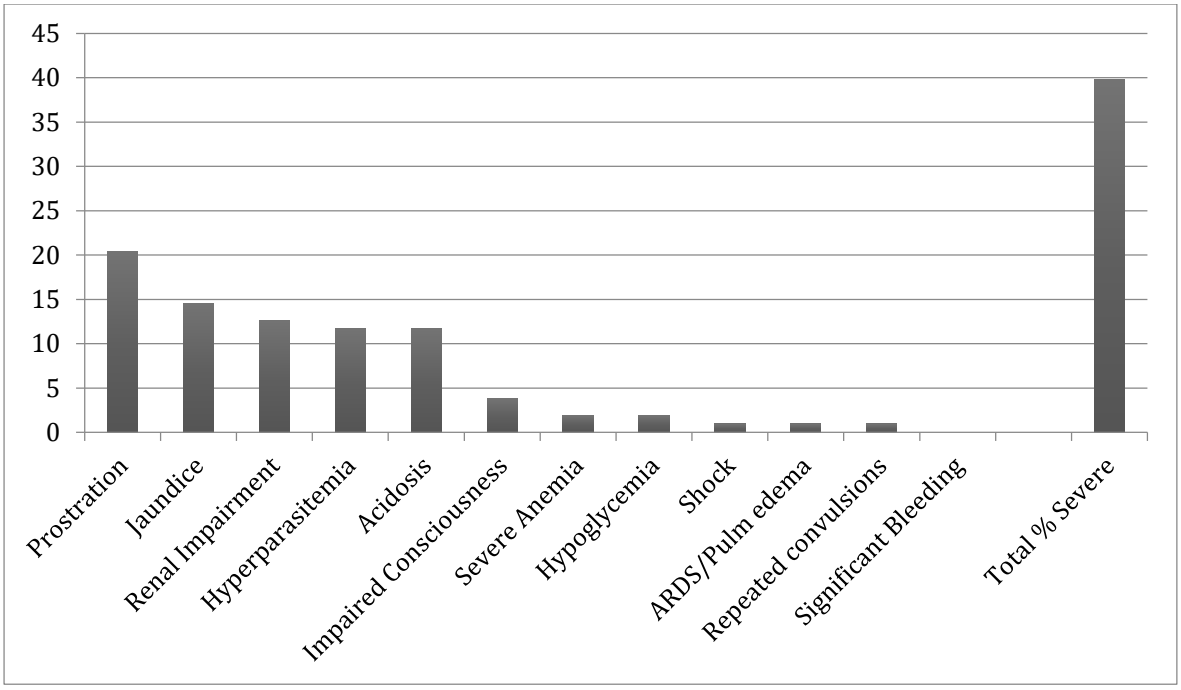

Figure 3. Percentage of participants with specified WHO features of Severity.

Table 5: Comparison between groups with severe malaria that received artesunate and those that did not.

	Severe Malaria (*n*=40)		
	Non-Artesunate (n=23)	Artesunate (n=17)	P
H/C Admission*	0 (0.0)	4 (23.5)	**0.026**
ICU admission†	0 (0.0)	8 (47.1)	**<0.001**
Ventilation	0 (0.0)	4 (40.0)	**0.026**
Haemodialysis	0 (0.0)	6 (35.3)	**0.003**
Blood Transfusion	2 (8.7)	6 (35.3)	0.053
Mortality	0 (0.0)	5 (29.4)	**0.009**

*High Care (H/C) similar to ICU but sperate from main ICU and usually not 1:1 nursing.

†Intensive Care Unit (ICU)

Discussion

There was a large number of severe malaria cases (39.9%) and a relatively high mortality rate (4.9%) over the study period. The majority of malaria cases attended to were young African male travellers that had visited their country of birth during the December festive period. These groups of travellers, that are increasingly representative of malaria infections in non-endemic areas around the world, are being referred to as travellers visiting friends and relatives (VFRs) (31). A large proportion of the study group were born and grew up in malaria endemic areas and whether semi-immunity to malaria is protective for severe malaria in our setting is suggested but remains unclear. The use of Artesunate, particularly in the sickest groups of patients managed in high care/ICU, appears to have been more widely adopted.

The study supports previous data from previous studies conducted in Gauteng that demonstrated a large seasonal peak in January associated with travel, predominantly to Mozambique, during the festive period (4,6,7). All malaria infections were contracted in sub-Saharan Africa. The participant characteristics were also similar in that the majority were young African male expatriates born in Mozambique that were resident in SA. The group were also similar to the group described by Cohen *et al* at the same facility 17 years ago, in that a significant proportion of the participants were semi-immune, having grown up in malaria endemic areas (6). The semi-immune group tended to have less prostration and a lower parasitaemia but there wasn't a statistically significant difference in the number with severe malaria. There is currently no reliable clinical biomarker to assess immunity but it is likely that immunity wanes the longer time is spent away from endemic areas (31). The median duration of residency for patients that grew up in malaria endemic areas was around

10 years. It is likely that the economic promises Gauteng offers will result continued numbers of malaria cases related to travellers VFRs.

There is a paucity of local and international data on the relative frequencies of these signs and symptoms in participants who present to hospital in non-endemic areas for care. The frequency of a few clinical findings reported by 2 international studies was similar but had some notable differences, which may be explained by higher rates of non-*falciparum* malaria in those studies. A higher percentage of participants reported headache, nausea and vomiting and abdominal pain/cramps. Where overlapping features were reported, comparison can be seen in Table 6 (6,15,16). The frequency of splenomegaly or pallor was notably low at 4.9% each. The most common clinical features are non-specific and thus clearly demonstrates the importance of a high clinical index of suspicion for malaria during peak periods. A detailed travel history and an awareness of areas with endemic transmission, both within and outside of SA are essential to the early recognition and diagnosis of malaria. This is especially important because a delayed diagnosis and institution of therapy is associated with adverse outcomes in malaria. This can be validated by the high cases fatality rates seen with odyssean malaria where there is often a delayed diagnosis due to lack of clinical suspicion (9). It is lastly important to note that although none of the participants in this study contracted malaria within Gauteng, the possibility of odyssean malaria does exist without a travel history and should be considered in unexplained acute febrile illness.

The study population demonstrated a large proportion (39.2% by the WHO clinical definition and 33.3% by the WHO research definition) of participants with severe

malaria. This was higher than previous studies conducted in Gauteng which demonstrated severe malaria in 10-30% of patients presenting for care (4,6,7). This may be partly accounted for by the fact that only patients admitted from casualty to the medical wards were included in the study, whereas in some studies patients seen and discharged from casualties were also included (4,6). However it is worth noting that in Cohen *et al* (6), 17% of participants were excluded because they were discharged before data could be collected. In this study the commonest feature of severity was prostration followed by jaundice, renal impairment and acidosis. It is worth considering that prostration in this study may be overestimated owing to self-reporting bias. In Cohen *et al* (6) the commonest features of severity were renal impairment, acidosis and hepatic dysfunction/jaundice (prostration was not listed as a feature of severity as the definitions were updated by the WHO in 2014) (6). Discounting prostration data from this study supports the previous findings on features in Cohen *et al* (6). In concordance with Cohen *et al*, acidosis was more commonly a feature of severity in HIV positive patients ($p<0.05$) (6).

On multivariate analysis it was found that a higher white blood cell count, adjusted OR=1.41 (95% CI:1.07-1.86) and probably a higher parasite level, OR=1.31 (95% CI:1.08-1.59) was associated with a higher risk of severe malaria. HIV infection and non-immunity were not shown to be a risk factor for the development of severe malaria in this study despite Cohen *et al* demonstrating the association between the risk for severe malaria with HIV in non-immune patients (6). This was not a primary objective of the study and it was not powered to detect this outcome and may be also be due to waning immunity related to duration of residency outside of malaria endemic areas (31). Despite not being demonstrated as a risk factor on multivariate

analysis a higher parasite level was observed in the non-immune versus semi-immune participants ($p<0.02$).

Around a third of the study participants were found to be HIV positive in this study, 62.5% (20/32) of which were newly diagnosed, highlighting the importance in overlap between the two conditions in our setting. This was similar to the 33% of patients found to be HIV positive by Cohen *et al* (6). In just under one fifth of participants HIV testing was not performed. It is important that all patients presenting with an acute febrile illness (including malaria) and a travel history be offered VCT. Severe malaria appeared more frequent in the non-immune group when compared to the semi-immune group, but the p-value was not statistically significant ($p=0.089$). Comparison of HIV positive and negative groups demonstrated that in this sample, HIV positive participants with malaria were more likely to present with acidosis as a feature of severity ($p<0.05$), were more likely to have a more prolonged hospital stay (median of 6 vs 4 days, $p=0.003$) and were more likely to require haemodialysis ($p=0.007$). Data has shown that malaria infection results in a significant decrease in CD4 count (17), but in participants within this sample there was no significant difference in CD4 count between immune and semi-immune participants with HIV co-infection ($p=0.232$). The vast majority of participants were asymptomatic for HIV infection in keeping with Cohen *et al* (6).

Despite evidence for mortality benefit as well as an improved safety profile (reduced risk of hypoglycaemia and QT prolongation) with the use of artesunate as compared to quinine for the management of severe malaria, only 17/40 (42.5%) of participants with severe malaria received artesunate based regimens (17,18,32). The mortality in

the group of participants that received artesunate was significantly higher than the non-artesunate group (p=0.009). This likely represents that, while artesunate was available at CHBAH through section 21 application during the study period, artesunate seems to have been used more frequently in the subset of participants with severe malaria that were more ill and required admission to high care or ICU and had a higher baseline risk of mortality; rather than suggesting that artesunate use was causal in the higher mortality rate. This higher use of artesunate in ICU and H/C is likely protocol driven and may related to the industry involved in section 21 application after hours and in busy general wards. Despite the limited use of artesunate in all participants with severe malaria, it appears from the data that clinician driven clinical decisions to treat some cases of severe malaria with quinine-based regimens did not appear to result in adverse outcomes in this group of participants. Artesunate was not available when prior studies were conducted in Gauteng (6,7). It appears from the data that the use of artemether-lumefantrine in both uncomplicated and after initial treatment in complicated malaria has been well adapted as more than 95% of participants received this anti-malarial.

Only one prior study determined the number of patients in Gauteng presenting with malaria, that had taken malaria prophylaxis. Dube *et al* reported on 4 patients (2%) having taken some form of malaria prophylaxis (7). The number of participants whom had taken malaria prophylaxis in this study was low despite many of them having had previous episode/s of malaria, similarly in other centres around the world (table 6) (15,16). The department of health has provided extensive guidelines on malaria prophylaxis, updated as recently as January 2019 (19). Unfortunately the

public healthcare sector in SA does not currently offer malaria prophylaxis to travellers as part of the current extended drug list (20).

Around 6% of participants received haemodialysis comparable to the 6.2% reported by Cohen *et al* (6) and the 7% in Akselrod *et al* (16) (Table 6). The number of admissions to ICU, at 7.8% was higher than the study in London by Francis *et al* (15), but was lower than the study in Washington by Akselrod *et al* (16) . The median length of stay was found to be 2 days longer than the study by Cohen *et al* (6) and similar to the study by Akselrod *et al* (16).

The case fatality rate can be said to be 3.9%, of which all patients died in ICU and received treatment with Artesunate. The case fatality rate was nearly four times the national average and twice the reported rate of previous studies in Gauteng tertiary facilities (1-2%) but similar to a larger study in Gauteng where the case fatality rate was 4% (4,6,7). The mortality rate far exceeded the studies conducted in Washington and London, which may be due health care access problems at the median duration of symptoms was more than 4 days longer (15,16) (Table 6).

Study strengths and limitations

Strengths of the study include the prospective design and the description of clinical characteristics that have not previously been extensively described as well as comparison to international work. Limitations included the relatively short data collection period limiting sample size and preventing reaching the target sample size,

and the study being conducted at a single centre referral hospital. There is possible lack of inclusion of a number of patients with very severe malaria that demised shortly after admission or that were not referred or whom were discharged from casualty inferring some degree of selection bias. Some of the comparative statistics had small sample sizes. Some participants were excluded due to inability to consent due to language barriers possibly resulting in exclusion bias. Some of the questionnaire relied on participant recall of symptomatology which may have resulted in recall bias. There are possible confounders due to the overlap of variables assessed that may be affected by both HIV and malaria such as renal dysfunction and anaemia. Another limitation was that not all data was available for analysis such as HIV results, CD4 counts and HIV viral loads.

Table 6. Comparison of relative frequencies of presenting clinical features of participants with malaria to hospitals in non-endemic regions.

Characteristic	Soweto, SA	Soweto, SA (6)	London, UK (15)	Washington, USA (16)
Number studied	102	336	133	100
Year	2016-2017	2001-2002	2013-2015	2000-2017
Age*	30 (18 - 72)	29 (15 - 49)	41 (IQR 30-50)	Mean = 41.9 (± SD 13.4)
Male sex	70.6%	78.3%	64.7%	60.0%
P. falciparum	99%	99%	76.7%	76.0%
Born in malarial area	62.7%	68%	-	58.6* (n=70)
Travel to sub-Saharan Africa	100% (Southern)	-	70.4% (West)	94% (East and West)
Prior malaria episode	22.5%	-	-	51%
Chemoprophylaxis	7.8%	-	12.0%	26%
Days since arrival from travel for *falciparum*	Mean 11.39 (± SD 7.3)	-	7 (IQR 9)	7 (IQR 9)
HIV infected	31.4% (n=83)	32.7%	8.3% (n=36)	1%[§]
Fever	91.2%	-	93.6%	92.0%
Chills/Rigors	95.1%	59.6%[†]	-	78.0%
Headache	90.2%	79.1%[†]	-	64.0%
Myalgias/arthralgias	63.7%	-	-	53.0%
Nausea/vomiting	66.7%	39.2%[†]	-	35.0%
Diarrhoea	32.4%	21.6%[†]	23.3%	26.0%
Abdominal pain	45.1%	-	-	18.0%
Weakness	19.6%	-	-	25.0%
Altered mentation	18.6%	-	-	9.0%
Severe malaria (Clin/Res)	39.2/33.3%	10.5%[‡]	36.3%	21.0%
Median parasite level	1.3% (0.0-18.0)	HIV^- 0.6 (0-25) HIV^+ 0.5 (0-22)	1.0% (IQR 2)	mean 2.7 (± SD 4.9)
Platelets $x10^9/L$*	64.5 (IQR 56.25)	-	90 (IQR 74)	mean 36.6 (± SD 6.6)
ICU/high care	7.8%	6.0%	4.5%	21.0%
Artesunate	18.6%	-	33.3%	1.0%
Quinine/Quinidine	18.6%	100%	-	38.0%
Artemether-lumefantrine	93.0%	-	-	19.0%
Dialysis	5.9%	6.3%	-	7.0%
Transfusion	7.8%	-	-	7.0%
Length of stay	5.0	3.0	-	4.36
Mortality	4.9%	0.1%	0.0%	0.0%

* Data presented according to source information, Median with range unless otherwise specified

[†] Data extrapolated from article (not specifically reported)

[‡] Study included patients seen and discharged from casualty

[§] 1 patient that refused follow up testing

Conclusion

Malaria continues to pose a significant problem to Southern Africa. CHBAH continues to manage a large number of severe malaria cases shortly after the festive season in December that are imported predominantly from southern Mozambique and Limpopo province. The presenting signs and symptoms were non-specific and highlight the need for a high index of suspicion during peak malaria months. A large number of participants were HIV positive and were newly diagnosed on admission. Despite proven mortality benefit and improved safety profile, there still appears to be limited use of Artesunate outside of high care and ICU environments that is likely limited by the section 21application process. The case fatality rate was higher than previously reported and was possibly underestimated.

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3.1 Appendix A

Information Document

Study Title: Malaria at Chris Hani Baragwanath Academic Hospital.

Introduction: Good Day**,** My name is:……..and I am currently working with a group of researchers at the University of the Witwatersrand. We are currently researching malaria at Chris Hani Baragwanath Academic Hospital. Research is a process whereby we collect and analyse information to improve our understanding about patients and their medical conditions. In this study we are collecting information about patients and the characteristics of the malaria parasites affecting them who present to Chris Hani Baragwanath Academic Hospital. We are collecting this information to better understand the condition in which patients present to the hospital, how patients are treated, what types of malaria patients have and how any other medical problems/genetic characteristics affect their outcomes. The participation and collection of this information does not affect or form part of your normal medical care.

Invitation to Participate: We are inviting you to kindly take part in our research study titled Malaria at Chris Hani Baragwanath Academic Hospital.

What participation includes: We will be asking all adult patients (18 years old and older) who have been diagnosed with malaria at Chris Hani Baragwanath Academic

Hospital to participate in the study. The study will involve us (the researchers) collecting medical information, which includes details from history and examination findings from your medical records, blood results and treatment charts. If we cannot find all the information required, we may ask your permission to ask some additional questions or ask your permission to do a short medical examination. The entire process is expected to take about thirty minutes and comprises the entirety of your participation. Your participation/ non-participation will not affect your length of stay in hospital, will not affect the treatment or quality of care you receive and will not result in any financial gain or loss. No additional blood samples would need to be taken, but with your permission we would be using some of the blood previously drawn, to look at some of the features of the malaria and levels of medications used to treat the malaria. Part of the study will include assessing how Human Immunodeficiency Virus (HIV) infection affects the severity and outcomes of patients suffering from malaria Infection. This information will only be collected if HIV status is known. Voluntary testing and counselling for HIV will not form part of the study. Every effort will be made to ensure this information remains confidential (please see section on confidentiality).

Risks: We the researchers have not identified any risks that may be incurred by participating in the study.

Benefits of being in the study: We the researchers do not expect you to benefit from participation in the study. No money or financial re-imbursement is offered, as no additional follow up is required. There will be no additional medications or treatment

modalities made available to participants that are not already available to the treating physicians.

You will be given access to relevant information on the study while involved in the project.

Participation in our study is voluntary: This means that your involvement in this study is your choice and will not affect any of the care you would normally receive. You may also decide at any point to withdraw your involvement should you change your mind. Withdrawal from the study will not affect the care you would normally receive. There will be separate consent form for your agreement to allow for further testing on blood samples already taken. Your refusal for further testing on these blood samples does not exclude you from participating in the clinical part of the study. Testing on blood samples includes testing the type and amount of malaria parasites in your blood. The amount or levels of medications present in your blood and the testing for some of your genetic characteristics that are thought to affect how patients respond to being infected by malaria.

Confidentiality: All efforts to maintain confidentiality will be maintained throughout the study and as such no identifying personal information will be made available to the public or public records. Although we cannot guarantee confidentiality we would want to assure the participant that every effort would be made to avoid any breach of confidentiality. In the case where personal information would have to be disclosed if so prescribed by South African Law, your records will be kept separate from our data and blood samples.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the University of the Witwatersrand human research committee.

If you would like any more information, please contact either one of the following individuals:

Contact Details of researchers:

1) Prof. Colin Menezes:

2) Prof. Alan Karstaedt:

3) Prof. Theresa Coetzer:

4) Prof. Robyn Van Zyl:

6) Dr Darren Fox: 011-933-0000/SMS0062

Contact details of REC administrator and chair – for reporting of any complaints or problems.

Should you not wish to discuss any details or concerns with one of the above researchers you may contact the University of the Witwatersrand human research committee, Professor Cleaton-Jones or Ms. Zanele Ndlovu on tel:011-717-1234.

Informed Consent to participate in the study

I have been informed by:……..……...… about the nature, conduct, benefits and risks of this study "Malaria at Chris Hani Baragwanath Academic Hospital". I have also received, read and understood the written information (Participant Information form and Consent form) regarding the study.

I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials, diagnosis and clinical information will be anonymously processed into the study report.

I may at any stage, without prejudice, withdraw my consent and participation in the study.

I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in this study.

Participant's Name: _____

(please print)

Participant's Signature: _____ **Date/Time** _____

I, _____ (please print) hereby confirm that the above participant has been informed fully about the nature, conduct and risks of the above study.

Person Obtaining

Consent Signature: _____ **Date/Time** _____

Witness' Name:

(If applicable) _____

Witness' Signature:

(If applicable) _____ **Date/Time**

Informed Consent to the use of blood samples previously taken for additional testing

I have been informed by:……, have read the information sheet above, and understand that as part of my participation in the study "Malaria at Chris Hani Baragwanath Academic Hospital" blood samples previously taken from me will be kept at the NHLS laboratory at Chris Hani Baragwanath Academic Hospital and will be transferred to the University of the Witwatersrand Medical School for further testing.

I am aware that testing on this blood would include and is limited to:

1. Testing to look for a specific type of the malaria parasite called gametocytes.
2. Testing to identify the type and genetics of the malaria parasite found in the blood sample
3. Testing for two genetic conditions that are thought to provide some protection from developing severe malaria. The two conditions are called cytochrome $b5^{T116S}$ polymorphism and G6PD deficiency
4. Analysing blood samples to ascertain the levels/concentration of medications present in the blood (Anti-malarial and Anti-retroviral if applicable)

Once these tests are completed the blood samples would be discarded via normal medical waste services available to the Pharmacology and Molecular Parasitology laboratories at the University of the Witwatersrand Medical School. These blood samples will be kept anonymous and only the study number will be used to identify the specimen. All efforts to maintain confidentiality will be practiced.

I hereby consent to the transport of blood specimens from the National Health Laboratory Service at Chris Hani Baragwanath Academic Hospital to the University of the Witwatersrand Medical School and to the additional testing on these blood samples as described above. I am further aware that I may withdraw my consent at any time, without prejudice, and acknowledge that I have been given ample opportunity to ask questions about testing to be done on my blood and the procedures involved.

Participant's Name: _____

(please print)

Participant's Signature: _____ **Date/Time** _____

I, _____ (please print) hereby confirm that the above participant has been informed fully about the, nature, conduct and risks of the above study.

Person Obtaining Consent Signature: _____ **Date/Time** _____

Witness' Name:

(If applicable)

_____
(please print)

Witness' Signature:

(If applicable) _____ **Date/Time**

3.2 Appendix B

Clinical Data Collection Sheet: Malaria at Chris Hani Baragwanath Academic Hospital

Demographics

Study Number					Race	Black	Indian	White	Coloured	Asian	
Gender	M	F			Residency						
Place of birth					Duration (yrs.)						
Pregnant	Y	N	Unknown		Age (years)						

Hospital stay

Notified?	Y	N	Unknown
Date of Admission (D/M/Y):			
Date of Discharge (D/M/Y):			
Date of Demise (D/M/Y):			
Length of Hospital Stay (days):			

Level of Care

General Ward	Y	N	Days	
Short Stay Ward	Y	N	Days	
High Care	Y	N	Days	
Intensive Care Unit	Y	N	Days	

Travel history

Recent travel history to endemic malaria area					Y	N
Country						
City						
Duration of stay (days)						
Number of previous visits	1	2	3	4	>4	
Time from return to current presentation (days)						
Was any prophylaxis taken?	Y	N	Drug			

Presenting symptoms

Headache		Weakness	
Fevers		Diarrhoea	
Lethargy		Decreased level of consciousness	
Chills			
Loss of appetite		Arthralgia	
Nausea		Myalgia	
Vomiting		Abdominal cramps	
Jaundice		Night sweats	
Confusion		Cola coloured urine	
Dizziness		Prostration	
Abnormal bleeding		Confusion	
Other - specify			

Blood Pressure	
Pulse Rate	
Temperature	
Respiratory Rate	
Baseline GCS	

Date of symptom onset	

Clinical examination (tick)

Prostration		Convulsions/seizures	
Confusion		Rash	
Jaundice		Pulmonary consolidation	
Pallor		Lymphadenopathy	
Splenomegaly		Haemaglobinuria	
Clinical dehydration		Hypoglycaemia	

Co-morbid HIV infection (tick)

HIV	Y	N	?	CD4		Viral Load			Newly Diagnosed		Y	N			
Treatment		Y		N		Duration (weeks)									
ART regimen		1	2	3		Bactrim Prophylaxis		Yes	No	Duration (wks.)					
Current WHO stage						Previous or baseline WHO stage				Date					
ARVs		ABC	AZT		TDF		3TC		d4T						
		FTC	ddi		EFV		NVP		ALUV						
Other						Unknown									

WHO staging reference (South African National HIV 2014 ART guidelines)

Clinical Stage	Clinical conditions or symptoms
Primary HIV infection	Asymptomatic Acute retroviral syndrome
Stage 1	Asymptomatic Persistent generalized lymphadenopathy
Stage 2	Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrheic dermatitis Fungal nail infections
Stage 3	Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for >1 month Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anaemia (haemoglobin<8 g/dL) Neutropenia (neutrophils <500 cells/µL) Chronic thrombocytopenia (platelets <50,000 cells/µL)
Stage 4	HIV wasting syndrome, as defined by the CDC Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month orvisceral herpes at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extra pulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Cryptococcosis, extra pulmonary (including meningitis) Disseminated non-Tuberculosis mycobacteria infection Progressive multifocal leukoencephalopathy Candida of the trachea, bronchi, or lungs Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) Recurrent non-typhoidal Salmonella bacteraemia Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy Symptomatic HIV-associated cardiomyopathy Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Other Co-morbidities: specify
1:
2:
3:
4:
5:

Clinical/Biochemical features of severe malaria (WHO 2015)

Tick box (Y/N) and specify value and units:

Reference: World Health Organization. Guidelines for the treatment of malaria, 3rd ed, WHO, Geneva 2015.			Value and Units	Note: WHO no longer qualifies a level of parasitaemia that defines severe malaria below 10% but states that counts above 4% (2% in non-endemic) put patients at high risk for developing severe malaria and developing treatment failure.			Value and Units
Hyper-parasitaemia	In the absence of any other severe features - >10%	Y N		Acidosis or acidaemia	Acidotic breathing or Bicarbonate < 15mmol/L or venous lactate ≥ 5mmol/L or Base deficit > 8 mmol/L	Y N	
	CDC > 5%	Y N					
Severe Anaemia	Hb<7g/dL or HCT<20% with parasite count >10,000/mcL	Y N		Hypoglycaemia	<2.2mmol/L	Y N	
Renal Impairment	Serum Urea> 20mmol/L or serum creatinine > 265 umol/L	Y N		Impaired consciousness	GCS<11	Y N	
Shock	Compensated: Capillary refill >3 secs	Y N		Jaundice	TB>50umol/L with a parasite count >100,000/mcL	Y N	
	Decompensated: SBP<80mmHg with poor perfusion (capp refill >3sec)	Y N					
Significant bleeding	Prolonged bleeding from gums, venepuncture sites or nose. Also malaena or haematemesis	Y N		Pulmonary oedema/ARDS	Confirmed on radiograph or RR>30 or Sats in RA < 92%	Y N	
Prostration or weakness	Unable to sit or walk without any other obvious neurological cause	Y N		Repeated convulsions/ seizures	More than 2 in 24 hours	Y N	

Diagnosis

Rapid test falciparum PCR	Result	Positive		Negative	
Thin/Thick smear	Result	Positive		Negative	
Parasite count	Initial smear	%		72hrs	%
Gametocytes	Initial smear	%		72hrs	%

Falciparum	
Vivax	
Ovale	
Malariae	

Management

Rx combination	tick	Specify duration of each medication (days)		Dosages of each drug (mg/dose) and doses/day	
Co-Artem®					
Quinine and Co-artem®					
Quinine and Clindamycin					
Quinine and Doxycycline					
Artesunate and Co-Artem®					
Artesunate and Doxycycline					
Artesunate and Clindamycin					
Other (specifiy):					

If Quinine given	Loading Dose? (20mg/kg)	Y	N
If Quinine given in renal failure	Dosages adjusted?	Y	N
What was the delay, if any, from the time patient seen to receiving first dose (hours)			

Intubated/Ventilated	Y	N	Duration (days)	
Dialysis	Y	N	Sessions	
Blood transfusions	Y	N	Total Units	

Blood Results (standard NHLS units)

Test	Admission	72 Hours	Discharge
WCC			
HB			
MCV			
HCT			
PLT			
Morphology			
Reticulocytes			
INR			
PTT			
Fibrinogen			
D-dimers			
Lactate (gas)			
G6PD			
TB			
CB			
TP			
Alb			
ALT			
AST			
ALP			
GGT			
Urea			
Creatinine			

Blood Cultures		
Date	**Organism/s**	**Sens.**

If lumbar puncture done provide results (standard NHLS units):

Appearance		**PMN**	
Protein		**Lymph**	
Glucose		**Eryth**	
Chloride		**GXP**	
VDRL		**MCS**	
TB culture		**India ink**	
Crypto Ag		**MCS**	

Outcome

Discharge Home	Y	N			
Demised	Y	N			
All-cause mortality	Y	N	Malaria Mortality	Y	N

3.3 Appendix C

Informed Consent in the case where the participant is unable to consent

This consent document is to be used in circumstances where the participant is unable to give informed consent based on clinical status. This includes participants who are not of sound mind; including those participants that are confused, have a psychiatric co-morbidity that would make the normal consent process impossible (psychosis), or is obtunded/unconscious or is heavily sedated in a high care or ICU setting.

The Information sheets is to be presented to the guardian (Spouse/closest family member/designated person/s in ICU in that order of preference) of the participant either in person or telephonically. It is to be explained that if the guardian gives consent to study participation that once/if the participant becomes of sound mind so that he/she would be able to consent to participate in the study that the study participant will be presented with the information in the information sheet and informed consent shall be attempted to be obtained again. If the specified person does not wish to participate they will no longer considered study participants from that point onward and any information/blood samples from that participant shall be discarded and not included in the data analysis. Information regarding reason for dropout will be sought and this information will be included as part of the methodology of the study.

Preliminary Consent to participate in study by Spouse/Relative/Guardian:

I have been informed by: ……..……...… about the nature, conduct, benefits and risks of this study "Malaria at Chris Hani Baragwanath Academic Hospital". I have also received, read and understood

the written information (Participant Information form and Consent form) regarding the study.

I can confirm that the participant is unable to him/herself give informed consent to participate in the study.

I am aware that the results of the study, including personal details relating to the participant…… ……., of whom I am the spouse/relative/guardian (circle that which applies), regarding sex, age, date of birth, initials, diagnosis and clinical information will be anonymously processed into the study report.

I may at any stage, without prejudice, withdraw consent and participation in the study on behalf of the participant.

I hereby understand that the consent process shall be repeated once/if the participant becomes

I have had sufficient opportunity to ask questions and (of my own free will) declare my willingness to allow the aforementioned participant to be included in the study.

Guardians Name_____ Date_____ Place _____

Signature_____

Witness 1 (If applicable) _____

Witness 2 (If applicable) _____

Person Obtaining Consent signature _____

Informed Consent to the use of blood samples previously taken for additional testing where the participant is unable to consent

I have been informed by: ……, have read the information sheet above, and understand that as part of the participant……'s participation in the study "Malaria at Chris Hani Baragwanath Academic Hospital" blood samples previously taken from me will be kept at the NHLS laboratory at Chris Hani Baragwanath Academic Hospital and will be transferred to the University of the Witwatersrand Medical School for further testing.

I am aware that testing on this blood would include and is limited to:

1. Testing to look for a specific type of the malaria parasite called gametocytes.
2. Testing to identify the type and genetics of the malaria parasite found in the blood sample
3. Testing for two genetic conditions that are thought to provide some protection from developing severe malaria. The two conditions are called cytochrome $b5^{T116S}$ polymorphism and G6PD deficiency
4. Analysing blood samples to ascertain the levels/concentration of medications present in the blood (Anti-malarial and Anti-retroviral if applicable)

Once these tests are completed the blood samples would be discarded via normal medical waste services available to the Pharmacology and Molecular Parasitology laboratories at the University of the Witwatersrand Medical School. These blood

samples will be kept anonymous and only the study number will be used to identify the specimen. All efforts to maintain confidentiality will be practiced.

I hereby consent to the transport of blood specimens from the National Health Laboratory Service at Chris Hani Baragwanath Academic Hospital to the University of the Witwatersrand Medical School and to the additional testing on these blood samples as described above. I am further aware that I may withdraw my consent at any time, without prejudice, and acknowledge that I have been given ample opportunity to ask questions about testing to be done on the blood samples from the above mentioned participant and the procedures involved.

Guardians Name_____ Date_____ Place _____

Guardian's relationship to the participant_____

Signature_____

Witness 1 (If applicable) _____

Witness 2 (If applicable) _____

Person Obtaining Consent signature _____

3.4 Appendix D

R14/49 Dr Darren Fox

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1611137

NAME: (Principal Investigator)	Dr Darren Fox
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Clinical Aspects and Outcomes of Patients with Malaria at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	Adhoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-Study under Primary Study M160549 Prof Colin Menezes
SUPERVISOR:	Colin Menezes and Alan Karstaedt
APPROVED BY:	Prof A Dhai, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/12/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 15/12/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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Mrs Sandra Benn
Postgraduate Office,
Faculty of Health Sciences,
Wits Medical School.

23 April 2020

Dear Mrs Benn,

RE: TURN-IT-IN REPORT ON MMED RESEARCH - Dr Darren Joshua Fox, student no. 0603611P

We wish to confirm that the "turn-it-in" report submitted by Dr Fox for his MMed research report entitled: CLINICAL ASPECTS AND OUTCOMES OF PATIENTS WITH MALARIA AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL, is satisfactory with no evidence of obvious plagiarism (<1% - 1%) in all the sections picked up by the software where the total similarity index of 10% was noted.

Sincerely,

A/Professor Colin Menezes

Professor Alan Karstaedt

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SENATE PLAGIARISM POLICY: APPENDIX ONE
I Darren Joshua Fox (Student number: 0603611P) am a student registered for the degree of Masters of Medicine in the academic year 2020

I hereby declare the following:

- - I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- - I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- - I have followed the required conventions in referencing the thoughts and ideas of others.
- - I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- - I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection)

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