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Characteristics of patients (expatriates and long-term travellers) with suspected malaria, being evacuated by fixed-wing air ambulances out of Sub-Saharan Africa to Johannesburg, South Africa. a retrospective case review, for the period July 2006 through June 2009

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CHARACTERISTICS OF PATIENTS (EXPATRIATES AND LONG-TERM TRAVELLERS) WITH SUSPECTED MALARIA, BEING EVACUATED BY FIXED-WING AIR AMBULANCES OUT OF SUB-SAHARAN AFRICA TO JOHANNESBURG, SOUTH AFRICA. A RETROSPECTIVE CASE REVIEW, FOR THE PERIOD JULY 2006 THROUGH JUNE 2009.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science (Medicine) Emergency Medicine

Johannesburg, 2011

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ABSTRACT

Background Promotion of job opportunities and tourism in African countries has led to an increase in expatriates in malaria endemic areas. A paucity of data exist on characteristics and numbers of expatriates and long-term travellers being evacuated from sub-Saharan Africa for suspected malaria infections diagnosed while still in Africa.

Methods A retrospective flight record review of a South African fixed-wing air-ambulance provider from June 2006 through July 2009 was performed. Adult expatriates and long-term travellers with suspected malaria being evacuated from sub-Saharan African countries to Johannesburg, South Africa were included.

Results Suspected malaria was the single most common diagnosis for dispatching air-ambulances with 81 (11.9%) of the 679 flights. Accuracy of the initial diagnosis, based on confirmation of malaria at the receiving facility was 78.4% for blood smears, 92.3% for rapid detection tests and 42.8% for clinical signs alone. *P. falciparum* (alone, or in combination with other *Plasmodium* species) was the most frequently isolated species at both the referring (100%) and receiving (88.2%) facilities in cases where the species was documented. The suspected malaria patients were predominantly male 69 (84.1%), with a mean age of 42.1 ±12.8 years, and were in sub-Saharan Africa for occupational reasons 65 (79.3%). Angola, the Democratic Republic of Congo and Mozambique were the countries of origin in 48 (58.5%) of the suspected malaria flights. Compliance on appropriate malaria chemoprophylaxis was documented in two (2.4%) suspected malaria patients. Intubation as a marker of severity was required for 15 (18.3%) patients, and one (1.2%) patient died in-flight. No statistically significant difference (p=0.50) was shown for intubation requirements when comparing patients who had utilised malaria chemoprophylaxis with the patients who had not utilised chemoprophylaxis.

Conclusions Patients presented in advanced stages of severe/complicated malaria with concurrent poor chemoprophylaxis utilisation and compliance. Appropriate chemoprophylaxis did not decrease the severity of presentation (based on intubation requirements) and did not guarantee complete malaria protection.

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LIST OF ABBREVIATIONS:

APf:	Annual *Plasmodium falciparum*
A*Pf*EIR:	Annual *P. falciparum* entomological inoculation rates
CAMTS:	Commission on Accreditation of Medical Transport Systems
DRC:	Democratic Republic of Congo
EIR:	Entomological inoculation rate
EURAMI:	European Air Medical Institute
GAN:	Global Assistance Network
GCS:	Glasgow Coma Scale
Hb:	Haemoglobin
Hgt:	Haemo-Gluco test
HRP-2:	Histidine-rich protein-2
ICU:	Intensive care unit
NCME:	Nearest centre for medical excellence
N/D:	Not documented
NMSS:	National Malaria Surveillance System
pLDH:	Parasite-specific lactate dehydrogenase
PRC	Packed red cells
RBC:	Red blood cells
RDT:	Rapid detection test
SD:	Standard Deviation
SBP:	Systolic blood pressure
TropNetEurop:	European Network on Imported Infectious Disease Surveillance
USP:	United States Pharmacopoeia
WHO:	World Health Organization

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Malaria.

Malaria is transmitted through exposure to bites of the female *Anopheles* mosquito. [1] The female requires a blood meal (protein), for the development of her eggs which are later laid in water. [2] During the blood meal (biting of a human), the mosquito inoculates sporozoites (from her saliva) into the human host, which infect the liver cells, where they undergo asexual replication and mature into schizonts. Merozoites are released as the schizonts rupture, and enter the bloodstream, infecting red blood cells. The merozoites then either go into the erythrocytic cycle, maturing again into schizonts (asexual replication) releasing meroizites within the red cells, or differentiate into gametocytes (sexual erythrocytic stage). The erythrocytic cycle parasites are responsible for the clinical manifestations of malaria. Gametocytes are ingested by an *Anopheles* mosquito (vector) during a blood meal and through a life cycle starting in the mosquito's stomach, make their way to the mosquito's salivary glands. This leads to a new human being infected during a blood meal and perpetuates the malaria life cycle. [1][3] Four species of malaria are known: *Plasmodium vivax, P. ovale, P. malariae* and *P. falciparum.*[4] *P. knowlensi* is a simian plasmodia usually found in long- and pig-tailed macaques, which has been known to cause clinical infections in humans. [4][5] *P. vivax* and *P. ovale* may produce dormant liver stage parasites, which may reactivate months to years later. [2] Malaria incubation periods range from seven to 30 days, with the shorter period usually seen with *P. falciparum*. [2]

Malaria infection is placed into two categories, uncomplicated and complicated. Uncomplicated malaria commonly presents with a combination of fever, chills, sweating, headache, nausea and vomiting, generalised body aches and malaise. Severe (complicated) malaria manifestations

may include cerebral malaria (abnormal behaviour, impaired consciousness, seizures or coma), haemolysis (anaemia, haemoglobinuria), respiratory failure (pulmonary oedema, acute respiratory distress syndrome), thrombocytopenia, acute renal failure, hyperparisitaemia (>5% of erythrocytes infected), hypoglycaemia, metabolic acidosis, cardiovascular collapse or shock. [2][6] Any pregnant patient or patient under five years should be considered as complicated malaria.

The majority of infections in sub-Saharan Africa are caused by the most lethal of the four species, *P. falciparum,* which is also found in Haiti, the Dominican Republic and Papua New Guinea. [7] *P. vivax* is usually found in Central America, India, Bangladesh and Pakistan. *P. ovale* and *P. vivax* are found mainly in South-East Asia and South America. *P. malariae and P. ovale* are both uncommon. [1][7][8] *P. knowlesi* is found in South-East Asia and can be misidentified as *P. malariae.* In a retrospective review by Cox-Singh et al., 316 (31%) of the 1018 stored blood samples and films were found to contain *P. knowlesi* (as confirmed by the polymerase chain reaction test method) as opposed to the initial erroneous diagnosis of *P. malariae*. [5] The blood samples were from Malaysian Borneo and Peninsular Malaysia obtained during the period 2001 to 2006. Four of the fatal cases had been incorrectly diagnosed with *P. malariae* hyperparasitaemia. All four cases presented with severe malaria complicated by marked hepatorenal dysfunction and resulted in death. [5]

The number of bites by an infectious mosquito per person per unit of time is referred to as the entomological inoculation rate (EIR). The EIR is thought to be the most direct measurement of transmission intensity. [9] In a meta-analysis (1980 through 2004) of annual *P. falciparum* (A*Pf*) EIR's, thus the number of *P. falciparum* positive mosquito bites per person per year, across 23 of the 54 African countries, it was found that more than 55% of annual *P. falciparum*

entomological inoculation rates (A*Pf*EIR) were from Kenya, Burkina Faso, Tanzania and Gambia. [9][10]

1.2 Confirmatory malaria testing modalities.

Empirical clinical diagnosis remains the most common method of malaria diagnosis in many sub-Saharan African regions which leads to over-diagnosis with resultant over-treatment due to this methods low sensitivity, the overlap of the malaria symptom complex with many other tropical diseases and co-infections. [11][12]The two main methods of confirmatory testing for malaria is utilisation of a rapid detection test (RDT), or by microscopy.

1.2.1 The rapid detection test.

RDTs incorporate immunochromatographic capture procedures, with monoclonal antibodies providing the indicator of infection. [11][12][13] The newer simpler tests work by dropping a specified amount of fingerpick blood droplets (5-15µL) into a designated area and then adding a specified amount of buffer droplets into another designated area. [4][8][14] As the blood migrates across a nitrocellulose membrane the parasite antigens are captured by monoclonal antibodies prepared against a malaria antigen target, in effect labelling them during the mobile phase. A further monoclonal antibody, applied to a strip of nitrocellulose then captures the antigen-antibody complex producing a visible coloured line in the immobile phase. The preferred target antigens are those which are abundant in both the sexual and asexual stages of the parasite.[13] Current tests focus on the detection of histidine-rich protein-2 (HRP-2), which is specific to *P*.

falciparum, and parasite-specific lactate dehydrogenase (pLDH) or *Plasmodium* aldolase enzymes from the parasite glycolytic pathway found in all four *Plasmodium* species. [13] *P. falciparum* may be detected with HRP-2, P. *falciparum*-specific pLDH isomer. *P. vivax* may be detected with *P. vivax*-specific pLDH.[4][11] Different isomers of pLDH do exist for each of the four Plasmodium species. [13]

Commercially available RDTs are available as two, three or four bands and contain different combinations of target antigens to suit local malaria epidemiology. [4][11] Two-band tests target HRP-2 and therefore detect *P. falciparum* only, whereas the three-band tests also detect other malaria parasite antigens (*P. ovale, P*. *malariae* and *P. vivax)* by targeting HRP-2 combined with either pLDH or aldolase. [14] The three bands have a control line, a line for *P. falciparum* and a third line for detection of antigens such as pan-*Plasmodium*-specific pLDH or aldolase, which are common to all four *Plasmodium* species. [4][8] The four-band RDT has a fourth line which detects *P. vivax* through a *P. vivax*-specific pLDH isomer. [4]

Results of RDT results are available within 5 to 20 minutes. A positive result shows a line in the control area as well as the *P. falciparum* and/or mixed area. Should the control line not be visible, then the test is invalid. A negative test will only show the control line. Visible lines may be rated as strong, medium, weak and faint and this test line intensity variation has been shown to correlate with the parasite densities in both aldolase assays as well as the HRP-2 assay. [4][8]

In a meta-analysis by Marx et al., the malaria results of 5747 non-immune returning travellers from malaria endemic areas were analysed to determine the accuracy of RDTs for ruling out malaria. [14] Studies were included if the RDTs were compared with expert microscopic examination or polymerase chain reaction tests. The meta-analysis found that when testing for P. *falciparum* the HRP-2-based tests were more accurate than the pLDH-based tests. *P.*

falciparum sensitivities were 88-99% for HRP-2 and 79-95% for pLDH*. P*. *vivax* sensitivities were 46-93% for HRP-2/Aldolase-based tests and 62-95% for pLDH-based tests. *P*. *ovale* and *P. malariae* showed low and variable sensitivities of 7-80% for HRP-2/aldolase-based tests and 36-95% for pLDH-based tests. [14] A study by Van der Palen et al. of the stored blood of 452 returned travellers using two types of RDTs (the two-band SD FK50 Malaria Ag *P. falciparum* test and the three-band SD FK60 Malaria Ag *P. falciparum*/Pan test) and referencing with microscopy, showed 21 false negative RDT results 15/21 with parasite densities <100/µl and no false negative readings with parasite densities above 400/µl. [8] Of the 21 false negative results, 20 were for *P. falciparum* and a single mixed sample (*P. falciparum* and *P. ovale*) gave a false negative result.[8] Overall sensitivities were 87.5% for *P. vivax*, 76.3% for *P. ovale* and 45.2% for *P. malariae*, although sensitivity increased to 92.6% and 90.5% for *P. vivax* and *P. ovale* respectively at parasite densities above 500/µl. Sensitivity for detection of *P. falciparum* was 93.5%, increasing to 97.6% and 100% at parasite densities higher than 100/µl and 1000/µl respectively.[8] Thus RDTs have limited exclusion power at low *P. falciparum* parasite densities and a lower sensitivity for non-*falciparum* species, especially *P. malariae*. [8]

The World Health Organisation (WHO) has recommended a minimal RDT sensitivity standard of 95% and specificity standard of 95% for P. *falciparum* densities of 100/µl. [4][11][14] The WHO has published a non-exhaustive list rating some of the commercially available RDTs based on the RDTs sensitivity. The WHO stipulates that RDTs must be able to detect 100 parasites/µl (0.002% parasitaemia) in all Plasmodium species. [13][15]

The air-ambulance service provider reviewed in this study utilises the three-band ICT Malaria Combo Cassette Test (marketed as U-Test in South Africa), which detects *P. falciparum* through HRP-2 and all four Plasmodium species through aldolase. Results are available within 10 minutes and the cassette is stored at 2-30ºC. [15][16] According to the WHO RDT ratings list,

this test has a *P. falciparum* detection score of ≥ 75% at 200 parasites/µl, a false positive rate of <10% and an invalid rate of <5%. This test did not meet the WHO minimal standards for detection of *P. vivax* >75% at 200 parasites/µl. [15]

False negative RDT results may be due to insufficient parasites to register a positive result or damage to the RDT itself causing reduced sensitivity. [16] False negative RDT results may also be due to the RDT not detecting the species of Plasmodium causing the illness, e.g. when a patient is infected with non-*falciparum* species where a HRP-2 based RDT is utilised. [12][13][16] Non-immune patients develop symptoms at lower parasite densities, which may result in more false negative tests than in semi-immune patients who develop symptoms at higher densities. [11][14]

The HRP-2 concentration increases as the parasite develops from the ring stage to the late trophozoite. Although it is found predominantly in the asexual stages, it is also found in gametocytes. [11] These HRP-2 producing gametocytes (which do not cause clinical illness) may persist, resulting in a false positive HRP-2 based RDT for up to 28 days post successful treatment. [4][8][11][16] Due to this HRP-2 persistence despite resolution of malaria symptoms and apparent parasite clearance from the host, RDTs have limited usefulness in monitoring of the therapeutic response. [13] HRP-2 based RDTs have also shown false positive results in patients with circulating rheumatoid factor. [11][16] Although pLDH based RDTs are thought to be more appropriate in monitoring treatment than the HRP-2 RDTs, it should be noted that pLDH is produced by the plasmodial gametocytes and may thus also cause the RDT to remain positive despite the absence of asexual parasite forms. [4][8]

Benefits of the RDT is that it does not require refrigeration, although temperature should be maintained between 2-30ºCelcius, has a long shelf life of up to 24 months, does not require an

energy source and can be utilised following simple instructions. It is ideal for remote areas where microscopy is not available, decreasing the dependence on clinical diagnosis alone. [4][8] RDTs offer a rapid diagnosis, requires little training and results are available quickly. [13] In remote areas, a positive RDT may result in expediting the initiation of appropriate malaria treatment and may be life-saving. A negative RDT, in contrast, may delay appropriate treatment if the user is not aware of its limitations. [8]

1.2.2 Microscopy.

Ideally, where diagnostic laboratories are available, an appropriately trained microscopist will prepare thick and thin blood films stained with Giemsa (pH 8.0) and examine a minimum of 200 (100-400) fields by light microscopy using a 500-times magnification.[4][8][12][13] The thick-blood film concentrates the layers of red blood cells (RBC) by a factor of 20-30, enhancing sensitivity, and detects low levels of parasitaemia as well as the reappearance of circulating parasites during infection recrudescence or relapse. The parasite densities in thick-blood films are estimated by counting the number of asexual parasites against 200 white blood cells and multiplying the parasites counted by 40. The parasite density is expressed as parasites/µl blood [2][8][13]

The thin-blood film emphasizes the morphological identification of the parasite species and thus provides greater specificity than the thick-blood film. Parasitaemia in thin-blood films are estimated by counting the number of parasitized RBC seen in 10000 RBC and expressing the number of parasitized RBC as a percentage. Thus 1.0% parasitaemia is equal to 50000 parasites/µl of blood assuming that 1µl of blood contains 5×10^6 RBC. [13] Microscopy is the gold standard in diagnosing malaria and sensitivity can be excellent with detection of parasite

densities as low as 5 parasites/µl (0.0001% parasitaemia). [4][11][14] Experienced microscopists are able to identify to the species level in 98% of all parasites seen. [13] The process of examining a thick-blood film takes 5-10 minutes when performed by an experienced microscopist and 30-45minutes when only thin-blood films are examined to achieve the same detection limit as thick films. [12] Microscopy is able to differentiate different species as well as quantify parasites and thus monitor response to malaria chemotherapy. [4][11][14]

It should be noted that, although discouraged by the WHO due to its unreliability, semi-quantitative expression of parasitaemia, expressed as 1+ to 4+, does still occur in Africa. [17] An approximate estimate of the percentage parasitaemia from the "+" method is: 1+ (<0.001%); 2+ (0.001-0.01%); 3+ (0.01-0.1%) and 4+ (>0.1%) (personal communication with Prof. J. Frean of the National Institute of Communicable Diseases – 2011 April 7). The extrapolation of a percentage parasitaemia from the "+" method of reporting is based on assumptions about the quality, method and thickness of the slide preparation, the average high power field size of the microscope, the average red cell count, as well as the film being interpreted by a good microscopist.

False negative microscopy results may occur with parasite densities less than 5-10 parasites/µl, or with sequestered parasites as seen in pregnant patients.[4][11] Patients with *P*. *falciparum* may also have parasites sequestered in the deep capillaries of the spleen, liver or bone marrow which may result in insufficient numbers of the parasite in the circulating blood. This may result in a false negative result on the blood films. [13] As parasite densities of *P. malariae* and *P. ovale* are often low, these mixed infections are often missed by microscopy. [11]

False positive microscopy results post successful malaria treatment may be due to observation of circulating parasites which are dead and have not yet been cleared by the host. [13]

The process of microscopy is time consuming and labour intensive and it requires appropriately trained competent microscopists as well as continued training to remain proficient, a microscope in good working order and access to consumables (slides, Giemsa), quality control and quality assurance. [4][11][12][13]

1.3 Malaria in Africa.

Worldwide in 2006, 3.3 billion people were at risk of contracting malaria, mainly with *P. falciparum*, with an estimated 247 million cases resulting in 881 000 deaths (mainly in children under five years of age). Nearly 80% (212 million) of the cases were in Africa, with 50% of these cases presenting in Nigeria, Democratic Republic of Congo (DRC), Ethiopia, Kenya and Tanzania. [18] Malaria eradication was made a top health priority by the World Health Organization (WHO) in the 1990's, leading to the launch of the Roll Back Malaria initiative in 1998, with the aim of developing a sector-wide approach to combating malaria, with a goal to halve malaria mortality rates by 2010. [19] Seven of the 45 African WHO countries/areas decreased malaria cases and deaths by 50% or more during 2000 to 2006 as a direct result of the WHO initiative. [20] As travel to Africa becomes more popular and more expatriates live in Africa for occupational reasons one can expect an increase in expatriate and long-term traveller malaria cases being diagnosed and requiring evacuation for complications. Malaria endemic areas are visited by an estimated 80 to 90 million travellers annually, with an estimated 10000 to 30000 travellers contracting malaria. [21][22]

1.4 Travellers to Africa.

The risk of malaria to travellers to African regions has been extrapolated as a figure per 100000 travellers to the region: 302/100000 for West Africa, 240/100000 for East Africa, 357/100000 for Central Africa, and 46/100 0000 for Southern Africa. [23] Sub-Saharan Africa (excluding South Africa) was found to have the greatest relative risk for malaria in returning travellers. [23] The above mentioned figures are from a study by Askling et.al. which was based on Swedish residents returning from malaria endemic areas during 1997 through 2003 and testing positive for malaria in Sweden. During this period a total of 857 residents contracted malaria, 75% from sub-Saharan Africa (93% of all *P. falciparum* cases). [23] A study by Kofoed et al. found that malaria was contracted in 158/100000 travellers returning to Denmark after visiting Gambia, and 714/100000 travellers visiting Ghana. [24] Of interest is that 10% of travellers to Ghana had apparently been treated for malaria in Ghana and did not have malaria on return to Denmark. These cases were not captured on the data base. [24] A shortcoming in all these statistics is that only cases of imported malaria to the specific country are documented as the patients present to medical facilities in their home country, and that travellers diagnosed or treated in Africa are not registered. [24][25]

1.4.1 European travellers

According to the European Network on Imported Infectious Disease Surveillance (TropNetEurop), 1659 cases of *P. falciparum* were imported into the European Union countries from 1999 to 2000. European travellers accounted for 52.4% (869) of the cases and immigrants accounted for 47.6% (790) of the cases. The reason for travel in the European travellers group was tourism (59.6%), visiting relatives/friends (21.6%), business (15.8%) or other reasons (3%).

Chemoprophylaxis was not utilised by 60.4% of the European travellers. The mortality rate was 0.6% (five patients) and the case-fatality rate among European patients with complications was 9.1%. More than half of European travellers were infected in West Africa. [25]

1.4.2 Travellers from the United States of America.

Approximately 27 million U.S. residents travelled to overseas destinations in 2000 [26] resulting in 825 imported malaria cases among U.S. residents, as reported to the National Malaria Surveillance System (NMSS). Cases diagnosed outside the United States or one of its territories (American Samoa; Guam; Northern Mariana Islands and Puerto Rico) were excluded. [27][28][29][30] Thus once again cases diagnosed or treated in Africa were omitted. In comparison, 713 malaria cases among U.S. residents were reported to the NMSS in 2006, with *P. falciparum* being the predominant species and the majority of cases having originated out of Africa. Six malaria-related fatalities occurred in the United States in 2006 with four of the six patients not having taken any chemoprophylaxis while travelling in malaria endemic areas. [31] During the period from 1963 to 2001, Newman et al. found that 123 malaria-related deaths occurred among U.S. travellers and 17 among military personnel. [27] *P. falciparum* caused 92.7% of the deaths, and *P. vivax* 3.3% of the deaths. Africa, notably Kenya and Nigeria, was the source of the majority of fatal imported malaria cases. Only seven of the 123 travellers who died were compliant on an appropriate chemoprophylaxis regimen. Cerebral malaria occurred in 48% of cases, renal failure in 44%, acute respiratory distress syndrome in 32%, anaemia in 21% and disseminated intravascular coagulation in 11% of cases. [27] The case fatality rate (1985-2001) for U.S. travellers with imported *P. falciparum* was 1.3%. [28][29]

1.4.3 British travellers.

In a study by Phillips-Howard et al. to identify the risk of malaria of British residents travelling abroad, 2948 randomly selected British residents completed a passenger survey at passport control of international airports in Britain in 1987. A further 1052 case reports of British residents with microscopically confirmed malaria infections in 1987 were also reviewed. [32] It was found that the annual infection rates extrapolated as a figure per 100000 travellers was: 555/100000 to Nigeria; 779/100000 to Ghana; 28/100000 to Gambia; 149/100000 to Kenya; 212/100000 to Tanzania; 138/100000 to Zambia and 789/100000 to Malawi. [32] The annual infection rate per 100000 travellers per African region was found to be 379/100000 for West Africa, 172/100000 for East Africa and 128/100000 for Central or Southern Africa. Malaria chemoprophylaxis was utilised by 77% of British travellers to West Africa, 83% to East Africa and 54% to Central and Southern Africa. [32] Although no actual figures were noted for compliance on chemoprophylaxis and compliance was merely stated as poor, travellers returning from West Africa had a 2.5 times higher rate of *P. falciparum* infection when not compliant on chemoprophylaxis. [32]

1.5 Chemoprophylaxis compliance in expatriates and long-term travellers.

Expatriates, for the purpose of this study are defined as non-immune individuals who reside for a period in a malaria-endemic country other than their original country of citizenship, with the purpose of completing an occupational (mainly) assignment, with the intent to return to their home country once the assignment period is completed. [33][34][35]The period of exposure to country-related hazards is usually longer with expatriates than with other travellers. [33] Expatriates who travel to areas with high malaria rates are particularly vulnerable. [36] In a

prospective study by Hill for the period June 1989 to May 1991, 784 U.S. resident travellers attended the International Traveler's Medical Service at the University of Connecticut prior to departure and agreed to complete a health questionnaire within two weeks of returning to the United States of America. [37] Travellers ages ranged from one to 85 years with a mean age of 44.1 ± SD 17.5 years. The duration of travel was 90 days or less, with 631 (80%) having travelled for 30 days or less and a median duration of 19 days (mean 24 ± 16 days). [37] All travellers received extensive counselling and written material on, amongst other issues, the prevention of malaria. 612 of the 784 travellers were prescribed malaria chemoprophylaxis: 63% chloroquine, 18% chloroquine plus proguanil, 17% mefloquine and the remaining 2% other unspecified chemoprophylaxis. Of the 608 travellers who completed the chemoprophylaxis compliance information on the postcard, 488 (80%) were completely compliant (taking the prescribed number of doses before, during and following their trip). Eight of the 612 travellers sought medical attention for fever of an unknown cause, with two having had *P. falciparum* malaria documented, four were treated presumptively for suspected malaria, and the remaining two were treated presumptively for pharyngitis and otitis media respectively. Of these six travellers treated for malaria, the diagnosis was made in Ghana (three), India (one), Kenya (one) and Nigeria (one). Five of these six travellers were on appropriate chemoprophylaxis, and the remaining traveller who was one of the two travellers with documented *P. falciparum,* purchased but never took the unspecified chemoprophylaxis. One malaria case required hospitalisation without mention of chemoprophylaxis utilisation. An additional film positive case was documented in a returned traveller increasing the total number of confirmed plus presumptive malaria cases to seven. All three documented malaria cases originated out of West Africa, without documentation of specific countries, with two travellers having used chloroquine/proguanil chemoprophylaxis and the third traveller not having utilised any chemoprophylaxis. In this study the incidence of documented malaria was estimated at 3.8/1000

travellers, and the incidence of documented plus presumptive malaria was estimated at 8.9/1000 travellers. [37]

In a study by Chen et al. it was found that long-term travellers, defined as travelling for longer than six months, have a higher risk of contracting malaria than short-term travellers. [35] It was also found that long-term travellers exhibited poor adherence to chemoprophylaxis regimens and underused personal protective measures. Chen et al. showed that most chemoprophylactic regimens, even when taken correctly, provided 75-95% protection against malaria and that no chemoprophylactic regimen was 100% effective. [38]

With the objective to elucidate the risk for travel-related diseases of European travellers to five chosen malaria-endemic tropical areas, Rack et al. proceeded with a questionnaire-based observational study of 658 adult German travellers who consulted the travel clinic of the Berlin Institute of Tropical Medicine. [39] The tropical areas were grouped into five groups including: Kenya/Tanzania; Senegal/Gambia; India/Nepal; Brazil and Thailand. It was found that 201 of the 658 subjects had travelled to tropical areas within sub-Saharan Africa with 167 people having travelled to Kenya/Tanzania and 34 to Senegal/Gambia during the study period of July 2003 through June 2004. [39] The mean duration of travel for all 658 travellers was 23.9 ±10.3 days with a range of 3-62 days. 276 (41.9%) of the 658 travellers took malaria chemoprophylaxis as follows: mefloquine 60.5%; atovaquone/proguanil 31.2%; doxycycline 5.8%; chloroquine/proguanil 1.8% and chloroquine 0.7%. Chemoprophylaxis compliance was reported by 268 (97.1%) of the 276 travellers. This unusually high rate of compliance may be due to the subset of travellers who visit travel clinics being more aware of potential medical problems and being more willing to take precautions to prevent them. [39]

1.6 Quality of care and anti-malarial drugs in Africa.

As the incubation period for malaria is seven to 30 days, it is fair to say that malaria management and diagnosis within sub-Saharan Africa will mainly be a problem for the long-term traveller and expatriate. Short-term travellers (six days or less) are more likely to present with malaria manifestations in their home country as 'imported malaria'. All travellers (short- and long-term) as well as expatriates would require knowledge of malaria manifestations and understand the urgency in going to the nearest appropriate facility to be tested. In many instances in Africa, this may require several hours over very poor terrain by motor vehicle, or even helicopter or light airplane flights as seen with the flooded plains in the Okavango Delta, Botswana. [40] Fixed-wing air ambulance evacuations dispatched by this particular air-ambulance service provider are usually limited to cases with manifestations of complicated malaria, or where the local facilities are not able to provide adequate treatment. Although evacuations may be internal within that country, the majority are to the nearest centre of medical excellence, which may be in Europe and South Africa, or to regional centres in Kenya. [41]

Once the traveller has tested positive for malaria another hurdle is encountered. Access to anti-malarial treatment in 18 of the 46 WHO African-region countries was on average 38%, and no African country reached the WHO 80% target. [18] The 18 African countries audited include: Angola; Benin; Burkina Faso; Cameroon; Central African Republic; Ethiopia; Gambia; Ghana; Guinea-Bissau; Ivory Coast; Malawi; Mali; Niger; Sao Tome and Principe; Senegal; Togo; Uganda and Zambia. [18] According to the WHO 2010 world health statistics, access to selected generic medicines which include anti-malarial treatment was on average 57% in the private sector of the 15 countries audited as shown in figure 1. [42] Access in the public sector was on average 39.1% in the 14 audited countries (excluding South Africa). [42]The traveller, through

medical/travel insurance or corporate sponsorship, may be in a privileged position to have access to private healthcare institutions (where they exist).

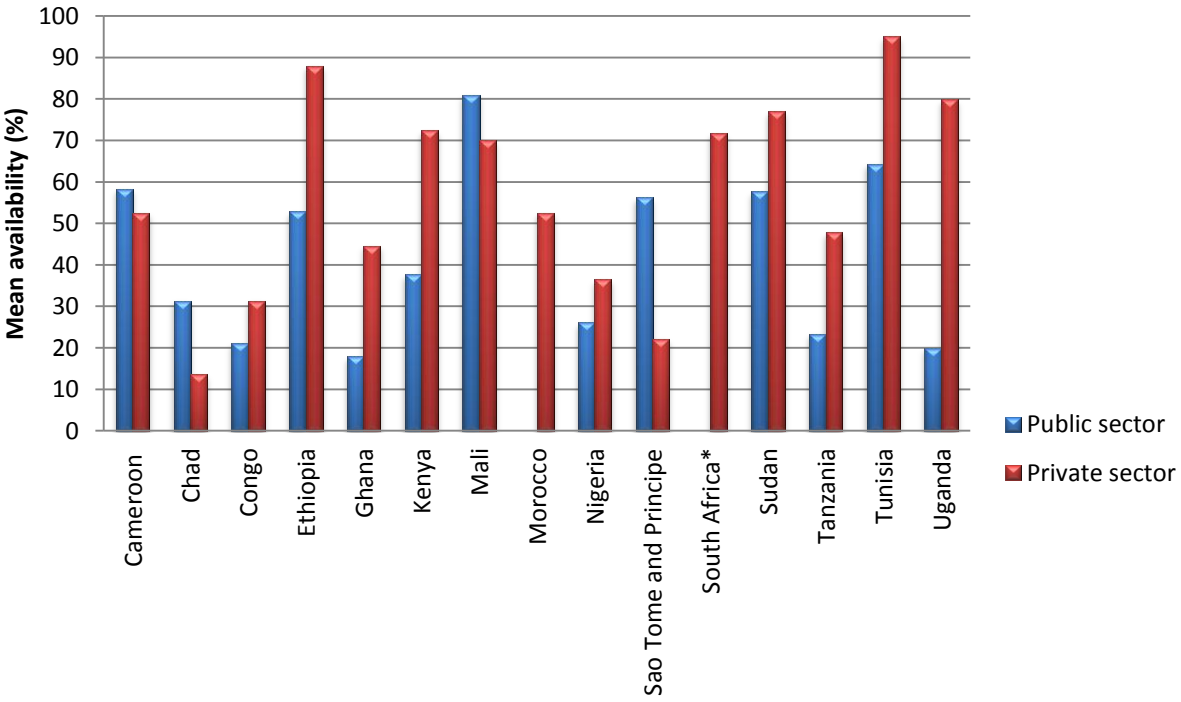


Figure 1: Mean availability of selected generic medicines. 2001-2008
Adapted from the WHO - World Health Statistics 2010.
(* Public sector not audited in South Africa)

In a study by Onwujekwe et.al. of 225 samples of anti-malarials (which included artesunate, dihydro-artemisnin, sulphadoxine-pyrimethamine, quinine and chloroquine) which were either collected or purchased in six Nigerian towns, it was found that 60 (37%) of the anti-malarials tested did not meet the United States Pharmacopoeia board specifications. [43] It was found that these drugs either contained sub-optimal quantities, or completely lacked in active ingredients. [43] What is surprising is that 78% of these drugs were obtained from private institutions in Nigeria. [43] In a study of artemisinin derivatives purchased in Kenya and the Democratic Republic of Congo by Atemnkeng et al., the percentage of active ingredient found ranged from 23% to 81% for tablet and intra-muscular injection formulations respectively. [44]

Thus we may believe a traveller is receiving appropriate treatment for uncomplicated malaria, when in actual fact the traveller is at great risk of developing complicated malaria. As expatriates and long-term travellers by definition stay in malaria endemic areas for longer periods than short term travellers, they are more likely to run out of their personal supply of malaria chemoprophylaxis, and thus increase their chances of purchasing these suboptimal or counterfeit drugs in Africa. [35] Thus, although being compliant with chemoprophylaxis, they may be purchasing chemoprophylaxis which may have little or no active ingredients or even unwittingly buy inappropriate chemoprophylaxis containing active ingredients which the local malaria subtypes have shown resistance to.

1.7 Fixed-wing air-ambulances in Africa.

An air-ambulance is either dedicated (permanently configured for medical evacuations), or is a charted aircraft that is medically configured for a specific flight. [45] An air-ambulance may be a propeller driven or powered by a jet engine. This will restrict the aircraft in terms of range and landing capabilities, e.g. a jet cannot land on a gravel runway and requires amongst other things a tarred runway in good condition of a certain length (dependent on the ambient temperature), working runway lights, air traffic control, instrument landing capabilities and confirmation of fuel availability. Benefits of a jet aircraft is the ability to fly longer distances requiring fewer technical (fuel) stops, faster air speed resulting in a shorter mission time and having a pressurised cabin allowing for a controlled cabin altitude environment. The pressurised cabin is vital when flying patients with conditions where air is trapped in confined spaces for example pneumocephalus or bowel obstruction. The benefit of a propeller driven aircraft is the ability to land on shorter non-tarred runways and thus have access to more remote areas in Africa. Propeller driven aircraft

may have an unpressurised cabin resulting in a less controlled cabin altitude environment and have a slower air-speed resulting in longer missions with potentially more technical stops. Several air-ambulance providers operate in Africa and are based in Angola, Botswana, Dakar, Gabon, Ivory Coast, Kenya, Namibia, Nigeria, South Africa, Sudan, Tanzania, Uganda, Zambia and Zimbabwe. These service providers vary in the type of fleet and staffing on the air-ambulance. Some service providers are purely paramedic based and other service providers have a doctor on every flight. [45][46] Each air-ambulance flight by this particular reviewed air-ambulance provider is staffed by a doctor and either a nurse trained in intensive care or an advanced life support paramedic. [46] This service provider has a fleet of three permanently configured dedicated air-ambulances, namely one Falcon 10 and two Lear Jet 35 aircraft which are based in Johannesburg, South Africa. [46] All three aircraft are fitted with a lifeport™ stretcher and the crew are able to provide a full intensive care unit (ICU) service including ventilation (non-invasive or invasive), defibrillation, cardiac pacing (internal or external), electric cardioversion, invasive blood pressure monitoring, multiple infusions of drugs through centrally placed lines, thrombolysis and advanced neonatal care. [46] An extensive range of equipment, with secondary back-up devices for all emergency equipment, as well as an array of essential medications are carried as standard on all flights.

International accreditation for air medical transport is obtainable from the European Air Medical Institute (EURAMI) [47] and the Commission on Accreditation of Medical Transport Systems (CAMTS). [48] EURAMI is based in Germany and CAMTS is based in the United States of America. Both these accreditation services require accredited service providers to adhere to stringent standards on safety, education, training and ethics to ensure optimal patient management and safety during aeromedical transport. Three air-ambulance service providers in Africa are internationally accredited. The Johannesburg based air-ambulance service provider utilised for this study is the only CAMTS accredited service provider in Africa, and is also in the

process of obtaining EURAMI accreditation. [48] The remaining two internationally accredited service providers are based in Nairobi and Johannesburg respectively and are both accredited with EURAMI. [47]

The air-ambulance service provider reviewed in this study is associated with the world's leading international healthcare, medical assistance, and security services company. [41] In general, air-ambulance missions are based on a fee for service agreement, whether through an insurance company, medical aid, corporate agreement or on a private basis. [41]

This air-ambulance service provider has the ability to land in any (African) country depending on logistical issues mentioned above, security issues and obtaining flight clearances. Flights have been done to locations as far as Yemen, Dubai, Senegal, Egypt and Diego Garcia. Safety is a very real issue in Africa and the medical assistance company associated with the air-ambulance service provider in this study has a security branch based in London which continuously monitors the worlds' security status in real time. [41] Security issues may restrict landing in a country completely or result in the inability to provide a bed-to-bed service for that specific country at that particular high security risk period. The bed-to-bed service may also be restricted in certain countries e.g. Nigeria where the flight on duty time of the pilots may result in having only one hour on the ground (time from landing to departure) if a direct turnaround is required. Should this time period be exceeded, the crew will have to spend an obligatory rest period in that country prior to departure as per the South African Civil Aviation Authority.

1.7.1 Process of air-ambulance flight activation.

The medical assistance company associated with the air-ambulance provider utilised in this study will receive a call for assistance, whereupon medical information as well as the patient's exact location is obtained as shown in figure 2. The reason for travel is usually documented by the alarm centre co-ordinator as this may assist with financial coverage decisions as certain insurance policies are only valid if the patient is for instance travelling for leisure and not for business reasons. In certain cases subcontractors may have coverage under the primary client so obtaining employment information is necessary. No information on reason for travel is required in private cases.

The initial assessment and recommendation is made by the co-ordinating doctor, who is present 24 hours a day in the alarm centre, and approved by the medical director of the medical assistance company. A decision is made on whether the patient requires an upgrade of care within the same town/city, country, to the closest appropriate regional medical hub in Africa, or if the medical condition warrants immediate activation of an air-ambulance to either Europe or South Africa. Once the decision is made for evacuation to South Africa, the case is handed over to the flight-desk which is staffed by a logistical coordinator and the flight-desk doctor.

The flight desk acts as an air-ambulance service provider to the medical assistance company, and although the flight desk is associated with the medical assistance company it is an independent entity. The flight desk may receive a direct call for an air-ambulance request from a person/company with no association with the medical assistance company. In these cases the flight desk doctor and co-ordinator will assess the patients' medical condition and logistical issues regarding current location. The most appropriate initial referral for stabilisation will be recommended where appropriate, whilst activating an air-ambulance.

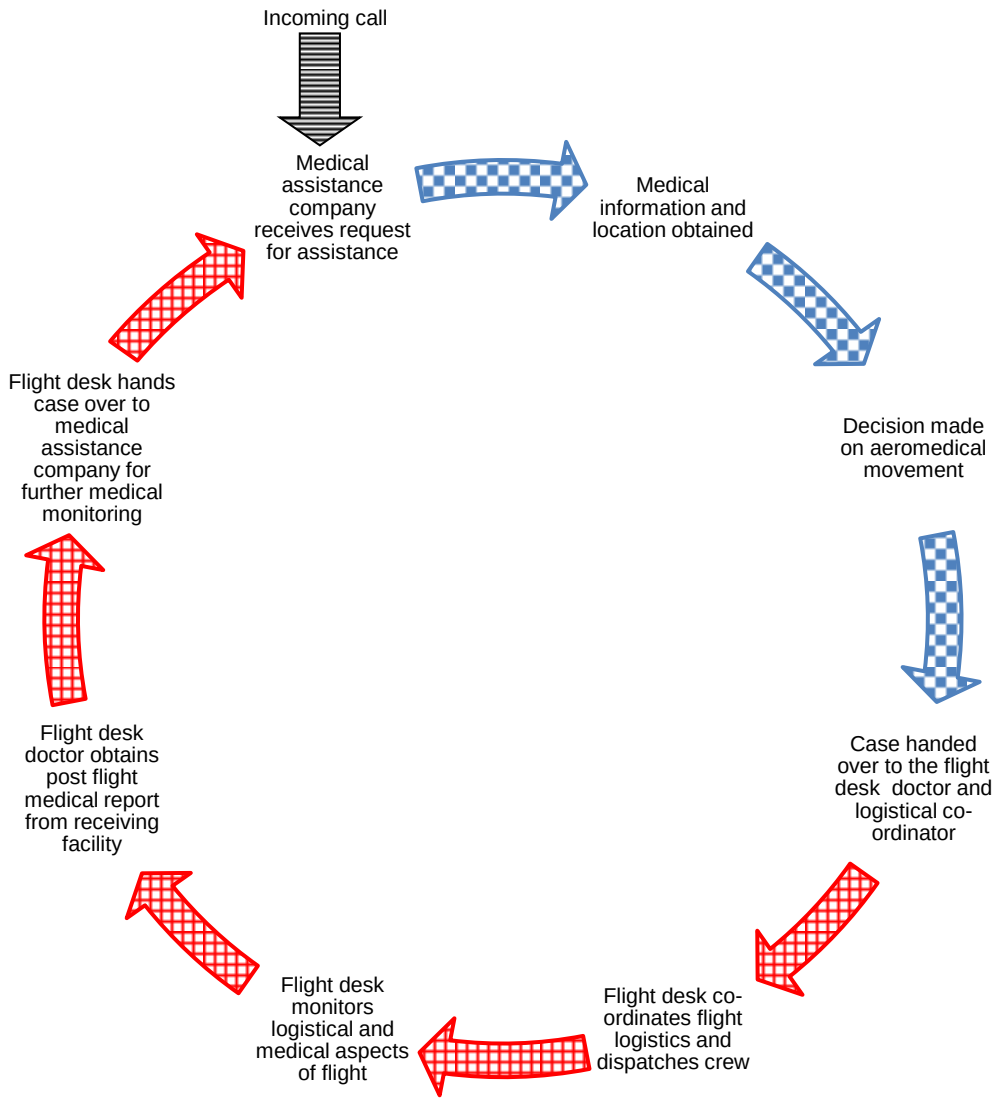


Figure 2: Operational overview of aeromedical movements.

As illustrated in figure 3 the mission is monitored by real-time satellite tracking of the air-ambulance. The flight crew call the flight-desk doctor in the alarm centre at multiple pre-ordained times during the mission. Once the crew have assessed and stabilised the patient a medical update is given to the flight-desk doctor. Medical advice is provided by the flight-desk doctor and the medical director in certain situations. Satellite phones are available on each flight

for in-flight emergencies. Upon landing the flight crew provide a medical update and again once handover is completed at the receiving facility. A post flight medical report is obtained by the flight-desk doctor from the receiving physician 1-2 hours after handover to allow for the majority of investigations to be completed. Depending on the client agreement, continuous medical monitoring may be provided until the time of discharge and/or repatriation to the patients' country of residence where required. Should extended medical monitoring be required, the case is handed over to the co-ordinating doctor in the alarm centre once the post-flight medical report has been obtained.



Figure 3: Example of real-time satellite tracking of a mission to Abuja, Nigeria.

1.7.2 Language barriers experienced by flight crew.

Air-ambulance evacuations out of Africa may be challenging as language barriers may restrict communication between the flight crew and the referring health care worker. Handover may be taken at either the referring hospital or at the airport, the latter in cases where there are security concerns or time constraints due to restricted flight-on-duty time of the pilots. These handovers are often undertaken without the benefit of a translator.

In certain situations no medical records may be available for the flight crew to review. As expatriates may not be fluent in English, this may present another hurdle in obtaining detailed, if any, information.

1.8 The need for upgrade of care in sub-Saharan Africa.

1.8.1 Identification of the nearest centre of medical excellence in sub-Saharan Africa.

The medical assistance company referred to in this study has a Global Assistance Network (GAN) which utilises a credentialing process based on assessments of individual medical practitioners and medical facilities worldwide. [49]

The GAN incorporates regular on-site inspections and surveys of clinics and hospitals to evaluate staff accreditation, equipment, sanitation and sterilisation techniques, laboratory equipment, staffing capabilities, origin of medication procurement and adherence to First World standards. A hospital or clinic may be deemed adequate to treat uncomplicated malaria, however when complications occur, these same facilities may be deemed substandard due to lack of ICU facilities or access to ancillary services such as haemodialysis.

Patients may be temporarily moved to one of these accredited regional medical hubs and then have a secondary movement either to South Africa or Europe if the severity of the medical condition outweighs the capabilities of the centre concerned.

In cases where a patient is geographically closer to Europe the patient may be evacuated to the nearest centre of medical excellence (NCME) in Europe where feasible. The major limiting factors are the availability of European air-ambulance service providers as well as visa restrictions, often necessitating the activation of the Johannesburg based provider. Despite being geographically closer to Europe, patients are often evacuated to South Africa as the patient reaches a centre of medical excellence sooner (often days) than if a flight to Europe had been waited for. Flights by the Johannesburg service provider to Europe will be restricted by visa requirements by the flight crew and pilots as European countries make no exception on visa requirements even in the emergency air-ambulance evacuation scenario. The same visa restrictions also restrict patients from obtaining emergency care in Europe. The South African Customs and Immigration Department issues a three month emergency medical visa on landing in South Africa, regardless of the patients' passport nationality, thus making South Africa a feasible destination in emergency situations. [50]In all cases the medical assistance company will look at the safest and fastest mode of evacuation to the most appropriate receiving facility. Where applicable, clients are presented with quotations and timelines of several different air-ambulance service providers to both European destinations and South Africa. The medical assistance company will advise the client on the urgency of the mission and which option would be the most appropriate. However in these circumstances, the decision on destination and which provider to utilise will rest with the client. Due to the air-ambulance service provider reviewed in this study being based in Johannesburg, the majority of missions will be flown to Johannesburg, South Africa as the NCME.

1.8.2 The need for fixed-wing air-ambulance evacuation to the NCME in sub-Saharan Africa.

A cohort study published in 2006 by Patel et al. over a period of one year (dates not specified), of 2020 British Foreign and Commonwealth Office staff and partners living abroad in Europe, Americas, Africa, Near East, Middle East, Asia, South Pacific and Australasia measured the incidence of illness or injury serious enough to require consultation with a doctor. [33] Ages ranged from 23 to 59 years with a mean age of 42 ±9.6 years. 43 (2%) of the 2020 patients required medical repatriation. One of these 43 repatriated patients was also grouped under the listing of 'certain infectious and parasitic diseases' as a diagnosis. A total of 55 patients were grouped under the 'certain infectious and parasitic diseases' diagnosis, with six of these cases requiring hospital admission. [33] Four cases of malaria were reported, with an estimated malaria incidence of 1% in malaria endemic countries. This low incidence is thought to be due to urban postings and effective pre-travel advice. [33] No definition was given for medical repatriation, and whether it implied fixed-wing, rotor-wing or medically escorted commercial air travel. No breakdown was given for the countries where the repatriation originated from, or what the destination country was and may thus not have involved Africa at all.

A study by Duchateau et al. reviewed all repatriation and evacuation records of a medical assistance company based in France. Medical movement was required by 402 patients during the period from August 2006 through July 2007.[51] Of the 402 patients 35 required urgent evacuation by air-ambulance with 15 (43%) of these originating out of sub-Saharan Africa. A further 367 patients required non-urgent medical movement, of which 69 patients were flown by air-ambulance mainly for logistical reasons, and the remaining 298 patients by a medically escorted commercial flight. 34 (9%) of the 367 non-urgent flights originated out of sub-Saharan Africa. Specific sub-Saharan countries of air-ambulance evacuation origin were unfortunately

not noted. Although no specific mention was made of the countries where the patients were evacuated to, the authors advised that patients were evacuated to the nearest centre where First World facilities were available. [51] The authors noted that the only country in sub-Saharan Africa with First World sanitary conditions was South Africa. [51][42] The medical assistance company in this study utilised their so called 'Marco Polo' program for evaluating medical facilities worldwide. According to this system, medical facilities with a high standard are limited to South Africa, Kenya and Ethiopia in sub-Saharan Africa. [51]

A paucity of published data exists on fixed-wing air-ambulance evacuations out of Africa for malaria as well as malaria incidence in long-term travellers and expatriates.

1.9 Overall aims of the study.

The aim of this study is to review the characteristics of patients (expatriates and long-term travellers) with suspected malaria being evacuated by fixed-wing air ambulances out of sub-Saharan Africa to Johannesburg, South Africa.

1.10 Study objectives.

The objectives of this study are to:

- Determine the number of long-term travellers and expatriates who required fixed-wing air-ambulance evacuation for suspected malaria out of sub-Saharan Africa.

- Compare the initial diagnosis of suspected malaria based on pre-dispatch information with the diagnosis at the receiving facility and thus determine the accuracy of the initial diagnosis.
- Determine the number of suspected malaria patients who are utilising malaria chemoprophylaxis as well as the type of chemoprophylaxis utilised and the compliance rate of the patients.
- Identify the presence of seasonal trends when compared to the specific countries wet and dry seasons.
- Determine the number of suspected malaria patients who require definitive airway management as well as the mortality rate as a marker of disease severity.
- Determine the incidence of specific malaria species as diagnosed at both the referring and the receiving facilities and to identify cases where the species isolated differed between the two facilities.
- Document patient demographics including age, gender and reason for travel.
- To assess the severity of malaria by documenting the clinical parameters of the suspected malaria patients. These parameters include the initial temperature, systolic blood pressure (SBP), blood glucose, heart rate, oxygen saturation, Glasgow Coma Scale (GCS), clinical anaemia, haemoglobin (Hb) level, clinical jaundice, average hourly urine output and presence of macroscopic haemoglobinuria.

CHAPTER 2: MATERIALS AND METHODS

All adult expatriate and long-term traveller patients, evacuated by fixed wing air-ambulance from a sub-Saharan African country to Johannesburg, South Africa with suspected malaria were included in the study.

Patients with suspected malaria were identified by reviewing all flight records for the period 1 July 2006 through 30 June 2009:

1. Patients with an initial air-ambulance dispatch diagnosis of suspected malaria, which was based on either a clinical picture indicative of malaria (without any confirmatory testing or even with an initial negative RDT or blood film), or a positive RDT or a positive blood film.
2. Any additional patients where the flight crew suspected malaria in the differential diagnosis were followed up.
3. Any additional patients with a fever or documented clinical signs which could fit in with a diagnosis of malaria were followed up.

Where documented in the post-flight medical report, the final diagnosis and malaria species isolated at the receiving facility were extracted.

No patient identifying information was utilised in this retrospective study and therefore informed consent from the patients was not required and not obtained. Permission from the air-ambulance provider management to utilise their flight records to complete the study was obtained. Ethics approval was obtained from the Witwatersrand Human Research Ethics Committee (Medical), clearance certificate reference: M10591.

2.1 Study design.

This is a descriptive observational retrospective study.

2.2 Study population.

Patients were identified during the period 1July 2006 through 30 June 2009. This time period was chosen as the electronic data storage system used by the air-ambulance service provider was upgraded resulting in limited to no access to the stored data prior to this period.

2.2.1 Inclusion criteria:

All expatriates and long-term travellers aged 18 years and older, with suspected malaria in sub-Saharan Africa where a fixed-wing air-ambulance to Johannesburg, South Africa was dispatched during the study period were included.

Expatriates were defined as:

- Non-immune individuals who reside for a period in a malaria-endemic country other than their original country of citizenship, with the purpose of completing an occupational (mainly) assignment, with the intent to return to their home country once the assignment period is completed.
- Nationality for the purpose of this study, was based on the nationality of the passport held by the patient. Thus patients born in malaria-endemic countries who had emigrated

to non malaria-endemic countries and were in possession of a passport from the new country of residence were seen as expatriates due to limitation of flight documentation to the contrary. These previously semi-immune travellers have lost (part of) their immunity during stays of six months or more in non-endemic areas.[52]

Long-term travellers were defined as:

- Non-immune individuals who travelled to malaria-endemic countries for a period of seven days or longer.

The diagnosis of suspected malaria was determined by:

- Patients with an initial air-ambulance dispatch diagnosis of suspected malaria, which was based on either a clinical picture indicative of malaria (without any confirmatory testing or even with an initial negative RDT or blood film), or a positive RDT or a positive blood film.
- Any additional patients where the flight crew suspected malaria in the differential diagnosis were followed up and included.
- Any additional patients with a fever or documented clinical signs which could fit in with a diagnosis of malaria were followed up and included if the final diagnosis was confirmed as malaria.

Table 1: List of sub-Saharan countries (Highlighted countries are malaria-free)

Angola	Equatorial Guinea	Mali	Somalia
Benin	Eritrea	Mauritania	(South Africa)
Botswana	Ethiopia	**Mauritius**	Sudan
Burkina Faso	Gabon	Mozambique	Swaziland
Burundi	Ghana	Namibia	Tanzania
Cameroon	Guinea	Niger	The Gambia
Cape Verde	Guinea-Bissau	Nigeria	Togo
Central African Republic	Ivory Coast	**Réunion**	Uganda
Chad	Kenya	Rwanda	Western Sahara
Comoros	**Lesotho**	Sao Tome and Principe	Zambia
Congo	Liberia	Senegal	Zimbabwe
Democratic Republic of Congo	Madagascar	**Seychelles**	
Djibouti	Malawi	Sierra Leone	

List adapted from: http://www.uis.unesco.org/profiles/EN/EDU/countries40350.html

2.2.2 Exclusion criteria:

- Semi-immune patients were excluded:

  Local nationals who have grown up in malaria-endemic areas and thus have a degree of malaria immunity due to repeated exposure to malaria.

  - The nationality was based on the nationality of the passport.
  - Patients with local African passports were assumed to live in the area due to limitation of flight documentation to the contrary.
- Missions where an alternative air-ambulance service provider was utilised by the air-ambulance provider utilised in this study were excluded due to limited access to in-flight medical records.
- Internal (fixed-wing air-ambulance movement within the same country) evacuations were excluded as they did not meet inclusion criteria.

- Cases where the receiving facility destination was not Johannesburg, South Africa were excluded. The air-ambulance provider utilised in this study was based in Johannesburg, South Africa and thus Johannesburg was expected to be the final destination.

2.3 Data captured.

The following parameters were collected from the flight records of a Johannesburg based internationally accredited fixed-wing air-ambulance service provider:

- The date of the mission, the country of air-ambulance evacuation origin and final destination.
- The initial air-ambulance dispatch diagnosis, the flight crew diagnosis and the receiving facility final diagnosis.
- The reason for travelling which was grouped into business/occupational and leisure.
- Patient demographics included age, gender, weight, nationality, travel history to malaria endemic areas in the past three months, malaria chemoprophylaxis utilisation, type of chemoprophylaxis utilised and the compliance thereof.
- The method of initial malaria diagnosis (RDT, blood film or clinical) as per the referring facility.
- *Plasmodium* species identified at both the referring and receiving facilities.
- Initial clinical data included the temperature, systolic blood pressure, blood glucose, heart rate, oxygen saturation, GCS, clinical anaemia, haemoglobin (Hb) level, clinical jaundice, average hourly urine output and presence of macroscopic haemoglobinuria.

- Any anti-malarial treatment administered during the flight (intravenous, intramuscular or oral anti-malarials).
- Definitive airway requirements and mortality at any stage of the mission was documented as a marker of severity. Decreased cerebral function with a decreased level of consciousness results in the loss of the ability to protect the airway necessitating intubation. Severe respiratory compromise will require intubation for ventilatory support.

2.4 Statistical analysis.

Data from case records for missions undertaken within the study period (1st July 2006 through 30th June 2009), were captured on the Microsoft® Office Word® 2007 data capture sheet in hard copy retrospectively.

Microsoft® Office Excel ®2007 was utilised for data entry from the data capture sheet into the data entry sheet.

Analysis was performed with EpiInfo™ version 3.5.1. Continuous variables were summarised as frequencies and percentages as well as means and standard deviations for age, weight, GCS, systolic BP, Hb level, heart rate, hourly urine output, temperature, blood glucose level, oxygen saturation and respiratory rate. Discrete variables were expressed as frequencies and percentages for gender, the reason for travel, nationalities, utilisation of chemoprophylaxis, compliance on chemoprophylaxis, clinical jaundice, clinical anaemia and the presence of macroscopic haemoglobinuria. The *P-fisher* exact score was utilised for assessing the statistical significance when comparing the intubation requirements for patients who had utilised chemoprophylaxis against the patients who had not utilised chemoprophylaxis as well as where chemoprophylaxis utilisation was not documented.

CHAPTER 3: RESULTS

A total of 997 patients were flown by fixed wing air-ambulance during the study period from 1st July 2006 through 30th June 2009. 679 patients complied with inclusion criteria and 318 patients were excluded. As more than one exclusion criteria may be relevant per excluded patient, for example in the case of a paediatric national patient, the exclusion criteria was applied in the order of the listed exclusion criteria as shown in table 2.

Table 2: Reasons for exclusion of patients.

Flights		
Excluded	318	
Aged less than 18 years		91 (28.6%)
Local nationals		171 (53.8%)
Internal flights within South Africa		41 (12.9%)
Origin of evacuation not from sub-Saharan Africa		12 (3.8%)
Patients flown to their home countries from Johannesburg		2 (0.6%)
Destination not Johannesburg		1 (0.3%)
Included	679	
Total flights	997	

3.1 Flight demographics.

3.1.1 Sub-Saharan countries of evacuation origin for all air-ambulance flights.

The 679 patients included in the study population were flown out of 30 of the 49 (excluding South Africa) sub-Saharan African countries which are listed in table 2. Angola and Zambia were the countries of origin in 272 (40.1%) of all 679 sub-Saharan fixed wing air-ambulance evacuations as shown in figure 4.

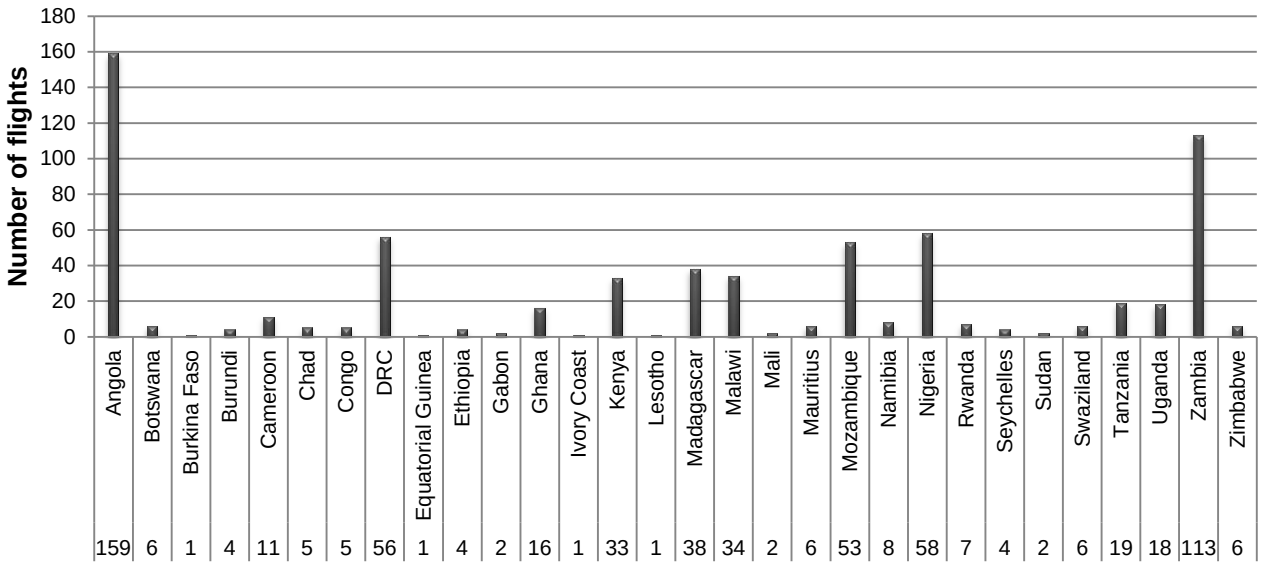


Figure 4: Sub-Saharan countries of evacuation origin for all air-ambulance flights.

3.1.2 Initial diagnosis at time of air-ambulance dispatch.

Figure 5 illustrates that malaria was the most common specific dispatch diagnosis, with 81 (11.9%) of the 679 flights due to an initial diagnosis of suspected malaria. Cardiac patients encompassed 124 (18.3%) of all patients flown and included a range of pathologies: dysrythmias, myocardial infarctions, angina and cardiac failure amongst others. 164 (24.2%) of

the 679 patients, were flown for other medical diagnoses. A total of 157 (23.1%) trauma related patients, 139 (20.5%) surgical patients and 14 (2.1%) obstetric patients were flown during the study period.

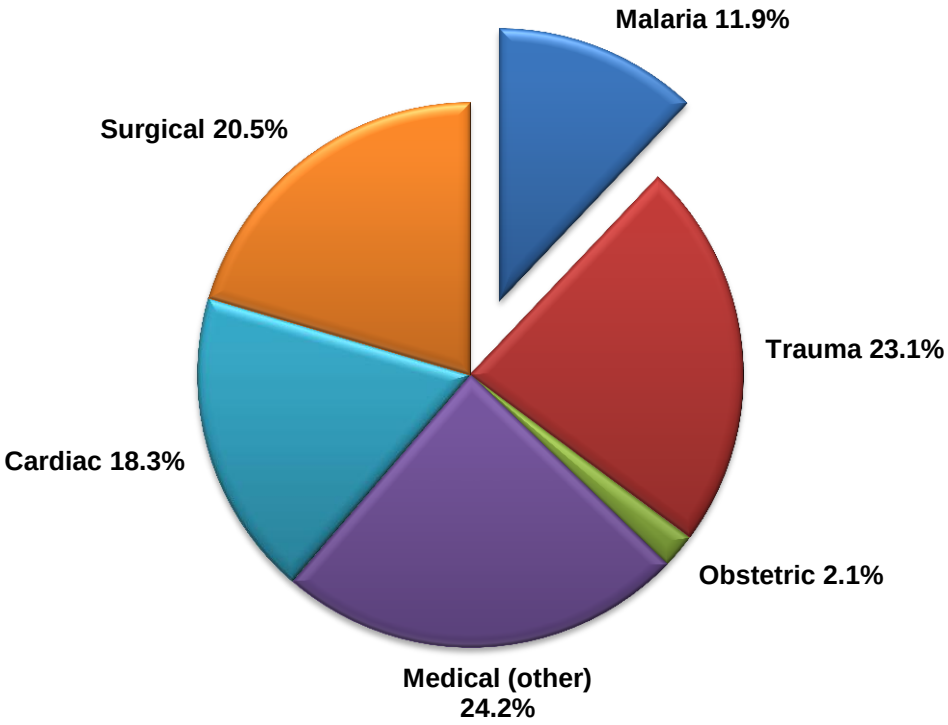


Figure 5: Initial diagnosis at time of air-ambulance dispatch.

3.1.3 Sub-Saharan countries of evacuation origin for suspected malaria air-ambulance flights.

As shown in figure 6 the five most common sub-Saharan countries of origin for air-ambulance flights for patients with suspected malaria on dispatch were Angola 20 (24.7%), the Democratic

Republic of Congo 15 (18.5%), Mozambique 13 (16.0%), Nigeria seven (8.6%) and Zambia six (7.4%).

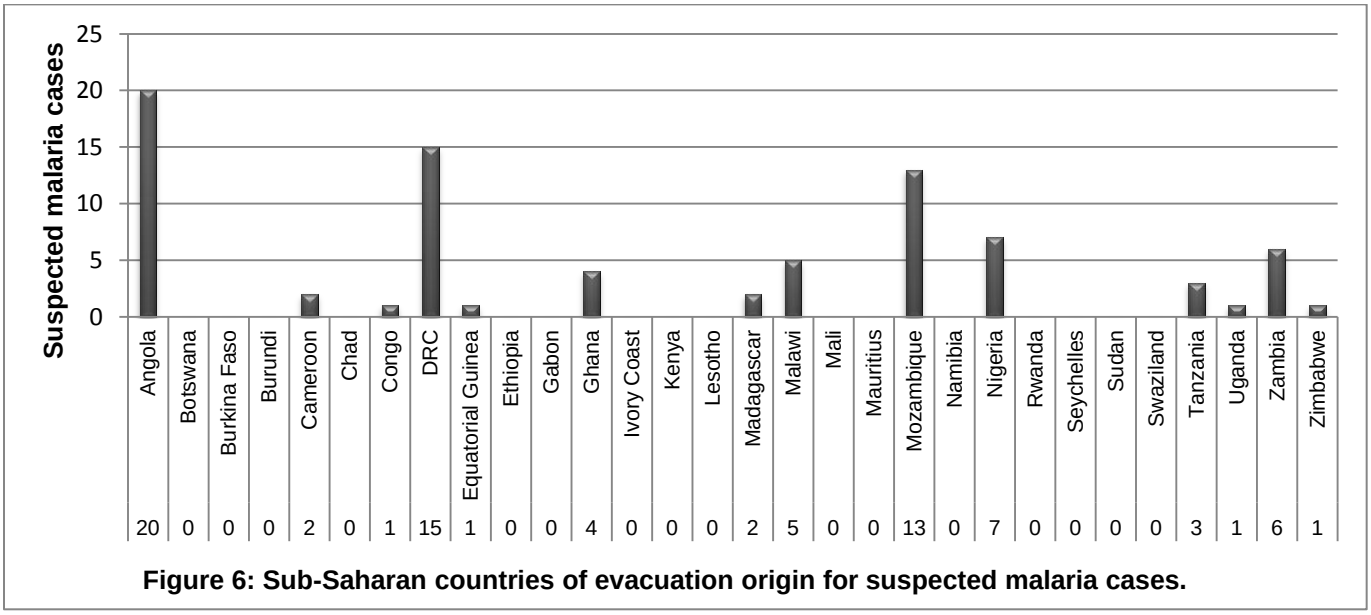


Figure 6: Sub-Saharan countries of evacuation origin for suspected malaria cases.

3.1.4 Proportion of suspected malaria flights of the total flights per sub-Saharan African country.

Figure 7 illustrates the proportion of suspected malaria flights of the total flights flown, with the following countries showing the highest proportions: Equatorial Guinea (100%); the Democratic Republic of Congo (26.8%); Ghana (25%); Mozambique (24.5%); Congo (20%) and Cameroon (18.2%).

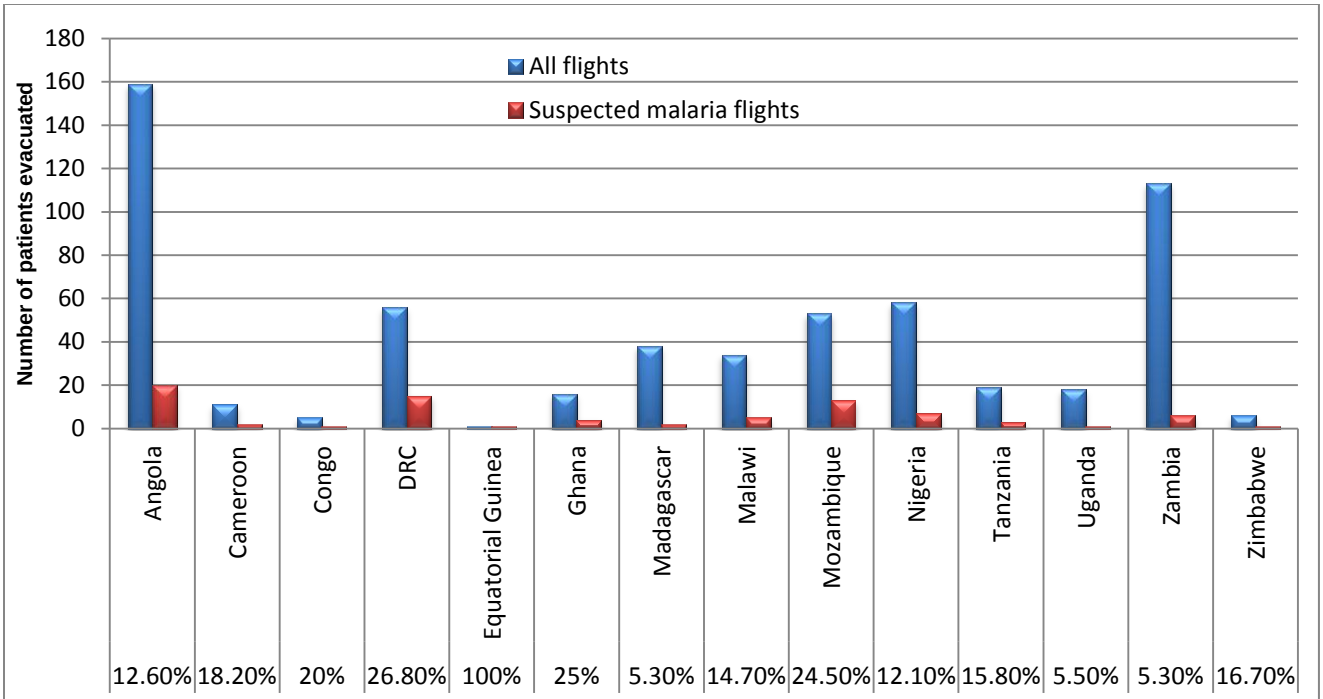


Figure 7: Proportion of suspected malaria flights compared to all flights flown per sub-Saharan African country of evacuation origin.

3.2 Comparison of initial diagnosis of suspected malaria with flight crew and final diagnosis.

Eighty-one cases were dispatched with an initial diagnosis of malaria and in one additional case the flight crew made the diagnosis of malaria after their initial assessment of the patient. The latter patient was flown from the Democratic Republic of Congo with an initial diagnosis of acute renal failure and jaundice and had had an initial negative RDT at the referring facility. After clinical assessment, the flight crew suspected malaria and repeated the RDT which was positive without documentation of the species isolated. There were no cases of a receiving hospital making the first diagnosis of malaria. Of the 82 cases, nine did not have a final diagnosis

documented at the receiving facility. Of these nine cases, one case did not have a documented initial method of malaria diagnosis, two cases were diagnosed on clinical symptoms alone and five cases had an initial diagnosis based on a positive blood film at the referring facility. A single case of an in-flight mortality was attributed to severe complicated malaria where the diagnosis was based on an initial 4+ (>0.1% parasitaemia) *P. Falciparum* positive film test, and so no confirmatory testing was done at the receiving facility. 12 cases were omitted from the confirmed malaria group as malaria was excluded at the receiving facility in Johannesburg. As illustrated in table 3, the final diagnosis in these 12 cases included trypanosomiasis, tick bite fever, viral encephalitis, tuberculous meningitis, appendicitis, diverticulitis, anaemia, cardiac pathologies and lower respiratory tract infections.

Table 3: Comparison of initial diagnosis of suspected malaria with final diagnosis at the receiving facility.

	(n)	Confirmed malaria (n)	Not malaria (n)
Diagnosis confirmed as malaria at receiving facility	61	61	
Diagnosis not documented at receiving facility	9		
Initial diagnosis based on positive smear		5	
Mortality in flight		1	
Initial diagnosis based on clinical signs alone			2
No initial method of diagnosis documented			1
Diagnosis not malaria at receiving facility	12		
Trypanosomiasis			1
Tick bite fever			1
Viral encephalitis			2
Tuberculous meningitis			1
Appendicitis			1
Diverticulitis			1
Anaemia			1
Cardiac pathologies			2
Lower respiratory tract infections			2
Total	82	67	15

The flight crew differed with the dispatch diagnosis of malaria in four cases, all of which were confirmed as not being malaria at the receiving hospitals. 61 of the cases had malaria confirmed by blood film at the receiving facility, with a total of 67 cases being grouped under the final confirmed malaria cases.

3.3 Accuracy of initial method of malaria diagnosis.

The method of initial malaria diagnosis at the referring facilities was based on blood films in 51 (61.4%) patients, RDTs in 13 (15.9%) patients, and clinical signs alone in 14 (16.9%) patients as shown in table 4.

Table 4: Accuracy of initial method of malaria diagnosis based on receiving facility final diagnosis.

Initial diagnostic method	n	Malaria confirmed n (%)	Not malaria	Not documented
Blood smear	51	40 (78.4%)	5 (9.8%)	6 (11.8%)
RDT	13	12 (92.3%)	1 (7.7%)	
Clinical	14	6 (42.8%)	6 (42.8%)	2 (14.2%)
Not documented	4	3 (75%)		1 (25%)

Of the 51 patients with an initial malaria blood film positive diagnosis, the diagnosis at the receiving facility was confirmed in 40 (78.4%) patients, excluded in five (9.8%) patients and not documented in six (11.8%) patients. One of the six patients died in-flight with no confirmatory malaria testing performed at the receiving facility.

The most accurate method of initial diagnosis appeared to be RDTs with the use of clinical signs alone as the least accurate.

3.4 Incidence of specific malaria species.

P. falciparum alone, or in combination with other *Plasmodium* species was the most commonly isolated species. Of the patients with a documented species, 28 (100%) of the patients at the referring facilities and15 (88.2%) of the 17 patients at the receiving facilities demonstrated *P.*

falciparum (alone or in combination). Forty-four (53.7%) of the 82 suspected malaria cases had no species isolation documented in the post-flight medical report as shown in table 5.

Table 5: Malaria species incidence.

Species isolation	Pre-dispatch	Receiving facility
P. falciparum	25 (30.5%)	13 (15.9%)
P. falciparum and *P. ovale*	2 (2.4%)	1 (1.2%)
P. falciparum and *P. malariae*	1 (1.2%)	1 (1.2%)
P. ovale and *P. vivax*		1 (1.2%)
Not otherwise specified - mixed		1 (1.2%)
Not tested (clinical)	7 (8.5%)	
Species not documented	40 (48.8%)	44 (53.7%)
Negative film	4 (4.9%)	9 (11.0%)
Negative RDT	3 (3.7%)	
Diagnosis not malaria		12 (14.6%)

P. falciparum was diagnosed in combination with *P. ovale* in two patients originating out of Nigeria and Madagascar respectively. The patient from Nigeria had a confirmatory film at the receiving hospital for both strains. Receiving facility species was not documented for the patient originating out of Madagascar.

P. malariae in combination with *P. falciparum* was diagnosed in 1 patient originating out of Mozambique, without confirmatory species isolation documentation at the receiving hospital.

A patient originating out of Uganda had an initial diagnosis of blood film positive for *P. falciparum*, whereas the blood film at the receiving facility isolated a combination of *P. ovale* and *P. vivax* and no *P. falciparum*.

Two patients flown out of Angola with an initial blood film diagnosis of *P. falciparum* malaria had different strains isolated at the receiving hospitals. In one patient *P. malariae* was also seen on

the film, and the other patient had a film which was documented as ‘not otherwise specified mixed’ at the receiving facility.

3.5 Seasonal trends of suspected malaria flights.

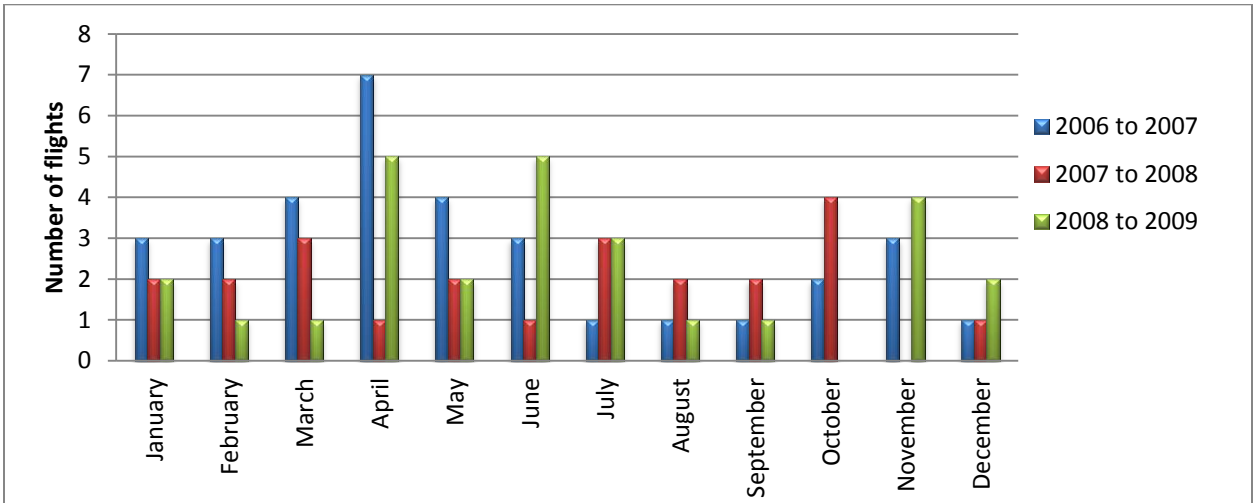


Figure 8: Monthly air-ambulance flights per year for suspected malaria cases.

April and June showed the highest incidence of suspected malaria cases being evacuated, with 13 (15.9%) and nine (11.0%) of all suspected malaria evacuations being flown in these months respectively over the three year period as shown in figure 8.

3.5.1 Seasonal trends of specific countries.

When considering the seasonal variation of malaria, the rainfall pattern of the region concerned needs to be taken into consideration. Each sub-Saharan African country has unique geography and climate variations resulting in specific seasonal variances as pertains to wet and dry

seasons. The five countries most frequently flown to as the country of origin for suspected malaria cases were reviewed individually with regards to seasonal trends.

Angola

Ten (50%) of suspected malaria flights originating out of Angola were flown during the wet season, although cases were flown steadily throughout the year. A peak of five (25%) of all Angolan flights occurred during the month of June, which falls within Angola's dry season.

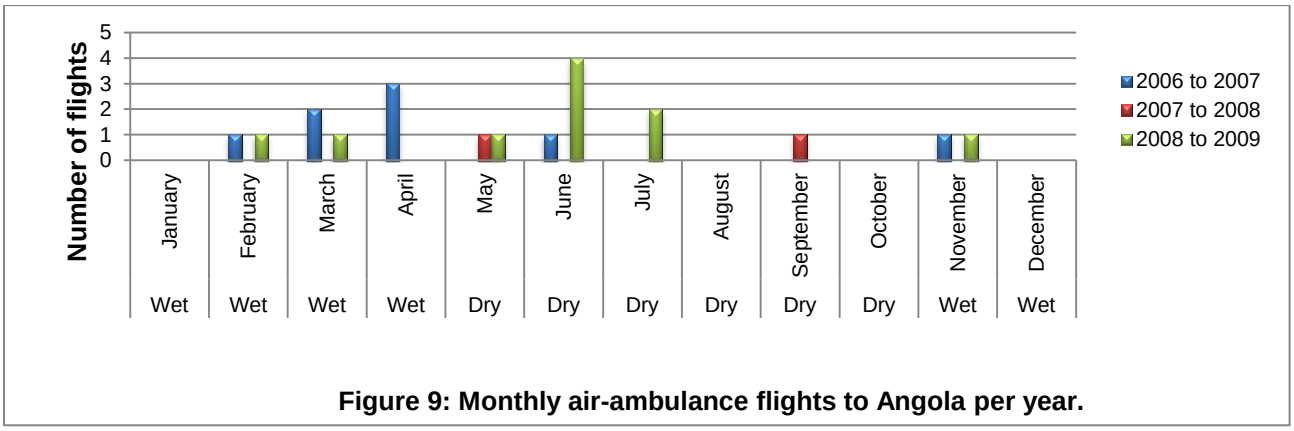


Figure 9: Monthly air-ambulance flights to Angola per year.

The Democratic Republic of Congo

All cases originating out of the Democratic Republic of Congo during this study period were flown out of either Kinshasa or Lubumbashi which are both situated in the south of the Democratic Republic of Congo. Although one patient was flown out of Zambia, the actual initial malaria diagnosis was made in the Democratic Republic of Congo and was thus included in the Democratic Republic of Congo group when considering seasonal trends.

Five (31.3%) of the Democratic Republic of Congo cases were flown during the southern regions wet season (November through March). The peak however, occurred during April and May (dry season) with seven (43.8%) of all the cases occurring during this period.

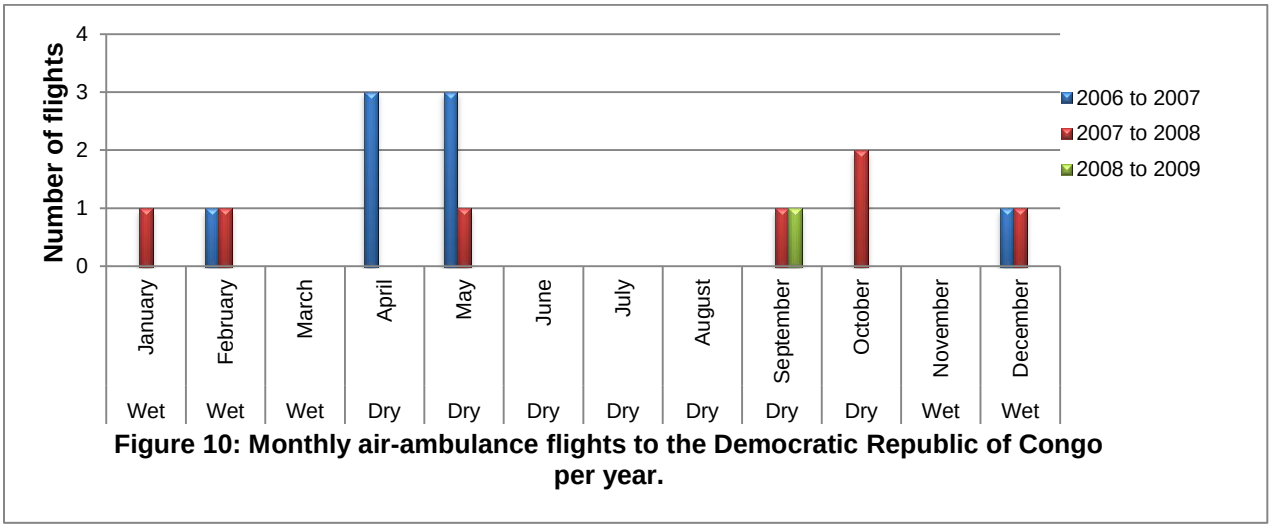


Figure 10: Monthly air-ambulance flights to the Democratic Republic of Congo per year.

Mozambique

The malaria cases flown out of Mozambique were widely distributed throughout the year. Four (30.8%) of the malaria flights originating out of Mozambique occurred during the country's rainy season.

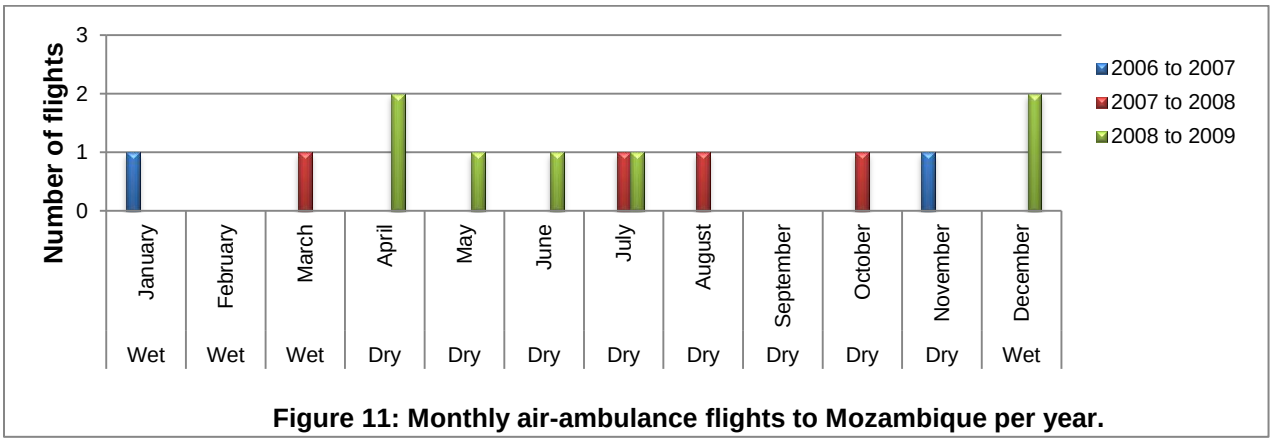


Figure 11: Monthly air-ambulance flights to Mozambique per year.

Nigeria

Four (57.2%) of the flights fell within the wet season, although the highest single month was November with two (28.6%) of the flights occurring here.

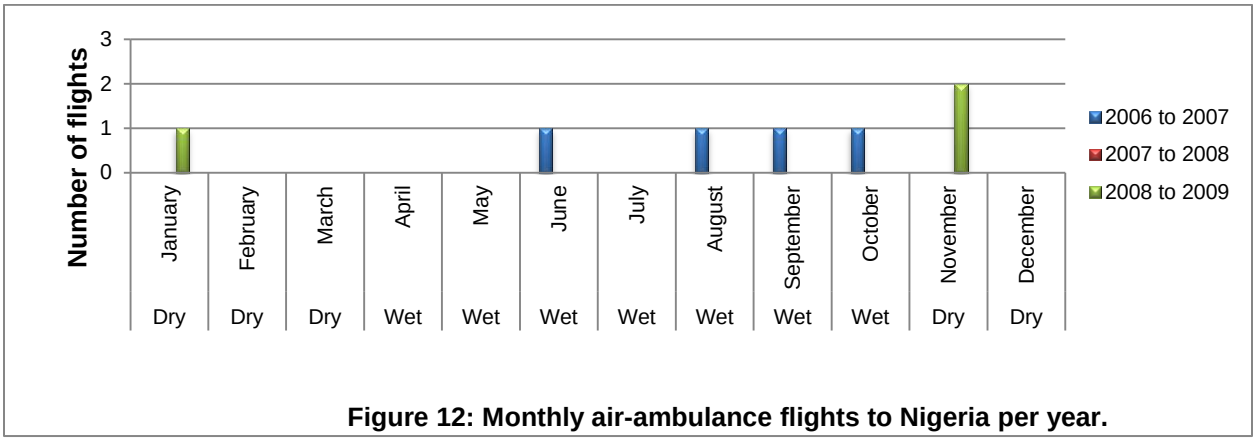


Figure 12: Monthly air-ambulance flights to Nigeria per year.

Zambia

Six (100%) of the suspected malaria evacuations originating out of Zambia occurred within the wet, humid season.

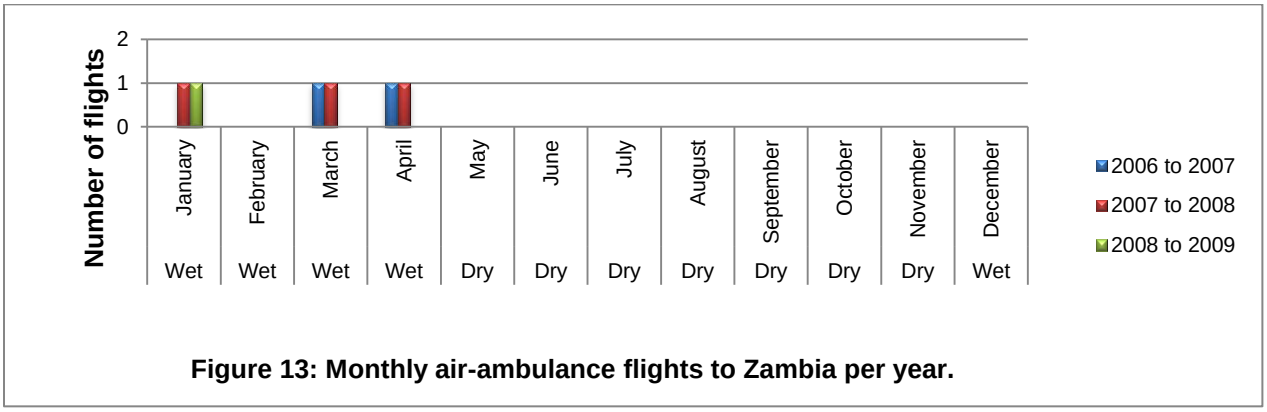


Figure 13: Monthly air-ambulance flights to Zambia per year.

3.5.2 Seasonal trends of all suspected malaria flights.

As shown in figure 14, no seasonal trend was evident when comparing suspected malaria flights flown during specific country's wet and dry seasons. Of the 82 flights, 42 (51.2%) of flights were flown during the specific country's wet seasons.

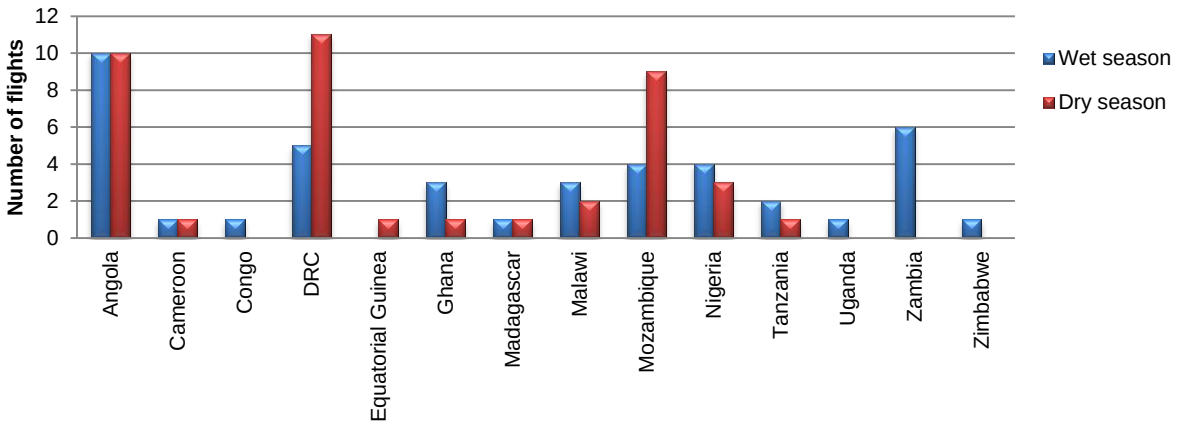


Figure 14: Seaonal trends of suspected malaria flights per country of evacuation origin. July 2006 through June 2009.

3.6 Suspected malaria patient demographics.

Age ranges, gender and the reason for travelling for all the flights as well as for suspected and confirmed malaria flights are shown in table 6. The weight of the suspected malaria patients ranged from 53 to 125 kg with a mean weight of 79.9 ±SD 15.9 kg.

Travel history

Travel history to malaria-endemic countries (other than the malaria-endemic sub-Saharan country of air-ambulance origin) in the preceding three months was obtained from 19 of the

suspected malaria patients and not documented in the remaining 63 patients. The reason the travel history was documented was to ascertain whether patients could potentially have been exposed to malaria species other than the species expected for the country from which they were evacuated. Of the 19 patients, five had confirmed travelling to other malaria-endemic countries in the preceding three months, which are listed in brackets after the country of air-ambulance evacuation origin. These countries included: Nigeria ("tropical areas"), Ghana (Nigeria), Angola (Cameroon), Zambia (the Democratic Republic of Congo) and Angola (China - province not specified). None of these five patients had documented Plasmodium species that were atypical for the country of diagnosis.

Table 6: Summary of patient demographics

	All flights (n=679)	Suspected malaria (n=82)	Confirmed malaria (n=67)
Age			
18-30 years	86 (12.7%)	17 (20.7%)	13 (19.4%)
31-40 years	151 (22.2%)	18 (22.0%)	15 (22.4%)
41-50 years	193 (28.4%)	26 (31.7%)	20 (29.9%)
51-60 years	181 (26.7%)	13 (15.9%)	12 (17.9%)
61-70 years	45 (6.6%)	8 (9.8%)	7 (10.4%)
>70 years	23 (3.4%)		
Mean age	45.8 ±12.7 years	42.1 ±12.8 years	42.9 ±12.8 years
Range	18-89 years	18-68 years	18-68 years
Gender			
Male	538(79.2%)	69 (84.1%)	56 (83.6%)
Female	141 (20.8%)	13 (15.9%)	11 (16.4%)
Reason for travel			
Business/occupation	405 (59.6%)	65 (79.3%)	54 (80.6%)
Leisure	48 (7.1%)	1 (1.2%)	1 (1.5%)
Not documented	226 (33.3%)	16 (19.5%)	12 (17.9%)

Nationality

Table 7 reflects the various nationalities of the patients evacuated for suspected malaria during the three year period. The vast majority of patients were South African citizens in 40 (48.8%) of the 82 cases.

Table 7: Nationalities of suspected malaria patients.

American	4 (4.9%)	Chinese	3 (3.7%)	Japanese	1 (1.2%)
Argentinean	1 (1.2%)	Croatian	1 (1.2%)	Korean	2 (2.4%)
Australian	1 (1.2%)	Filipino	1 (1.2%)	Portuguese	5 (6.1%)
Belgian	1 (1.2%)	French	6 (7.3%)	South African	40 (48.8%)
Brazilian	1 (1.2%)	Indian	1 (1.2%)	Swiss	1 (1.2%)
British	7 (8.5%)	Irish	1 (1.2%)	Taiwanese	1 (1.2%)
Canadian	1 (1.2%)	Israeli	2 (2.4%)	Thai	1 (1.2%)

3.7 Malaria chemoprophylaxis utilisation and compliance.

Of the 82 patients with an initial and flight crew diagnosis of suspected malaria, only 11 (13.4%) had utilised malaria chemoprophylaxis and 51 (62.2%) had not. Of the 20 (24.4%) patients where malaria chemoprophylaxis utilisation was not documented, six patients required intubation or had already been intubated by the referring facility, and a further two patients had a GCS of 13/15 and 11/15 respectively, and were therefore unable to provide a chemoprophylaxis history.

Of the 11 patients who had utilised malaria chemoprophylaxis, two were non-compliant, two were compliant and there was no documentation on the other seven patients. The first non-compliant patient stopped taking his chloroquine chemoprophylaxis one month prior to the malaria diagnosis in Angola due to side effects including gastro-intestinal symptoms and dry hands. The second non-compliant patient stopped taking his mefloquine chemoprophylaxis due to side effects including morning nausea and sleepiness one week prior to the malaria diagnosis in Madagascar.

The choice of chemoprophylaxis was appropriate for the country of origin in seven of the eight patients who had the type of chemoprophylaxis utilised documented by the flight crew. One patient originating out of Angola utilised chloroquine (Nivaquine®, Daramal®, Plasmaquine®, Rolab-Chloroquine®) as chemoprophylaxis. Mefloquine (Lariam®, Mefliam®) was the most popular chemoprophylaxis choice, and was utilised by four (36.4%) patients, followed by doxycycline (Vibramycin®, Doxitab®, Cyclidox®) utilisation by two (18.2%) patients. Atovaquone-proguanil (Malanil®, Malarone®) was utilised by one (9%) patient. The remaining three (27.3%) patients did not have the type of chemoprophylaxis documented.

Two (18.2%) of the 11 patients who had utilised malaria chemoprophylaxis required intubation. The first patient was evacuated out of Angola during the wet month of November. As this patient was in severe respiratory failure with a respiratory rate of 50 breaths/min and oxygen saturation readings of 61% on supplemental oxygen the crew elected to intubate the patient emergently and obtained chemoprophylaxis information from a colleague post intubation. The colleague confirmed chemoprophylaxis compliance although the type of chemoprophylaxis utilised could not be recalled. The latter patient was evacuated out of Mozambique during the dry month of October. This patient had already been intubated by the referring facility and the accompanying medical records documented atovaquone-proguanil utilisation without mentioning compliance.

Of the 71 patients where chemoprophylaxis was either not utilised or not documented, 13 (18.3%) required intubation. The 13 patients were flown out of Angola, Congo, the Democratic Republic of Congo, Ghana, Mozambique, Nigeria and Madagascar with four of these flights during each specific country's wet months and three during the country's dry months as shown in table 8.

No statistically significant difference (*P-Fisher exact* = 0.50) was shown for intubation requirements when comparing patients who had utilised malaria chemoprophylaxis with the patients who had not, nor when comparing intubation requirements of patients who had utilised chemoprophylaxis with patients where chemoprophylaxis utilisation was not documented (*P-Fischer exact* = 0.39). When comparing patients who had utilised malaria chemoprophylaxis with the patients who had not utilised chemoprophylaxis or where chemoprophylaxis was not documented, no statistically significant difference (*P-Fischer exact* = 0.68) was shown.

Table 8: Intubation requirements compared to chemoprophylaxis utilisation.

Chemoprophylaxis utilised (11)		**Air-ambulance country of origin**	**Wet season**	**Dry season**
Intubated	2 (18.2%)	Angola	1	
		Mozambique		1
Not intubated	9 (81.8%)			
Chemoprophylaxis not utilised (51)				
Intubated	7 (13.7%)	Congo	1	
		Democratic Republic of Congo		1
		Madagascar	1	
		Mozambique		1
		Nigeria	2	1
Not intubated	44 (86.3%)			
Chemoprophylaxis usage not documented (20)				
Intubated	6 (30.0%)	Angola	1	
		Ghana	1	
		Democratic Republic of Congo	2	1
		Mozambique		1
Not intubated	14 (70.0%)			

Intubation requirements comparing chemoprophylaxis utilised vs. not utilised *P-fisher* = 0.50
Intubation requirements comparing chemoprophylaxis utilised vs. not documented *P-fisher* = 0.39
Intubation requirements comparing chemoprophylaxis utilised vs. not utilised/documented *P-fisher* = 0.68

3.8 Initial clinical parameters of suspected malaria patients.

Glasgow Coma Scale

As shown in table 9, the GCS ranged from 4/15 to 15/15 with a mean GCS of 14.2 ±2.1. The majority of the suspected malaria patients, 61 (74.4%) had an initial GCS of 15/15, and 13 (15.9%) patients had an initial GCS of 9/15 to 14/15. The three (3.6%) patients with a GCS score of between 4/15 to 8/15 were all intubated by the flight crew for airway protection.

Table 9: Summary of initial clinical parameters of suspected malaria patients

GCS	**n (%)**	**Systolic BP**	**n (%)**	**Heart rate**	**n (%)**
3/15:	0	70-90mmHg	5 (6.1%)	<60bpm	2 (2.4%)
4-8/15:	3 (3.6%)	91-110mmHg	21 (25.6%)	60-100bpm	60 (73.2%)
9-14/15:	13 (15.9%)	111-130mmHg	29 (35.4%)	101-140bpm	18 (22.0%)
15/15:	61 (74.4%)	131-150mmHg	21 (25.6%)	>140bpm	2 (2.4%)
Intubation in situ	5 (6.1%)	>150mmHg	6 (7.3%)		
Range	4-15/15	Range	77-180mmHg	Range	46-150bpm
Mean	14.2 SD ± 2.1	Mean	121.0 SD ±20mmHg	Mean	88.9 SD ± 21bpm
Hb	**n (%)**	**Hourly urine output**	**n (%)**	**Temperature**	**n (%)**
< 5.0 g/dL	1 (1.2%)	<0.5 ml/kg/hr	7 (8.5%)	<37.5°C	61 (74.4%)
5.0-7.0 g/dL	2 (2.4%)	0.5-1.0ml/kg/hr	10 (12.2%)	37.5-38.4°C	13 (15.9%)
7.1-10.0 g/dL	9 (11.0%)	1.1-2.0 ml/kg/hr	13 (15.9%)	>38.4°C	7 (8.5%)
>10.0 g/dL	38 (46.3%)	>2.0 ml/kg/hr	11 (13.4%)	Not documented	1 (1.2%)
Not documented	32 (39.1%)	Self voiding - nil	33 (40.2%)		
		Self voiding - passed	8 (9.8%)		
Range	4.4-17.0 g/dL	Range	0.2-24ml/kg/hr	Range	35.4-39.8°C
Mean	11.9 SD ±3 g/dL	Mean	2.1 SD ±3.7ml/kg/hr	Mean	37.0 SD ±1.0°C
Blood glucose	**n (%)**	**Oxygen saturation**	**n (%)**	**Respiratory rate**	**n (%)**
<3.5 mmol/L	2 (2.4%)	< 80%	2 (2.4%)	8-11/min	1 (1.2%)
3.5-8.0 mmol/L	66 (80.5%)	80-90%	1 (1.2%)	12-20/min	56 (68.3%)
>8.0 mmol/L	14 (17.1%)	>90%	79 (96.4%)	21-29/min	19 (23.2%)
				≥30/min	6 (7.3%)
Range	2.4-31.2 mmol/L	Range	61-100%	Range	10-50/min
Mean	6.7 SD ± 3.5 mmol/L	Mean	96 SD ±5.1%	Mean	19.7 SD ± 7.7/min
Clinical anaemia	**n (%)**	**Macroscopic haemoglobinuria**	**n (%)**	**Clinical jaundice**	**n (%)**
Yes	20 (24.4%)	Yes	13 (15.9%)	Yes	25 (30.5%)
No	48 (58.5%)	No	19 (23.2%)	No	49 (59.8%)
Not documented	14 (17.1%)	Not documented	50 (60.9%)	Not documented	8 (9.7%)

Systolic blood pressure

Suspected malaria patients presented with a systolic BP ranging from 77 to 180mmHg with a mean of 121 ± 20 mmHg. Five (6.1%) of the 82 patients presented with systolic BP readings of equal or less than 90 mmHg. Two of these hypotensive patients had already been intubated by the referring facility upon flight crew assessment. Table 10 depicts the associated clinical parameters for the afore-mentioned five patients who presented with systolic BP readings of equal or less than 90 mmHg.

Table 10: Clinical parameters of patients with an initial systolic BP ≤90mmHg.

SBP	Heart rate	GCS	Urine output	Clinical anaemia	Hb
90 mmHg	90 bpm	15/15	Spontaneous voiding x1/2.5hrs	No	N/D
88 mmHg	82 bpm	Intubated	Nil spontaneous voiding/4hrs	No	N/D
90 mmHg	80 bpm	15/15	Nil spontaneous voiding/2.5hrs	Yes	N/D
77 mmHg	65 bpm	15/15	0.8 ml/kg/hr	No	13.3 g/dL
77 mmHg	128 bpm	Intubated	0.2ml/kg/hr	N/D	10.5 g/dL

One of the five patients presenting with hypotension was on an adrenaline infusion of 1.8mcg/kg/min from the referring facility in the Democratic Republic of Congo. This patient presented with a systolic BP of 77mmHg and heart rate of 128bpm and had already been intubated.

One patient from Congo presented with a systolic BP of 91 mmHg on a dopamine infusion, without documentation of the infusion dose, which was changed to a combination of adrenaline and dobutamine infusions by the flight crew. The flight crew initiated inotropic infusions in a further five patients. One of the five patients was hypotensive on presentation and four patients became hypotensive during the evacuation necessitating inotropic support. The patient who died in-flight received adrenaline as part of the resuscitation as per Advanced Cardiac Life Support® principles.

Heart rate

The patients' heart rates ranged from 46 to 150bpm with a mean of 88.9 SD ± 21 bpm. Two (2.4%) patients presented with bradycardias, defined as a heart rate of less than 60 bpm. The first patient developed a second-degree heart block with a heart rate of 46 bpm when intravenous quinine was initiated at the referring hospital in the Democratic Republic of Congo. The second patient, flown out of Madagascar, had a sinus bradycardia with an initial heart rate of 49bpm. This patient tolerated intravenous quinine administered during the flight. Both patients presenting with bradycardias had adequate peripheral perfusion. One patient who presented with an initial heart rate of 67 bpm in a sinus rhythm had apparently received atropine at the referring facility in Equatorial Guinea. This patient tolerated an intravenous quinine loading dose administered by the flight crew. Twenty patients presented with tachycardias, defined as a heart rate of more than 100 bpm. The two patients with the fastest heart rates both presented with sinus tachycardias of 149bpm and 150bpm respectively and had adequate peripheral perfusion and systolic blood pressures of more than 90mmHg. One of the 20 tachycardic patients presented with a systolic BP of 77mmHg.

Haemoglobin level

The Hb as measured by means of the i-STAT® blood gas analyser on initial assessment by the flight crew showed a range of 4.4-17 g/dL and a mean Hb of 11.9 SD ± 3.0 g/dL. The i-STAT® provides real-time laboratory results within two minutes. Quality control checks are performed utilising a metal electronic cartridge simulator prior to each air-ambulance flight as well as prior to utilisation. Of the 82 suspected malaria patients, nine (11%) patients had an initial Hb of between 7.1-10.0 g/dL with two of these patients having received three and two units of packed red cells (PRC) at the referring facilities in Cameroon and Malawi respectively prior to flight crew assessment as shown in table 11. Two (2.4%) patients had a Hb level of between 5.0 to 7.0

g/dL and neither had received blood transfusions at the referring facility nor from the flight crew. One (1.2%) patient flown out of the Democratic Republic of Congo had an initial Hb of 4.4 g/dL, and the flight crew administered two units of emergency O-negative packed red cells during the flight. For the purpose of this study anaemia was defined as a Hb level of less than 10 g/dL, thus 12 (14.6%) of the suspected malaria patients were anaemic. 38 (46.3%) patients had a Hb measurement of more than 10.0 g/dL with no documentation on a Hb measurement in the remaining 32 (39.0%) patients.

Table 11: Clinical parameters of patients with a Hb <10.0 g/dL.

Hb (g/dL)	SBP (mmHg)	HR (bpm)	Sats	Intubation	PRC transfusion
4.4	160	112	99%	No	2U by crew
6.1	108	82	98%	No	
6.4	97	81	91%	No	
7.5	145	105	79%	By flight crew	
7.8	127	109	98%	No	2U at referring facility
8.2	113	46	97%	No	
8.2	115	94	100%	No	
8.2	180	113	98%	By flight crew	
8.5	110	75	100%	No	
8.8	157	72	97%	No	
8.8	99	149	99%	No	
9.2	118	69	100%	No	3U at referring facility

Clinical anaemia

Clinical anaemia, as per assessment of the presence of pallor by the flight crew doctor, was present in 20 (24.4%) of the 82 suspected malaria patients, with 14 (70.0%) of these 20 patients having had a Hb level checked upon assessment. Of these 14 patients, four (28.6%) had a Hb level of more than 10 g/dL, seven (50.0%) had a Hb level of 7.1 to 10 g/dL, two (14.3%) had a Hb level of 5.0 to 7.0 g/dL and one (7.1%) patient had a critically low Hb of less than 4.4 g/dL. Thus in 10 (71.4%) of the 14 patients the blood gas analyser haemoglobin measurement confirmed the clinical diagnosis of anaemia. Two patients with Hb values of 7.5 and 8.2 g/dL respectively required intubation with the former patient dying during the flight. Of the 20 patients

who presented with clinical anaemia seven (35.0%) patients also presented with clinical jaundice and two (10%) patients also presented with macroscopic haemoglobinuria.

Table 12: Clinical parameters of patients presenting with clinical anaemia.

Hb (g/dL)	SBP (mmHg)	Heart rate (bpm)	Oxygen saturation	GCS	Intubated	Macroscopic haemoglobinuria	Clinical jaundice	Supplemental oxygen in situ
4.4	160	112	99%	15	No	N/D	No	No
6.1	108	82	98%	15	No	N/D	No	No
6.4	97	81	91%	15	No	No	Yes	No
7.5	145	105	79%	8	By flight crew	No	Yes	Yes
7.8	127	109	98%	14	No	N/D	No	No
8.2	115	94	100%	15	No	No	Yes	No
8.5	110	75	100%	15	No	No	No	No
8.8	99	149	99%	14	No	N/D	No	No
8.8	157	72	97%	15	No	N/D	Yes	No
9.2	118	69	100%	15	No	N/D	Yes	No
10.5	122	67	100%	15	No	No	Yes	No
12.6	137	62	96%	15	No	No	Yes	No
12.9	112	83	100%	10	By flight crew	N/D	No	No
15.6	151	110	99%	Intubated	In situ	Yes	No	Yes
ND	118	76	97%	15	No	Yes	N/D	No
ND	117	75	96%	15	No	No	No	No
ND	113	78	93%	15	No	No	No	No
ND	135	72	98%	15	No	No	N/D	No
ND	90	80	94%	15	No	N/D	No	No
ND	107	62	99%	15	No	No	No	No

Macroscopic haemoglobinuria

The presence of macroscopic haemoglobinuria as a sign of haemolysis was documented in 13 (15.9%) of the suspected malaria patients, absent in 19 (23.2%) patients and not documented in the remaining 50 (60.9%) patients. Table 13 illustrates that concurrent clinical jaundice was present in five (38.5%) of the 13 patients with macroscopic haemoglobinuria. The Hb levels were higher than 10 g/dL in all six patients who underwent testing and urine output was more than 0.5 ml/kg/hr in all seven patients where hourly urine output was measured. The systolic BP was more than 90mmHg in all 13 patients with macroscopic haemoglobinuria.

Table 13 : Suspected malaria patients with macroscopic haemoglobinuria.

Clinical jaundice	Clinical anaemia	Hb	Urine output	SBP (mmHg)
Yes	No	N/D	3.2 ml/kg/hr	109
No	N/D	14.2 g/dL	2.7 ml/kg/hr	140
Yes	No	14.2 g/dL	Spontaneous voiding x2/9hrs	142
Yes	N/D	10.9 g/dL	1.6 ml/kg/hr	113
N/D	N/D	N/D	Nil spontaneous voiding/4hrs	120
Yes	No	N/D	4.7 ml/kg/hr	149
No	No	N/D	Nil spontaneous voiding/3hrs	102
No	No	11.2 g/dL	1.3 ml/kg/hr	132
No	Yes	N/D	Spontaneous voiding x1/6hrs	118
No	Yes	15.6 g/dL	1.0 ml/kg/hr	151
Yes	No	N/D	Nil spontaneous voiding/4hrs	147
No	No	N/D	Spontaneous voiding x1/4hrs	110
No	No	12.2 g/dL	0.7 ml/kg/hr	91

Hourly urine output

Oliguria, defined as an average urine output of less than 0.5ml/kg/hr was documented in seven (8.5%) of the suspected malaria patients. One of these seven patients had presented with concurrent initial hypotension with a systolic BP of 77mmHg. Urine output in the 41 patients where hourly urine output volumes were documented ranged from 0.2 to 24ml/kg/hr with a mean output of 2.1 ± 3.7ml/kg/hr.

Of the 11 patients with polyuria, defined as urine output of more than 2.0ml/kg/hr, one patient had an output of 24ml/kg/hr and had received furosemide from both the referring facility and the flight crew. In this patient the crew diagnosis as well as the final diagnosis at the receiving facility was atrial fibrillation with congestive cardiac failure and not malaria. No patient presenting with polyuria had hyperglycaemia on initial assessment, and presented with blood glucose levels ranging from 3.9 to 8.2 mmol/l.

Clinical jaundice

Clinical jaundice was present in 25 (30.5%) patients and absent in 49 (59.8%) patients. No documentation regarding the presence or absence of jaundice was made in the remaining eight

(9.7%) patients. Macroscopic haemoglobinuria was present in five (20.0%) of the 25 clinically jaundiced patients, absent in six (24.0%) patients and not documented in the remaining 14 (56.0%) patients. Of the 25 clinically jaundiced patients five (20.0%) had a Hb measurement of less than 10 g/dL with a range of 6.4 to 9.2 g/dL, 13 (52.0%) patients had a Hb measurement of more than 10 g/dL and the remaining seven (28.0%) patients did not have a Hb documented.

Temperature

The temperature readings of the suspected malaria patients ranged from 35.4-39.8ºC with a mean temperature of 37.0 SD ± 1.0 ºC. Seven (8.5%) of the 82 suspected malaria patients had an initial temperature higher than 38.4ºC.

Blood glucose level

The initial blood glucose levels as measured by finger prick testing ranged from 2.4 to 31.2 mmol/L with a mean level of 6.7 SD ± 3.5 mmol/L. The two patients with the lowest blood glucose levels presented with values of 2.4 mmol/L and 2.9 mmol/L respectively. Both patients had received intravenous quinine infusions prior to flight crew arrival, and neither were on any glucose containing intravenous fluids at the time of assessment. Intravenous quinine was appropriately administered in a 5% dextrose infusion to the first patient during the flight from Angola as it was due, and the patient remained persistently hypoglycemic necessitating four administrations of 50ml 50% dextrose by the flight crew. A patient flown from the Democratic Republic of Congo presented with an initial blood glucose level of 31.2 mmol/L whilst on a 5% dextrose saline infusion. This patient was not known to have diabetes and required insulin during the flight after the dextrose infusion was stopped to control his blood glucose levels.

Oxygen saturation

Upon assessment the suspected malaria patients' oxygen saturation readings ranged from 61-100% with a mean of 96.0 SD± 5.1%. The majority of patients, 79 (96.4%) presented with initial oxygen saturation readings of more than 90%. Three patients presented with initial oxygen saturation readings of less than 90%. Two of these patients were receiving supplemental oxygen at the time of assessment. The first patient from Angola had saturation reading of 61% and the second patient from the Democratic Republic of Congo had saturation readings of 79%. One patient from Ghana who presented with oxygen saturation readings of 84% was not on supplemental oxygen at the time of assessment. All three patients were subsequently intubated by the flight crew. In total, 19 (23.2%) of the 82 suspected malaria patients were receiving supplemental oxygen therapy at the time of initial assessment by the flight crew.

Respiratory rate

The respiratory rate ranged from 10 to 50 breaths per minute with a mean of 19.7 SD ± 7.7 breaths per minute. As shown in table 14, six patients presented with marked tachypnoea, defined as a respiratory rate of equal/more than 30 breaths per minute. Of these six patients, three presented with oxygen saturation readings of less than 90% and four of the six tachypnoeic patients were intubated by the flight crew.

Table 14: Initial clinical respiratory parameters in tachypnoeic patients.

Respiratory rate (breaths/min)	Oxygen saturation	Supplemental oxygen	Intubation	GCS
32	99%	Yes	No	11
36	97%	Yes	No	15
36	100%	No	By flight crew	10
46	79%	Yes	By flight crew	8
47	84%	No	By flight crew	9
50	61%	Yes	By flight crew	15

3.8.1 Intubation requirements.

A total of 15 (18.3%) of the 82 patients in the suspected malaria group required intubation and ventilation as shown in table 15. Ten of these intubations were performed by the flight crew post initial patient assessment. All intubations performed by the referring facilities as well as the flight crew were orotracheal intubations.

The indications for the 10 flight crew intubations were due to a depressed level of consciousness (GCS) in seven patients which ranged from 4/15 to 14/15, severe respiratory failure in one patient and a combination of depressed level of consciousness and respiratory failure in two patients. The remaining five patients had already been intubated by the referral facility prior to the flight crew arrival.

Twelve of the 15 intubated patients had a final diagnosis of *P. falciparum* at the receiving facility. Two of these patients had been flown with an initial diagnosis of *P. falciparum* combined with *P. ovale*. One patient who had been flown out of the Democratic Republic of Congo with an initial diagnosis of *P. falciparum* had *P. malariae* identified at the receiving facility. *P. vivax* was identified in one patient flown out of Angola without a documented initial species identification from the referring facility. One patient died in-flight which was attributed to the 4+ *P. falciparum* film positive severe complicated malaria by the air-ambulance service provider.

Patients requiring intubation by the flight crew were flown out of Nigeria, Ghana, Angola, Mozambique, Congo and the Democratic Republic of Congo. Six of these 10 flights were during the wet season for that specific country.

Thirteen of the 15 patients were receiving intravenous quinine as part of the treatment regimen from the referring facility and two patients did not have any documentation on the referring facility treatment regimens. The crew administered loading doses of intravenous quinine to the latter two patients and the next due dosage in a further seven patients. Five patients were not due their next intravenous quinine dose during the flight and no anti-malarials were administered to a patient where the crew differed with the referring facility diagnosis of malaria. The latter patient who was flown from Ghana was confirmed to have pneumonia at the receiving facility. Five patients were on concurrent antibiotics as part of the treatment regimen from the referring facility, including ceftriazone, cefuroxime and cefotaxime. Two patients were on inotropic support upon crew assessment, including one patient who was hypotensive despite being on an adrenaline infusion. The flight crew provided inotropic support to these two patients as well as a further three patients. Adrenaline was provided as part of the resuscitation of the patient who died in-flight.

Of the five patients who were intubated by the referral facility one was hypotensive with a systolic BP of 77 mmHg, and three patients were tachycardic including the aforementioned hypotensive patient. All five patients presented with saturation levels of more than 90% on supplemental oxygen with artificial ventilation. Patients were flown out of Mozambique, Angola, Madagascar and the Democratic Republic of Congo as illustrated in table 15. Although one patient was flown out of Zambia, by this air-ambulance service provider, it was part of a staged evacuation originating out of the Democratic Republic of Congo where the malaria diagnosis was made.

Table 15: Initial clinical parameters of intubated patients.

Reason for intubation	GCS	SBP	HR	RR	SpO2	O2	Hgt	Referring facility sp.	Receiving facility sp.	Country	Season
Decreased GCS	4	113	106	16	95%	No	5.1	N/D	P.f	DRC	Wet
	8	132	124	26	100%	Yes	5.3	P.f	P.f	Nigeria	Wet
	10	150	130	26	95%	No	15.3	P.f	P.f	Mozambique	Dry
	10	180	113	18	98%	Yes	15.1	P.f + P.o	P.f	Nigeria	Dry
	10	112	83	36	100%	No	4.1	N/D	P.f	Mozambique	Dry
	14	91	95	28	94%	Yes	6.7	N/D	P.f	Congo	Wet
	14	111	120	28	98%	Yes	5.7	P.f	N/D	Nigeria	Wet
GCS and respiratory	8	145	105	46	79%	Yes	7	P.f	P.m	DRC	Dry
	9	139	117	47	84%	No	4.1	N/D	N/A	Ghana	Wet
Respiratory	15	140	122	30	61%	Yes	4.6	N/D	P.v	Angola	Wet
In situ	N/A	77	128	14	93%	Yes	8.2	N/D	P.f	DRC	Wet
	N/A	151	110	16	99%	Yes	4.2	P.f	P.f	Mozambique	Dry
	N/A	101	88	12	100%	Yes	6.3	N/D	P.f	Zambia (DRC)	Dry
	N/A	118	75	14	100%	Yes	6.4	N/D	P.f	Angola	Wet
	N/A	135	125	12	94%	Yes	5.6	P.f +P.o	P.f	Madagascar	Wet

3.9 Malaria treatment administered by the referring facility and during the air-ambulance flight.

Forty-nine of the 82 patients were on intravenous quinine as part of the treatment regimen from the referring facility as shown in table 17. Seven of the 49 patients were changed to intravenous quinine by the referring facility after initially being on artemesinin derivatives which included oral artemether-lumefantrine (coartem®) in four patients, artemether as monotherapy without specification of administration route in one patient, oral artemether-lumefantrine combined with intramuscular artemether in one patient, and artemether with sulfadoxine-pyrimethamine (fansidar®) in one patient.

Of the 49 patients, 24 patients were on intravenous quinine alone and 13 patients were on intravenous quinine in combination with an antibiotic. Four patients were on third generation

cephalosporins (ceftriazone, cefotaxime), one patient received a second generation cephalosporin (cefuroxime), two patients were receiving penicillin and beta-lactamase inhibitor combinations (amoxicillin/clavulanic acid), three patients received tetracyclines (doxycycline), two patients were administered quinolones (ciprofloxacin), and one patient was administered a nitroimidazole derivative (metronidazole).

The flight crew administered the next due intravenous quinine dose to 19 of the 49 patients. Twenty-nine of the 49 patients were not due their next dose during flight, and in one case the crew elected not to give intravenous quinine as the flight crew disagreed with the initial diagnosis of malaria. In one case intravenous quinine had been changed to intravenous artesunate by the referring facility which was not due during the flight. A further seven patients received an initial loading dose of intravenous quinine from the flight crew, totalling 26 intravenous quinine administrations during flight by the flight crew.

Nine patients were not administered intravenous quinine by the referring facility or the flight crew. Four of these patients were on oral artemether-lumefantrine and two patients on intravenous artesunate. A patient, who had forgotten to take the 200mg oral artesunate as part of his sulfadoxine-pyrimethamine combination regimen took the tablets during flight. One patient from Malawi was on oral halofantrine (after initially being on artemether-lumefantrine) which was not due during the flight. Intramuscular artemether 80mg was administered by the flight crew in one patient as it was due during the flight.

The flight crew differed with the referring facility diagnosis of suspected malaria in four cases and did not administer any anti-malarial treatment during the flight. In all four cases the diagnosis was confirmed not to be malaria. One patient flown out of Angola had already completed his sulfadoxine-pyrimethamine (fansidar®) course. Two patients flown from Zambia

and Angola respectively had no documentation regarding treatment administered at the referring facility. A patient who was flown out of Ghana had received a loading dose of intravenous quinine and had a follow-up negative malaria film at the referring facility. The diagnosis was confirmed as pneumonia at the receiving facility.

Anti-malarial treatment was deferred in a further six patients, including an 18 week pregnant patient from Zambia, until a definitive diagnosis was made at the receiving facility. Three of the six patients had completed a course of artemether-lumefantrine, one had completed a sulfadoxine-pyrimethamine with artesunate course and the no documentation on the referring facility treatment was received in one patient from Angola.

One patient from the Democratic Republic of Congo had developed a second degree heart block on intravenous quinine which was subsequently stopped by the referring facility and one patient from Mozambique refused intravenous quinine administration by the flight crew after having completed her artemether-lumefantrine course in Mozambique.

Table 16: Referring facility and flight crew anti-malarial treatment.

Referring facility treatment regimens	(n)	IV quinine due (n)	IV quinine not due (n)	IV quinine loading dose (n)	Other anti-malarials due (n)	Other anti-malarials not due (n)	Not malaria (n)
IV Quinine	24	13	11				
IV Quinine and antibiotic	14	3	10				1
Other [a] then changed to IV quinine	7	2	5				
Other [b] then changed to IV quinine and antibiotics	4	1	3				
Other [c] and antibiotic	3			3			
Atovaquone-proguanil	1			1			
Crew unsure of treatment received	5			3			2
Other [d]	9				3	6	
Other [e] and antibiotic	5				2	3	
IV quinine then changed to IV artesunate	1					1	
IV quinine stopped due to side effects	1						
Deferred treatment	6						
Patient refused IV quinine after completing artemether-lumefantrine course	1						
Completed sulfadoxine-pyrimethamine course	1						1

[a] Artemether-lumifantrine, artemether, sulfadoxine-pyrimethamine
[b] Artemther-lumifantrine, sulhfadoxine-pyrimethamine, doxycycline
[c] Artemether-lumifantrine, artesunate, artemether
[d] Artemether-lumifantrine, artesunate IV, artesunate + sulfadoxine-pyrimethamine, IMI artemether, halofantrine
[e] Arthemether-lumifantrine, artemether, quinine

CHAPTER 4: DISCUSSION

4.1 Summary of results.

This 3-year retrospective study reviewed flight documentation of 679 adult expatriates and long-term travellers who were evacuated by fixed-wing air-ambulance from 30 of the 49 (excluding South Africa) sub-Saharan African countries to Johannesburg, South Africa. Suspected malaria cases were flown out of 14 sub-Saharan African countries, which included: Angola; Cameroon; Congo; the Democratic Republic of Congo; Equatorial Guinea; Ghana; Madagascar; Malawi; Mozambique; Nigeria; Tanzania; Uganda; Zambia and Zimbabwe. Patients were mainly evacuated out of Eastern and Central Africa with the majority of flights originating out of Angola, Mozambique and the Democratic Republic of Congo. No suspected malaria cases were flown out of Lesotho, Mauritius, Réunion and Seychelles which are malaria-free. [53]

Suspected malaria was the most common specific diagnosis at the time of air-ambulance dispatch when compared to the other clinical groupings of trauma, surgical, obstetric, cardiac and other medical diagnoses. The majority of suspected malaria patients were correctly diagnosed at the referring facility. RDTs were the most accurate diagnostic method and clinical signs alone were the least accurate. *P. falciparum* was the most commonly isolated species at both the referring and receiving facilities, however the majority of patients did not have specific species documented at both facilities. Malaria species isolated at the referring and receiving facilities were expected for the country of origin except for one case flown out of Angola.

No seasonal trend could be demonstrated as flights for suspected malaria occurred in similar numbers over the wet and dry seasons when reviewing the five countries most commonly flown to during the study period. Suspected malaria patients were predominantly male with a mean age of 42.1 years and travelling for business or occupational reasons. The majority of patients were South African Nationals.

Malaria chemoprophylaxis was poorly utilised with only 2.4% of patients being compliant on appropriate chemoprohylaxis. One in five of the suspected malaria patients required intubation as a marker of disease severity. One patient died in-flight as a result of severe malaria. No specific malaria treatment regimen could be identified for a specific country. The majority of complicated malaria patients flown out of sub-Saharan Africa were still receiving intravenous quinine and not artesunate as treatment for complicated malaria.

4.2 Limitations of the study.

Records utilised for this review were from one air-ambulance provider (operating out of Johannesburg), which is contracted to specific corporate clients and medical/travel insurance companies. The fee-for-service operational policy of this air-ambulance provider will select for a specific study patient population and thus results are not reflective of the entire expatriate and long-term traveller population in sub-Saharan Africa. The profile of patients flown may thus be influenced by availability of financial backing rather than on clinical presentation of the disease alone. A further limitation of this study is that data from other air-ambulance providers operating out of South Africa have not been included in this review. This, combined with the relatively short period reviewed has resulted in a small sample size.

There is a paucity of data in the literature on expatriates being evacuated for suspected malaria from sub-Saharan African countries. This limits the ability to compare results of this study with previous studies. There was also no widely accepted definition in the literature as to what defines a long-term traveller.

Data captured was dependent on the thoroughness of pre-flight, in-flight and post-flight documentation. For several parameters, incomplete documentation may have resulted in skewed results due to small sub-groups for analysis. Limited documentation was most apparent regarding *Plasmodium* species isolation at the receiving facilities, with more than half of the patients having no documentation on species isolated. Therefore the size of this sub-group analysed was much smaller than expected. Nearly a quarter of patients had no documentation on the utilisation of chemoprophylaxis resulting in a small sub-group of patients who were documented to be compliant on chemoprophylaxis.

The format and structure of the in-flight medical report form ensured the capturing of similar basic information as shown in appendix A. The quality of the post-flight medical report varied from case to case with regards to the extent of the information obtained and documented. The measure of the detail in the post-flight medical report is largely dependent on the medical assistance company's client expectations. For certain clients a basic report confirming safe admission is expected whereas other clients may expect continuous daily medical monitoring with detailed updates to their in-house medical team. As the initial, and in some cases final post-flight medical report is obtained within 1-2 hours post admission, the malaria film results may not be available at that time. This means that data captured from the post-flight medical report may be incomplete, especially with regards to malaria species identification.

Air-ambulance evacuations out of Africa may be challenging as language barriers may be encountered. In certain cases, handover may be taken either at the referring hospital or at the airport for security or flight-on-duty issues, without the presence of an English speaking health care worker. At times no medical records may be available for the flight crew to review. As expatriates may not be fluent in English, this may present another hurdle in obtaining detailed, if any, information. The potential impact of these language barriers on the results of this review is difficult to gauge. Information regarding malaria chemoprophylaxis and treatment administered may have been lost in translation and thus skewed results.

No data were available on the exact time of malaria diagnosis, the period of illness prior to the diagnosis or the timelines of when malaria treatment was started. This limited the ability to ascertain delays in help-seeking behaviour as a reason for the severity of illness upon presentation of the suspected malaria patients.

4.3 Background.

The medical assistance company associated with the air-ambulance service provider utilised in this study services the world's largest oil and gas, mining, and large-scale construction companies, as well as large military and civil departments, government institutions, embassies and non-governmental organizations. [41] The company is based in Johannesburg and is the Africa branch of 27 alarm centres worldwide. [41] Due to geographical proximity, sub-Saharan African countries are expected to be the countries of origin for the majority of evacuations. Patients located geographically closer to Europe may be flown to South Africa instead of Europe due to visa restrictions (which pertain to pilots, flight crew and patients), as well as the limited

availability of European air-ambulance service providers. The medical assistance company will recommend the safest, fastest and most appropriate local referral or mode of transport based on the medical condition of the patient and the adequacy of the local medical infrastructure.

4.4 Malaria in Africa.

An estimated 212 million malaria infections occurred in the Africa region during 2006, with 106 million of these cases presenting in Nigeria, the Democratic Republic of Congo, Ethiopia , Kenya and Tanzania. [18] Because of the high prevalence of the disease in sub-Saharan Africa, coupled with the fact that that the study patient population were expatriates (non-immune), it is not surprising that malaria was found to be the most common specific initial diagnosis affecting 81 (11.9%) of the 679 patients flown.

4.5 Diagnosis of malaria.

Of the 82 initial and crew diagnosed suspected malaria patients, the diagnosis at the receiving facility was confirmed as malaria in 61 patients, and excluded in 12 patients. Several symptoms and signs of malaria are shared by other disease processes. It is thus not surprising that the diagnosis of malaria was incorrectly made in 12 cases. Nine patients had no documented confirmatory test results from the receiving facility. Of these nine patients, one patient did not have a documented initial method of malaria diagnosis and two patients were diagnosed on clinical symptoms alone. Due to the method of initial diagnosis these three cases were not

included in the final confirmed malaria group. One patient who was flown with a 4+ *P. falciparum* film died in-flight and was accepted as a confirmed malaria case due to the species identified and the documented hyper-parasitaemia. The remaining five patients had an initial diagnosis based on a positive blood film from the referring facility. Without documentation on the time of initiation and duration of treatment prior to the flight crew assessment, these five cases were accepted as confirmed malaria cases without receiving facility confirmation of the diagnosis. Thus of the 82 suspected malaria cases, 67 were confirmed.

The method of diagnosis at the referring facility was mainly based on blood films and RDTs. Of interest is that a 92.3% of suspected malaria cases were confirmed to be malaria at the receiving facilities for initial diagnoses based on RDTs when compared to the 78.4% of patients diagnosed initially with blood films. This may have been due to a larger proportion of patients initially diagnosed with blood films not having the final diagnosis documented at the receiving facility when compared to patients initially diagnosed by RDTs. The higher accuracy with patients initially diagnosed by RDTs may also have been due to a smaller chance of human error in reading RDTs, which require little training to interpret results, rather than isolating parasites accurately through a microscope in remote areas. [13] Although RDTs have demonstrated decreased sensitivity with decreasing parasite densities, a positive result will exclude other pathologies presenting with similar signs and symptoms as malaria and thus expedite appropriate malaria treatment. [8][14] As a lay person can utilise a RDT, it decreases dependence on clinical diagnosis in remote areas where access to microscopy and/or the level of training of the microscopist may be limited. Users need to be informed of the RDT's limitations as far as false negative results are concerned and should consider initiating treatment even in cases of a negative test result where there is a high clinical index of suspicion of malaria, especially if the patient's condition deteriorates. [14]

The microscopy results at the receiving facility which showed no parasites (negative film) may have been due to completion of treatment and resolution of malaria parasites by the time of arrival at the receiving facility, or incorrect initial diagnosis at the referring facility. False negative microscopy results may also occur with parasite densities less than 5-10 parasites/µl, or with sequestration of *P. falciparum* parasites in the deep capillaries of the spleen, liver or bone marrow as well as in pregnant patients. [4][11] *P. falciparum* sequestration may thus result in insufficient numbers of the parasite in the circulating blood leading to a negative blood film. [13] As parasite densities of *P. malariae* and *P. ovale* are often low, these mixed infections are often missed by microscopy, leading to false negative results. [11] Initial referring facility tests may also have been several days old by the time the air-ambulance provider was contacted for assistance, although without documentation delineating the timeframes of treatment initiation this could not be proven. In certain cases a dual pathology may have been present at the outset, with malaria resolution and only the second pathology present on arrival at the receiving facility as seen in one case flown out of Zambia. In this case the follow-up film was negative at the time of evacuation and the flight crew diagnosed atrial fibrillation complicated by congestive cardiac failure which was confirmed as the diagnosis at the receiving facility.

4.6 Malaria species incidence.

P. falciparum alone or in combination with other *Plasmodium* species was isolated in 15 (88.2%) of the 17 cases where the species was documented at the receiving facilities. This incidence is higher than the 40.6% -76.8% *P. falciparum* (alone or in combination) documented in other studies. [23][24] Although it can be assumed that the majority of complicated malaria cases will be

due to *P. falciparum*, it is unfortunate that no species identification was recorded in more than half of the suspected malaria patients at the receiving facilities.

Cases of an initial RDT positive malaria diagnosis could not be included into the *P. falciparum* group unless specific mention was made of the species isolated in the test. Commercially available RDTs are available as two, three or four band tests and contain different combinations of target antigens isolating different species of malaria to suit local malaria epidemiology. [4][11] Information regarding the specific type of RDT used at the referring facility was not always available. Thus the initial referring facility isolation of *P. falciparum* may have been higher, however it cannot be assumed as a positive RDT may refer to a species other than *P. falciparum* or even a combination of *Plasmodium* species.

P. falciparum was diagnosed in combination with *P. ovale* in two patients originating out of Nigeria and Madagascar respectively. The patient from Nigeria had a confirmatory film at the receiving hospital for both strains. Receiving facility species was not documented for the patient originating out of Madagascar. Both Nigeria and Madagascar have mosquitoes infected with *P. ovale*, which account for an estimated 5% of the *Plasmodium* infections in both Nigeria and Madagascar. [53]

P. malariae in combination with *P. falciparum* was diagnosed in one patient originating out of Mozambique, without confirmatory species isolation documentation at the receiving hospital. *P. malariae* is a species that is known to be found in Mozambique and was thus not an unexpected finding. [53]

A patient originating out of Uganda had an initial diagnosis of blood film positive for *P. falciparum*, whereas the blood film at the receiving facility isolated a combination of *P. ovale* and *P. vivax*, both of which strains are found in Uganda. [53]

Two patients flown out of Angola with an initial blood film diagnosis of *P. falciparum* malaria had different strains isolated at the receiving hospitals. In one patient *P. malariae* was also seen on the receiving facility film, which is unusual as it is not an expected species in Angola. [53] The latter patient had only travelled to the United States of America (without specifying the routing to/from the United States of America to Angola), and Angola in the preceding three months. As malaria is not found in the United States of America or any of its territories [30][53], this may mean that *P. malariae* has now spread to Angola, or that the patient had been infected during the routing to/from Angola. The second patient flown out of Angola had a film which was documented as 'not otherwise specified mixed' at the receiving facility.

Thus, in all cases except the one case flown out of Angola, the species isolated initially and at the receiving facility were expected for the country of origin.

4.7 Seasonal trends.

Seasonal variation has to be compared to a specific country, as each sub-Saharan African country has unique geography and climate variations resulting in specific seasonal variances. The majority of suspected malaria flights originated out of the following five countries:

Angola

Angola has two main seasons, the wet cooler months of November through April, and the dry warmer months of May through October.[54] Half of suspected malaria flights originating out of Angola were flown during the wet season, although cases were flown steadily throughout the year. A peak of 25% of all Angolan flights occurred during the month of June, which falls within Angola's dry season.

The Democratic Republic of Congo

The Democratic Republic of Congo straddles the equator and has a rather unique seasonal distribution. The central region has an equatorial climate and a high annual rainfall of 1700mm annually. The northern and southern regions have reversed seasons, with the wet season in the north from April through October, and November through March in the south. [55] The Democratic Republic of Congo has 3 distinct regions each with its own wet season, resulting in a wet region at any given time of the year. Thus unless specific areas are stipulated, the Democratic Republic of Congo as an entity has year-round wet seasons.

All cases originating out of the Democratic Republic of Congo during this study period were flown out of either Kinshasa or Lubumbashi which are both situated in the south of the Democratic Republic of Congo. Although one patient was flown out of Zambia, the actual initial malaria diagnosis was made in the Democratic Republic of Congo and was thus included in the Democratic Republic of Congo group when looking at seasonal trends. Even though the 31.3% of the cases originating out of the Democratic Republic of Congo were flown during the southern region's wet season (November through March), the actual peak was during April and May with 43.8% of cases being flown during this period. The true origin and exact location of malaria infection within the Democratic Republic of Congo was not always documented, so certain malaria cases may have been infected in the north, or on the equator, and the south may have been purely the port of exit.

Mozambique

The suspected malaria cases flown out of Mozambique were distributed throughout the year. Only 30.8% of the malaria flights originating out of Mozambique occurred during the country's rainy season which starts in December through March. [56]

Nigeria

Nigeria has a tropical climate with the rainy season extending from April to October, with June being the wettest month. [57] The majority of flights fell within the wet season. However, the most number of flights in a single month occurred in November, which falls within the dry season.

Zambia

Zambia has three distinct seasons with December through April being warm, wet and humid, May through August is cool and dry and September through November is hot and dry. [56] All of the suspected malaria evacuations originating out of Zambia occurred within the wet, humid season.

Of interest is that there was a peak in flights for both Nigeria and the Democratic Republic of Congo in the dry month immediately following the last wet month of each respective country. These peaks are in keeping with the findings of the WHO, who found the risk of malaria infection was found to be the highest at the end of the rainy season or soon thereafter. [52] These peaks may be due to *P. falciparum's* incubation period which ranges from 7 to 30 days, resulting in cases that may have been infected during the end of the wet season to present in the following month which falls within the dry season. [2]

No seasonal variation was shown when reviewing all suspected malaria flights, with near equal numbers of patients flown during the wet and dry seasons. The importance of this may be that travellers and expatriates should be advised to utilise malaria chemoprophylaxis throughout the year. Suspected malaria cases were flown throughout the year from all countries except for Zambia where all flights occurred during the wet season.

4.8 Suspected malaria patient demographics.

Expatriates and long-term travellers with a diagnosis of suspected malaria in this study showed a predominantly male distribution of 84.1%. This is in keeping with the 62.9-64.8% male majority found in previous studies of European travellers returning from Africa with imported malaria. [25][32] Of the cases where the reason for travel was documented, 65 (98.5%) of the 66 suspected malaria patients were in sub-Saharan Africa for business/occupational reasons. Leisure was the purpose for travel in only one suspected malaria patient - a female, flown out of Ghana. Business/occupation as the reason for travel ranged from 23.2% - 29.8% in studies of American and European travellers returning home with imported malaria. [25][27]The predominantly male gender discrepancy as well as business/occupation as the main reason for travel, was most likely due to the spectrum of clients serviced by the medical assistance company. These clients are often based on remote sites, mines, military postings and offshore oil installations in sub-Saharan Africa and one would thus expect the majority of staff to be male. The mean age of the suspected malaria patients was 42.1 (range 18-68 years), which is in keeping with the mean age of 35.8 (range 1-86 years) to 44.1 years documented in other studies of European and American travellers returning from Africa with imported malaria. [25][37]

When considering the respective nationalities of the patients flown, it was found that the majority were South African citizens. The reason for this might be that companies seeking skilled labour may source such labour from countries in close geographical proximity to the area of need so as to curtail travel expenditure when employees move between their home country and place of work.

4.9 Malaria chemoprophylaxis.

Malaria chemoprophylaxis whilst working and travelling in malaria-endemic areas was utilised in 11 (13.4%) of suspected malaria patients with only two of these 11 patients confirming compliance. Thus, only two (2.4%) of all 82 suspected malaria patients were compliant on chemoprophylaxis. As 20 (24.4%) of the suspected malaria cases did not have malaria chemoprophylaxis documented the results could be skewed. The rate of chemoprophylaxis utilisation found in this study was lower than several studies which showed chemoprophylaxis utilisation rates ranging from 19.0 - 83%, and chemoprophylaxis compliance rates on appropriate regimens ranging from 5.7 – 97.1%. [25][27][32][35][37] The higher figures in compliance rates were found in studies where travellers visited travel clinics. These travellers may have received appropriate detailed pre-travel advice resulting in an increased awareness of the risks associated with malaria and have been more willing to take precautions to prevent malaria.

All patients, save one, were on appropriate chemoprophylaxis for the country of evacuation origin. The aforementioned patient was flown out of Angola and had utilised chloroquine inappropriately, as all sub-Saharan countries except Western Sahara, have shown chloroquine resistance as shown in figure 15. [53][58] Mefloquine was the most popular chemoprophylaxis

choice, followed by doxycycline and atovaquone-proguanil. These three pharmacological agents offer protection from all four malaria species and are recommended types of chemoprophylaxis for the 14 sub-Saharan African countries of evacuation origin for the suspected malaria patients. [53]

The fact that two patients were known to become infected with malaria whilst being compliant on appropriate chemoprophylaxis highlights that no chemoprophylactic regimen offers complete protection. At most chemoprophylactic regimens offer 75-95% protection from malaria infection even when taken correctly. [35][52] Patients may stop taking chemoprophylaxis or change their anti-malarial agent based on adverse effects, a perceived low risk of malaria or on the advice of medical staff or local colleagues. [35] Of the two patients who defaulted chemoprophylaxis, one patient stopped taking his chloroquine due to gastro-intestinal side-effects and dry hands, whereas the second patient stopped taking his mefloquine due to the side effects of sleepiness and morning nausea.

Offshore oil-rigs may advise their employees that no chemoprophylaxis is required whilst off-shore, due to the distance from the mainland, resulting in a higher risk of forgetting to take chemoprophylaxis prior to disembarkation to the mainland after the tour of duty ends (personal communication with oil rig doctor, offshore Nigeria – 2010 August). Certain remote site companies do not have a malaria chemoprophylaxis policy in place and prefer to rather treat malaria early than prevent it (personal communication with mine site doctor, the Democratic Republic of Congo – 2011 February).

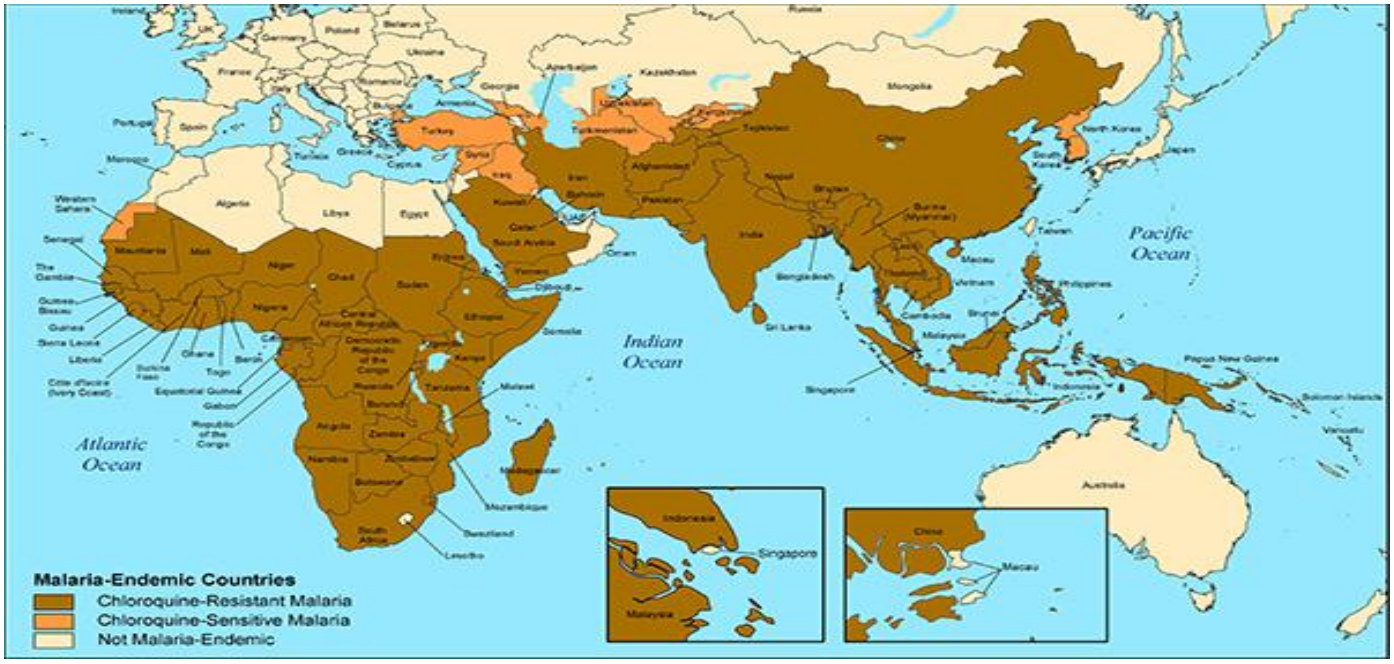


Figure 15: Malaria-endemic countries in the Eastern Hemisphere.
Utilised with kind permission from the Centres for Diseases Control, and available from:
URL:http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria.aspx#989

4.10 Counterfeit and sub-standard anti-malarials.

Long-term travellers and expatriates are more likely to purchase their anti-malarials in the sub-Saharan country of temporary residence due to their prolonged period of stay in that country. Anti-malarials obtained in Nigeria and tested in one study showed that 37% of the anti-malarials tested lacked active ingredient or contained sub-optimal quantities of the active ingredients. [43] 78% of the drugs tested were obtained from private Nigerian institutions. The potential dangers of ineffective anti-malarial agents is self-evident. The fact that the majority of these sub-standard drugs were purchased from private institutions is even more disconcerting. Thus patients may receive treatment for uncomplicated malaria from a private institution and unwittingly receive sub-standard drugs, increasing their risk of progressing to complicated malaria as potentially no

active ingredient is being administered. A patient may be compliant on an appropriate chemoprophylaxis regimen, procured locally in sub-Saharan Africa, whilst sub-optimal or even no active ingredient may be present in the chemoprophylaxis. [35][43] This may result in travellers not identifying malaria symptoms for what they are at an early stage, as malaria infection is not suspected due to a false sense of protection.

Utilisation of sub-standard drugs may result in malaria resistance to the specific agent as sub-therapeutic levels are administered, selectively killing susceptible parasites whilst leaving resistant parasites to flourish. [44] Counterfeit anti-malarials with too much active ingredient may precipitate toxic or adverse effects resulting in discontinuation of malaria prophylaxis or treatment with dire consequences. Education of travellers by travel clinics, physicians and companies deploying employees to malaria-endemic countries on the dangers associated with purchasing medication in sub-Saharan Africa, excluding South Africa, is the key to avoid using counterfeit and sub-standard anti-malarials. Travellers should ensure adequate stock of anti-malarials are procured from a reliable source for the duration of their stay. Alternatively they would need to arrange a shipment of anti-malarials, or return to their home country frequently to procure further stock. [35]

An additional aggravating situation is that access to anti-malarial treatment is limited. It is estimated that in 18 of the 46 WHO African-region countries, access to anti-malarials was on average only 38%. [18] Suspected malaria flights originated out of six of these 18 countries including: Angola; Cameroon; Ghana; Malawi; Uganda and Zambia.

So in summary, there is limited access to anti-malarial drugs (both prophylactic and therapeutic) which are often of questionable efficacy.

4.11 Clinical presentations.

Suspected malaria patients in this study presented with a wide range of organ systems affected including central nervous system, haematological, renal, endocrine, respiratory and cardiovascular systems. An interesting finding was the incidence of patients (19.5%) displaying cerebral compromise suggesting and advanced disease process at the time of assessment by the flight crew.

Although a quarter of patients with documented Hb levels had a Hb of less than 10 g/dL only three patients received RPC transfusions. This may have been due to patients being clinically stable despite the low Hb level. The importance of the ability of the air-ambulance service provider to obtain and transport appropriate emergency blood products is emphasised with patients presenting with Hb levels as low as 4.4 g/dL.

In a review by Dondorp et al. it was found that anaemia in severe malaria resulted from a combination of parasitized RBC destruction at schizont rupture, ineffective erythropoiesis as well as accelerated removal of RBC (both parasitized and un-parasitized).[59] In severe *P. falciparum*, red cells have reduced deformability which may cause microcirculatory flow obstruction and are prone to being filtered out by the spleen, contributing to anaemia in malaria. [59]

Macroscopic haemoglobinuria as a sign of intravascular haemolysis was documented in 15.9% of the 82 patients. None of the aforementioned patients had blackwater fever, defined as severe, acute intravascular haemolysis with haemoglobinuria and a dramatic fall in Hb value.[60] A study by Bruneel et al. documented the characteristics of 21 European patients who presented with blackwater fever in France between 1990 and 1999 after living in sub-Saharan Africa. [60] The duration of residence in Africa ranged from 4 to 37 years with a mean of 18.1

±8.9 years. The country of residence was the Central African Republic, Ivory Coast, Cameroon Guinea, Gabon, Congo, Burkina Faso, Benin and Togo. None of the 21 patients had utilised malaria chemoprophylaxis. All 21 patients presented with macroscopic haemoglobinuria, fatigue, jaundice and a slate-grey skin colour. The Hb level ranged from 3.0 to 9.0 g/dL with a mean of 5.3 ± 1.5 g/dL. [60]

Less than 10% of the suspected malaria patients had demonstrable pyrexia of more than 38.4ºC, which may be due to the fluctuations in pyrexia typically found in malaria. Administration of antipyretic agents such as paracetamol could also have resulted in fewer patients having increased temperature measurements. The fever found in malaria is due to merozoites being released from the red blood cells during the erythrocytic cycle of malaria -triggering an immune response. [1][3]

Both patients who were found to have hypoglycaemia with blood glucose levels of 2.4 mmol/L and 2.9 mmol/L respectively, had received intravenous quinine at the referring facility and were not on glucose containing fluids at the time of assessment. The former patient received the next due dose of intravenous quinine in a glucose containing fluid and remained persistently hypoglycaemic during the flight necessitating repeated intravenous dextrose administration. This case emphasises the need for continual blood glucose monitoring in patients receiving quinine, even when quinine is administered in a glucose containing fluid.

Clinical jaundice was documented in a third of the suspected malaria patients. 20% of the clinically jaundiced patients presented with concurrent macroscopic haemoglobinuria. Jaundice in malaria may be due to pre-hepatic haemolysis or due to hepatitis from the opportunistic infections leading to sepsis.

4.12 Intubation as a marker of severity.

Intubation was used as a marker of severity of illness. The need for intubation may be to afford airway protection or to facilitate ventilation. The loss of the ability to protect the airway indicates decreased cerebral function, whereas the need for intubation for mechanical ventilation indicates decreased pulmonary function. Intubation and ventilation may also be required for other conditions such as metabolic derangements. Intubation was required in 18.3% of the 82 suspected malaria cases. 10 of the 15 patients were intubated by the flight crew, seven for a depressed level of consciousness and two for a combination of respiratory failure and depressed level of consciousness and one for respiratory failure. Five of the patients were already intubated at the time of assessment by the flight crew without clear documentation of the reason(s) for intubation.

The severity of illness on presentation could be attributed to several factors, although it should be noted that no flight crew documentation was available to substantiate the following:

i) Delayed help-seeking behaviour which may be due to a lack of education on malaria prior to travel leading to the inability to recognise early malaria symptoms [27], a fear of job loss due to absenteeism, the limited availability/ accessibility to healthcare in remote areas in sub-Saharan Africa or even cultural beliefs with self-treatment initially with traditional/herbal remedies.

ii) A delay in initial accurate diagnosis which may be due to limited or no medical facilities, the lack of RDTs or access to reliable microscopy. Initial false negative RDTs which may be due to insufficient parasites to register a positive result as non-immune patients present with clinical symptoms at lower parasite densities. RDT cassette damage may reduce the sensitivity. A false negative RDT result may also occur when the RDT utilised fails to detect the *Plasmodium* species causing the

illness. Initial false negative microscopy may be due to parasite densities less than 5-10 parasites/µl, or with sequestered *P*. *falciparum* parasites which may result in insufficient numbers of the parasite in the circulating blood. [4][11][13] As parasite densities of *P. malariae* and *P. ovale* are often low, these mixed infections are often missed by microscopy. [11] Malaria could present with flu-like symptoms resulting in initial self-treatment with flu remedies.

iii) A delay in initiation of appropriate malaria treatment may be due to inadequate medication supplied to remote sites or clinics or an incorrect initial diagnosis.

iv) Failed treatment may be due to inadequate exposure to the active anti-malarial ingredient (under-dosing of standard medication, vomiting, sub-optimal active ingredients in counterfeit medication), not utilising recommended combination therapies, poor adherence or drug resistance. [61] In one case a patient forgot to take the oral artesunate as part of his sulfadoxine-pyrimethamine combination regimen. Patients, unless specifically instructed to do so, may first complete one blister pack prior to starting on the next instead of taking the two tablets in combination.

v) Patients may have underlying co-morbid conditions resulting in diminished baseline physiological reserve.

vi) Patients may be pregnant which makes any infection of malaria complicated by definition.

vii) Admission to hospital may result in noscocomial infections and/or complications from treatment administered e.g. hypoglycaemia and dysrhythmias from intravenous quinine.

No statistically significant difference (p=0.50) was shown for intubation requirements when comparing patients who had utilised malaria chemoprophylaxis with the patients who had not, nor when comparing intubation requirements of patients who had utilised chemoprophylaxis with

patients where chemoprophylaxis utilisation was not documented (p=0.39). It should be noted that the sub-groups utilised for analysis were small.

None of the patients in this study were deemed unfit to fly due to the severity of the condition after the assessment by the flight crew. The initial assessment by the flight crew of the patient who died in-flight was that the patient was fit to fly and stable for transport. Crew may under exceptional circumstances request to stand down an air-ambulance flight post patient assessment. These rare cases are escalated to the air-ambulance service provider's medical director who will make the decision on whether to proceed with the mission or not after weighing up all available information. The case-fatality rate in this study was 1.2% which is higher than the 0.6-0.9% mortality rates documented in other studies. [25][27] It should be noted that the mortality rate in this study only includes the single death in-flight and may have been even higher as this study did not follow-up patients to the time of discharge from the receiving facilities.

4.13 Malaria treatment administered at the referring facility and during the air-ambulance flight.

The majority (59.8%) of suspected malaria patients were on intravenous quinine as part of the treatment regimen from the referring facility, with half of these patients also on an antibiotic. The flight crew administered intravenous quinine to 26 patients during the flight with seven of these patients receiving the initial loading dose from the flight crew and the remainder (19 patients) requiring the next due dose during the evacuation mission. The balance of the patients already receiving quinine were not due the next dose for the duration of the mission.

A treatment regime of an anti-malarial (oral, intravenous or intramuscular) in combination with an antibiotic was initiated by the referring facility in 31.7% of patients. The choice of antibiotics included third generation cephalosporins (ceftriazone, cefotaxime), second generation cephalosporins (cefuroxime), penicillins (amoxicillin), penicillin and beta-lactamase inhibitor combinations (amoxicillin/clavulanic acid), tetracyclines (doxycycline), quinolones (ciprofloxacin), and nitroimidazole derivatives (metronidazole).

The WHO recommends doxycycline or clindamycin as part of the second line treatment regimens when used in combination with either artesunate or quinine. [61] The WHO also recommends a third generation cephalosporin with gram-negative and gram-positive cover, or an antibiotic with proven efficacy against the causative pathogen in opportunistic infections in malaria. [61] One patient who had received ciprofloxacin for a urinary tract infection was the only patient with a documented reason for antibiotic choice. The reason(s) for specific antibiotic selection(s) and the reasoning behind antibiotic initiation was not documented in the remaining cases and thus appropriateness could not be assessed.

Oral antimalarial regimens included artemesinin derivatives (artemether-lumefantrine, artemether, artesunate), sulfadoxine-pyrimethamine , atovaquone-proguanil, halofantrine, oral quinine and artemether combined with sulfadoxine-pyrimethamine. Intravenous treatment regimens included quinine or artesunate. Artemether was the only treatment regimen administered intramuscularly.

No specific correlation was shown with the choice of anti-malarial treatment regimens to the countries where evacuations originated from. Artemether-lumefantrine was administered as a sole anti-malarial agent or in combination with other antimalarials and/or antibiotics in a quarter

of the 82 suspected malaria patients. These patients were flown from Nigeria, Mozambique, Malawi, Angola, the Democratic Republic of Congo, Zambia, Madagascar and Ghana.

Sulfadoxine-pyrimethamine in combination with an artemesinin based derivative was administered to patients flown from Nigeria, Mozambique and Zambia. Sulfadoxine-pyrimethamine was administered to patients flown from Zimbabwe and Angola. Artesunate was administered to patients originating from Tanzania, Equatorial Guinea and Mozambique. Artemether as mono-therapy was administered to patients originating from Angola, Ghana, Mozambique and Uganda. Halofantrine in combination with artemether-lumefantrine, oral quinine and atovaquone-proguanil were administered to patients originating from Malawi, the Democratic Republic of Congo and Angola. It should be noted that in certain cases the patients had completed the anti-malarial course and/or had been initiated on intravenous quinine for severe malaria at the time of flight crew assessment.

In two cases the patients had received a combination of medications without documentation as to when and why medications were initiated and/or discontinued by the referring facility. One patient from Zambia had received artemether-lumefantrine, doxycycline, sulfadoxine-pyrimethamine, ciprofloxacin and cefotaxime. The second patient from Ghana had received artemether, ciprofloxacin, cefuroxime and amoxicillin/clavulanic acid. Injudicious administration of medication may lead to drug reactions and interactions. [61]

CHAPTER 5: CONCLUSIONS

This retrospective analysis has yielded some interesting results. Suspected malaria was the single most common diagnosis for dispatching air-ambulances during the review period. Patients in this study presented in advanced stages of severe/complicated malaria with 18.3% of patients requiring intubation as a marker of severity and one patient dying in-flight. These findings would suggest that malaria poses a material danger to expatriates and long-term travellers in sub-Saharan Africa.

Despite the dangers of malaria, the utilisation of malaria chemoprophylaxis by the study population in this review was alarmingly low with only 2.4% of suspected malaria cases confirming compliance. However, this review also found that the utilisation of malaria chemoprophylaxis did not decrease the severity of presentation (based on intubation requirements) and did not guarantee complete malaria protection. No statistically significant difference could be found in intubation requirements when compared to chemoprophylaxis utilisation, although it should be noted that the sub-group for this analysis was very small.

This review emphasises the important role that RDTs have in detection of malaria in remote sites. 92.3% of cases diagnosed initially by RDTs were confirmed to be malaria at the receiving facility. Notwithstanding, the limitations of the RDTs should be borne in mind. False negative results due to low parasite loads or the inability of certain RDTs to detect the species of Plasmodium causing the illness could lead to malaria going untreated.

Another interesting finding of the review was the incongruity of treatment regimens for malaria in various countries particularly regarding the addition of antibiotic second-line regimens. These

finding would suggest that the WHO protocols for treatment of malaria and not widely being adhered to.

5.1 Recommendations for future work.

Future studies should review the effect of flight crew management for suspected malaria cases during flights and whether outcomes improve. Additional parameters documented should include clinical features (prostration, convulsions, abnormal bleeding), biochemical features (acidosis, hepatic impairment, hypoxia) as well as haematological features (parasitaemia level, platelet level) as these are additional indicators of severe malaria. [61] These studies should also review the long-term outcomes of the patients who were evacuated, as this will provide a more accurate mortality figure.

A study reviewing all the malaria cases monitored by the medical assistance company (associated with the air-ambulance service provider utilised in this study) will provide more accurate figures of malaria infections in expatriates in sub-Saharan Africa – whether evacuated or not. It will also be of interest to compare the number of expatriates requiring evacuation compared to the total number of monitored expatriate patients.

APPENDIX A: Example of the in-flight medical report form utilised by flight crew.

Air Rescue Africa
Tel:- +27 11 541 1100
Fax:- +27 86 554 3884

Pre-flight evaluation Page 1

Date:_____ Case Number:_____
Patient:_____ Sex: M F Age:_____ Wt:_____
Aircraft Type and Registration:_____
Routing and Destination:_____
Crew 1:_____ Crew 2:_____ Crew 3:_____
Medical Hx:_____

Medications:_____

Allergies:_____
Hx of Presenting Condition:_____

ATD Base:_____ ATA Destination:_____ ATD Destination:_____ ATA Base:_____

General Assessment

Primary Survey

A_____
B_____
C_____
D_____

Secondary Survey

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Secondary Survey Cont. **Page 2**

Date:	Pt:	Case No:

Provisional Diagnosis: _____

Medications

Time	Medication	Dose	Route	Sign

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In-flight monitoring		Altitude							Cabin Alt								Page 3
	Date:	Pt:							Case No:								
	Time:																
	B.P. ^ v	220															
		200															
	H.R. ●	180															
		160															
		140															
		120															
		100															
		80															
		60															
		40															
Vital Signs	MAP																
	ECG Rhythm																
	R.R.																
	ET CO_2																
	FI O_2																
	O_2 Saturation %																
	Temp °C																
	Dextrose																
	CVP / IBP																
Airway Management	ETT cm Teeth																
	ETT Cuff Pressure																
	A/E																
	Vent rate																
	Vent mode																
	Tidal Vol																
	Min Vol																
	PEEP																
	Peak Airway Pressure																
	IE Ratio																
Neurovascular Assessment	Pupils (L)																
	(R)																
	Eye Opening																
	Verbal																
	Motor																
	Mot/Sen Arm L/R																
	Mot/Sen Leg L/R																
	Pulses/Perfusion Arm L/R																
	Pulses/Perfusion Leg L/R																
	Pain	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Infusions																	
	Incubator Temp																
	Foetal HR																

Air Rescue Africa
Tel:- +27 11 541 1100
Fax:- +27 11 541 1058

In-flight record

Date: Pt: Case No:

IV Fluids / Infusions

Infusions	Concentration	Vol	Ml/Hr	Dose	Time Started

Time	Site	Gauge	IV Fluid	Vol Up	Rate	Total Volume Infused

Intake / Output

Time	PO	IV	Total	Time	Urine	NGT	Blood/Stool	Total
Intake over ____ hours				Output over ____ hours				

Transport Notes

Handover

Date: Time:
Patients Vitals: BP HR RR SpO_2
Temp HGT
Neuro Status: E M V = /15 Motor Sens Prop
Valuables:
Valuables handed over to:
Medical Crew: Signature: Signature:
Receiving facility:
Doctor: RN:
Signature: Signature:

APPENDIX B: University of the Witwatersrand Human Research Ethics Committee (Medical) clearance certificate.

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Renske van der Walt

CLEARANCE CERTIFICATE	**M10591**
PROJECT	Characteristics of Patients (Expatriates and Long-Term Travellers) with Suspected Malaria, being Evacuated by Fixed-Wing air Ambulances out of Sub-Saharan Africa to Johannesburg, South Africa: A Retrospective Case Review.....
INVESTIGATORS	Dr Renske van der Walt.
DEPARTMENT	Department of Emergency Medicine
DATE CONSIDERED	28/05/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 31/05/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr R Dickerson

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX C: Air-ambulance provider access to database authorisation letter**.**

19 November 2009

Dr Renske van der Walt
47 Keurboom Cres
Dowerglen Ext 3
1609

Dear Renske

Access to Air Rescue Africa Patient Records

I refer to your communication dated 18 November 2009.
I confirm that you have unrestricted to the requested medical records. Please note that the records may not be copied or removed from the premises without permission.

Kind regards



Dr F Lamond
Regional Medical Director
International SOS
Southern Africa

Tel :011 541 1037
Fax : 011 541 1060

International SOS Assistance (Pty) Ltd
72, New Road, Midrand. P.O. Box 4561, Halfway House 1685
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Reg. no. 1985/003274/07,Licensed Financial Services Provider, Licence No. 18861
A.P.A. Vaissié (Chairman)(French), I.M. Cornish (Regional General Manager),
J.A. Jacobsz, L. Sabourin(French) T.V. van Stryp (Managing)

Worldwide reach Human touch

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