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MALARIA

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CONTENTS

MALARIA

BURDENSOME INTRODUCTION

Malaria, that annoying buzzing entity that we just can't seem to eradicate completely.
By the end of the 20th century, this parasite had claimed almost 3 million lives annually, the majority of those being African children.

Annually, Malaria is responsible for the death of at least three quarters of a million people worldwide[1] and is the most common cause of serious imported infection in non-endemic areas.[2-4] It is endemic throughout most of the tropics and subtropics[2-4] and surveillance programs have shown that most cases of falciparum malaria, the most common form to result in severe disease, are acquired in sub-Saharan Africa.[5-8]

So it should not come as a surprise that when the Millennium Development Goals (MDG) set to be achieved by 2015, were put forward in the year 2000, a world-wide decrease in the incidence of Malaria earned a place, as part of MDG 6C. 2015 is here, and D-day has come, the question of whether this goal has been achieved will need to be answered…

Despite the World Health Organisation (WHO) putting forth an optimistic report in 2014, the truth is that, when one takes into account the current data at hand, or rather, as some authorities will argue, the lack thereof, the answer unfortunately is not a resounding yes.

By 2012, the estimated global incidence had fallen by 29%, and estimated global malaria mortality rates (which take account of population growth) had fallen by 42%, equating to 3.3 million lives saved since 2000.[9]

The accuracy of these figures have however been brought into question, especially as febrile illness and death in children may be caused by a great many potential aetiologies, wherein malaria may easily have been overlooked during work-up in some instances, especially in non-endemic areas.[10]

Also, by 2012, data obtained from the 103 countries that were endemic for malaria in 2000, were significantly skewed. The 41 countries carrying about 80% of the estimated case load, were unable to provide adequate surveillance data on confirmed cases, and data collected deemed to be adequate for the assessment of trends in incidence and mortality, came predominantly from the 62 countries with lower incidence and transmission rates.[10] In order for any estimation of regional and global trends to therefore be made, statistical modeling had to be used, the results being nothing short of a wild guess in the dark, with uncertainty intervals a mile wide.[10]

With above limitations in mind, the data at hand were as follows:
In 2012, Africa accounted for 165 million of the estimated 207 million cases of malaria (95% uncertainty interval, 135–287 million) and 562 000 of the estimated 627 000 malaria deaths (95% uncertainty interval, 473 000–789 000).[9,10 Table1]

Just two countries, Nigeria and the Democratic Republic of Congo, generated 40% of total estimated cases globally. Yet there are grounds for cautious optimism.[9,10]

Cases/deaths per year (thousands)	2000		2004		2008		2012	
WHO region	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Africa	174 000	802	190 000	791	181 000	677	165 000	562
Americas	2000	2.1	2000	1.6	1000	1	1000	0.8
Eastern Mediterranean	16 000	22	15 000	20	13 000	18	13 000	18
European		0.003		0.001			0.002	0
South-east Asia	31 000	49	31 000	45	29 000	46	27 000	42
Western Pacific	3000	6.9	3000	6.1	2000	3.9	1000	3.5
Global total	226 000	881	240 000	864	225 000	747	207 000	627
Lower limit	151 000	670	158 000	656	146 000	569	135 000	473
Upper limit	304 000	1113	325 000	1094	307 000	937	287 000	789

Table 1: Estimated total number of indigenous Malaria cases and deaths by WHO region from 2000-2012[9,10]

A meta-analysis conducted on data from a multitude of local surveys evaluating infection prevalence across 49 endemic African areas, have indeed shown a reduction in malaria transmission rates, albeit modest, for the period from 2000-2010.[9,10] Also, another positive finding, if the data on which it is based is indeed accurate, is that the malaria mortality rate in children under the age of 5 years have decreased by 54% between 2000-2012, which accounts for about 20% of the overall mortality reduction in this age group, for the same epoch.[9,10] Therefore, looking again at the MDG, control of Malaria played a significant part in achieving the 4th goal, which stated the aim of a 2/3^{rds} reduction in under 5 mortality rate between 1990 and 2015.[9,10]

SOUTH AFRICAN STATISTICS?

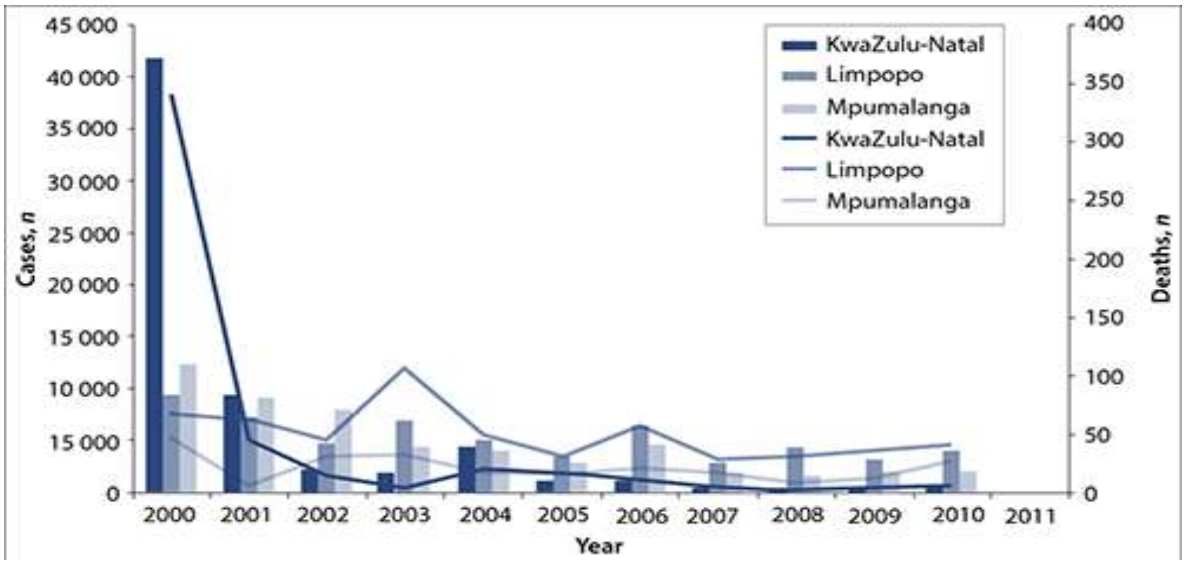
Through the ongoing efforts of the South African Malaria Programme, the 10 year period between 2000 and 2010 has seen an 85% reduction in confirmed cases of Malaria in 2010 compared to the year 2000 (9669 vs. 64622 cases), and a reduction in mortality of 80% (453 to 87) for the same reporting period.[11-15] In 2007, South Africa was identified as a candidate country for possible malaria elimination, which WHO at that time, defined as zero local malaria transmission in a specific geographical area.[14]

The National Department of Health subsequently drafted a Malaria Elimination Strategy for South Africa. The goal of the strategic plan is to reach malaria elimination by 2018, and to prevent the re-introduction of malaria into the country.[12,13,15]

A Monitoring and Evaluation Plan was developed to track indicators for the Malaria Elimination Strategy for South Africa.[12,13,15] One of the main indicators around which this strategy centers, is appropriate surveillance activities, and subsequent follow up of cases identified, which need to be implemented nationwide, through the notification of all malaria cases, in both public and private health facilities, within 24 hours of diagnosis.[12,13,15] Other indicators looked at, would be to have each reported case investigated and reported on within 72 hours, at provincial and national level, stratification of malaria according to case classification, as well as an indicator to track the malaria foci identified.[11-15]

Disease control and elimination efforts are focused mostly within the 3 endemic malaria regions in South Africa, the north-eastern areas of KwaZulu-Natal (KZN), Mpumalanga and Limpopo provinces, that carry the majority of the disease burden.[16] With these strategies in place, the current incidence in South Africa has effectively been decreased to 1 case per 1000 of the population at risk.[49] Control has therefore been achieved and the next aim is now to attempt elimination of malaria.
Of the 3 provinces, KZN has shown the greatest decrease in case numbers as well as in number of malaria-associated deaths, with Limpopo now being the largest contributor to malaria incidence.[16] TABLE 2

**TABLE 2: Malaria cases and deaths reported in South Africa, 1995 - 2011 (source: Malaria Research Unit, Medical Research Council*).*[16]



PATHOPHYSIOLOGY

It's quite scary to think that an insect weighing less than 2.5 mg and rarely being larger in size than 1.5cm, can spread such devastation as is being suggested by these figures. It took the human race quite a while to catch onto the fact that the infection causing fever, splenomegaly and generalised ill-health were being transmitted by mosquitoes though!

There are 4 main species which result in the clinical presentation now recognised as malarial infection, Plasmodium Falciparum, Plasmodium Ovale, Plasmodium Vivax and Plasmodium Malariae.[17,18] A fifth, Plasmodium Knowlesi, is also now being recognised as a zoonotic cause of malaria, found mainly in parts of Malaysia. Of these, it is the Falciparum species which account for most of the severe case presentations and mortality associated with the disease.[17,18]

Essentially, these parasites complete their lifecycle in 2 hosts, the human and the anopheles mosquito. When a female mosquito takes a meal from an infected human, it ingests gametocytes present in the person's blood.[17,18] Within the stomach of the mosquito, the microgametocytes (male) lose their flagella and enter the macrogametocytes (female) forming zygotes.[17] The zygotes in turn become motile and elongated, now known as ookinetes, which subsequently invade the midgut wall of the mosquito, where they develop into oocysts. The oocysts grow, rupture and release sporozoites, which make their way to the mosquito's salivary glands. This process takes roughly 10-18 days.[18] When these mosquitoes then subsequently bite an unsuspecting human, inoculation of the sporozoites perpetuates the malaria life cycle.[17]

The following sequence of events then transpires in the infected individual. The inoculated sporozoites infect liver cells and mature into schizonts over 7-10 days. With their rupture, merozoites are released into the bloodstream, where they are rapidly taken up into erythrocytes.[17] (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) The parasites undergo asexual multiplication in the erythrocytes, forming trophozoites which then again mature into schizonts.[17,18] This occurs over a period of 24-72hours, depending on species.[17,18] The mature schizonts then rupture, causing haemolysis and further releasing merozoites which will once again be taken up into erythrocytes. Some parasites differentiate into sexual erythrocytic stages (gametocytes) which complete the cycle if/when subsequently taken up by the mosquito as discussed above.[17,18]

The clinical manifestations of the disease are a result of the asexual stages or erythrocytic stage of the lifecycle, coinciding with the rupture of erythrocytes and release of merozoites.[18]

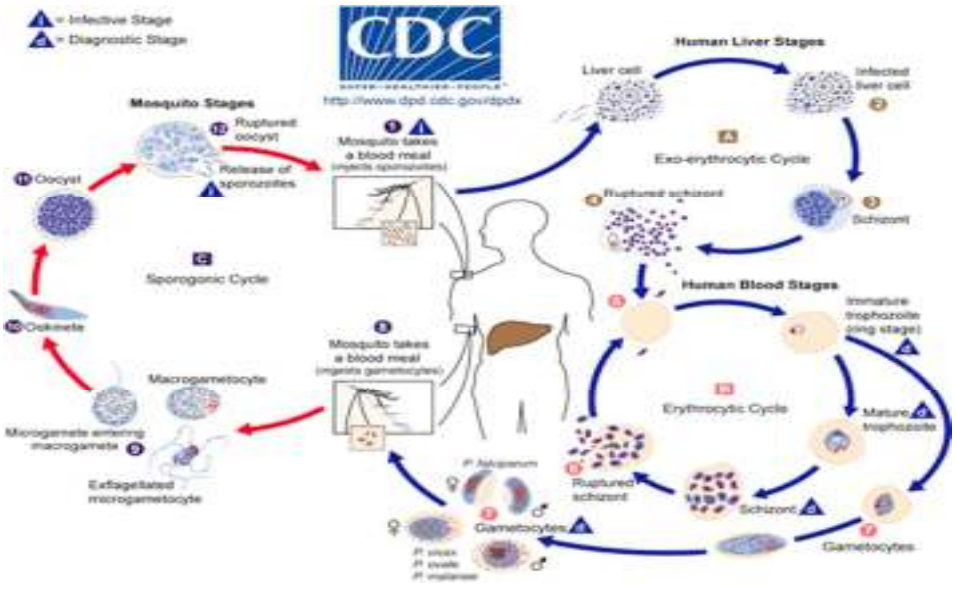


Figure: Life cycle of the malaria parasite. Reproduced with permission from the Centers for Disease Control and Prevention[17]

The incubation period for falciparum malaria is usually 12-14 days, and in other species may be slightly longer. The presence of parasites within red cells results in reduction of its cell membrane deformability, with a resultant increase in its osmotic fragility contributing to haemolysis. Following infection with P.Falciparum, red blood cell membranes express a specific membrane glyco-protein (P.falciparum erythrocyte membrane protein 1, Pfemp1) which mediates sequestration of infected red cells and binding to endothelial surfaces.[18] This results in occlusion of capillaries and small venules of vital organs such as lungs, liver, heart, spleen and kidney. Infected erythrocytes may also adhere to non-infected red cells, in a process known as rosetting, which further contributes to the microvascular occlusion.[24]

In response to infection, pro-inflammatory cytokines, including IL-1 and TNF-α, triggers an up-regulation of endothelial receptors, thereby contributing to the sequestration of infected red cells. Capillary bed occlusion results in obstruction to flow in microvasculature with subsequent tissue hypoperfusion and lactic acidosis.[18,22] An interesting phenomenon that has been observed is the apparent immunity that people living in high endemic areas seem to have developed, most likely due to repeated exposure. They rarely become critically ill when infected and may not even become symptomatic.[19] The mechanism of this immunity has not quite been elucidated, but what is known is that the immunity is rapidly lost when the person moves out of the endemic area.[20] These people have been found to be at quite a high risk of developing severe malaria upon later return to an endemic area, most likely as they wrongly assume themselves to be “immune” as they never got sick when they were living in such an area and therefore would be less likely to take the necessary precautions.[19,20]

A secondary and somewhat concerning route of disease transmission is via blood transfusions, sharing of needles between iv drug users or subsequent to a needlestick injury, following an organ transplant and through placental transfer.[24] The South African National Blood Service as well as most malaria-endemic countries in sub-Saharan Africa, do not screen donor blood for the presence of the parasite, but they do issue a warning label on the blood product that was collected from either within a malaria endemic area or in the event that the donor recently traveled to such an area. Pre-transfusion screening could be a reasonable cost-effective option in the prevention of transfusion-transmitted malaria in endemic areas, that is, if such a method existed.[53] None of the available methods are either practical, affordable or of adequate sensitivity to be of use to most sub-Saharan countries.[53]

In the United States, and various non-endemic developed countries, individuals with a history of contracting malaria, recent travel to an endemic area with exposure time of >24 hrs, and immigrants from endemic areas, are not considered eligible to donate blood for a period of 3 years from the time of exposure. Thereafter, a thorough clinical examination is required before they will be considered safe. All potential blood donors are therefore questioned extensively regarding recent travel, which has effectively resulted in extremely low incidences of malaria transmission via this route.

The problem faced in sub-Saharan African countries however, especially in endemic areas, is that rejection of such a nature as described above, would result in a significantly compromised banked blood supply, which in itself would lead to considerable morbidity and mortality.[53] The prevalence of parasitaemia in African donors depends on the transmission season as well as the local endemicity, for eg. Northern Nigeria where endemicity is especially high, it may be as great as 55%.[53] Median prevalence being about 10.2% of which Plasmodium Falciparum accounts for the majority. These donors are often asymptomatic with very low parasite counts, which may escape detection despite screening being done.[53]

The most recent data on the incidence of transfusion-transmitted malaria, date back to 2005, with the frequency in non-endemic countries reported as less than 0.2 cases per million recipients, and up to 50 cases per million in endemic areas.[53]

An alternative strategy currently employed, especially since the subsidising and low cost provision of artemisin-based combination therapy (ACT) from 2010 in various endemic areas, is to give blood transfusion recipients concomitant anti-malarial prophylaxis.[53] Thusfar, it has shown reasonable efficacy, although exact figures on the incidence are not available. Previously used agents such as chloroquine for the same purpose, resulted in the development of widespread resistance to the agent, which proponents of the ACT strategy hope will be less likely with combination therapy.[53]

DISEASE PRESENTATION

Symptoms and signs of malaria tend to start appearing on average 10-14 days after being bitten by a disease carrying mosquito. There are a number of patient and disease related factors that may influence the presentation. As mentioned, patients who have taken prophylaxis inappropriately, or who have been on certain antibiotics such as doxycycline within the time period of travel and infection, may present only later. Also as briefly mentioned in the lifecycle stages, some species may remain dormant in the liver with sporadic rupture of schizonts and release of merozoites occurring months later.[21] Plasmodium Falciparum tends to result in severe disease, and carries the highest mortality rate of all the implicated species.

Population groups at risk for development of severe disease:[21]

- Young, infants and children < 5yrs of age
- Elderly > 65 yrs
- Patient from non-endemic area (ie. Travellers)
- Pregnant (as well as in postpartum period)
- Patient's who have had a splenectomy
- Immune compromised individuals (incl HIV)[21]

The increased susceptibility for developing severe infection seen in the parturient, occurs secondary to the well-described alterations in acquired immune responses associated with pregnancy as well as sequestration of the parasite in the placenta.[24] The symptoms and signs are also quite non-specific, sharing features with a number of other infections, making the differential diagnosis wide. A high index of suspicion should be held however in any patient with a recent travel history to an endemic area, presenting with a fever, as well as any patient with fever without a obvious explanation or cause.[21]

Typical signs and symptoms in uncomplicated cases:[21]

- Fever
- Headache
- Rigors
- Myalgia
- Nausea and vomiting
- Lethargy
- Dizziness
- Loss of apetite/poor feeding
- Cough
- Splenomegaly

Features suggestive of severe disease:[21,22]

- Prostration
- Impaired consciousness
- Multiple convulsions
- Respiratory distress (acidotic breathing) or ARDS
- Cardiovascular collapse
- Abnormal bleeding
- Jaundice
- Haemoglobinuria[21]

Differential diagnoses to consider:
Community acquired gram positive and negative bacterial infection, presenting as meningitis, encephalitis, pneumonia, gastro-enteritis, other parasitic infections such as Rickettsia, Viral haemorrhagic fevers, Leptospirosis to name but a few.

Many of the manifestations seen in severe disease occur as a consequence of the change in structure and function of parasitised erythrocytes which result in microvascular occlusion in multiple sites[24] as mentioned in the pathophysiology section above.[24] The resultant cytokine release, triggers a systemic inflammatory response, has a direct myocardial depressant effect and stimulates inducible nitric oxide synthetase leading to widespread vasodilatation and a hyperdynamic circulation.[24] Despite the nitric oxide induced vasodilation, sequestration of red cells still result in occlusion. Cytokine-induced mitochondrial dysfunction, gives rise to a functional cellular hypoxia which ultimately results in patient demise due to impaired oxygen utilisation and not solely as a consequence of capillary occlusion mediated hypoperfusion.[24]

DIAGNOSIS

After evaluation of any patient presenting with symptoms and signs as discussed, or in the event of a slightly atypical presentation in a patient with a recent travel history to an endemic area, especially if deemed at risk of complications, a high index of suspicion should prompt appropriate investigations to detect the presence of Malaria timeously.

Diagnostic Blood tests:
Microscopic examination of a Giemsa stained blood film remains the gold standard[18]
Both thick and thin blood peripheral blood smears should be done:

- Thick film : higher sensitivity for diagnosis
- Thin smear : more accurate speciation and quantification of parasitaemia[18]
- Rapid malarial antigen tests: detect a parasite-associated protein or enzyme. Most detect both a pan-species and a falciparum specific target, but usually do not provide definitive speciation or quantification of parasitic load (should be used as an adjunct and not replace blood film analysis)[18]

Tests done for prognostication/identifying markers of severity:[18]
Investigations as per the laboratory indices recommended by the WHO, tabled below.

Other investigations:
CXR: Especially if respiratory symptoms present: Severe cases are prone to develop ARDS, cardiogenic pulmonary oedema, as well as there also being a high incidence of secondary/concomitant bacterial infection.

CT Brain/MRI:
If patient presents with seizures, signs of raised intracranial pressure; mainly to rule out other potential causes before declaring it as cerebral malaria.

In patients with confirmed Malaria, it is important to exclude co-infection with HIV, in light of these patients being at increased risk of developing severe disease, as the immune suppression translates to subsequent higher parasite loads. Efficacy of treatment is also reduced in these patients.[25,26]
In women of child-bearing age, exclusion of pregnancy is essential.

Determination of the severity of malaria infection rests on both clinical and laboratory indices. These have been defined by the WHO.[22]

Criteria for severe malaria: From WHO guidelines[22]

Clinical features	Laboratory features
Cerebral malaria: impaired consciousness or coma, convulsions or both	Hypoglycaemia < 2.2mmol/l
Prostration: generalised weakness, patient unable to sit up or walk without assistance	Metabolic acidosis (HCO3 < 15mmol/l or pH <7.35)
Acute Respiratory Distress Syndrome	Severe normocytic anaemia (Hb < 5g/dl, Hct <15%)
Circulatory collapse/Shock: Adults SBP < 70mmHg and children < 50mmHg	Hyperparasitaemia (>2% or 100000 µl in low intensity transmission areas or >5% or 250000 µl in areas of high stable transmission intensity)
Jaundice in the setting of other organ dysfunction	Hyperlactataemia >5 mmol/l
Haemoglobinuria	Acute Kidney injury (s-creat > 265 µmol/l)
Abnormal spontaneous bleeding	Haemoglobinuria
Radiological evidence of pulmonary oedema	
Infants/children: failure to feed	

Requires one or more of above clinical or laboratory parameters with confirmed Plasmodium falciparum parasitaemia in order for the patient to be classified as having severe Malaria.[22]

TREATMENT

The decision on treatment location ie. Hospital admission, referral to higher level of care, or primary health care facility, as well as the specific drugs to be used must take a number of factors into account [21]

- species of protozoa
- patient characteristics (age, pregnancy, allergies, other chronic meds etc)
- disease severity
- resistance pattern of the disease in the endemic area where it was contracted
- presence of nausea and vomiting[21]

As severe disease may develop rapidly, initiation of anti-malarial agents should be within a health care facility, with ongoing monitoring to ensure early recognition of deterioration. Especially if the contracted species is confirmed to be Plasmodium Falciparum.[21]

The WHO recommends the first line treatment of all **uncomplicated** cases to be an artemisin-based combination therapy (ACT), this includes children over 5kg and women in their second and third trimesters of pregnancy.[21,22]
The combination of artemisin-lumefantrine is well tolerated and the treatment course quite short, 6 doses over 3 days. It has been shown to produce a rapid clinical and parasitological response, decrease further transmission and produce higher cure rates when compared to quinine, and by not using a single agent as monotherapy, the development of treatment resistance may be delayed.[21,22]

Dosage recommendations [21,22,23]

ARTEMETHER-LUMEFANTRINE (oral) 1 tablet contains artemether 20 mg plus lumefantrine 120 mg.	**5 -<15 kg:** One tablet stat, followed by one after 8 hours and then one twice daily on each of the following two days (total course = 6 tablets) **15-<25 kg:** Two tablets stat, followed by two after 8 hours and then two twice daily on each of the following two days (total course = 12 tablets) **25-<35 kg:** Three tablets stat, followed by three after 8 hours and then three twice daily on each of the following two days (total course = 18 tablets) **35-<65 kg:** Four tablets stat, followed by four after 8 hours and then four twice daily on each of the following two days (total course = 24 tablets). **>65 kg:** Dose as for >35 kg above, although inadequate experience in this weight group justifies closer monitoring of treatment response. *NOTE: Administer with food/milk containing at least 1.3 g fat (100 ml milk) to ensure adequate absorption.*

In pregnant patients in their first trimester and children less than 5kg, the recommended chemotherapeutic agents are Quinine and Clindamycin.
Important to note; when this treatment regime is used, the course spans over 7 days.

Quinine (plus either doxycycline or clindamycin)

QUININE (oral) 1 tablet usually contains 300 mg quinine sulphate	10 mg salt/kg body weight (maximum usually 600 mg) every 8 hours for 7 days.
DOXYCYCLINE (oral) 1 capsule/tablet contains 50 or 100 mg doxycycline	Use in combination with quinine as soon as oral medication can be tolerated: 3.5 mg/kg daily for at least 7 days. NOTE: Avoid in pregnancy and children under 8 years old.
CLINDAMYCIN (oral) 1 tablet contains 150 mg clindamycin	Use in combination with quinine in pregnancy and children <8 years as soon as oral medication can be tolerated: 10 mg/kg twice daily for 7 days

WHO recommended treatment for other species[22]

Species	1st line therapy	2nd line therapy[22]
Vivax malaria	Chloroquine plus primaquine for quinine-sensitive strains	ACT plus primaquine for quinine resistant strains
Ovale malaria	Chloroquine plus primaquine	
Malariae malaria	Chloroquine[22]	

In patients presenting with severe disease, or with rapid symptom progression, treatment aims are as follows:

- Identifying and managing acute life-threatening complications
- Organ support, general measures of care
- Directed pharmacological management
- Frequent re-evaluation and prompt management of new complications[21,22]

First line therapy for severe disease, as endorsed and recommended by the WHO, is Intravenous Artesunate. Compared with Quinine, it is easier to administer and has a much better side-effect profile.[24] A large randomised control trial comparing the two drugs, showed a 35% reduction in case fatality rate with the use of artesunate, which translates into an absolute mortality of 15% compared to 22% for Quinine.[27]
Quinine should only be used as first line treatment if intravenous artesunate is either unavailable or if the patient has a history of a previous severe anaphylactic reaction to it.[24] Due to its narrow therapeutic index and high incidence of severe side effects, when Quinine is used, extreme vigilance and monitoring of patients are required.[24]

Artesunate IV preparation	2.4mg/kg at 0,12 and 24 hrs from dx then daily to complete 7 days As soon as patient able to take orally: Switch to oral ACT as soon as able to swallow.
alternative	
Quinine IV	20mg/kg loading dose in 5% dextrose solution over 4hours, followed by: 10mg/kg ivi preparations given over 4 hours every 8 hours **PLUS** Clindamycin iv/po 450mg 8 hrly Or Doxycycline po 200mg dly for 7 days

PERIOPERATIVE AND ICU MANAGEMENT

The most frequent surgical procedures that patients who have contracted malaria may present with, relates to the associated splenic enlargement with potential rupture or haematoma.[24] Another commonly performed surgical procedure which may be shrouded by the presence of the parasite, is caesarian delivery.
Important preoperative considerations would be concerning the species of parasite and severity of infection, as well as the degree of organ impairment.[24] Appropriate treatment should have been initiated, including appropriate resuscitative measures in consultation with intensive care physicians. Elective or non-urgent surgery should be postponed until the patient has been fully treated.
Many of the intra-operative concerns and challenges are relevant in the critical care setting as well, and will therefore be discussed concurrently.[24]

Risk stratification of adult patients utilising scoring systems have been proposed, mainly focusing on identifying patients likely to have a poor outcome. Two scoring systems by different research groups have been developed, but not been externally validated to my knowledge, making their usefulness questionable especially in resource-poor settings.[18]

The C-A-M score (Coma-Acidosis-Malaria) below, by Hanson and colleagues, was derived from data from the SEAQUAMAT trial:[27,28]

Variable	0 (normal)	1 (deranged)	2 (very deranged)
Base deficit	<2	2 - <10	>10
GCS	15	>10 - 14	<10

A total score of < 2 accurately identified patients who survived (positive predictive value (PPV) of 95.8%).[28] Although an increasingly higher score was associated with a similarly increasing mortality risk, the PPV for mortality does not reach the same clinical value as that for survival with a low score.[28] It is also not validated for use in children, and the patient population in question were from a low transmission area.[28] However, compared to similar predictive risk scoring systems used for other medical illnesses such as pneumonia and ischaemic heart disease for example, it achieves similar or better area under the receiver operating curve (AUROC) values.[28] The usefulness of bicarbonate levels (BCAM) or respiratory rate (RCAM) as surrogates for acidosis (ie: replacing base deficit) were also evaluated in those patients included in the SEQUAMAT data series, who were admitted in units where blood gas analysis was unavailable.[28] Cut off values used for BCAM and RCAM respectively were as follows: > 24mmol/l = 0, > 15 < 24 = 1, <15 = 2, and <20 bpm = 0, 20-39 = 1, ≥40 = 2. Using bicarbonate resulted in only slightly inferior AUROC compared to the CAM score, and when pooled data analysis was performed, a BCAM score of <2 was associated with a PPV of 95.7% for patient survival, very similar to that achieved with the CAM score using base deficit.[28] Respiratory rate as surrogate was shown to correlate poorly with the level of acidosis, and was significantly inferior to the CAM score.[28]

Overall Performance of the Three Scores as a Predictor of Survival (Data from Derivation and Validation Series Pooled)[28]

Score	PPV %, 95%CI	No of deaths/pts with low score
CAM	95.8% (93 – 97.7)	14/331
BCAM	95.7% (92.1 – 97.9)	10/230
RCAM	92.2% (89.1 – 94.7)	29/374

Note: BCAM, bicarbonate-based Coma Acidosis Malaria (CAM); PPV, positive predictive value; CI, Confidence interval; RCAM, respiratory rate-based CAM [28]

A preceding malaria score for adults (MSA), developed by Mishra and colleagues[29] has slightly more substance to it, although the C-A-M score in its' simplicity is in fact an improvement on the MSA, in terms of early identification and triage of patients requiring ICU admission.[28] As the MSA includes mechanical ventilation as a derivative, its use is limited to patients with severe disease, as defined by the WHO,

already admitted to a critical care unit, and is primarily aimed at predicting mortality risk in patients with complicated malaria. Once again and as the name specifies, extrapolation to the paediatric population is not possible, mainly due to the observation that in spite of similar initial presentation, clinical and laboratory parameters, children tend to have much lower mortality rates.[29]

Following an analysis of all known factors associated with elevated risk for the development of severe malaria, including age and pregnancy, as well as the parameters put forth by the WHO, the following variables were associated with the most significant increase in mortality risk; cerebral malaria, severe anaemia, acute kidney injury and respiratory failure requiring ventilatory support.[29] Some factors frequently associated with severe disease such as jaundice, hypoglycaemia, seizures and pregnancy were not found to impact negatively on survival despite their presence at time of illness.[29]

For each of the 4 parameters found to be associated with the highest risk of poor outcome, an odds ratio for mortality were then determined, following which each were allocated a point depending on their respective odds ratios, in ascending order.[29]

Score calculation for each parameter follows an all-or-nothing principle, with the score per parameter being 0 if absent, and given the allocated point as below for each variable, if present.

Severe anaemia (Hb < 5g/dl) 1 point
Acute kidney injury (Creat > 265 µmol/l) 2 points
Respiratory distress requiring mechanical ventilation 3 points
Cerebral malaria (unarousable coma) 4 points[29]

The MSA ranges from 0 to 10.[29]
Associated mortality: 0-2 points = 2%
3-4 points = 10%
5-6 points = 40%
≥ 7 points = 90%[29]
Using a cut-off value of 5, the reported sensitivity for mortality was 89.9%, specificity of 70.6% and a PPV of 94.1%[29] Similar to the CAM score, the predictive value for patient survival was actually better than for mortality.[18]

Preoperative checklist:

Aim to determine disease severity and species of parasite, and degree of organ impairment.

What treatment regimen is patient receiving? Quinine vs Artesunate. Of concern is the associated side-effects seen with Quinine. Artesunate is generally well tolerated, with a 1:3000 incidence of anaphylaxis and post-treatment haemolysis occasionally being reported.[18]

Quinine deserves a closer look however. The three main areas to which your attention should be focused are its' metabolic, cardiac and neuromuscular effects.

Side effect	Mechanism	Management thereof
Hypoglycaemia	Stimulates insulin release from pancreas.[24]	Regular glucose monitoring, esp with change in consciousness or if seizures occur. Consider continuous dextrose infusion as preventative strategy.[24]
Cardiac arrhythmias	Blocks fast Na channels in myocardium, which prolongs action potential duration and repolarisation time.[24]	Baseline ECG and continuous cardiovascular monitoring for early detection of QT prolongation.[24]
Prolonged neuromuscular blockade	Blocks presynaptic Na channels, and potentiates depolarisation post-synaptically, with a consequent overall decrease in motor endplate excitability.[24]	Essential to monitor neuromuscular block with nerve stimulator and ensure adequate reversal prior to extubation. Prolonged blockade may necessitate post-op ventilation.[24]

Systemic evaluation and associated special investigations (S/I)

Resp: Severe distress can occur in up to 20% of patients.
Multifactorial aetiology: severe anaemia, non-cardiogenic pulmonary oedema, frequently there may be a co-existing lower respiratory tract infection as well as the compensatory hyperventilation in response to the metabolic acidosis.[30]
Progession to acute lung injury/acute respiratory distress syndrome may occur and is thought to be due to parasite sequestration in pulmonary capillaries and host immune response led by cytokine release, both resulting in direct lung damage.[30]

S/I: Pulse oximetry, assess need for urgent intubation and ventilation, or potential post-operative ventilation. Need for supplemental oxygen. Arterial blood gas analysis. CXR

CVS: Some patients may develop ischaemic cardiomyopathy secondary to erythrocyte sequestration in coronary vessels.[31] Direct myocardial damage as evidenced by raised levels of BNP seen in patients with severe disease, may occur secondary to host inflammatory cytokine release, parasite toxins, the associated metabolic acidosis as well as the decreased levels of nitric oxide that have been demonstrated.[32] Conduction abnormalities and arrhythmias secondary to quinine therapy should also be looked for as discussed above.[33] In general however, cardiac function has been found to be remarkably preserved.

S/I: Baseline ECG, transthoracic echo if evidence of cardiac failure, cardiac biomarkers.

CNS: Cerebral malaria is one of the most devastating complications, and is rapidly fatal if left untreated. Altered level of consciousness being the main presenting feature, in the presence of confirmed peripheral parasitaemia, following exclusion of hypoglycaemia and other causes of coma.[34] Once again, sequestration of red cells in cerebral vessels, resulting in local tissue hypoxia, inflammation and acidosis, with eventual venous congestion effects the rise in intracranial pressure (ICP), altered sensorium and convulsions.[35] In patients presenting with seizures, airway protection and aspiration prevention is paramount, and control should be established with benzodiazepines.[24] Document GCS, patients with impaired pre-operative neurological functioning are likely to deteriorate post-operatively.
Evaluate patient for signs of raised ICP:
Headache, nausea and vomiting are quite non-specific
Diplopia, unilateral pupillary dilation
Papilloedema on fundoscopy
Other lateralising signs

Renal: An estimated 30% of imported cases develop acute kidney injury.[36] Once again its' development is as a consequence of multiple factors, including pyrexia, hypovolaemia, haemolysis and rhabdomyolysis, sepsis and hyperparasitaemia.[37] These culminate in acute tubular injury with oliguric renal failure. The renal impairment also further contributes to the metabolic acidosis.[37] In patients with clinical evidence of fluid overload, pre-operative dialysis may be appropriate. Cardiogenic pulmonary oedema may develop rapidly in patients who are anaemic with renal failure, which may be prevented by early renal replacement therapy.[38]

S/I: Electrolytes, urea and creatinine levels. Calcium and magnesium levels are often low as well and need to be replaced, as they will result in QT prolongation with risk of developing ventricular dysrhythmias, especially with concomitant use of Quinine.

GIT and hepatic: The presence of hepatic dysfunction is deemed a poor prognostic indicator.[39] The jaundice and hyperbilirubinaemia are due to both direct hepatocellular damage as well as haemolysis. Consequent to the hepatic dysfunction is the development of hypoglycaemia, acidosis, a coagulopathy and altered drug handling. The catabolic state induced by malaria, results in hypoalbuminaemia.[24]
A massively enlarged spleen may be present, due to its role in sequestration and destruction of deformed red cells, especially in acute infection.[40] In patients complaining of left upper quadrant pain, splenic rupture, haematoma or infarction may be the cause. Patients who have had previous infection may have had a splenectomy done at the time, and this must be elicited from

the history as specific antibiotic prophylaxis is necessary.[24]

Haem: Varying degrees of anaemia, thrombocytopenia and coagulopathy may be present. Rarely, rapid intravascular haemolysis may occur, with rhabdomyolysis and severe anaemia. (Blackwater fever). Usually follows initiation of therapy with chloroquine in semi-immune patients.[24] Guidelines with regards to transfusion triggers are mainly based on expert opinion. The WHO has set out one such approach, advocating the following:
In endemic malaria areas: transfuse when Hct falls below 15% or an Hb < 5g/dl
Non-endemic, low transmission areas: Hct < 20% or an Hb < 7g/dl[22]

As spontaneous bleeding is rarely seen even with very low platelet levels, the suggestion has been to only transfuse platelets in the absence of bleeding when platelet levels are below 10 x $10^9.L^{-1}$, or if a surgical procedure is planned, to transfuse when levels fall below 50 x $10^9.L^{-1}$ [41]

Metabolic: Malaria is often complicated by hypoglycaemia, due to massive glucose consumption by parasites, hepatic dysfunction with impaired gluconeogenesis, the hypermetabolic state with hyperpyrexia and anorexia.[42,43] Features to look for include autonomic symptoms; sweating, tachycardia, tachypnoea and anxiety.

Metabolic acidosis arises from a culmination of organ dysfunction induced by the parasite, tissue hypoxia, impaired bicarbonate handling by kidneys and hepatic dysfunction being the main contributors.[44] It's presence and degree is an important indicator of disease severity and predictive of mortality.[44]

Specific peri-operative considerations:[24]

Premedication:
Sedative agents are best avoided, as any degree of respiratory depression could result in an increase in PaCO2 with the resultant cerebral vasodilation potential for cerebellar herniation in patients with pre-existing elevated ICP.

Induction goals:
Use induction agents that are not associated with an elevation in CBF:
- Both Propofol and Thiopentone may be used, depending on the patients haemodynamic parameters.
- The use of ketamine is discouraged as it results in an increase in CBF and therefore ICP.

Avoid surges in ICP and hypercapnia:
- Blunting the intubation response is therefore quite important, with no specific technique being advocated. A potent opioid would likely be more appropriate than a beta-blocker or vasodilator in a haemodynamically unstable patient.

Maintenance goals:
Avoid cerebral vasodilation / ICP elevation:
- Head elevation, avoid ties around neck, assess pupils regularly, maintain normocarbia.
- Most volatile agents induce cerebral vasodilation, however Isoflurane does this the least as well as having the added property of decreasing CSF production, and is therefore the preferred volatile agent to use.
- Mannitol and furosemide should be available for acute lowering of ICP, if needed, although as a general measure, most studies have found Mannitol to result in prolonged coma without any outcome benefit and is therefore not advocated for the management of cerebral oedema.

A lung protective ventilation strategy is generally advocated for all patients:
- However, in the presence of cerebral malaria and raised intracranial pressure, these strategies may have to be sacrificed in order to maintain normocarbia.

Careful fluid management as discussed below:
- The value of invasive monitoring to guide and optimise fluid therapy is questionable. (see text on fluid therapy)
- Patients may rapidly and unpredictably develop pulmonary oedema, which has a poor prognosis attached to it.
- This may require high concentrations of FiO2 to be administered, judicious use of PEEP and diuretics.

- Early use of inotropes is preferable to excessive fluid boluses.

Avoid hypoglycaemia:
- The use of 10% dextrose as maintenance in normal saline, with half-hourly glucose monitoring. (This is important in all patients with severe malaria, not only those receiving Quinine)

In the presence of renal impairment:
- Neuromuscular relaxants such as atracurium or cisatracurium are preferred due to their organ independent elimination kinetics.
- Suxamethonium may be used safely if pre-operative potassium levels are normal and no associated neuropathy exists. But repeat doses are ill-advised.
- Consideration of the drug interactions between the neuromuscular relaxants and anti-malarial agents are paramount when the patient is receiving Quinine.
- Monitoring of the blockade with a nerve stimulator is mandatory, and if unavailable, using lower doses is strongly advocated.

If extubation planned at the end of surgery:
- Limit the use of sedative agents, and use short acting opioids.

Appropriate transfusion strategy. (as dicussed above)
Temperature monitoring in all patients.

Safe and appropriate extubation:
Ensure full neuromuscular blockade reversal
Blunt extubation response
Ensure appropriate post-op level of care

Neuraxials?
Most of the literature addressing this issue, are case reports on women undergoing caesarian section delivery. The patients' clinical condition should guide the appropriate anaesthetic strategy.
Patients should be carefully evaluated for the presence of any contra-indications such as raised ICP in cerebral malaria, or coagulation abnormalities such as DIC or thrombocytopenia which frequently complicate the disease.

The paediatrician should be involved and notified about the maternal diagnosis so that timely intervention can be instituted should the neonate show signs of congenital malaria.

Fluid Therapy

Despite current methods used in determining intravascular volume status consistently indicating or suggesting that patients with severe falciparum malaria are hypovolaemic, resuscitation with high volumes of fluid has not translated into improvement in indices of tissue perfusion such as lactate and base excess or oxygen delivery, and also has not shown any amelioration of acute renal dysfunction.[45]

Instead, development of acute pulmonary oedema occurs rapidly, often with associated worsening of tissue perfusion due to capillary leakage and subsequent interstitial oedema further impairing tissue oxygen delivery, in spite of being clinically hypo or normovolaemic at the time of its development.[45]

The explanation put forward for this observation, lies in the pathophysiological occurrence of red cell sequestration to the activated endothelium of capillaries, and the resultant obstruction of blood flow.[45] Regardless of adequate perfusion pressure and intravascular volume, the delivery of oxygen is hampered by the physical obstruction to flow, therefore, not reaching intended tissues. The result of overzealous fluid administration is the leaking of fluid and subsequent interstitial oedema, in the face of an already damaged endothelium, which then further impairs tissue oxygen delivery.[45]

The current recommendation of the WHO is to use 0.9% Normal Saline as the primary resuscitative fluid, however, there are concerns regarding the risk of acidosis and acute kidney injury with the use of high chloride-containing solutions which must be considered.[46] The efficacy and safety of balanced solutions have not been studied in this population, although some mortality benefit have been shown in critically ill patients.[47]

Due to concerns associated with colloid solutions increasing the risk of developing acute kidney injury and bleeding, it cannot be safely advocated especially in patients with severe malaria where these complications occur frequently as part of the disease process itself.[45]

The conclusion is that no single fluid strategy can confidently be put forward for the adult patient with severe malaria. It does seem however that in most instances, a conservative approach is the safest option.[45]

Shock remains a medical emergency requiring prompt intervention. Fluid resuscitation should be accompanied by frequent reassessment, and early institution of vasopressor or inotropic support as deemed appropriate, whilst potential contributing factors are actively excluded eg. Co-existing bacterial infection or occult bleeding.[45]

The transfusion strategy as put forward by the WHO should be adhered to. Keep in mind that with high parasitic loads, haemolysis is ongoing and the need for transfusion as the disease progresses should be anticipated.

Current data suggests that patients who develop anuria are very unlikely to respond to fluid therapy and renal replacement therapy should be instituted early.[45]

Finally, in patients with adequate perfusion and urine output, fluid should be limited to maintenance only of 1-2ml/kg/hr.

The figure that follows is a suggested approach to fluid management by Hanson et al.[45]

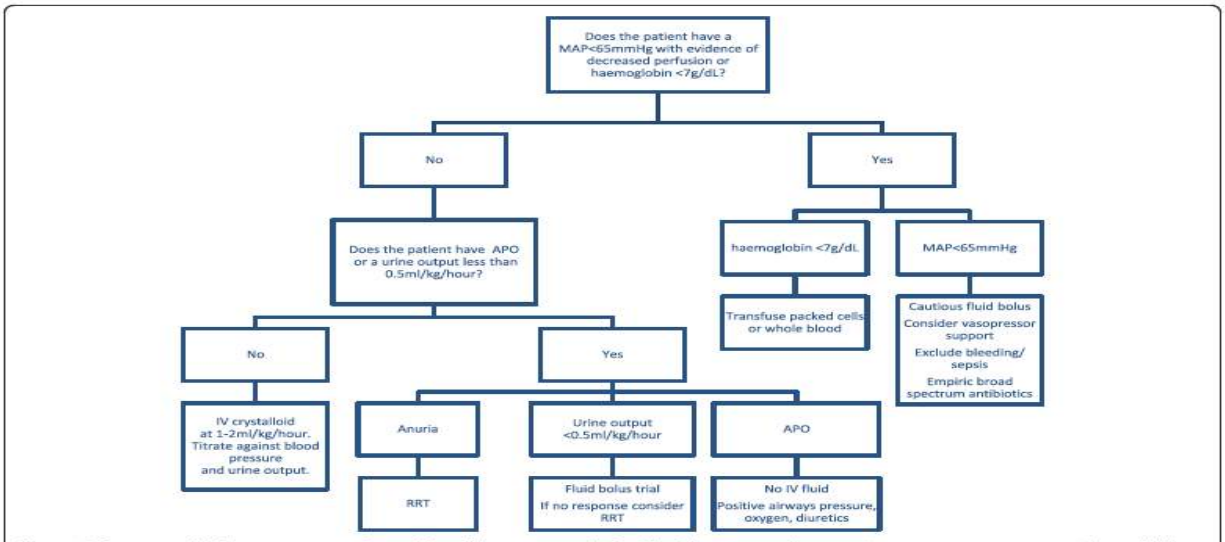


Figure 2 Suggested fluid management for adults with severe malaria. All of the proposed supportive care measures may not be available at sites where patients with severe malaria are initially managed. Early transfer to centers where these services are available is indicated, when possible. Maintenance fluid: the suggested 1 to 2 mL/kg per hour should take into consideration and include other administered fluids: antibiotic therapy, vasopressor infusions, and so on. Crystalloid: Based on plasma electrolytes, consider balanced solutions if available. Fluid bolus: 5 mL/kg crystalloid over 15 minutes; titrate bolus frequency against clinical response. APO, acute pulmonary edema; IV, intravenous; MAP, mean arterial pressure; RRT, renal replacement therapy, hemofiltration preferred if available.

PREVENTATIVE STRATEGIES

Implementation of surveillance programs play an essential role; these serve to identify local as well as imported cases, provide data of current endemicity and the need for chemoprophylaxis in certain areas as well as information with regard to resistance patterns.

General strategies shown to be effective when implemented appropriately:

- Avoid being outside between dusk and dawn in endemic areas especially during known high risk seasonal periods
- Wearing long sleeved trousers and shirts during abovementioned periods
- Sleeping underneath mosquito nets
- Appropriate use of chemoprophylaxis
- Spraying endemic areas with DDT (indoor residual spraying) or pyrethroids for vector control
- Avoidance of travel to high risk areas when pregnant, or with children below the age of 5.
- Creation of public awareness and education programs should also be implemented.

The latest recommended chemoprophylaxis are tabled below.[48]

Table I: Recommended options for malaria chemoprophylaxis

Active Ingredient	Indicated from	Regimen
Adult tablets: Atovaquone-proguanil (250 mg and 100 mg, respectively)	40 kg	• A daily dose started at least one day before entering the area, once daily while in the area, and once daily for seven days after leaving the area. • See package insert for dose.
Paediatric tablets: Atovaquone-proguanil (62.5 mg and 25 mg, respectively)	11 kg	
Mefloquine (250-mg tablets)	5 kg (or three months of age)	• A weekly dose started at least one week prior to entering the malaria area, once weekly while there, and one a week for four weeks after leaving the area. • See package insert for dose.
Doxycycline (50-100 mg)	8 years of age	• A daily dose started at least one day before entering the area, once daily while in the area, and once daily for four weeks after leaving the area. • See package insert for dose.

48

ELIMINATION / ERADICATION STRATEGIES

A malaria-free South Africa seems to be a not so far-fetched possibility. In order to achieve such a feat we do need to do our homework carefully however, ensuring optimal timing, financial feasibility and that the technical and operational aspects of such a strategy are all in line.[49]

The WHO recommendations advise that interventions should target a larger geographical area and that surveillance and case reporting need to be up-scaled significantly.[50] This includes buy-in of clinical and laboratory services in order to ensure success. As can be appreciated from the time-lines being set out for achievement of malaria elimination, this is not an overnight project, but will be quite time-consuming, requiring hard and continuous work and may have significant costs attached to it.[49]

At present, the three target provinces are not in the same phase for potential elimination, with Limpopo especially showing static figures over the past few years. A study recently conducted to determine South Africa's appropriate readiness to achieve elimination, revealed various gaps in our knowledge due to inconsistent data capturing in the affected regions.[49] Although indoor residual spraying are occurring satisfactorily, there has been no recent data on the effectiveness of agents in use and resistance patterns. Also, case data have not been uniformly reported on, and many of those reported on only occurred after a lag period.[49] Data on rapid detection tests use, quantities of ACT dispensed and numbers of positive tests or smears have also not been captured in any of the affected provinces.[49] Substantial improvement in these areas are pertinent for effective implementation of elimination strategies.[49]

A key point made by the authors, was the necessity of neighbouring countries to institute similar measures if we are to be successful, especially Mozambique and Zimbabwe.[49] As a result of the political turmoil in the latter, there has been a breakdown in their malaria program due to lack of financial support from the government, and this could account for the large number of cases reported in Limpopo.[49]

Ongoing governmental funding and political backing are essential requirements, not only to achieve elimination, but also to sustain it.[49] All the effort and hard work could be reduced to nothing, resulting in an unwanted rebound, as occurred in Sri Lanka and India due to underfunding.[49]

In areas fulfilling WHO criteria for elimination, up scaling and intensification of vector control and case monitoring have already started despite these shortcomings in information mentioned. The hope is that these escalated efforts, will be accompanied by an improvement in data collection and follow up.[49]

Keep a close eye on 2018…….

CONCLUSION

Malaria is a deadly parasite. Plasmodium Falciparum should never be underestimated. Patients may rapidly develop multiple organ failure requiring expeditious recognition and active, intensive management.

Apart from the critical care physicians amongst us, our role may not be overwhelmingly obvious. And as our country has been earmarked for elimination of the disease, implying low disease prevalence, malaria is not exactly a frequent addition on our list of differential diagnoses.

However, our neighbouring countries are still significantly affected, and border crossing, whether illegal or legal, occurs on a daily basis, with these so-called imported cases contributing most to our disease burden.

The message is therefore, to maintain a high index of suspicion when a febrile patient with a non-typical South African surname happens to be booked for an emergency Caesarian section or laparotomy. Rapid tests should be available in order to make a quick diagnosis, and considerations mentioned in the text above be kept in mind.

And to those amazing individuals who participate in projects such as Operation Smile for example, that may place you in an area of high endemicity, take care of yourselves first and foremost, and also, carefully evaluate those children. Here you may be able to make a significant difference, through the early identification and diagnosis of the disease, potentially setting a chain of events in motion so that they may receive the appropriate treatment. Also, the opportunity for patient, or in most cases parental education, should not be allowed to slip by.

Prevention is better than cure, and as a vaccine is not available, prophylaxis is the only armour we have at present……..Or is it? To conclude, just a word on some interesting developments in the scientific world.

Genetic modification of mosquitoes, rendering them incapable of being infected by and thereby pass on the parasite. It has been done, a gene in the parasites' gut controlling SM1 peptide has been successfully turned on by scientists.[51] This effectively halts the developmental stages of the parasite whilst in the mosquito, rendering it harmless.[51] But…. There's always one isn't there? Any such modification generally results in a weaker species.[51] Therefore, releasing it into the wild would be like handing Superman some Kryptonite. In the survival game, only the strong survive.

A second option, used in the past to engineer the extinction of the melon fly and screwworm as examples, is the sterile insect technique (SIT). What this entails is the release of a large number of sterilized male insects, to out-compete the wild male population for the single mating opportunity.[52] This strategy can be repeated multiple times until eradication of the targeted species has been achieved.

Concerns about the potential impact on the ecosystem and its untold repercussions have mostly prevented implementation. 2 large scale attempts previously made were both disrupted. Civil war broke out in El-Salvador and hysteria in India (some unfounded accusations were made about it being done to gain data for future biological warfare purposes).[51,52] A 3rd genetic modification aimed once again at the male species ensures all sperms are male. The short-term effect would be less mosquito bites, as males generally do not bite, and in the long run, an eventual complete eradication.[52]

Intriguing right?
Concerns however have been voiced. What if the mutation makes the mosquitoes able to carry another deadly disease, or the parasite adapts to the new genetic makeup, resulting in modification of the disease for which we then have no cure? Mosquitoes not only bite humans, how is the genetic change going to impact on other species in the food chain. What if it becomes transferable?

And as mentioned before, we cannot with absolute certainty assume that eradication will not have a significant ecological impact. Thus, until our clever lab friends figure out a way to appease the weary, just be safe out there.

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