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Impacts of Antimalarial Drugs on Malarial Management Outcome of African Regions

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Abstract

Introduction*:** The burden of managing malaria is lowering worldwide but it is still a threat in the African region. Understanding the current practices for malaria management can help to determine the gaps that need to be filled in order to achieve effective malaria management in Africa. This systematic review focuses on the actions implemented for malaria management in Africa. These include identification of the current malaria management practices, availability of antimalarial drugs, and evaluation of the affordability and quality of the available drugs. ***Methods: A comprehensive literature search was undertaken on online scientific databases such as PubMed and Cochrane. The following search terms were utilised - 'malaria', 'management', 'Africa', 'antimalarial drugs', 'antimalarial', and 'quality'. The studies were limited by years of publication (2015-2020), and stringent inclusion and exclusion criteria were pre-specified to screen for and select the most relevant research articles. The quality of the data available was assessed using Critical Appraisal Skills Programme (CASP) tool. The PRISMA guidelines were adhered to for this systematic review. ***Results*:** The findings of this systematic review address four main themes - the quality of management of malaria in the African region, the management of malaria in pregnancy in the African region, the assessment of diagnostic tests for malaria in the African region, the effectiveness of specific interventions as regards the incidence and management of malaria, and the availability of, and adherence to anti-malarial drugs in the African region. ***Conclusion*:** There is a lack of standardisation and harmonization of the indicators and metrics of health quality where the management of malaria is concerned. There are variations in what is construed to be the full malaria case management pathway, the importance of counselling during the prescription process is inappropriately understated. There is a lack of knowledge when it comes to managing malaria in pregnancy, and pregnant patients are not acknowledged as high-risk patients. There is also inconsistency regarding the intermittent preventive treatment policy for malaria in pregnancy; only 39 out of 47 African countries have such a policy. Although RDTs have a moderate performance vis-à-vis the gold standard microscopy test, their cost-effectiveness has not yet been definitively determined. While antimalarials are widely available in both public and private sectors, their price mark-up remains a financial barrier to the community, especially in hard-to-reach rural areas. Finally, an increasing mobile phone penetration throughout the African region suggests that mobile health solutions could address the top reasons for non-adherence to anti-malarial therapy; namely, forgetfulness and a lack of health literacy.

1. INTRODUCTION

Malaria is a mosquitoborne disease that causes chills, fever and tiredness. Although many antimalarial drugs are available for the treatment of malaria, severe cases of malaria are still a global problem and can result in fatality. There are various species of malarial parasites with varying severity and morbidity rates. *Plasmodium falciparum* remains the most common cause of severe malaria throughout the world.

1.1 Past and present of malaria in Africa

A French army doctor named Charles Louis Alphonse Laveran first observed the crescent-shaped bodies in the blood of soldiers infected by malaria in 1880. He also mentioned the different stages of the malarial parasite, namely the female and male gametocyte, followed by the schizont stage, and finally the trophozoite stage. Ronald Ross identified the transmission of the protozoa through female Anopheles, and also discovered the lifecycle of the protozoa in the mosquito (Arrow, Panosian, & Gelband, 2004).

In early times, this disease originated from the Asian sub-continent, and was spread to the African and European continents (Snow *et al*., 2017). The African regions are the most affected because of their humid

climate. The number of cases of malaria in Africa was 24% from 2010 to 2015, when compared to 40% cases in the beginning of the 20th century. However, the African region still accounts for the largest number of malaria cases in the world (Snow *et al*., 2017).

1.2 Demographics

The worldwide statistics suggest that there were 228 million cases of malaria across the world in 2018 (WHO, 2020). Almost 40,500 individuals suffering from malaria died in 2018. Children below 5 years of age accounted for 67% of the mortalities. It has also been noted that the African sub-continent is responsible for 94% of all malaria cases across the world (WHO, 2020). Furthermore, in 2018, Nigeria accounted for 25% (1/4) of all cases of malaria around the world, the Democratic Republic of the Congo accounted for 12%, Uganda 5%, and Côte d'Ivoire and Niger 4% (WHO, 2020).

1.3 Cause and Transmission

The protozoan species has a sexual and an asexual lifecycle; the sexual cycle occurs in the vector mosquito while the asexual cycle takes place in the host. When the female Anopheles mosquito bites a human, the parasite is transferred into the human blood in the form of a sporozoite. These sporozoites then enter the hepatocytes, where the asexual cycle of the parasite begins. The parasites then enter the erythrocytes and cause them to rupture (Talapko, Škrlec, Alebić, Jukić, & Včev, 2019).

In the asexual cycle, the sporozoites transferred to humans during a mosquito's blood meal infect the liver cells, converting into schizonts, thereby releasing merozoites after rupture. The merozoites infect the red blood cells, and the parasites multiply in the erythrocytes. They reach the immature trophozoite stage and later mature into schizonts, which rupture releasing merozoites. When the parasites enter the erythrocytes, they can be clinically diagnosed (Dean & McEntyre, 1999).

In the sexual cycle, the male and female gametocytes of the malarial parasites are ingested by an Anopheles mosquito during a blood meal. The parasite undergoes multiplication within the mosquito to form sporogonic cycle C. The zygotes are formed and develop into oocysts. The rupture of oocysts releases sporozoites, which are transferred into humans through the salivary glands of a mosquito (Dean & McEntyre, 1999).

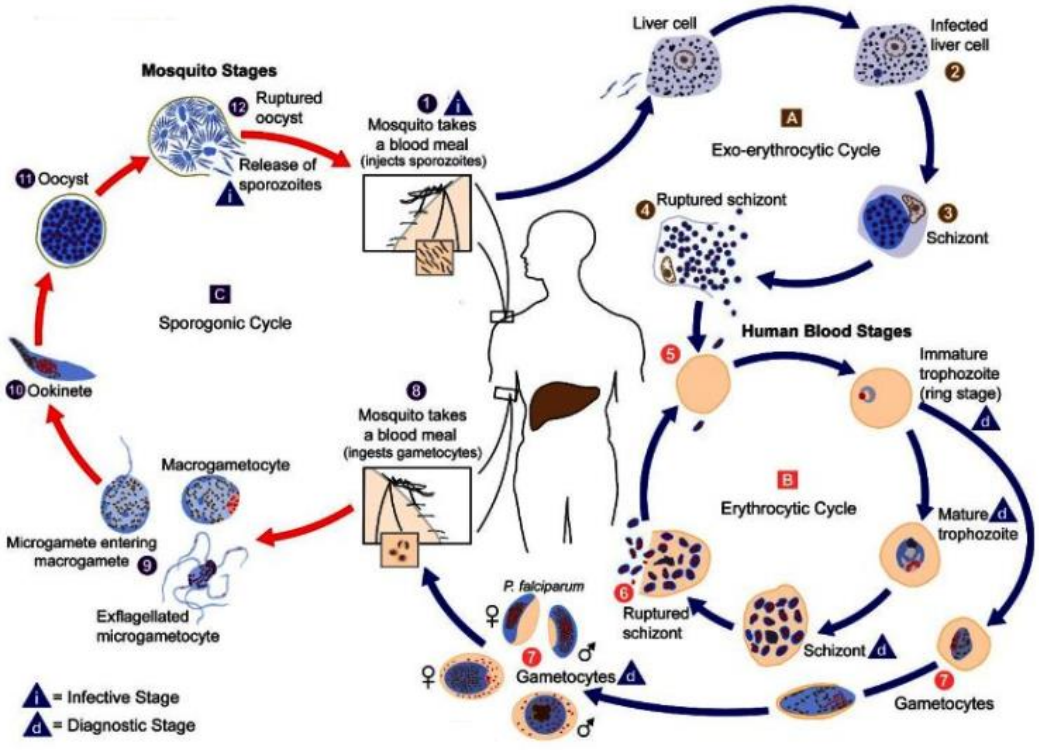

Figure 1: Sexual and asexual cycle of the malarial parasite (Dean & McEntyre, 1999)

Turning to the transmission of malaria in the African regions, the most important factor to be considered is the tropical atmosphere. Mosquitoes are more prevalent in Africa due to the dense forests, excessive rains and humid climate. The eggs of the female Anopheles convert into larvae, which develop into mosquitoes (WHO, 2020). Most of these larvae are present in accumulated water bodies like puddles of mud and collected fresh water. The accumulation of water in topical African countries is high, thereby

providing a favourable environment for the female Anopheles to grow in number.

The transmission rate depends upon the viability of this mosquito. The longer the lifespan of female Anopheles mosquitoes, the higher the transmission rate of the malaria parasite. African mosquito vectors have a strong human biting habit, and a long life span, which is why they help the parasite to complete its asexual cycle of reproduction in humans, and then be transmitted to others (WHO, 2020). The high transmission rate can also be attributed to the failure to prevent malaria at the community level. There is often a lack of the facilities required to restrict the transmission from the vector to healthy humans.

Temperature, humidity and rainfall pattern also impact the survival of the female Anopheles mosquitoes and thereby impact the rate of transmission. Malaria is usually caused in particular seasons when the environment is favourable for transmission, and is most common during the rainy season. The people in the African sub-continent have low immunity because of poor nutrition, which leads to zero or very low immunity towards malaria (WHO, 2020). All these factors contribute to the high percentage of malaria causation, and transmission of this disease in the African regions.

1.4 Management of malaria

1.4.1 Diagnosis of malaria in African regions

In malaria-prone countries of Africa, it is essential to diagnose the disease in the early stages. This can help to alleviate the severity of the disease, and thereby reduce the mortality rate associated with malaria. Most often, the costly drugs for malaria cannot be used for prophylaxis and they are only used for patients suffering from life-threatening malaria. Traditionally, diagnosis is based on the frequency and intensity of the fever (Shillcutt *et al*., 2020). However, with this method, many patients who are not infected by the malarial parasite are diagnosed with the disease and administered antimalarial drugs, thereby causing an increase in drug resistance.

The presence of the malaria parasite in the blood can be detected by using a microscope. The World Health Organization suggests a rapid diagnostic test (RDT) or blood analysis, along with presumptive treatment, when a person complains of malaria-like symptoms. The RDT test is based on the detection of histidine rich proteins-2(HRP-2), which is a sensitive test for the detection of *P. falciparum* strains (Shillcutt et al., 2020). The cost of these diagnostic tests is lower than that of the drug treatment for severe malaria. RDTs can provide results in as little as 20 minutes, which is super-fast (Shillcutt *et al*., 2020). The data suggest that timely diagnosis using microscopic analysis and RDTs can reduce the transmission and control the severity of malaria in the malaria-endemic countries of Africa.

1.4.2 Drugs available to treat malaria in African regions

Itodo and Emmanuel (2017) analysed the pathogens in the blood of African malaria patients, and discovered five relevant gene sequences, each with a different geographical distribution. They also discovered various molecular causes of sulfadoxine resistance in the malaria pathogen, and different resistance patterns in East and West Africa. The discovery of different forms of resistance was particularly important here because it shows why sulfadoxine does not work in all regions of Africa (Itodo & Emmanuel, 2017). The socio-economic divisions, climate, and humidity play an important role in the transmission and management of the disease in Africa (Zautner, *et al*., 2018). This is a strong reason for identifying the most vulnerable sections of the population based on geographical location and socio-economic status for the prevention of the transmission of malaria and the control of numbers of cases.

According to the World Health Organization recommendations, the treatment of patients diagnosed with malaria should begin within 24 hours of diagnosis. The drug treatment for malaria depends upon the clinical condition of the patients, the type of malarial parasite strain, allergies, the presence of pregnancy, drug resistance and any underlying complications.

There is a decision tree suggested by World Health Organization for the treatment of patients diagnosed with malaria in African regions. The effectiveness of the treatment also depends upon patients' adherence to the treatment. If adherence is high, the patient can be cured in the given time period. A lack of treatment adherence results in treatment failure and drug resistance (Shillcutt *et al*., 2020).

In the case of a true negative test, antibiotics are prescribed that can treat bacterial or viral infections, but no antimalarial drugs are prescribed. If treatment fails or there is a delay in diagnosis, the disease progresses to the severe stage. In severe conditions, hospitalisation of the patient is required. The most common and low-cost drugs available for prophylaxis and the primary treatment of malaria in African countries are quinine and chloroquine. Other drugs used only after diagnosis of malaria are ACTs, mefloquine and primaquine (WHO, 2020). According to the World Health Organization, patients who have a true positive test for malaria should be administered artemisinin-based combination therapy (ACT). Drugs like chloroquine and mefloquine are not effective in many African regions because of drug resistance. Primaquine is used as an adjunct for parasites like *P. vivax, P. falciparum, and P. ovale.* This drug, however, is

effective only when the parasite is in the hypnozoite stage. Primaquine is not recommended during pregnancy or for patients who are deficient in G6PD (glucose-6-phosphate dehydrogenase) (Winstanley, Ward, Snow, & Breckenridge, 2004).

For the severe symptoms of malaria caused by *P. falciparum*, artesunate is recommended by the World Health Organization. In the absence of this drug, a combination of parental artemether and quinine is recommended. Intravenous drugs doses are to be completed, followed by oral anti-malarials and drugs like doxycycline and clindamycin, if needed. Doxycycline does not show any antimalarial effect but it is used in patients who are resistant to mefloquine. Doxycycline has adverse effects like photosensitisation, which poses a question over its use. Halofantrine (Halfan®) is an official treatment in Africa but because of its impact on the heart, it is administered only under strict medical supervision (Steketee & Nahlen, 2017).

Although there is a system in place in African countries to treat malaria, there are several informal approaches to treating the disease that result in resistance and an increase in the severity of the disease. The cost of drugs and drug treatment is borne by the patients, according to most of the healthcare facilities in Africa (Winstanley, Ward, Snow, & Breckenridge, Therapy of Falciparum Malaria in Sub-Saharan Africa: from Molecule to Policy, 2004). This makes drug treatment a major burden for individuals with malaria, and they discontinue the treatment when they start to feel better. However, this results in the relapse of malaria with greater severity. Standardised procedures make it possible to correlate data throughout geographical areas and over time, in order to establish a national commitment to eradicating the disease (Zautner, *et al*., 2018).

1.4.3 Vaccines available in African regions

Vaccines can be an important alternative to prevent malaria in malaria-pandemic countries. GlaxoSmithKline have been developing a malaria vaccine for 30 years. This vaccine, RTS,S/AS01, has received approval for human trials. The pilot study for this vaccine was undertaken on a population of 720,000 in Malawi over a period of 50 months. This vaccine is now undergoing phase III trials, which tests the adverse events associated with the vaccine (Benn, 2020).

In the past, many vaccines were developed for malaria but none of them showed efficacy. The RTS vaccine is the most recent vaccine and it consists of antigens from all the stages of the parasite's lifecycle. These antigens are administered using empty hepatitis virus particles. The malaria parasite is very complex in nature and therefore developing a vaccine is challenging in nature. The clinical trials of this vaccine consisted of trials on two different groups. The first group consisted of 5–7-year-old children, who received a dose of RTS,S/AS01 or a similar vaccine. The second group consisted of children aged 6–14 weeks. RTS,S/AS01 was administered in these children along with the pentavalent vaccine (World Health Organization, 2020).

Along with these vaccines, there are many others starting with clinical trials. However, the efficacy of these vaccines is not clear. There are various areas for development for the malaria vaccine. Some researchers are trying to develop vaccines that would attack the DNA of the parasite. The clinical testing for this type of vaccine has been started in Kenya and Gambia. Some researchers are also developing a vaccine that could prevent the transmission of the disease. This vaccine is a transmission-blocking vaccine, useful for controlling the severity of malaria in malaria-pandemic countries (Scott, *et al*., 2018).

1.4.4 New drug development

According to the current data, the WHO has listed 14 antimalarial drugs in the essential drug list. These drugs are to be administered as prophylaxis or for the treatment of malaria. This drug list includes artemisinin and its derivatives: amodiaquine, piperaquine, lumefantrine, proguanil, pyrimethamine, pyronaridine, and tafenoquine (Tse, Korsik, & Todd, 2019). Novel drugs are under research and attention is focused on novel mechanisms of action and freedom from resistance. Along with traditional drug discovery techniques, combinations of various antimalarial drugs are also under study to improve efficacy and reduce resistance. An example of such a combination of drugs is methylene blue combined with primaquine. Many novel antimalarial drugs have entered the clinical research phase but failed in the trials.

There has also been the development of NPC1161B, which is chiral in nature and a derivative of 8-aminoquinoline. This drug is still in the pre-clinical study stage. Merck developed MK4815 in 2012, and it is also in the pre-clinical study phase, due to some safety issues. A novel drug of the class trioxane, named CDRI 97/78, was synthesised by the Council of Scientific and Industrial Research in India. It passed the pre-clinical studies and the first clinical trial on humans. N-tert butyl isoquine/GSK369796, was synthesised at Liverpool School of Tropical Medicine as an alternative to amodiaquine. This novel drug has also completed the pre-clinical trials and is in the first stage of human clinical trials. All the novel antimalarial drugs are still in the trial phase and the existing drugs are either very costly or show parasite resistance in patients in African regions.

1.5 Aim of research

There has been a malaria pandemic in the African regions for many years. Although there has

been immense progress in antimalarial drug development worldwide, the number of malaria cases has not reduced to a significant level in African regions. The aim of this research is, therefore, to assess the impacts of antimalarial drugs on Malarial management outcome of African Regions,

This can provide substantial input on the delays between interventions and treatment outcomes, and potentially scope for improving overall malaria management in Africa.

2. LITERATURE REVIEW

2.1 What is malaria?

Malaria is a disease transmitted by female Anopheles mosquitoes. Four parasites of the Plasmodium species, namely *P. vivax*, *P. malariae*, *P. ovale*, and *P. falciparum*, can cause malaria in humans. The severity depends upon the species of the Plasmodium, with *P. falciparum* being considered the most severe of all (Talapko, Škrlec, Alebić, Jukić, & Včev, 2019). Malaria is potentially life threatening.

2.2 Malaria in Africa

Africa is one of many developing countries in the world, and there are a number of factors that lead to increasing numbers of malaria infections in the region each year. These include a lack of basic infrastructure and education, poor hygiene conditions, poverty, heavy rains and the poor health condition of the people (Sachs & Malaney, 2002). The low levels of education mean that the people of Africa have not indulged in industrialisation, and this is a major hurdle to the manufacture of their own antimalarial drugs. Africa is therefore highly dependent on antimalarial drugs from other countries, which are therefore costly and of low affordability for the citizens of Africa.

There has been a favourable association with neighbouring continents and authorities which has allowed Africa nations to receive grants and conduct programmes to combat malaria (Winstanley, Ward, Snow, & Breckenridge, 2004). There are several drug policies in many of the African nations, but drug resistance is also creating a tremendous problem for the management of malaria in many parts of Africa.

2.3 Community perceptions about malaria

The beliefs and the traditions of Africa also affect their health parameters. Many research studies report that Africans pay a lot of attention to spiritual and social health, along with physical health. They also believe that until they are not able to work properly, they are in good health.

This means that they avoid going to the doctor until their health conditions worsen, and they are no longer able to work. In research carried out by the World Health Organization (WHO, 2012), 69% of respondents in African regions reported malaria to be the most common disease prevailing in their neighbourhoods and 53% of respondents suggested that fever was the main disease. Almost 85–90% of respondents were dependent on public health services for treating disease. In rural areas, people preferred traditional healers: 13.8% of respondents stated that they took informal medicines while 14.7% suggested faith-based medicine, which did not include a proper healthcare system.

The level of awareness of both communicable and non-communicable diseases was high in most of the countries in the World Health Organization's research. However, the findings revealed that medical service facilities were inadequate in most of the countries in Africa. Over one-third (39.1%) of the respondents suggested that drugs and equipment were unavailable, resulting in treatment delays and deaths, while 27.7% of the respondents suggested that the attitude of the healthcare providers was not good and hence affected treatment. Just over 13% of the respondents suggested that there were long queues for treatment at public healthcare centres, resulting in treatment delays (WHO, 2012). They also stated that the healthcare centres could not prevent mosquito bites within their premises. Even newborns suffered from mosquito bites in hospital, suggesting that hospital management was neglecting essential healthcare services. Most of the respondents stated that the financial barrier was the main reason for not visiting healthcare centres and opting for traditional medicine. The health insurance ratio is quite low in African countries – only one-third of the total population have health insurance (WHO, 2012).

The government and the health institutes are entering into a partnership to provide adequate health services throughout Africa (WHO, 2012). However, because of poverty, the large population and illiteracy within the community, the efforts taken bare not showing the desired effects. Communities and individuals throughout the sub-continent are facing difficulties with accessing a decent level of healthcare.

2.4 Diagnosis of malaria in Africa

Although fever is the main symptom used for the diagnosis of malaria, the use of blood tests is recommended to observe the malarial parasite in the blood. Other symptoms of malaria include myalgia, sweating, dizziness, headache and gastrointestinal disturbances. Several algorithms to diagnose malaria have been developed, especially for children in the African Region. However, because of the common tendency to have a fever, these algorithms were not found to be very effective in diagnosing malaria. The anthropological data depict the use of several terminologies in the local languages to indicate malaria: for example, "soumaya" describes symptoms like

malaria in the Burkino Fasso region of Africa (Winstanley, Ward, Snow, & Breckenridge, Therapy of Falciparum Malaria in Sub-Saharan Africa: from Molecule to Policy, 2004).

2.5 Prevention of malaria in Africa

The prevention of malaria is possible by preventing the transmission of the vector. There are two forms of vector control practised in Africa. The first is the use of insecticide-treated mosquito nets (ITNs), and the other method is spraying insecticides using the indoor residual spraying (IRS) method. Insecticide-treated nets are a powerful tool to reduce the contact between the parasite containing the vector and humans (World Health Organization, 2020). Prevention can occur on a large scale through the distribution of these nets in communities susceptible to malaria. People should be educated on the correct use of mosquito nets and their associated health benefits. Research shows that half of the population at risk of malaria was prevented from contracting the disease through the use of ITNs in 2018.

The IRS programme has to be carried out twice a year inside and outside every house in communities that are high in risk. The zone of prevention can be wide depending upon the area covered by the IRS programme. Statistics suggest that there was a 5% decline in malaria cases in 2010 through the implementation of the IRS method (World Health Organization, 2020). Pyrethroid insecticides are the cheapest alternatives to the IRS programmes, but their use is diminishing today because newer and cost-effectiveoptions are available.

2.5.1 Intermittent prevention of malaria in pregnant women

Women face changes in immunity during pregnancy, and therefore they are at high risk of diseases and infections during this time. A malarial infection during pregnancy can affect the fetus as well, resulting in the low birth weight of the fetus, the risk of death of the fetus, intrauterine growth retardation, maternal anaemia or premature delivery. Women in Africa are at a high risk of malaria during the first and second trimesters. The risk increases when they are infected with the human immunodeficiency virus (HIV). Pregnant women residing in the high-risk zones for malaria must undergo intermittent prevention treatment (IPTp). This involves the compulsory administration of antimalarial drugs, namely sulfadoxine-pyrimethamine, to pregnant women. A malarial parasite test is not necessary, and this medication is given as a prophylaxis for malaria. IPTp is to be given at every antenatal visit. Folic acid interacts with sulfadoxine-pyrimethamine and reduces the efficacy of the antimalarial drugs. It is therefore recommended that women take 0.4 mg of folic acid while the antimalarial drug is being administered during pregnancy (CDC, 2018).

2.5.2 Larval control

Intervention to prevent malaria in the larval stage of the mosquitoes has been proved to be effective in many parts of the endemic. The breeding of *Anopheles gambiae can take place in pools of water created by excessive rains in African regions. The larval stage of Anopheles occurs in these areas and then the larva is transferred to the vectors. The formation of these sites can be identified or prevented before the formation of adult mosquitoes from the larval stage* (CDC, 2018). *The habitats where the larvae are formed can be drained and filled in therebyestroying the sites for mosquito breeding. These sources can be reduced using chemical and biological controls.*

Chemical insecticides like oils help in surfacing the larvae and pupae thereby preventing their growth and transmission. Toxins from the bacterium Bacillus thuringiensis can be applied as a chemical insecticide to destroy the larvae of the mosquito, but these chemicals only destroy the larvae of mosquitoes, black flies and midges. Chemicals such as methoprene can be applied to mosquito-prone areas to restrict the growth and population of mosquitoes (CDC, 2018).

2.5.3 Biological control

Fungi and mermethid nematodes are used for the destruction of the larval stage of mosquitoes in African regions. Mosquito fish are also an alternative that can be used in puddles where the larvae of mosquito breed and develop. Biological controls show efficacy and are cost effective, but they are not used widely.

2.5.4 Other interventions

Fogging is found to be an effective alternative for larval destruction in malaria-prone areas. However, fogging and spraying at the right time is essential for the effectiveness of the treatment. Repeat fogging is required to cover every part of the environment, but this is practically not possible. The cost and required frequency of the application of fogging create a barrier to the application of these interventions in developing countries. Personal protection can be applied to protect from mosquito bites. Using mosquito repellents, light-coloured clothes and long-sleeved clothes can help with the prevention of malaria (CDC, 2018). Prevention is always better than treatment, and measures should be taken to prevent the cause and the spread of malaria in pandemic areas.

2.6 Antimalarial drugs available in African countries

Antimalarial drugs are categorised into three classes depending on their structure and mechanism of

action. These classes are Aryl amino alcohol compounds, Antifolate compounds and artemisinin compounds (Arrow, Panosian, & Gelband, 2004).

Aryl amino alcohol compounds include amodiaquine, quinine, quinidine, chloroquine, halofantrine, lumefantrine, mefloquine, tafenoquine and piperaquine. Quinine and chloroquine are the most frequently prescribed first-line agents for malaria throughout the world. However, because of drug resistance, many countries have stopped the use of chloroquine. Chloroquine acts by interfering with the heme dimerisation process. This prevents the formation of hemozoin (Arrow, Panosian, & Gelband, 2004).

The anti-folate compounds include proguanil, pyrimethamine, chlorproguanil and trimethoprim. These drugs interfere with folic acid synthesis by inhibiting the enzyme dihydrofolate reductase-thymidylate synthase (DHFR). These drugs are also prescribed profoundly throughout the world. Pyrimethamine, however, has been discontinued because of *P. falciparum*'s resistance to the drug (Arrow, Panosian, & Gelband, 2004). The resistance to antimalarial drugs has caused a sharp increase in the cases of malaria in Africa in the last few years. Number of malarial cases in Africa per year is described in the chart below. The figures are in millions.

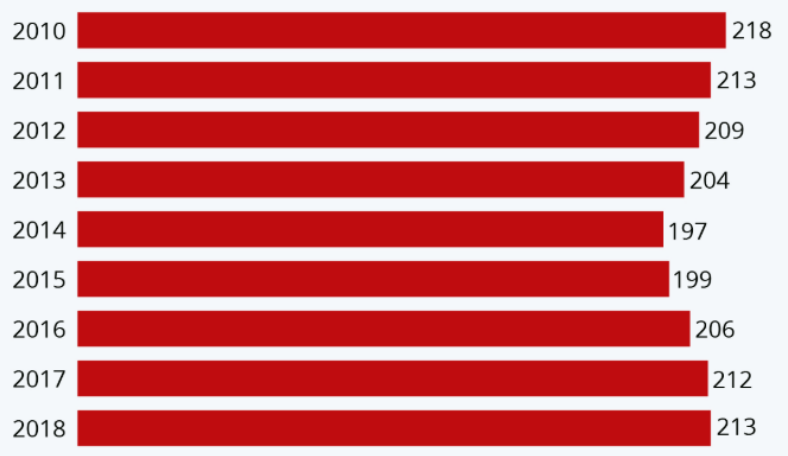

Figure 2: Increases in the cases of malaria in Africa because of resistance to antimalarial drugs (Willem Roper, 2020)

Artemisinin compounds like artemisinin, artemether, dihydroartemisinin and artesunate form the third and most recent class of antimalarial drugs. These drugs are effective in the destruction of the parasite during the asexual cycle in humans. They usually act on the medium- sized rings and schizont stage of the parasite. This category of drugs is highly useful and no species of *Plasmodium* show resistance to it. It acts by lipid peroxidation, which causes the death of the malarial parasite in the blood cells.

Chloroquine (CQ) used to be the most abundantly used antimalarial drug in African countries. It was used as the first-line treatment even for malaria caused by *P.falciparum* until resistance was developed in patients. Later in the 1960s, sulfadoxine-pyrimethamine (SP) was introduced. This drug was also withdrawn owing to its decline in efficacy, which may be due to resistance. In the last decade, artemisinin-based combination therapies (ACTs) have been used widely in most African countries. South Africa first recommended the use of ACTs in 2001 while Malawi and Botswana continued to use SP until 2007. The Demographic Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS) present the data on the antimalarial drugs used in 40 African countries from 1999 to 2011. Countries like Burundi, DRC and Zimbabwe showed moderate resistance to SP and hence they continued using the drug for a long time. The cost impacts the availability of anti-malarial drugs in African countries and the cost of ACTs is 25 times higher than that of CQ and SP. This results in a disparity in the availability of ACTs in many regions of Africa (Flegg *et al.*, 2013).

To reduce the costs of artemisinin-based drugs in African countries, the World Health Organization (WHO) has created technical support programmes meant for the development and production of ACTs. Artemisinin is basically extracted from Artemisia annua, which is native to China. However, its cultivation is carried out widely in Tanzania. With the available technology, the extraction and manufacturing of the drug would be cost effective in Africa. The quality of the medicines would also be acceptable as the entire process would be monitored and facilitated by the WHO. Currently, Tanzania exports the artemisinin grown there to Europe. To encourage the development of drug extraction and manufacturing in Africa, the Canadian International Development Agency (CIDA) has funded this project with US$6.5 million (WHO, 2003).

2.7.1 Quality of the available antimalarial drugs

Although there are strict regulations for the quality of clinical drugs on a worldwide level, there have been many discrepancies in the quality of the drugs available in developed nations and those available in poor nations. Most of the antimalarial medicines supplied to African countries are manufactured by local generic companies that do not have global accreditation or certification.

One study carried out in Nigeria shows that 50% of the antimalarial drugs available in Nigeria failed to comply with the specifications mentioned in the British pharmacopoeia. The quantity of active ingredients differed from the labelled claim, while some of the medicines did not have any active pharmaceutical ingredients at all. In a study, it was revealed that 100% of the chloroquine phosphate syrups failed the quality assurance tests, which means that none of the samples were fit for administration. The examination of other antimalarial drugs suggested that 22% of the samples failed the quality tests, and 8% of the available quinine samples failed the tests (Taylor, Shakoor, & Behrens, 2001). Substandard drugs are not effective against the disease, and they increase the severity of the disease as well as drug resistance.

One research study carried out to determine the quality of antimalarial drugs in Africa reported that the quality of drugs is sub-standard in the African region. In 21 surveys capturing data from 21 different African countries, 35% of the survey respondents suggested that the antimalarial drugs failed the chemical tests. More than one third (36%) of samples did not meet the packaging requirements, and 20% of samples did not comply with the classification and labelling requirements (Nayyar, Breman, Newton, & Herrington, 2012).

These results suggest that wrong claims are being made about the antimalarial drugs available in African countries. Apart from the quality of the drugs, the packaging and labelling also have flaws, which means that the drugs do not pass the requirements of the African drug regulatory authorities. The distribution of antimalarial drugs is poor and their production is also unregulated, which leads to questions over the overall quality and safety of the drugs.

Amin & Kokwaro (2007) carried out a systematic review to analyse the quality of antimalarial drugs in the African sub-continent. They analysed samples from various countries to determine their overall quality. The results of the review suggest that most of the drugs passed the tests for uniformity of weight. This means that the tablet weight is conform for antimalarial drugs. However, this test does not confirm the content uniformity, which assures the exact amount of the active ingredient in the tablets. Most of the drugs failed the in-vitro dissolution test. This means that the formulation method or the ingredients used to manufacture the tablets had some issues, and this occurred especially with SP. The drugs containing artemisinin showed a high level of failure against pharmacopoeial standards. All the samples of artemisinin taken from Nairobi and Kenya failed the quality tests.

2.7.2 Drug authorities and quality of drugs

The legal framework in the African sub-continent is weak, which results in a weak hold over basic healthcare services in the African region. Artemisinin is the most recently approved drug for the treatment of *P. falciparum*. The cost of this drug is much higher than the first line of agents. Prescriptions of artemisinin-based drugs are an effective treatment, but the poor quality of artemisinin and the lack of responsibility of healthcare authorities have resulted in poor treatment outcomes for malaria in Africa. The quality of these artemisinin-based drugs is not assured and it is not granted by global drug regulations. The documentation for quality is also poor in African countries.

Akulayi *et al*., (2017) carried out a survey in the medicine outlets of several African countries, namely Benin, Nigeria, Kinshasa, Katanga, Tanzania, Kenya, Madagascar, Zambia and Uganda. The survey was carried out from 2009 to 2015 to determine the quality of antimalarial drugs in non-regulated markets. The availability and distribution of antimalarial drugs in these countries were also assessed through this survey. Almost 83% of the anti-malarial drugs available in Kinshasa were non-approved. Katanga also has a high percentage of non- approved drugs (53%), followed by Nigeria (48%), Kenya (42%) and Uganda (33%). These statistics are for public sector medicine outlets. The presence of non-approved drugs in the private sector was also high, although lower than in the public sector. Non-approved drugs in the private sector were the highest in Kinshasa (40%) and the lowest in Zambia (8%). The availability of drugs in public sector drug stores was lower than in the private sector. Non-approved antimalarial drugs included artemether-lumefrantine (AL) and dihydroartemisinin-piperaquine (DHA PPQ). These tablets were mostly imported and distributed throughout the country through drug stores.

2.8 Management of malaria in Africa

Because of poverty and the social and spiritual beliefs of Africans, home-based management of malaria (HMM) is the preferred treatment for malaria across the whole of Africa. Members of the community treat children and adults with pre-packed antimalarial drugs. This type of management is preferred because of the large numbers of malaria patients. There are insufficient medical facilities for a huge population, therefore HMM is promoted. Usually, HMM comprises ACTs on

a huge scale. Individuals are resistant to the first line of antimalarial drugs like chloroquine and primaquine. Therefore, it has been proposed that effective new drugs like ACTs should be incorporated into HMM (Hopkins, Talisuna, Whitty, & Staedk, 2007).

The cases included in this study of home based management of malaria were those that used community-based or home-based treatments for malaria. The inclusion criteria for the research were an intervention for malaria using antimalarial drugs, treatment by community members who were not experts in medical science, the use of health indicators for mortality and morbidity associated with the disease, and lastly treatment based in Africa. Six research studies were included in the review. The trials were carried out during the season when the transmission of malaria is at its highest, and the subjects all took a prophylaxis using chloroquine. Out of six case studies, two studies did not show any impact of HMM. One study depicted a decrease in the prevalence of malaria, but the mortality rate was unaffected by HMM. One study suggested that the severity of malaria was reduced considerably by HMM, while another showed that the risk of progression of malaria was reduced by the HMM programme. Only one of the studies reported a positive endpoint from the mortality point of view (Hopkins, Talisuna, Whitty, & Staedk, 2007).

From the above case studies, it is clear that HMM is beneficial for reducing the mortality and morbidity rates in the communities of Africa. However, drug resistance and patient compliance for drugs need to be updated and monitored in order to increase the efficacy of the HMM programme across Africa (Hopkins, Talisuna, Whitty, & Staedk, 2007). Policy decision making and programme development help to limit the cases of malaria in the entire African sub-continent.

A cross-sectional study was carried out to assess the performance of antimalarial drugs, and the availability of the same in Bangui city. The availability of the drugs was checked with non-official drug stores, pharmacies and wholesalers. Chloroquine was the most abundantly available drug on the market. Artemisinin derivatives were also sold commonly in the drug stores. Most of the healthcare centres prescribed drugs without any formal test for malaria. Drugs like amodiaquine-sulfadoxine/pyrimethamine were not prescribed to a great extent. According to the national guidelines, the prescription of drugs should be based on the diagnosis of the disease. This guideline is violated almost everywhere in Bangui city. Control over the use of drugs, especially artemisinin combinations, is necessary. Over-usage of the drug can result in drug resistance and associated side effects (Manirakiza, Njuimo, Faou, Malvy, & Millet, 2010).

The number of caregivers visiting the drug stores ranged from 15% to 83%. Most of the Kenyan population used shop-bought drugs for treating fever. Residents of Togo avoided taking their children to the healthcare centre, and only 20% of people took their children to the healthcare practitioner. Medicine sellers are commonly available in the rural and urban areas of Africa, thereby promoting self-medication. There are no regulated spaces for medicine, and over- the-counter drugs are promoted. Drug stores and kiosks are everywhere, and therefore people go to the drug store to buy pills rather than visiting the healthcare centre. This is because healthcare centres are located further away than drug stores (Breman, Alilio, & White, 2007).

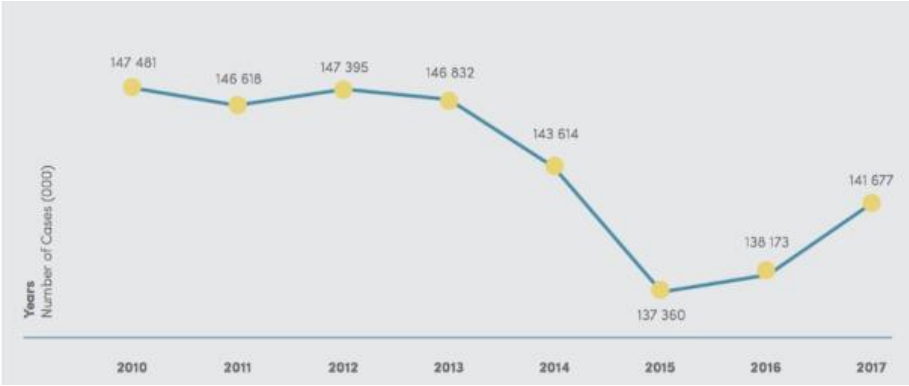

Figure 3: Burden of malaria because of poor malaria management in Africa (WHO-Africa, 2020)

2.9 Research aims and objectives

After studying the literature thoroughly, the aim of the research was finalised. From the literature survey it was evident that malaria is a major health problem in African countries. In spite of the treatment and availability of the latest drugs in African countries, there is an increasing number of malarial cases in most of the countries in Africa. Although several interventions have been carried out to reduce the cases of malaria in Africa, the number of cases has not reduced significantly. This points to a problem in the implementation of the interventions aimed at preventing malaria. The availability of antimalarial drugs is the key to treating the disease. Their quality and affordability

can impact the treatment outcome. A sub-standard quality of drugs and the unaffordability of newer antimalarial drugs can therefore result in poor malaria management in African countries. For this reason, the literature review will focus on the quality and availability of antimalarial drugs in all parts of Africa. Thus, our aim is to evaluate the effectiveness of antimalarial drug use in Africa. The main objectives of this research are to evaluate the underlying medical practices for malaria management in Africa, while evaluating the availability of antimalarial drugs, and the quality of the available antimalarial drugs. Overall, the research tries to understand the impact of the quality and availability of antimalarial drugs on the management *of malaria in Africa.*

2.10 Need for a systematic review

Systematic reviews clearly identify, evaluate and help to integrate the available information in order to assess a clearly defined research question (Cooper, 2003). A systematic review can have a qualitative or a quantitative aspect. It is a reliable, reproducible method for selecting and appraising the data from the literature and gaining insights on outcomes. This research has a clear research question, which needs to be assessed by collecting relevant research articles, followed by their evaluation, and the integration of the information available in the literature. This is the reason why a systematic review is the best possible approach to fulfil the aims and objectives of this research.

3. METHODOLOGY

3.1 Systematic Review

A literature review has a broad definition with the process varying with the requirement, the availability of literature, and the research question. Literature review helps in understanding the available literature and learnings of a particular topic. The medical and nursing sector requires a thorough review of the literature using a predefined system. PRISMA and PIO are two of the methods used to approach a research question using systematic literature reviews. A good literature review helps a researcher to develop clear research goals. This is because the literature review provides various perspectives for the research goals. This narrows down the goals of the research and helps the researcher to focus on the exact research question. A literature review helps to obtain the evidence on which the research is based. With a good-quality literature review, there is a defined objective, and relevant results are obtained to justify the objective (Maggio, Sewell, & Artino, 2016). The quality of the literature review is very important – a thorough literature review prevents the repetition of results, and ensures a strong methodology, reliable results and an expansion of knowledge.

3.1.1 Systematic review process

The literature review process involves several steps. These steps are complex in nature and require database resources for obtaining peer-reviewed journals published in high-impact journals.

3.1.2 Framing of the research question

The first step for a systematic literature review is framing a research question pertaining to the research. The research question should clearly define the area of research and its aim. It should not be complicated and should not be very broad (Khan, Kunz, Kleijnen, & Antes, 2003). The research question directly impacts the quality of the systematic review because the literature search is based on the key terms associated with the literature question. The PIO (Population, Intervention, Outcome) framework shall be used to deconstruct the research question; this is delineated in Table 1 below.

Table 1: PIO Framework

Population	People living in the African region
Intervention	Diagnostic tests and anti-malarial drugs
Outcome	Appropriate management of malaria

3.1.3 Literature survey of the relevant work

This important step involves searching the relevant literature and excluding studies that are not relevant. This segregation of the articles is based on clear inclusion and exclusion criteria. Hence, the inclusion and exclusion criteria for the population, study type, time of research and geography of the research should be finalised prior to the literature review. After excluding research articles that do not fit the inclusion criteria at each step, the remaining studies are assessed for their quality.

3.1.4 Determining the quality of studies

The quality of a study depends upon the factors of the research, the statistical parameters, any biases involved, the population, the randomisatiron factors, and the presentation of research data relevant to the research aim. The data provided in the research articles should be in concordance with the hypothesis of the literature review (Khan, Kunz, Kleijnen, & Antes, 2003). The shortlisted research articles are then segregated based on their quality, and the final research articles are selected based on various parameters. Appraisal tools such as the Critical Appraisal Skills Program (CASP) tools are utilised to determine the quality of studies; those of a sufficient quality are subsequently included for review purposes in the systematic review. The CASP tool enables an assessment of the relevance and trustworthiness of the outcomes of research studies that have been published

in peer-reviewed journals. The CASP checklist is centred on three main sections: the validity of the results, the outcome of the results and whether the outcome of the research study would improve patient outcomes in a clinical setting. As such, the following CASP tools were utilised in this research for the appraisal of relevant articles: (1) the CASP checklist for systematic reviews; (2) the CASP checklist for qualitative studies; and (3) the CASP checklist for randomised clinical trials.

3.1.5. Data extraction

Data extraction was conducted by an independent researcher to limit the introduction of bias and errors that might occur during the initial data extraction process. The following data were extracted from relevant articles: the date of publication, the aims and objectives, the design and methodology, the outcome/results and the strengths/limitations.

3.1.6. Data analysis

Once the list of included research papers is finalised, the data from all the research papers are interpreted based on the research question. This method should be transparent and in correlation with the research question. A systematic review is conducted on the basis of arriving at a conclusion that is dependent on the outcome of the results from the reviewed articles. This results in increased power and accuracy that would otherwise not be seen in individual studies. As such, the strength of evidence (outcome of the studies if significant) is taken into consideration as well as study heterogeneity. The results and outcomes from each of the reviewed articles included in the systematic review are presented in a tabular manner or in a descriptive format.

3.2 Limitations of a systematic review

The researcher conducting the literature review should possess adequate knowledge about various research methods, the population, types of research and the implications of the research. A detailed understanding of statistical analysis and the statistical significance of the results is also required. The area of research is diverse, as each author presenting a research paper presents a large volume of research. A researcher carrying out a systematic review has to go through the details of each research paper and match them with their own research question, thereby drawing important conclusions (Gerrish & Lacey, 2010). This makes the systematic literature review process time consuming and cumbersome. Failure to understand the exact results of the research papers included in the review can result in the failure of the entire review (Hemingway, 2009). At times, biasness, a small population size and non-randomised studies can lead to results that cannot be applied to different communities.

3.3 Research question

The research question for this research is: "Are the steps taken for the management of malaria optimum in African countries?" The aim of the research is to understand the flaws in the management of malaria in African countries. In order to gain an understanding of the management of malaria in the African region, the research objectives are as follows:

- To evaluate the underlying medical practices for the treatment of malaria in African countries.
- To evaluate the availability of antimalarial drugs in the African region.
- To evaluate the quality of anti-malarial drugs available in Africa.

3.4 Research strategy

A systematic literature search was conducted using two databases. The electronic databases of PubMed and Cochrane were used for this purpose. PubMed can help to locate free research articles published in MEDLINE (NIH, 2020). Cochrane is based on the latest research, which is essential for our review. Thus, Cochrane and PubMed were deemed to be sufficient for obtaining quality data across worldwide journals. The search terminologies employed for this literature survey were "Antimalarial drugs" OR "antimalarial" AND "quality" AND "malaria" AND "management" AND "Africa". A combination of the above search terminologies was used to find all the articles pertaining to the research question.

The search was conducted for articles published between 2015 and 2020. This filter was necessary to meet the requirements of a systematic review, which requires recently published research. The initial search was carried out on the 27th July 2020. The secondary search was also carried out on the same day. The results obtained from both databases were studied thoroughly against the exclusion and inclusion criteria before incorporating them into the study.

Table 2: Search criteria and years of search

Search database	Years searched	Search terminology
PubMed	2015-2020	"Malaria", "management", "Africa" "Antimalarial drugs", "antimalarial", "quality"
Cochrane	2015-2020	"Malaria", "management", "Africa" "Antimalarial drugs", "antimalarial", "quality"

3.5 Inclusion criteria

- The publication date of the research article should be between 01/01/2015 and 10/07/2020. This criterion is particularly important for keeping the research recent and avoiding obsolete data from the past.
- Only publications published in the English language were included.
- Research studies carried out in African countries were included, as per the research question. The research focusses on malaria management in Africa, so the geography of the studies are important.
- Research published in peer review journals were included.
- Full-text articles were included.
- Several study types were included: randomised controlled trials (RCTs), parallel RCTs, randomised pilot trials, cohort studies, case studies, and observational studies.
- The study population had to be humans as the research question revolves around the management of malaria in the African population.
- The age of the study population had to be above five years of age. This is an important inclusion criterion from the efficacy and safety point of view.
- The study population had to be at a threat of malaria, or suffering from malaria. This is important in view of the aim of the research.
- The interventions included drug-administered patients, patient counselling and healthcare monitoring. The interventions had to be based on the requirement of healthcare management to improve the efficacy of a treatment. Patient counselling and healthcare monitoring are very important for assessing the resistance and effectiveness of antimalarial treatment.

3.6 Exclusion criteria

- The research is based on malaria management in African countries, therefore antimalarial research carried out in countries other than Africa were excluded.
- Articles published before 2015 were excluded, as the research is based on a recent scenario.
- Research articles published in languages other than English were excluded.
- Articles with abstracts only, editorial pieces and letters to editors were excluded.
- This research targets population study and disease management, therefore in-vivo or in-vitro animal studies pertaining to antimalarial drugs were excluded.
- Systematic literature reviews require the collection of original research articles, which means that already existing literature reviews and meta-analyses cannot be included.
- Studies based in Africa but focusing on diseases other than malaria, or correlating other diseases with malaria, were excluded.

Table 3: Example of search strategy for the research

Search number	Search term	PubMed result
#1	“Malaria”	39,626
#2	“Management”	1,378,534
#3	“Africa”	178,779
#4	“Antimalarial”	25,139
#5	“Antimalarial drugs”	9,189
#6	“Quality”	1,076
#7	#1AND #2AND #3	2,713
#8	#4OR #5	27,390
#9	#7 AND #8 AND #6	202
#10	#9 and filters for publication date, English, and studies on humans	54

3.7 Data extraction and the selection of studies

A systematic flowchart was followed to extract the available data and screen the studies based on the inclusion and exclusion criterion. The first step was obtaining the search results using the two search engines. The second step was removing the duplicate articles by carefully observing their titles and content. The third step was selecting the most relevant articles by carefully following the inclusion criteria. This criterion requires the researcher to check the design and duration of the research, the setting and country of research, the eligibility criteria employed, participant characteristics, intervention and control group information, outcomes and demographics. A PRISMA flowchart was prepared according to the guidelines provided by Moher, Liberati, Tetzlaff, & Altman (2009).

The search in PubMed resulted in 202 articles using all the keywords. The Cochrane search yielded three studies using the key words “malaria” AND “management” AND “Africa” AND “Quality” AND “antimalarial”. The PRISMA flowchart for this research study is presented at the end of this chapter.

3.8 Data analysis and quality assessment

The first step of the data analysis in a systematic literature review is the formulation of a research question, which has already been done here. The methodology for carrying out a literature review must be transparent and reproducible – this is very important for obtaining unbiased results. The participant recruitment, study design and duration of a study are important criteria for the evaluation of each study. The quality of the research is assessed based on the quality scores, and the integration of all the quality parameters in the study.

The prediction models play an important role in determining the quality of the research articles. It is important to identify the variables included in the study, the type of interventions employed, and any additional characteristics of the study that reflect or influence the primary and secondary outcomes of the study. The internal and external validity of the resources have to be analysed to assess the quality of the research. Systematic reviews help to examine studies in a methodological way so as to collect relevant information in the area of interest of the researcher. The only drawback faced by a researcher in systematic research is the variability in the studies and the quality of the outcomes of the research studies (Berg *et al.*, 2013).

The step-by-step appraisal of the data helps to prevent an overload of information or missing important information from a large pool of data. The segregated data are not analysed from a clinical point of view to find their clinical relevance with the aim of the experiment. The quality assessment of the screened research articles is an important step in systematic literature. This is because research sometimes contains factors that can negatively affect the results of the research. Bias is one such factor that needs to be tested before finalising the retained resources for the research. Bias in a study will not lead to valid results or an accurate interpretation of the research question. Cochrane Collaboration's tool is generally used by researchers for quality assessment of the available data. The bias pertaining to the recruitment stage, analysis, performance and reporting stage is taken into consideration when designating a score to each research paper. Blinding of the participants, randomisation and allocation concealment are some of the criteria that need to be analysed using this tool. The systematic review took into account the use of the CASP tool, for enhanced data analysis. CASP was found to be effective and it incorporated various aspects to review evidence-based practices. The results, the validity of the results and the application of the results to a general population are key for a valid research study (Nadelson & Nadelson, 2014).

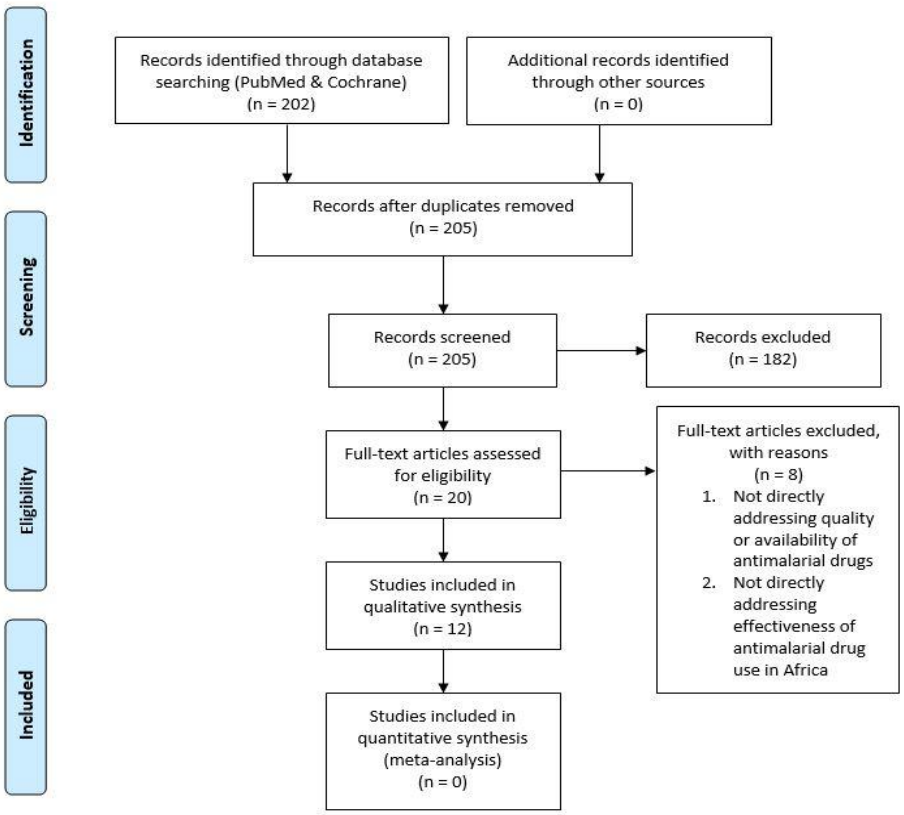

Figure 4: PRISMA flowchart for the systematic literature review

4. RESULTS

This results chapter provides an overview of the findings that emerged following the processes described in Chapter 3 above. As also noted in the previous chapter, twelve research studies were selected for inclusion within this review. These were: i) Adjel *et al*., (2016); (ii) Candrinho *et al*., (2019); (iii) Davlantes *et al*., (2019); (iv) Gerstl *et al*., (2015); (v) Kwarteng *et al*., (2019); (vi) Mbonye *et al*., (2016); (vii) O'Meara *et al*., (2018); (viii) Ssempiira *et al*., (2018); (ix) Steinhardt *et al*., (2019); (x) Wang *et al*., (2018); (xi) Wanja *et al*., (2016); and (xii) Yitbarek *et al*., (2016). Both the collective and individual findings from these studies will therefore form the focus of this chapter. In order to provide a robust and rigorous overview of all of the key aspects involved across this body of work, this chapter seeks to address a number of issues.

Firstly, Section 4.1 provides a summary overview of the studies that were selected for review. This largely descriptive aspect of the findings will provide insights into the aims and approaches taken by the selected studies via use of a data extraction table, as well as providing an overview of the approaches taken by these papers. This will provide the necessary context for the remaining, more critical, focused sections within this chapter. Section 4.2 will then consider the methodological quality of the included pieces of work, utilising CASP tools to appraise the included papers. Alongside the application of CASP analysis, a more general critique, based upon the accepted principles of good research practice and reporting, will be applied in order to provide a robust critique of the methodological quality of this body of work. Having summarised the approaches and outlined the strengths and limitations of each study, Section 4.3 then explores the findings conveyed within this selection of studies. This section also presents a narrative analysis of the data synthesised from these studies.

4.1 Summary of included articles

Of the twelve studies that were selected for review, the vast majority of them (n=10) adopted a positivist approach to data collection and analysis, with the remaining two studies adopting what can be viewed as a post-positivist approach. Positivism is perhaps the predominant paradigm within medical and health-related research, and it has remained so over the core of decades of such work (Everest, 2014). It is an approach that places direct emphasis on the importance of the scientific method (hypothesising, manipulating, testing, observing and comparing) and it dictates that any true knowledge should be derived from such an approach (Everest, 2014). However, it should be noted that whilst in recent years this framework has been responsible for numerous epidemiological, diagnostic and treatment-related advances in health research, there are a number of limitations of adopting a purely positivist approach (Corry, Porter & McKenna, 2019). This is in part because there has been an increased focus in recent years on the importance of individuals' experience of care, and their lived experience of good or bad care quality (Corry *et al*., 2019). Whilst positivism can advance knowledge on issues such as cause and effect, it has little ballast behind it when it comes to individual factors like lived experience (Bunniss & Kelly, 2010). In recent years, therefore, the interpretivist paradigm has seen an upsurge of interest within medical and health-related research (Broom & Willis, 2007); however it is noteworthy that within the selected studies for this current review, there was no such study. This perhaps points to insufficient attention being paid to the lived experiences of this population relating to the treatment for, or the prevention of, malaria. It should be noted on this point that two of the selected studies – those conducted by Adjel *et al*., (2016) and Kwarteng *et al*., (2019) – adopted a mixed methodological approach in alignment with the post-positivist paradigm. This paradigm seeks to draw on the strengths of both positivist work and interpretivist work (Weaver & Olson, 2006), and is typified by the mixed methodological work contained within these studies. Indeed, post-positivism has become as influential, perhaps even more so, than positivism in recent years (Corry *et al*., 2019). However, it should also be noted that mixed methodological studies, unless completed to a high standard across both the quantitative and qualitative branches, run the risk of becoming a watered-down version of both of these p

Whilst there is little variation in the paradigms and epistemological approaches taken by authors across this body of work, there is also little variation in terms of the range of methodological designs utilised. Within the ten solely quantitative studies that were selected, the dominant method used was that of a cross-sectional study, which was utilised by Candrinho *et al*., (2019), Davlantes *et al*., (2019), Gerstl *et al*., (2015), Mbonye *et al*., (2016), Wang *et al*., (2018), and Yitbarek *et al*., (2016). Of the two mixed-methods studies, both Adjel *et al*., (2016) and Kwarteng *et al*., (2019) also adopted a cross-sectional approach for the quantitative branch of their investigation. This means that 60% of the quantitative studies and 100% of the mixed-methods studies utilised the cross-sectional approach. Despite this relative homogeneity in research design, there was a wide range of key outcomes that were measured across these studies, and there was a high enough degree of heterogeneity to prevent the data synthesis adopting a meta-analytical approach. Of the remaining four studies within this review, two were cluster-randomised controlled trials (C-RCTs) (O'Meara *et al*., 2018; Steinhardt *et al*., 2019), one adopted an observational study approach (Wanja *et al*., 2016) and one adopted a statistical modelling approach, utilising Bayesian spatio-temporal negative binomial models from retrospective data (Ssempiira *et al*., 2018).

Whilst the heterogeneity of the methods and outcomes used by these twelve studies prevents a comprehensive meta-analytical approach to data synthesis, there is a positive opportunity for analysis. This is because a narrative synthesis approach can provide a broad overview of the differing areas of importance in relation to the phenomena of interest. It is of note, however, that many of these studies have limitations in terms of the choice of methods used, and this should be taken into account before synthesising and generalising from the data. For example, cross-sectional studies are by far the most common approach within this body of work. Whilst this design is both pragmatic and able to recruit large samples of participants (Cresswell, 2014), it should be noted that correlational analyses, which are typically employed within the data analysis of such studies, cannot be used to then infer issues of causation (Cresswell, 2014). In other words, such studies can provide insights into the directionality and strength of relationships between particular variables, but that is all; cause and effect are in essence out of bounds for these papers. On the other hand, the C-RCT's by O'Meara *et al*., (2018) and Steinhardt *et al*., (2019) are designs that enable such an inference to be made, due to their ability to control for a number of potential biases and confounding variables, and the assignation of participants to control or comparison groups (Cresswell, 2014). As such, these studies represent the gold standard of primary research data collection (Dannels, 2018). The benefits of naturalistic-style studies, using either the observational approach of Wanja *et al*., (2016) or the statistical modelling of real-world data as completed by Ssempiira *et al.,* (2018), are that they can elucidate insights of a large scale nature, although it should be noted that they are at risk of bias stemming from a number of potentially confounding factors that, due to the nature of the design, cannot be controlled for (Cresswell, 2014).

It is also of note that the unit of measurement employed across this body of work is, as a result of these differing designs, is different across studies. For example, whilst the majority of studies examined individual participants, Wang *et al*., (2016) sampled drug stores, and Mbonye *et al*., (2016) and Davlantes *et al*., (2019) examined healthcare facilities. Some studies examined healthcare professionals (e.g. Yitbarek *et al*., 2016), whilst others examined members of the general population (e.g. Gerstl *et al*., 2015). It is therefore not possible within the data extraction process to produce summaries of the total number of participants who were sampled by the body of work as a whole, nor to provide an overview of the demographic characteristics or outcome variables related to the studies, as would be the case in other systematic reviews of the literature. This is another reason for the narrative synthesis of data that will be presented in Section 4.3, but should also be considered a limitation of the work as a whole, for whilst this review can provide a broad overview of the issues relating to the research question, the nature of the data selected makes it impossible for added depth of analysis to be produced. Table 4 below is the data extraction table and it provides an overview of the core aspects of each of the selected individual studies, including their aims and core findings. Amongst other data that have already been touched upon – such as the range of methodologies employed – this also indicates the breadth of geographic data being collected. A total of eight different African countries are represented within this body of work, which provides a generalisability to the data that can help to answer the research question for this review.

Table 4: Data extraction table

Author (year)	Research aims	Study design	Study Population (country)	Core findings
Adjel *et al.*, (2016)	To explore if Affordable Medicine Facility-malaria (AMFm) improves access to ACTs	Mixed methods: Cross-sectional survey and qualitative	n = 285 (Ghana)	AMFm is effective in providing ACTs through local chemist stores, big concern though re the quality of the drugs
Candrinho *et al*., (2019)	To evaluate the quality of malaria management services in Mozambique	Cross-sectional survey	n = 319 healthcare providers, n = 1,840 patients (Mozambique)	The most significant gap in malaria case management was a failure to test febrile patients; only 46% of patients in Maputo Province were tested
Davlantes *et al*., (2019)	To assess the quality of malaria management and case reporting	Cross-sectional survey	n = 126 facilities (Guinea)	Differences re test accessibility were evident between establishments, indicating regional-based quality issues
Gerstl *et al.*, (2015)	To understand the reasons for non-adherence to fixed-dose	Cross-sectional survey	n =148 (Democratic Republic of	Non-adherence = 25%. Core reasons for non-adherence included sickness/adverse effects; lack of

Author (year)	Research aims	Study design	Study Population (country)	Core findings
	combination (FDC) of artesunate–amodiaquine (ASAQ)		Congo)	food/sugar; forgetfulness; and lack of comprehension of instructions
Kwarteng *et al*., (2019)	To determine the accuracy of and perceptions about malaria rapid diagnostic test (mRDT) kits in rural Ghana	Mixed methods: Cross-sectional survey, focus groups, interviews	n = 1,797 including children and adults (Ghana)	Test-based management of malaria was effective and was deemed acceptable and feasible by the community and stakeholders
Mbonye *et al*., (2016)	To examine quality of care for pregnant women at risk of malaria in the private sector	Cross-sectional survey	n = 241 facilities (Uganda)	Only 40.7% of private clinics managed febrile illnesses in this patient population. appropriately 28.2% in drug shops and 16.7% in pharmacies
O'Meara *et al*., (2018)	To evaluate the public health impact of an innovative strategy	Cluster-randomised controlled trial	n = 7,416 from 32 communities (Kenya)	Significant differences in malaria detection and treatment outcomes between the intervention and control arms
Ssempiira *et al*., (2018)	To determine the impact of vector control interventions and ACT on malaria management	Determining the space-time patterns of disease incidence	N/A (Uganda)	Vector control interventions reduced the incidence of malaria, and ACT treatment improved the management of malaria
Steinhardt *et al*., (2019)	To examine the effectiveness of text messages to health workers re malaria management	Cluster-randomised controlled trial	n = 2,536 (Malawi)	Intervention arm of CRCT resulted in an increase in the proportion of patients with uncomplicated malaria who were managed appropriately
Wang *et al*., (2018)	To assess the dispensing practices for antimalarial drugs in drug stores	Cross-sectional survey	n = 48 drug stores (Uganda)	Out of 48 drug shops identified, only 1 was licensed with the records office. 94% of the drug shops were stocked with intravenous anti-malarials.
Wanja *et al*., (2016)	To evaluate the diagnostic performance of various RDTs against the gold standard for detection	Observational study	n = 500 (Kenya)	It was concluded that RDTs could considerably improve the quality of malaria case management in endemic regions
Yitbarek *et al*., (2016)	To assess the performance of laboratory professionals in malaria diagnosis	Cross-sectional survey	n = 60 (Ethiopia)	Agreement between laboratory professionals and expert microscopists over malaria parasites and species identification was extremely low

4.2 Critical appraisal of included studies

This section will now consider the methodological rigour of the studies selected for this review. This will comprise both CASP methodology (a CASP data matrix relating to the selected studies can be found in the appendix to this work) and referring to accepted best practice considerations for conducting and reporting primary research studies. On the whole, according to the CASP checklists that were utilised to assess the rigour of these studies, this selection was a moderately strong example of research in this field. There were a number of CASP elements for which all of these studies scored well. For example, all of the included pieces of work provided a strong background to their investigation, clearly identified the aims and objectives of their work, and provided coherent explanations and rationales behind their choice of research design. As the CASP data matrix in the appendix shows, across many of the CASP criteria, these studies fared well, and taken together, they represent a body of work that can be viewed to have produced results of a valid nature that may be of use to those working in the field. However, CASP, whilst providing a good insight into the reporting of studies, does not seek to comprehensively critique every aspect of a study, and the discussion will now turn to

critiquing both the strengths and limitations of the selected studies in a more focused and specific manner. To this end, the RCTs will first be discussed, followed by the cross-sectional studies, the mixed methodology studies, and the naturalistic studies.

For the two RCT studies (O'Meara et al. (2018) and Steinhardt *et al*., (2019)), allocation to both the control and intervention groups followed a suitable randomisation procedure, following which all of the participants were treated in the same manner. It is also of note that both studies accounted for participant flow through the trials in accordance with the standards of the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (Schulz, Altman & Moher, 2010). However, although these two studies in particular can be considered to be particularly robust, a caveat regarding the lack of blinding within the study conducted by O'Meara *et al*., (2018) should be held in mind. This, although noted to be a pragmatic consideration on the part of the authors, does raise the risk of bias within the data collection processes that may invalidate or confound the results. This was, however, the sole area of concern across the two RCTs that were included in this review.

With regard to the studies that adopted a cross-sectional approach, which for this discussion will also include the mixed methodological work of Adjel *et al*., (2016) and Kwarteng *et al*., (2019), again the CASP appraisal indicated that their results were worthy of consideration. The core issue that was common in this body of work, however – aside from the limitations of the cross-sectional design that were noted previously – is the reporting of statistical procedures within this sub-sample of studies. Although it is good practice to conduct and report a statistical power analysis, to both generate insight into a requisite sample size and to ensure that the risks of Type II errors or false negative findings are minimised (Nayak, 2010), none of the selected studies outwardly reported conducting an *a priori* power analysis. Although this may seem like a small complaint, this is nevertheless a concerning omission from the reporting of these studies, and it limits the aura of rigour that they otherwise convey. Similarly, although it is considered good practice to report the effect sizes of inferential statistical tests – a prerequisite requirement within the reporting standards of many quality peer-reviewed journals (Appelbaum *et al*., 2018) – this was not done across the entirety of these papers. Because effect size is such an important consideration to determine clinical significance, not just the statistical significance of findings (Coe, 2002), and because it can also be used to inform future studies' power analyses (Coehn, 1992), this is a further cause for concern. It should be noted however that the analysis conducted for the qualitative branches of the work by Adjel *et al*., (2016) and Kwarteng *et al*., (2019) was well reported, the analytical frameworks were identified, and the reporting was in line with best practice guidelines (e.g. White, Woodfield & Ritchie, 2003).

Finally, the observational study conducted by Wanja *et al*., (2016) and the statistical modelling conducted by Ssempiira *et al.,* (2018) will be briefly discussed. As with all other studies within this review, the authors provide a strong sense of what was being done and why, and there is transparent reporting throughout. The modelling work conducted by Ssempiira *et al*., (2018) is complex, yet they clearly outline the key findings, whilst providing sufficient data for others to test the reliability of these findings. For example, they provide open access links to climatic data processing, Bayesian variable selection, a district-level indicator estimate, and statistical modelling files related to their work. This is in line with best practice conventions relating to transparency in science (Lewandowsky & Bishop, 2016).

In summary, therefore, this selection of papers can be considered to be fairly robust, and it can be judged to provide insights into this topic that are of relevance to the research question at hand, and which are also reliable in nature. There are a number of concerns with some of the reporting contained within this body of work, specifically around some of the statistical analysis and sample size work, or around the blinding of participants in the RCT conducted by O'Meara *et al*., (2018). However, these limitations, whilst limiting in nature, should not be considered to outweigh the positive aspects of these studies, nor the importance of the results that they convey. They should of course be held in mind when considering the impact of the results, but for the most part this is a solid selection of studies that have been well designed and reported, and which provide novel insights into an important topic. This will be discussed in the following section.

4.3 Data synthesis

Whilst the heterogeneous nature of the data collected by the included studies rules out the opportunity to conduct a meta-analysis or meta-synthesis on the data, a narrative analysis of their findings will nevertheless take place within this section, and it will provide core insights that can be used to answer the research question that has guided the conduct of this review. Three core areas were identified from the synthesis of the data from these twelve studies, and this triumvirate will be discussed below.

The first area relates to the management of malaria in African countries. This area comprises of the findings stemming from the work of Kwarteng *et al*., (2019), Gerstl *et al*., (2015), Ssempiira *et al*., (2018), Steinhardt *et al*., (2019), Wang *et al*., (2018), Wanja *et al*., (2016), and Yitbarek *et al*., (2016). As such, this is

one of the most commonly covered areas of work within this selection of identified studies. The narrative that these combined studies tell is wide and far reaching, and it goes a long way towards answering the research question for this current review. Starting broadly, the statistical modelling conducted by Ssempiira *et al.,* (2018) suggested that the use of ITNs and the prescription of ACTs had been core contributors to the reduction in the incidence of malaria in Uganda over the course of time. The statistical modelling – noted to be robust and rigorous in nature – therefore indicated that these interventions had been effective within this region, and can perhaps provide a model from which other countries in Africa can learn. The use of specific measures to manage and identify cases is key to the success reported by Ssempiira *et al*., (2018), yet it is by no means universal within this body of literature. For example, whilst RDTs for malaria were considered to be both effective and acceptable for the Ghanaian participants sampled in the work of Kwarteng *et al*., (2019), issues with clinician knowledge or skills in detecting malaria from lab tests were identified within the work of Yitbarek *et al*., (2016), which was based in Ethiopia. The management of malaria cases was also an issue highlighted within the work of Steinhardt *et al*., (2019), who found that a text messaging *nudge* system for clinicians could be effective in achieving better rates of case management. Although this is positive, more needs to be done to engage patients and inform them about the evidence-based means of managing their condition. This is evidenced by the study of Gerstl *et al*., (2015), which reported a 25% non-compliance with medication rate within its Congolese participants. Furthermore, the work of Wang *et al*., (2016), based in Uganda, stated that patients tended to obtain their antimalarial medication from private drug stores, which issued inadequate dosage, thus causing poor management of the condition. In summary of this first aspect of the findings, therefore, we can say that there are clearly some good and some bad practices in evidence across the African region, which may be due to the differing management approaches taken by different countries. What is clear, however, is that regardless of this, more needs to be done to ensure that patients are informed and empowered about the most effective and evidence-based means of treating the condition.

The second area to stem from this synthesis of the study data relates to antimalarial drug availability within the African countries included in this review. This relates primarily to the findings of Adjei *et al*., (2016) and O'Meara *et al*., (2018). Adjei *et al*., (2016), whose study was based in Ghana, conducted a large-scale survey across four geographic regions within the country. The authors found that the availability of ACTs was high and that there was adequate knowledge on the part of the drug providers about the condition. However, they also found that there were issues with the quality assurance processes with regard to drug provision, something that will be discussed in more detail in the next talking point. O'Meara *et al*., (2018) provide further, high-quality evidence, and the use of a cluster-point of randomisation, rather than participants being randomised at the unit of the individual, mitigated the biases that could potentially confound their findings. Within this trial intervention, those who were found to be malaria positive were provided with a discount voucher for a quality-assured ACT drug regimen. This voucher could be redeemed at any retail medicine outlet. A total of 32,404 participants were tested for malaria between July 2015 and May 2017 and ACT vouchers were allocated to 10,870 participants (O'Meara *et al*., 2018). The findings from the 18-month follow-up indicated that the use of free testing procedures and discounted access to appropriate medication could significantly improve the management of malaria. Because of the rigour of this particular design, and the robustness with which it was conducted and reported, these findings should be considered of particular interest to other countries in the region (this trial was based in Kenya) as a means of providing better access to antimalarial drugs within normally hard-to-reach populations.

The final area to be discussed relates to the quality of clinical knowledge within the African countries included in this review. This primarily refers to the work of Candrinho *et al.*, (2019), Davlantes *et al*., (2019), and Mbonye *et al*., (2016). For example, the work of Candrinho *et al*., (2019) was based in three different provinces of Mozambique and it recruited 1,845 participants, of whom 1,325 were thought to have malaria. This study identified a poor use of antimalarial drugs, with those in Maputo only managing 14% of cases in an appropriate manner (i.e. via correct dosage administration of medication). Furthermore, only 58–62% of patients received the correct prescription of antimalarial drugs. Taken together, clinicians' knowledge and skills appear to be a core barrier in this study to the effective usage of antimalarial medication, and this represents an area that could be addressed in the future. This is further underlined in the work of Davlantes *et al*., (2019), whose cross-sectional work identified that in healthcare facilities considered to have good levels of knowledge and staff training, high rates of concordance with best practice were noted. This was compared to lower levels of concordance in lower tiered services, indicating that there is scope for improving correct case management practices for treating malaria, and that this can be done by empowering and providing additional training to clinicians who work in this area. Finally, Mbonye *et al*., (2016) examined treatment provision in Uganda, and noted that the treatment provided to patients by those working in pharmacies was poor compared to those working in drug shops. The best levels of treatment provision – i.e. that most likely to be in line with best

practice malaria treatment guidelines – were judged to be more prevalent in private clinics compared to drug shops or pharmacies. The following chapter will seek to place these findings into a wider context.

5. DISCUSSION

5.1 Malaria management in Africa

5.1.1 Assessment of the Quality of Management of Malaria in the African Region

Several insights can be gleaned from the 12 research articles included in this systematic review. Of note, a comprehensive assessment of the current management principles of malaria in the African region can be conducted using the results from these 12 research articles. Of the 12 research articles included in this systematic review, the cross-sectional survey conducted by Davlantes *et al*., (2019) is instrumental in tracking the quality of management of malaria in the African region. As previously iterated in the results section of this systematic review, Davlantes *et al*., (2019) observed that there was a 100% availability of RDTs and ACTs in Guinean health facilities which were perceived to have a high or intermediate quality of malaria case management and reporting (Davlantes *et al*., 2019). Conversely, the availability of RDTs and ACTs in Guinean health facilities which were perceived to have a low quality of malaria case management and reporting, was only 82%, and 86%, respectively. As regards the correctness of the management of malaria cases, it was 85% in both the high and intermediate quality health facilities, but just 52% in the low quality health facilities; the researchers concluded that there were areas in Guinea which required much more attention in an endeavour to improve the management and case reporting of malaria. The findings proffered by the researchers are important to discuss because of the stratification between high, intermediate, and low quality health facilities in Guinea. The researchers determined the quality of a Guinean health facility based on the corrected fever testing proportion as a proxy measure – this measure looked at the number of febrile patients who are tested for malaria by observing the rate of malaria testing amongst all patients presenting to a health facility without documented malaria. As for the perceived quality of data recording, the researchers looked at the ratio of RDTs reported consumed to the number of suspected malaria cases as a proxy measure.

In contrast to these assessments of the quality of malaria management services in public health facilities, Candrinho *et al*., (2019) estimated the quality of malaria case management using standard indicators obtained from the exit interview and re-examination data. Adequate treatment was defined as oral quinine for pregnant women in the first trimester testing positive during re-examination, ACT for other patients testing positive during re-examination, and the abstinence from anti-malarial drugs for any patients testing negative during re-examination. The appropriate management of a suspect malaria case was defined by the researchers as testing via RDT or microscopy, as well as the management with the appropriate dose in accordance with the results from the re-examination (Candrinho *et al*., 2019). The authors also looked at similar metrics of quality as Davlantes *et al*., (2019) – they assessed the subset of patients with febrile illness who tested positive by RDT, but went on further to track these patients throughout the full malaria case management pathway. This pathway consisted of checking for the correct treatment, correct dose of anti-malarial drugs prescribed, and even the ability of patients to recite back their correct dosing schedule. The authors also looked at the effectiveness of counselling provided to malaria patients.

In this sense, the two aforementioned studies reveal that there is a lack of consistency in how quality of malaria management and case reporting is measured in different parts of Africa. Evidently, this cross-sectional study which was conducted in Mozambique demonstrates a higher standard for measuring quality of malaria management than what was utilised in the Guinean study. The development of a consistent set of quality indicators to be used throughout the region of Africa could be beneficial for the following reasons. First, a set of malaria-specific indicators could be better able to capture different aspects of healthcare quality which are relevant for the enhancement of patient care. Second, the harmonization of healthcare quality standards or metrics by which the management of malaria cases or case reporting throughout countries in the African region could facilitate better country and region-wide tracking and evaluation of healthcare facilities (Busse *et al*., 2019).

Scoping the assessment of the management of malaria in the African region further to treatment adherence, it is useful to explore the results proffered by Gerstl *et al*., (2015) (Gerstl *et al*., 2015). In this study which was conducted in the Democratic Republic of the Congo, researchers sought to measure adherence and identify reasons for non-adherence to a 3-day fixed-dose combination of artesunate-amodiaquine. This study highlights a limitation of the aforementioned quality-assessment study conducted by Candrinho *et al*., (2019). Although Candrinho *et al*., (2019) designed their study to track patients through the full malaria case management pathway, the Gerstl *et al*., (2015) study highlights that adherence to the prescribed treatment regimen requires meticulous and constant monitoring at the health-center level. If efforts are undertaken at the national or regional level to harmonize health quality metrics for evaluating the quality of malaria case management and malaria case reporting, an endeavour to incorporate treatment adherence into the full malaria case management pathway is recommended for these reasons.

Looking beyond the design and results of these studies, it is prudent to consider how the quality of malaria management is tracked and measured in regions outside of Africa. In Asia, specific indicators are used in the performance frameworks for Global Fund supported malaria grants; these indicators are categorized as follows – impact, outcome, output, and input. A total of 1,205 indicators are used to assess a bevy of service delivery areas such as prevention, behavioural change and communication, prevention in pregnancy, treatment, diagnosis, drug resistance, monitoring and evaluation and coordination amongst others (Zhao *et al*., 2011). Examples of specific indicators include all-cause mortality amongst children younger than 5 years of age, the number of insecticide-treated nets distributed to people, and the number of people attending malaria advocacy meetings. In order to address the heterogeneity of these indicators, the Global Fund developed an Indicator Guidance Sheet (TGF, 2020) for malaria which delineates 34 indicators including the number of reported malaria cases monthly and annually, the malaria test positivity rate, the proportion of pregnant women attending antenatal care clinics who received three or more doses of intermittent preventative treatment for malaria, the number of active foci of malaria, and the annual parasite incidence amongst others. Health policy makers in Africa or researchers/clinicians who are eager to harmonize standards for measuring quality could emulate this Indicator Guidance Sheet or adapt this Guidance Sheet to the unique needs of Africa.

5.1.2 Malaria Management in Pregnancy in the African Region

Of the 12 studies evaluated in this systematic review, one of them was specifically scoped towards the management of malaria in pregnancy. Mbonye *et al*., (2016) sought to explore ways of enhancing the quality of care in the private sector which provides 50% of health services in Uganda (Mbonye *et al*., 2016). The researchers observed that the management of febrile illnesses amongst pregnant women in accordance with national management guidelines was poor; only 40.7% of private clinics managed febrile illnesses in this patient population appropriately, and this figure dropped to 28.2% in drug shops and just 16.7% in pharmacies. Even though the majority of providers (exceeding 75%) at private facilities prescribed sulfadoxine-pyrimethamine for the intermittent preventative treatment, ACT was still prescribed at drug shops, private clinics, and pharmacies for the prevention of malaria in pregnant patients with febrile illness. The researchers opined that that this was due to a lack of knowledge that pregnant women are at a considered to be at high risk of contracting malaria. They also observed that there were discrepancies between National Malaria Control programmes and reproductive health programmes pertaining to the timing and dosing of intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (Mbonye *et al*., 2016). This is an important point for discussion as it highlights the fact that guidelines at the local, national, and even regional level could be outdated and inconsistent, leading to confusion amongst healthcare practitioners who implement malaria prevention programmes in pregnancy. Even though the WHO recommends ACT for the management of uncomplicated falciparum malaria during the second and third trimesters of pregnancy, as well as quinine in conjunction with clindamycin for the first trimester of pregnancy, several African countries have national policies which recommend the prescription of quinine throughout pregnancy (Mbonye *et al*., 2016). One study found that 39 out of 47 African countries surveyed had an intermittent preventive treatment policy for malaria in pregnancy; it is unclear if all 39 countries adhere to the WHO recommendations stipulated above. For the eight remaining countries which did not have any policies relating to the intermittent preventive treatment of malaria in pregnancy (i.e. Botswana, Cape Verde, Burundi, Djibouti, Ethiopia, Eritrea, South Africa, and Swaziland), efforts by their respective health ministries should be undertaken to ensure that these policies are not only implemented, but that they implemented in line with the current and best available evidence (WHO guidelines).

5.1.3 Assessment of Diagnostic Tests for Malaria in the African Region

Several studies included in this systematic review provided an assessment of the diagnostic tests for malaria routinely utilized in the African region. O'Meara *et al*., (2018) sought to evaluate the public health impact of an innovative strategy targeting ACT subsidies to malaria cases which had been confirmed by coupling free diagnostic testing with an ACT subsidy which was dependent on the diagnosis (O'Meara *et al*., 2018). In this cluster-randomized controlled trial in Kenya, the researchers observed that 50.5% of patients in the interventional arm had a malaria diagnostic test for a recent fever, as opposed to just 43.4% in the control arm. This was coupled with an increase in the rational use of ACTs in the interventional arm from 41.7% to 59.6%, representing a 40% increase at the 18-month interval. These results suggest that diagnosis-dependent ACT subsidies can have a beneficial impact on the diagnostic testing for malaria, with further downstream effects on the population-wide rational use of ACTs. Wanja *et al*., (2016) sought to evaluate the diagnostic performance of various RDTs against the gold standard for the detection malaria parasites (i.e. microscopy) (Wanja *et al*., 2016). The researchers observed that the evaluated RDTs (i.e. First Response, CareStart, SD Bioline and Binax Now) had moderate performance vis-à-vis microscopy and concluded that they could considerably improve the quality of malaria case management in endemic regions within Kenya.

However, the authors did not perform a cost-effectiveness analysis of these RDTs; it is unclear from the study whether the RDTs are a cost-effective diagnostic modality and whether or not the cost of the RDTs would preclude effective implementation of these RDTs in the field. Future research could be scoped to delineating the cost-effectiveness of these RDTs and compare them not only with the gold standard, but with each other to better inform health policy makers in Africa. The wider literature reports that RDTs have the potential to be cost-effective in most parts of sub-Saharan Africa; this cost-effectiveness is thought to be secondary to improvements in the management and health outcomes related to non-malarial febrile illnesses as well as savings from antimalarial drug costs (Shillcutt *et al*., 2008).

As regards the gold standard for the diagnosis of malaria, Yitbarek *et al*., (2016) sought to evaluate the performance of laboratory professionals in the diagnosis of malaria in health facilities in Addis Ababa and Ethiopia (Yitbarek *et al*., 2016). While not an assessment of the diagnostic tests for malaria per se, it is worth noting that the general agreement between the laboratory professionals and expert microscopists for the detection of malaria parasites and species identification was extremely low. This suggests that the human element (i.e. laboratory personnel) in the process of malaria diagnosis represents a significantly weak link which deserves attention. Indeed, another recently published study from Tanzania demonstrated that there was poor performance in parasite counting, warranting regular training and quality assessments to enhance the skills of microscopists (Ngasala and Bushukatale, 2019). Apart from the diagnostic accuracy and reliability of RDTs, the perceptions held by patients using these RDTs should also be discussed. In this vein, the study conducted by Kwarteng *et al*., (2019) is useful; the researchers revealed that a high proportion of patients presenting to private licensed chemical shops with fever or other signs and symptoms of malaria and who were tested with an RDT received the recommended malaria treatment (Kwarteng *et al*., 2019). This RDT-based management of private licensed chemical shop attendants was perceived to be feasible and acceptable not only by the community, but other stakeholders such as district health authorities, community opinion leaders, health insurance managers and private licensed chemical shop attendants, despite being contrary to current policy recommendations. These findings, together with those presented by O'Meara *et al.,* (2018), suggest that the subsidization of both the RDT and subsequent ACT therapy indicated for the specific type of malaria could be beneficial at the community level. Indeed, the literature suggests that the combined healthcare costs of both the RDT and ACT represents a significant barrier to patients in the community, especially in rural areas (Ezenduka *et al*., 2017).

5.2 Antimalarial Drug Availability & Adherence in the African Region

Not many studies in this systematic review directly addressed the availability of antimalarial drugs in the African region. Nevertheless, some studies do provide insights related to this theme. For example, Adjei *et al*., (2016) sought to evaluate the effectiveness of subsidies in increasing the access to ACT in Ghana and documented the malaria management practices in both the household and community levels during this period of subsidy (Adjei *et al.,* 2016). The researchers found that subsidising ACTs resulted in an increase in the availability of ACTs, especially in hard-to-reach areas within 8 countries in sub-Saharan Africa. One interesting point to note from the study is that not all retailers were compliant with the recommended selling price despite the ACTs being subsidised – this raises affordability concerns for patients without health insurance in these hard-to-reach areas. Enforcing compliance to the recommended selling price could also be challenging, as retailers could mark-up these drugs to maximise their profits. Indeed, the evidence suggests that non-artemisinin therapies are marked up by 40% in Nigeria and by 100% in Zambia, while ACTs are marked-up 22% in Nigeria and 71% in Zambia (Palafox *et al*., 2016). Health ministries and policy makers should consider various factors of market structure such as provider conduct, consumer demand and competition in order to institute policies that mitigate against excessive drug price mark-ups whilst ensuring that retailers remain profitable to encourage the sale of subsidised ACTs to the community.

Wang *et al*., (2018) sought to identify drug shops in Uganda to assess the practice of anti-malarial dispensing (Wang *et al*., 2018). Out of 48 drug shops identified, only 1 was licensed with the records office. 94% of the drug shops were stocked with intravenous anti-malarials, and more than half of all individuals receiving anti-malarials purchased them through the private sector. These findings suggest that the private sector has an equal, if not larger part to play than the public sector as regards the availability of ACTs and other anti-malarials, despite the fact that most of the private sector drug ships are unlicensed and unregulated. Even though the lack of regulatory oversight and quality assurance processes make the private sector appear unfavourable, the evidence suggests that 46.7% of individuals obtain their anti-malarials from them (Wang *et al*., 2018). This is a crucial point for health ministries and healthcare policy makers – efforts to subsidize anti-malarials and RDTs, as well as efforts to prevent the unscrupulous drug price mark-up for profit should be undertaken not just within the public sector core of healthcare service providers, but should also extend outwards to encapsulate private sector entities.

As regards adherence to antimalarial therapy, Gerstl *et al*., (2015) sought to measure it as well as delineate reasons for non-adherence to a 3-day FDC of artesunate-amodiaquine (Gerstl *et al*., 2015). The researchers found that total non-adherence amongst 148 patients was 25% and that the top reasons for non-adherence were as follows – sickness/adverse effects associated with drug intake, lack of food/sugar to consume together with drugs, forgetfulness, and lack of comprehension of instructions (Gerstl *et al*., 2015). These are extremely insightful results, as they reaffirm the importance of assessing the social determinants of health of the community, as well as in ensuring that health literacy is achieved by the patient during the prescription process. Indeed, the results from the Candrinho *et al*., (2019) study demonstrate that counselling is an indispensable component of the full malaria case management pathway.

5.3 Effectiveness of Interventions to Improve Incidence & Management of Malaria

Three studies in this systematic review assessed the effectiveness of various interventions in attenuating the incidence of malaria and/or enhancing the management of malaria. Ssempiira *et al*., (2018) found that vector-control interventions (insecticide-treated nets) and case management with ACT in Uganda were effective in reducing the incidence of malaria (Ssempiira *et al*., 2018). Steinhardt *et al*., (2019) found that a mobile health solution which leveraged text messaging resulted in an increase in the proportion of patients with uncomplicated malaria who were managed appropriately (Steinhardt *et al*., 2019). Mobile phone penetration rates have reached 63% in sub-Saharan Africa and were projected to pass 70% by 2015; latest figures suggest that the mobile phone penetration will reach 84% by 2025 (Betjeman *et al*., 2013). This suggests that mobile health could be a viable strategy for improving not only the malaria case management by healthcare professionals, but also be used to improve the adherence of malaria patients to anti-malarial drugs. Indeed, harking back to results presented by Gerstl *et al*., (2015), forgetfulness was the third most common reason for total non-adherence to anti-malarial drugs (Gerstl *et al*., 2015). Mobile phone applications could be developed to tackle this issue by sending timely reminders to patients, as well as to improve health literacy by reaffirming what was communicated to the patient during the counselling session as part of the prescription process. However, the cost of the development and promulgation of such mobile or tele-health solutions should also be taken into consideration; they may not be as cost-effective as some of the other interventions discussed in this systematic review.

5.4 Strengths & Limitations of the Systematic Review

This systematic review has several strengths and limitations. First, the review was characterised by a robust search strategy which resulted in a total of 12 studies for final inclusion. These 12 studies were extremely heterogenous and diverse in nature; taking reference from Table 4 above, it is evident that all 12 studies assessed various aspects of malaria case reporting and management. These aspects include, but are not limited to, the quality of management of malaria in the African region, the management of malaria in pregnancy in the African region, the assessment of diagnostic tests for malaria in the African region, and the availability of, and adherence to anti-malarial drugs in the African region. Second, all 12 studies were conducted in various parts of the African region, including Ghana, the Democratic Republic of Congo, Uganda, Malawi, Mozambique, Ethiopia, Guinea, and Kenya. Hence, the perspectives and results presented by the 12 studies could be considered to be generally representative of the wider African region. Third, the total study population that is collated across all 12 studies exceeds 10,000 individuals and 1,000 healthcare or healthcare-associated facilities. These are large numbers, and hence, the systematic review is not limited by a small collective study population. Fourth, all 12 studies are relatively recent publications, with the oldest study being published in 2015. Furthermore, the studies were diverse in their design; the systematic review consisted of studies which were qualitative in nature (e.g. questionnaire-based interviews and cross-sectional surveys) and quantitative in nature (e.g. cluster-randomized controlled trials) Hence, it is not unreasonable to assume that the perspectives and insights gleaned from the systematic review are generalizable and contextualizable to current practice in the African region.

Despite these strengths, this systematic review is not bereft of its limitations. Although the 12 studies address various themes as iterated previously, not all of the objectives of this systematic review were achieved. For example, one of the objectives of this systematic review was to assess the quality of the available anti-malarial drugs. However, only two studies addressed the quality of the anti-malarial drugs in the African region directly. Although it was mentioned that the heterogeneity and diversity of the included studies is a strength, it could similarly be construed as a limitation. This is because all 12 studies did not have a clear consensus regarding their aims and objectives; as a result of this, four themes were generated by the systematic review, but each theme did not have a strong core of evidence. Indeed, each theme that was discussed relied on a core of 2-4 studies which addressed that respective theme. On hindsight, a more focussed search strategy could have been developed to address the objectives of this systematic review.

6. SUMMARY

Rapid diagnostic tests play an important role in the early detection of malaria, resulting in effective malaria management. The likelihood of being diagnosed depends on the availability of the diagnostic test kits. Apart from diagnosis, the availability and quality of antimalarial drugs are very important for determining the efficacy and the impact of the treatment. Spurious or low- quality antimalarial drugs are not adequately effective and they result in poor patient health status, even with excellent diagnostic and treatment facilities. It is not just the quality of the antimalarial drugs that affects the treatment outcome, but also the quality of the treatment process, monitoring, diagnosis and dosing. From the research studies reviewed it was identified that the peak of malaria occurs biannually. Compliance in terms of patient adherence to FDC treatment was found to be 75% in a study carried out in the Republic of Congo.

6.1 Diagnosis of malaria

The cross-sectional study carried out in Mozambique clearly suggested that there was a gap in the training and supervision of microbiologists, which led to the ineffective diagnosis of malaria. Improvisation in RDTs can improve the overall malaria management. A study in Mozambique suggested that antimalarial prescriptions were being given even before diagnosis. This could be a major factor contributing towards drug resistance and inadequate health responses even after drug treatment. More than 90% of the microbiologists in a study carried out in Ethiopia made one or more than one mistake when carrying out tests for malaria. This indicates a high level of training lag in the country. The sensitivity, specificity and accuracy of RDT kits like First Response (FR), CareStart (CS), SD Bioline (SD) and Binax were found to be much higher than microscopic tests and the PCR method. This suggests that a rational implementation of RDTs prior to treatment could improve malarial management practices in Africa. In a large cross-sectional study it was clear that adequate diagnosis plays a key role in the treatment of malaria. This study provided RDTs to the patients showing symptoms of malaria and it reported a 40% improvement in the treatment of malaria within 18 months.

6.2 Drug availability and quality

A study of Uganda confirmed that there are adequate stocks of oral and parenteral antimalarial drugs in the country. However, the licensure procedure for running a pharmacy is not followed and only one out of forty-eight shops had a licence to sell medications. Most of the patients preferred to purchase antimalarial drugs from privately owned stores, which did not have a licence. This is a major flaw in drug dispensing practices and it may result in adverse health outcomes. The availability of antimalarial drugs like ACT was adequate, as reported by a large study carried out in Ghana. The quality of the drugs, however, was sub-standard, resulting in the low efficacy of the drug. There were major differences between the malaria management practices, the dispensing of antimalarial drugs and the quality of drugs in various regions of Africa. The factors responsible for this difference in malaria management were training, supervision, treatment facilities, testing facilities, age of patients and type of facility.

6.3 Strengths and limitations of the research

This review thoroughly studied 12 research studies based in different countries of Africa, thus providing an overview of the malarial management practices throughout Africa. The focus of the studies included in this review ranged from diagnosis, drug treatment, drug quality, patient adherence and malarial interventions, to the pattern of the disease. Thus, all the factors pertaining to malarial management were taken into consideration, suggestin that the study can shed light on the overall strengths and weaknesses of malaria management programmes in Africa. The PRISMA model provides an adequate framework for screening the research articles, resulting in the inclusion of the most relevant ones. The quality of the included research papers was assessed using all the parameters of the CASP tool.

The studies reviewed were based on interviews, surveys, observation and questionnaires, which can result in personal errors. Some of the studies involved space-time patterns of disease incidence and prediction models that are based on technology and might not be realistic. There were very few randomised control trials included in this review, which means that the test group was not compared with the control group as most of the studies were observational studies.

6.4 CONCLUSION

The findings of this systematic review address four main themes - the quality of management of malaria in the African region, the management of malaria in pregnancy in the African region, the assessment of diagnostic tests for malaria in the African region, the effectiveness of specific interventions as regards the incidence and management of malaria, and the availability of, and adherence to anti-malarial drugs in the African region. First, there is a lack of standardisation and harmonization of the indicators and metrics of health quality where the management of malaria is concerned. Second, there are variations in what is construed to be the full malaria case management pathway, the importance of counselling during the prescription process is inappropriately understated. Third, there is a lack of knowledge when it comes to managing malaria in pregnancy, and pregnant patients are not acknowledged as high-risk patients. There is also inconsistency regarding the intermittent preventive treatment policy for malaria in pregnancy;

only 39 out of 47 African countries have such a policy. Fourth, although RDTs have a moderate performance vis-à-vis the gold standard microscopy test, their cost-effectiveness has not yet been definitively determined. The performance of laboratory personnel in conducting the gold standard microscopy test is also lacking and requires attention. Fifth, while antimalarials are widely available in both public and private sectors, their price mark-up remains a financial barrier to the community, especially in hard-to-reach rural areas. Finally, an increasing mobile phone penetration throughout the African region suggests that mobile health solutions could address the top reasons for non-adherence to anti-malarial therapy; namely, forgetfulness and a lack of health literacy.

6.5 Future Research Suggestion

Future research should focus on public policies and medical regulations aimed at malaria management in Africa. This would help to identify the lag in the distribution, supply and dispensing of diagnostic kits and antimalarial drugs within Africa. Researcher could also focus on the regulations pertaining to the stepwise management of malaria in Africa according to the medical guidelines. Malaria affects children the most, so future research could investigate the morbidities and mortalities associated with malaria in children below the age of 5 years.

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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8. Appendices

Table: CASP tool for determining the quality of the research articles

Question	(Kwarteng, et al., 2019)	(Gerstl, et al., 2015)	(Candrinho, et al., 2019)	(Ssempiira, et al., 2018)	(Steinhardt, et al., 2019)	(Adjei, et al., 2016)
Clearly focussed question	Yes	Yes	Yes	Yes	Yes	Yes
Was the study an RCT?	No	No	No	No	Yes	No
Was the allocation of the control and intervention groups appropriate?	NA	NA	NA	NA	Yes	NA
Blinding done for study groups?	NA	NA	NA	NA	Yes	NA
Did all participants contribute to the results?	Yes	Yes	Yes	Yes	Yes	Yes
Same data collection for all participants?	Yes	Yes	Yes	Yes	Yes	Yes
Was the number of participants sufficient to eliminate non-representation?	Yes	Yes	Yes	Yes	Yes	Yes
Major outcomes and representation of the same	The incorporation of diagnosis before treatment was effective for managing malaria	There was no adherence to antimalarial drugs, which needs to be improved	Lack of training and supervision, resulting in gaps in diagnosis and in the treatment of malaria	Vector control interventions and ACT administration were effective in preventing malaria	Text messages did not improve the diagnosis and treatment practices in community health workers	Market share of ACT was high

Question	(Wang, *et al.*, 2018)	(Yitbarek, Nega, Tasew, Taye, & Desta, 2016)	(Davlantes, et al., 2019)	(Mbonye, et al., 2016)	(Wanja, et al., 2016)	(O'Meara, et al., 2018)
Clearly focussed question	Yes	Yes	Yes	Yes	Yes	Yes
Was the study an RCT?	No	No	No	No	No	Yes
Was the allocation of the control and intervention groups appropriate?	NA	NA	NA	NA	NA	Yes
Blinding done for study groups?	NA	NA	NA	NA	NA	No

Question	(Wang, *et al*., 2018)	(Yitbarek, Nega, Tasew, Taye, & Desta, 2016)	(Davlantes, et al., 2019)	(Mbonye, et al., 2016)	(Wanja, et al., 2016)	(O'Meara, et al., 2018)
Did all participants contribute to the results?	Yes	Yes	Yes	Yes	Yes	Yes
Same data collection for all participants?	Yes	Yes	Yes	Yes	Yes	Yes
Was the number of participants sufficient to eliminate non-representation?	No	No	Yes	No	No	Yes
Major outcomes and representation of the same	Inadequate drug dispensing by drug store owners was responsible for inadequate malaria management	The deficiencies of micro-biologists led to discrepancies in diagnosis of malaria	Incorrect malaria case management was found in many instances	Pregnant women were not treated for malaria according to the guidelines	RDTs were beneficial for the diagnosis of malaria, but need training and improvement	Diagnosis followed by treatment with discounted ACT was required for correct malaria management