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Malaria: What are the Needs for Diagnosis, Treatment and Control?

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Abstract

According to the World Health Organization, malaria has been noted for many years in the world causing a life threatening effects. Despite progress in fighting malaria worldwide, the disease kills 236,000 – 635,000 peoples annually. The objective of this re-view is to indicate the current situations of malaria on epidemiology, clinical presentations, diagnosis, treatment approach and control strategies, with enumerating the identified challenges. Literatures and available information written on the malaria epidemiology, clinical manifestation, diagnosis, treatment and control strategies were reviewed from different electronic archives of institutional websites and databases such as Scopus, HINARI, Pub Med, Scopus, Medline and Google scholar sources. Children less than five years of age living in Sub-Saharan Africa are mainly the affected groups. Although rapid diagnostic and molecular tests for malaria are increasing in prevalence and importance, the standard method for malaria diagnosis in much of the world remains microscopy. As recommended by the World Health Organization, the management of suspected malaria cases relies on early diagnosis and effective treatment based on artemisinin-combined therapy. Likewise, including Ethiopia, most Sub-Saharan African countries with *Plasmodium falciparum* malaria has adopted artemisinin-combined therapies as a first-line treatment; with Arthemeter Lumefantrine now the first line treatment for uncomplicated falciparum malaria in Ethiopia. In areas where chloroquine is still effective, *P. vivax* malaria should be treated with this drug. Where resistance to chloroquine has been documented, *P. vivax* malaria should be treated with an appropriate artemisinin-combined therapy. Most reviews and findings revealed that the control and elimination of malaria require expanded coverage of and access to effective malaria control interventions such as insecticide-treated nets, indoor residual spraying, intermittent preventive treatment, diagnostic testing and appropriate treatment. In malaria endemic areas, parasite resistance to most commonly used anti-malarial drugs, poor community participation, the absence of new technologies for effective control and eradication, difficulties on the diagnostic tools, insecticide resistance in the vector and changing of biting behavior of the vectors are involving problems to eradicate malaria. More operational researches and adapted evaluation methods are needed to better address challenges for malaria control and elimination. In addition, the global malaria community needs to work together, to ensure the early steps towards malaria eradication.

Keywords: Malaria; Plasmodium; Diagnosis; Treatment; Control; Mosquito

Introduction

Malaria is caused by infection with obligate intracellular, single-celled protozoa of one of the four species of plasmodium; *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* [1-3]. Recent human cases due to *Plasmodium knowlesi* were reported [2,4,5,6]. Of these, *P. falciparum* and *P. vivax* are the most predominant epidemiologically [1,2]. Malaria is transmitted when a competent vector, the different species of female anopheles mosquitoes, take a blood meal from somebody already infected with malaria [3,7]. About 400 species of Anopheles mosquitoes have been described and approximately 30 of these species are potential vectors of malaria that affect humans [2,8].

Malaria is the world's most deadly and life-threatening parasitic disease [4,9,10]. The disease is one of the most common parasitic diseases in tropical regions, affecting more than 300 million people per year, largely (with 90%) in the sub-Saharan African countries [4,11,12]. The World Health Organization (WHO) estimated 655,000 deaths in 2010 (13), 660,000 deaths in 2011 [14], 627,000 deaths in 2012 [1] and 438, 000 deaths in 2015 [2] directly attributed to malaria, approximately half of the world population being at risk of getting the infection [1,14]. Malaria accounted for just 5% of under-five deaths globally in 2015, and 10% of under-five deaths in sub-Saharan Africa, where it is now the fourth highest cause of death [2]. Initial data, in some African countries, showed that the combination of widespread distribution of LLIN to all households and nationwide distribution of ACT in the public sector was associated with substantial declines of malaria in the past years [15].

Malaria is a major public health problem in several parts of Ethiopia with the majority (68%) of the county's population is living in malaria risky areas. It is responsible for 70,000 deaths every year and accounting for about 17% of outpatient visits to different health institutes [16].

Malaria transmission involves different interlinked factors, from complex natural environment to man-made factors [17]. The transmission is mainly affected by the presence and absence of mosquito vectors, human activities, temperature, climate change and weather condition [18,19].

A laboratory diagnosis of malaria is one possibility in the management of a patient presenting with symptoms. To improve the quality care of the patients, many diagnostic procedures have been developed which aim to have an accurate diagnosis, to reduce the time

of preparation and training needed [13,20]. Till now peripheral blood smear (PBS) remains the gold standard for the diagnosis of Plasmodium species. But malaria rapid diagnostic tests (RDTs) are available to quickly identify malaria cases and as point-of-care test in health institutions where blood smear based diagnosis is not available [21].

Malaria control is an increasingly important focus for the international body concerned with public health and disease control. Because fighting malaria has become a priority in reaching six of the eight Millennium Development Goals [22]. Malaria can be prevented and treated more or less by using cost-effective interventions [2]. In malaria endemic areas of sub-Saharan African countries, including in Ethiopia, long-lasting insecticidal nets (LLIN), indoor residual spraying (IRS), and treatment with artemisinin-based combination therapy (ACT) are the major control tools to ultimately reduce the burden of malaria [23-26].

In this review, the epidemiology, clinical presentation and pathogenesis of malaria are reviewed, along with the current control strategies and treatment opportunities as well as vaccine development.

Methods

A literature survey was done with the aim to identify all relevant studies that examined for the epidemiology, pathogenesis, diagnosis, treatment and control of malaria from peer-reviewed journals and literatures. Computer-aid was used for a keyword search of the following electronic databases: PubMed, PubMed Central, MEDLINE, and CINAHL, Web of Science, Science Direct, HINARI Access to Research in Health Programmes, Scopus/Scimago, DOAJ, Global Health, Google Scholar. Next, electronic archives of institutional websites such as WHO, RBM, CDC and Federal Ministry of Health Ethiopia. Books, Dissertations, and unpublished documents ("grey literature") were considered.

Too old literatures and non-reputable journals were excluded from the search.

The epidemiology of malaria

Globally, an estimated 3.2 billion population in 97 countries are at risk of contracting the disease [1,4], and 1.2 billion are at high risk (>1 in 1000 chance of getting malaria per year). In 2013, about 198 million cases of malaria occurred worldwide (uncertainty range 124–283 million) and the disease led to 584,000 deaths (uncertainty range 367,000–755,000) [4]. The burden and transmission of the disease are serious in most of the tropical and the WHO African Region with unevenly distributed. About 90% of all malaria deaths occur in the areas, and in children aged below 5 years, accounting for 78% of deaths and among women [1,4,27]. The majority of deaths are occurred due to *P. falciparum* [13].

By 2015, the estimated number of malaria cases were 214 million (range: 149–303 million), and the total number of malaria deaths estimated to be 438, 000 (ranging: 236 000–635 000). Most cases in this year are occurred in the sub-Saharan African Region, followed by the South-East Asia Region and the Eastern Mediterranean Region Similarly, it is estimated that in 2015 most deaths (90%) were reported in the WHO African Region, followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%) [2].

P. falciparum shows predominance in Africa [28], New Guinea, and Haiti; whereas *P. vivax* infection commonly occurs in Asia and Central America [29]. For example, more than 80% of *P. vivax* malaria cases are estimated to occur in three countries (Ethiopia, India and Pakistan) [2]. But the incidence of the two plasmodium species is approximately the same in some areas such as South America, the India, east Asia, and Oceania. *P. malariae* is can occur in sub-Saharan Africa, but it is rare. *P. ovale* is encountered in Asia but unusual outside of Africa, and comprises <1% of the cases [28,30].

Malaria transmission and burden is affected by different factors. Climate seasonality, rainfall pattern, vegetation availability, presence of surface water, temperature and human activities are major factors affecting the geographical distribution of malaria and the mosquito vectors. The detailed analysis of all such variables is the future research agenda. But periods of prolonged drought could reduce the transmission of the diseases. Occurrence of fluctuated high rainfall pattern, different humidity or warmer temperatures can cause uneven distribution and pattern of malaria [31,32]. Results of different studies imply that endemic malaria will become an increasing problem in the African highlands, this is because of climate change [18,19,33,34]. In addition, according to the WHO and World Meteorological Organization malaria is one of the most known climate sensitive infection, showing a significant association of malaria incidence with changes in temperature, rainfall and humidity. When the temperature increases by 2–3 degrees of Celsius the number of the population who are vulnerable and at risk of contracting malaria would be increased by up to 5% [35].

Ethiopia is one of the seriously affected countries in sub-Saharan Africa [22]. The national guidelines and different research findings indicated for the epidemiological importance of malaria in Ethiopia. They reported that most of the populations are seriously suffered from both of Plasmodium species as *Plasmodium falciparum* and *P. vivax*. The dominant anopheles species transmitting the malaria are *Anopheles arabiensis* with high variability in different transmission strata [26,36]. Recent reports showed that there is a considerable decrease in malaria cases in the country, but it continues to be one of the major public health issues in different parts of the country [37]. According to the report of the Federal Ministry of Health, approximately 52 million peoples (68%) of Ethiopia live in malaria-endemic areas, chiefly at altitudes below 2,000 meters [16,38]. This variation is occurred by geography, human activities, climate seasonality and recent scale up of control activities [36].

The transmission of malaria in Ethiopia is seasonal and uneven [16]. The transmission peaks bi-annually from September to December and from April to May, with higher transmission rate in the former period. The transmission is corresponding with the major harvesting periods in rural areas. And this could lead to severe economic burden for the country in different ways. Major epidemics happen in every 5 to 8 years with focal epidemics as the predominant form [39,40].

The clinical presentations of malaria

Clinical findings in malaria are extremely diverse and may range in severity from mild headache to serious complications leading to death, particularly in falciparum malaria [41]. The first initial symptoms of malaria are not specific, varied and similar to the symptoms of some systemic viral illnesses. They comprised of headache, abdominal discomforts, lassitude, fatigue, and muscle and joint pains, commonly followed by fever, chills, perspiration, anorexia, vomiting and malaise [5,42].

From the four Plasmodia species, *Plasmodium vivax* and *P. ovale* are causing relapsing infection in that secondary infections can be generated from latent parasites in the liver. Previous infection with *P. vivax*, *P. falciparum*, and *P. malariae* did not prevent infection; there was some reduction in the frequency and intensity of fever and parasitaemia level [43].

Because of these general symptoms, malaria is often over-diagnosed based on the patient's symptoms alone. If, ineffective medications are given, or when the treatment is delayed at this early stage, the parasite burden of the disease continues to worsen, especially in falciparum malaria. According to the report of WHO, severe malaria attributes to a parasitemic person with one or more of the following abnormalities: metabolic acidosis [44], hypoglycaemia, renal failure, neurologic focal signs, respiratory abnormalities, intravascular hemolysis [45,46], black water fever, cerebral malaria, prostration, impaired consciousness, seizures, circulatory collapse, jaundice, hemoglobinuria and severe anemia (with hemoglobin level of <5 g/dL or hematocrit <15%) [47,48]. These disease conditions frequently observed in children followed by adults. Impaired consciousness occurred in adults and children; seizures and severe anemia common in children; whereas renal failure and jaundice are more frequently observed among adults [48,49]. At these stages of the disease, the lethality in individuals receiving treatment is typically 10–20%. But, if not treated, the fatality increases on the majority of the cases [44,45,47].

As parasites tending to consume the glucose, there is production of hypoglycemia in those infected patients with *P. falciparum* [45,49]. The other most severe complication of malaria is cerebral malaria, marked by impaired consciousness, coma, neurologic abnormalities and seizures [45,47,50,51]. If left untreated, cerebral malaria is probably nearly always fatal. Even when treated, cerebral malaria has an approximate 20% of mortality rate in adults and 15% in children [49]. Complicated malaria in pregnant women and in patients with HIV co-infection has increased morbidity and mortality [52,53].

P. vivax could be responsible for some life threatening complications, such as thrombocythopenia, among children in malaria endemic regions, but the number of haemolysed RBCs during *P. vivax* infection is minimal. Thus, the incidence of severe anemia associated with *P. vivax* might occur as a result of rigor inflammatory reactions due to cytokines activation and proinflammatory response [30]. *P. vivax* caused severe malaria complications documented few studies [54] strengthen the fact that this parasite is no longer benign and further studies have to be conducted.

The pathogenesis of malaria

Human infection with malaria begins when a female Anopheles mosquito species inoculates Plasmodia sporozoites into the blood system while blood meal. Once inside the body, the parasite moves to the liver, where it enters a hepatocyte and develops. From there, it enters the blood stream and multiplies inside the red blood cells. This complex life cycle of development of the Plasmodium parasite gives way to the different clinical symptoms on human [12,58,59].

The invasion, alteration, and destruction of red blood cells by the malaria parasites, local and systemic circulatory changes, and the related metabolic abnormalities are all important in the pathophysiology of malaria [12,59].

From the four plasmodia species *P. falciparum* is lethal as it invades red blood cells of all ages making the infection difficult to be destroyed by the human immune system. Whereas, *P. vivax* and *P. ovale* are invade only young reticulocytes. *P. falciparum* has a natural affinity for soft tissues causing sequestration in the brain, kidneys, and blood vessels, and consequently causing different complications that contribute to the severity and fatality of malaria [12,54].

Proliferation of the parasite within the host's erythrocyte takes place by using hemoglobin as predominant source of nutrition for the parasites. The malaria parasite digests hemoglobin within the digestive vacuole through the sequential metabolic processes involving multiple proteases. Massive degradation of the hemoglobin generates large amount of toxic heme. Malaria parasite, however, evolves distinct mechanism for detoxification of heme through its conversion into an insoluble crystalline pigment known as hemozoin. Hemozoin synthesis is an indispensable process for the parasite and is the target of action of several antimalarials [60].

More so, malaria pathogenesis could be explained by *Plasmodium falciparum* erythrocyte membrane protein mediated sequestration of parasitized erythrocytes. This protein helps the parasite infected red blood cells (IRBC) adheres to blood elements including non-infected erythrocytes, leukocytes, and wall of endothelial cells of microcirculation. These binding events enable parasitized erythrocytes to sequester and avoid clearance by the spleen and also contribute to disease by causing microvascular inflammation and obstruction [61,62]. Cytoadherance of IRBCs on human dermal microvascular endothelial cells (HDMECs) is responsible for pathogenesis of malaria. IRBCs were observed to tether, roll, and adhere on resting HDMECs, rossets will be formed causing clogging of capillaries. IRBCs interact synergistically with multiple adhesion molecules on vascular endothelium. The rolling of IRBCs may be the rate-limiting step in cytoadherance [63].

Different factors participate in the neuropathogenesis of malaria. They seem to include abnormally high production of cell-derived cytokines such as tumor necrosis factor (TNF) and interferon (IFN) - induced by infected erythrocytes [47,64]. These cytokines may play an important role in causing certain pathological changes, by up-regulating the expression of cell surface markers like ICAM-1 (intracellular adhesion molecule-1) and chondroitin sulfate A, thus leading to the sequestration of infected erythrocytes, leukocytes and monocytes in the cerebral capillaries [26,64-66].

Malaria diagnosis

Early and effective malaria diagnosis is the main thrust of the management and control of the disease [5,55,56]. Although malaria diagnosis involves microscopy, rapid diagnostic tests, and polymerase chain reaction (highly sensitive but too complex) most of the diagnostic approaches in sub-Saharan Africa are based on the clinical findings and on the parasitological detection of parasites in both thick and thin blood films. In the case of clinical diagnosis, fever or history of fever during the last 48 hours is the means of diagnostic approach, as fever is the cardinal symptom of malaria. Although clinical diagnosis is least expensive, it is imprecise as the clinical presentations used to confirm are not specific and similar with manifestations of other febrile illnesses. So that confirmatory diagnoses are required to decide which patients should be treated with respect to each plasmodium species [5,47]. High sensitivity and specificity of diagnosis in malaria endemic areas is important for the most susceptible groups, viz. children, pregnant mothers and the non-immune individuals, in whom malaria is rapidly fatal, while high specificity will avoid unnecessary treatments by anti-malarials [47].

Microscopic method of examination is laborious and requires considerable expertise in its interpretation, particularly at low-density parasitaemia. Moreover, in patients with plasmodium falciparum malaria, sometimes the parasites can be sequestered and cannot detect sequestered *P. falciparum* parasites. Thus, a *P. falciparum* infection could be missed due to absence of the parasite in the peripheral blood film in this case [57]. Regarding the sensitivity issue, studies revealed superiority of RDT (with a better sensitivity of 97%) over a single set of Giemsa blood smears (85% sensitivity) performed under routine clinical laboratory conditions, particularly for the diagnosis of *P. falciparum* [58].

Although rapid diagnostic and molecular tests for malaria diagnosis are available and in use, the gold standard for the diagnosis of malaria in most of the world is the microscopic thick and thin blood film examinations and identification of *Plasmodium* species in Giemsa-stains (Figure 1) [59]. Microscopic diagnosis with Giemsa-stained blood film, despite laborious and needing reliable equipments, continues through its advantages of cost, accessibility, and relative sensitivity [47,56,60]. This technique is also used in the evaluation of the level of parasitaemia [40,61]. But microscopic confirmation of suspected malaria is cumbersome and requires trained personnel, microscopes and a source of electricity.

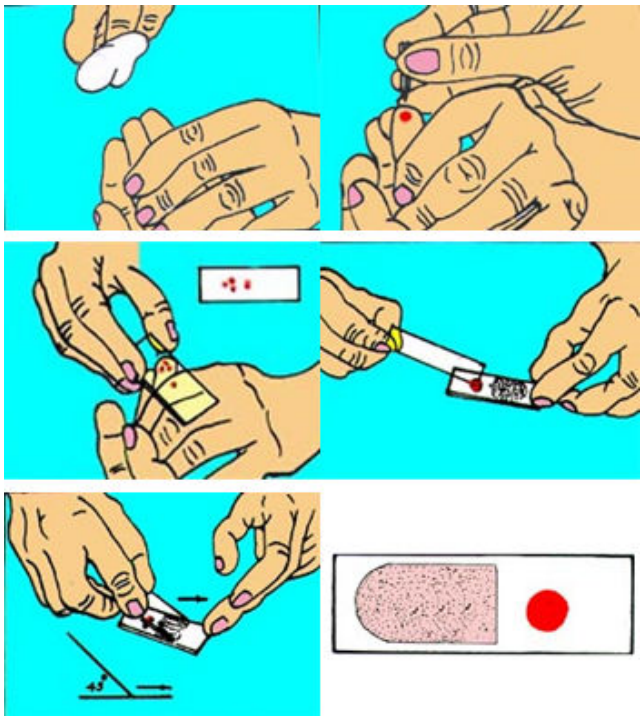

Figure 1: A schematic diagram of blood film microscopy.

In remote malarious areas where microscopy is inaccessible, the use of RDTs is great value for reliable diagnosis of malaria for treatment decisions as well as for guiding the use of different anti-malarial drugs. RDTs are simple and effective for rapid diagnosis of malaria to help in implication of control measures in different areas [21,39,62]. RDTs sometimes called "dipsticks" used to detect plasmodium parasite-specific circulating antigens in a finger pierce blood (Figure 2). The use of RDTs in some instances may lead to false positive results since circulating parasite antigens may stay in the bloodstream for some periods of time even after elimination of parasites. For example, Pf HRP-2 based kits may demonstrate plasmodium positive results even up to 3 weeks after periods of treatment and parasite clearance [39,61,63]. The other difficulty behind using RDT is the genetic variability in the Pf HRP-2 gene. The tests are usually available in different test kits as dipstick, plastic card/cassette. The tests contain antibodies conjugated to latex particles that bind to the circulating antigens. The principle is based on the detection of the histidine-rich-2 protein that specific to *P. falciparum* but usually combined with the detection of other circulating antigens common to all plasmodium parasites, such as aldolases or dehydrogenases [64,65]. In addition, these combined tests can identify both of the *P. falciparum* and non-*P. falciparum* (*P. vivax*, *P. ovale* and *P. malariae*) infections [65].

The advantages of using rapid diagnostic tests are: they do not need complex instruments, electricity, reducing referrals, and the patient's results are available in short periods of time (within minutes) then further reduction in dropout rates [66,67].

The third technique of malaria diagnosis is molecular technique using polymerase chain reaction (PCR). It detects parasite DNA and can identify infections below the threshold of detection for microscopy and RDTs. Although polymerase chain reaction is highly sensitive, it remain too complex for field deployment, requires sophisticated laboratory infrastructure and advanced training [68]. In addition, detection of antibodies to specific plasmodia is neither sensitive nor specific enough to be of use in the management of patients suspected of having malaria disease.

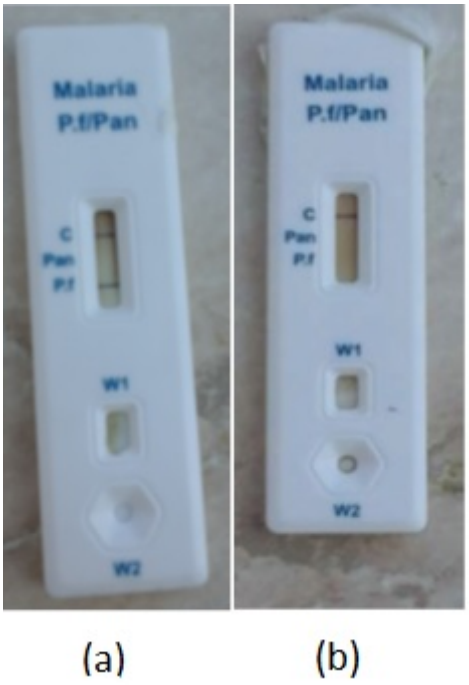

Figure 2: A schematic diagram of RDT of malaria parasites (a) positive for *Plasmodium* spp. and (b) negative for *Plasmodium* species.

Treatment strategies of malaria

Prompt and appropriate chemotherapy is the mainstay for the control of malaria spread [39,69]. In view of widespread drug resistance, treatment should follow national recommended protocols [70]. In previous years, chloroquine was successful in treating almost all cases of malaria. But recent findings revealed that chloroquine-resistant *Plasmodium falciparum* has been found with increasing occurrence in different countries [71-73]. In addition, Sulfadoxine-Pyrimethamine resistant strains of *P. falciparum* were emerged before 2004. As a result, the first line of drug for the treatment of *P. falciparum* malaria cases was changed from sulfadoxine-pyrimethamine to artemether lumefantrine after the mentioned year as above [36]. For instance, one study conducted in Ghana showed that sulfadoxine-pyrimethamine was substandard in treating malaria cases [74]. In areas where SP implementation, growing resistance to sulfadoxine-pyrimethamine is an emerging challenge [75]. In contrast, using sulfadoxine-pyrimethamine (SP) as an intermittent preventive therapy against the disease during pregnancy is becoming a policy in most sub-Sahara African regions before years [74].

Most countries with *P. falciparum* malaria have adopted ACTs as a first-line treatment. WHO recommends that uncomplicated *P. falciparum* cases must be treated with ACT [47]. In areas where chloroquine is still effective, *P. vivax* malaria should be treated with this drug. Where resistance to chloroquine has been documented, *P. vivax* malaria should be treated with an appropriate ACT. But to prevent relapses in *P. vivax* or *P. ovale*, both chloroquine and ACT should be combined with a 14-day course of primaquine (except pregnant women and infants aged less than 6 months), but with side effects such as haemolysis to subjects who are glucose-6-phosphate dehydrogenase (G6PD) deficient (gene frequency typically 3-30% in areas where malaria is endemic; >180 different genetic variants [76,77]. In areas where there is a threat of artemisinin resistance and in areas targeted for malaria for *P. falciparum* elimination, a single primaquine dose (0.25 mg/kg) should be supplied to *P. falciparum* patients during the initial day of their ACT treatment. In 2013, ACTs had been adopted as national policy for first-line treatment in 79 of 88 world countries where *P. falciparum* is endemic. A single dose of primaquine was being used for gametocidal treatment of *P. falciparum* cases in 37 low-transmission countries to further reduce malaria transmission. In 55 of 56 countries with transmission of *P. vivax* malaria, primaquine was being used for treatment of the hypnozoite stage of *P. vivax* malaria [4]. Studies recommended combination drug therapies provided effective cure and slow down the emergence of drug resistance [78].

Full doses of effective antimalarial treatment should be given promptly in the initial treatment of severe malaria in adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women). This should be followed by 3 days full dose of effective ACT orally. Two classes of medicine are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids (quinine and quinidine) [79].

Current treatment strategy in Ethiopia recommends artemether lumefantrine (AL) and chloroquine as the first line of drug to treat un-complicated P. falciparum and *P. vivax* patients, respectively. Mixed infections with *P. falciparum* are treated with AL [26,80]. But a study conducted in southern Ethiopia indicated that evidence of clinical treatment failure for *P. vivax* after chloroquine and this is most likely due to chloroquine resistance [81]. This shows a need to call for an increased in drug resistance monitoring and re-evaluation of treatment guidelines.

In Ethiopia, malaria treatment has been intricate due to the emergence of resistant plasmodium strains to the currently available anti-malarials. Therefore, new drugs need to be developed for drug-resistant parasite strains. As previous findings indicated many of the presently available drugs were discovered from different anti-malarial medicinal plants and their products. The different findings revealed for the presence of exhibiting, promising and potential antimalarial plants [81-89]. The results of different studies showed that efforts should be done to preserve and further assessment of these potent anti-malarial plants [85,88]. And the safety and effectiveness of the described plants need to be further evaluated comprehensively, by giving priority to those with highest anti-malarial activity, before recommending them for wider use and further phytochemical and pharmacological assessments [90].

Control strategies of malaria

Fighting malaria has become a priority in reaching six of the eight Millennium Development Goals in many countries [22]. Progress made in malaria control during the past decade has prompted increasing global dialogue on malaria elimination and eradication [91]. During 2000 – 2013, the improvement of effective malaria prevention and control efforts saved approximately 4.2 million lives, with 92% of those are children aged less than 5 years, and global malaria mortality was decreased by 30% from which 34% are in sub-Saharan African region [4]. Despite these accomplishments, around 214 million malaria cases occurred worldwide in 2015, and responsible for approximately 438,000 deaths [2].

According to World Malaria report [22], the combination of tools and methods has to be designed and employed. The main intervention strategies are vector control (which reduces transmission of parasites from humans to mosquitoes and then back to humans), which is achieved largely through the use of insecticide-treated mosquito nets (ITNs) and house spraying by indoor residual spraying (IRS); chemotherapy; and case management including rapid diagnosis and treatment of infections) [2,92]. Because drug and vaccine development may not be sufficient to halt transmission, vector-based initiatives in other areas have proved effective [93].

Empirical confirmation shows the effectiveness of ITNs in reducing incidences of the disease [94]. IRS is an additional highly efficient means for rapid, large-scale effects on both mosquito populations and the disease magnitude [95]. Good trials on implementation of IRS were demonstrated in southern African regions [95,96] and India [97]. Similarly, in Ethiopia, about one third of the population was protected by indoor residual spraying in 2013 [2].

In many settings of sub-Saharan Africa, use of LLIN, IRS and malaria case management with ACT made around 50% of reduction of malaria incidence and deaths [23,24,26]. In addition, use of ITNs reduces malaria mortality rates by an estimated 55% in children below 5 years of age in sub-Saharan Africa [98,99].

As stated in the above and as per the recommendation of WHO, prompt diagnosis and effective chemotherapy remains the vital strategies in malaria prevention and control [4,100]. Parasitological confirmation by light microscopy or rapid diagnostic tests is recommended in all malaria cases before the starting of antimalarial treatment [2]. Chemoprevention is particularly effective in pregnant women and young children. Administration of SP during antenatal

clinic visits in the 2nd and 3rd trimesters of pregnancy has been revealed that reduction in severe maternal anaemia [101], and low birth weight of neonates [102]. As a result, for the good achievement of pre-elimination strategies of malaria, ensuring of optimal healthcare for the population through accessing the highly sensitive diagnostic techniques and prompt treatments are essential [103].

The challenges of control strategies

Challenges in the endemic areas, are associated with increasing in vector resistance to current-generation insecticides [104-107], the shifting behavior of mosquitoes, leading to an increased outdoor biting hence evading insecticide-treated surfaces [108-110], and shortfalls in funding for control of malaria [105] collectively lead to a plateau in the reduction of malaria prevalence.

Outdoor biting behavior of Anopheles mosquitoes, causes risk of infection among sleeping household inhabitants [111]. Although studies showed malaria transmission is occurring both indoors and outdoors [112], most of the malaria control didn't include tools that target both indoor and outdoor transmissions. Anopheles mosquitoes are zoophagic and mainly feed on bovine blood meals than humans. So, the zoophagic nature of vectors is another challenge for the control (linked to scale-up of vector control interventions) [113].

Drug resistance to *P. falciparum* has also been shown to develop faster than with other Plasmodium species. It is owing to these factors that malaria infection that is predominantly due to *P. falciparum* causes grave consequences [5,114]. In addition, increasing prevalence of chloroquine resistance has led to an increase in complicated malaria in different regions of the world [4]. In recent years, there have been raised in insecticide resistant mosquito species and anti-malarial drug-resistant plasmodium strains and the changing in epidemiology of malaria due to the scaled-up intervention measures. As a result, new and effective strategies are needed to continue and then improve the good progresses in malaria control and further to move beyond control to the elimination strategy [115].

In some countries like Brazil, mosquito control approaches, especially spraying of homes with available insecticides, have been phased out for the past ten years unless alternative tools developed to improve the currently employing control approaches [116].

Despite millions of dollars of overseas development assistance over the last ten years in ITN, and more recently the resurrection of the use of IRS, the epidemiological impact of vector control remains uncertain due to an absence of nationwide basic parasite and vector-based field studies [117].

Malaria spread and transmission classically clusters in logging sites and farming areas that cause immense environmental changes (altering vector biology and favoring the transmission of the disease) and attract the non-immune migrating individuals/travelers to malaria risky areas [116]. In addition, poverty and low levels of education are significant determinants and challenges for the effective control strategies [4].

Ethiopia is a low-income country, with huge number of population are living in malarious areas and getting malaria infections. The potential for malaria epidemics and the highly variable rain patterns with complex geographical features complicate forecasts for malaria commodities at the remote rural community level, and provide challenges to maintaining medical supply chains. Because of Ethiopia's enormous agriculture-led development and mining industries in malaria risk areas in recent years, there have been massive seasonal population influxes with predominantly male migratory labor forces moving to the western lowlands.

The other challenges of malaria control involve lack of community participation for new strategies, closing intelligence gaps regarding surveillance of insecticide and drug resistances, questions on the quality of available anti-malarial medicines; building capacity to better monitor insecticide resistance and mosquito behavioral changes [118]. Therefore, in future operational researches and adapted evaluation methods and adapt to new technologies are needed to better address challenges for effective malaria control and eradication. In addition, the global malaria community needs to work together, ensuring the early steps towards the end goal of malaria elimination are taken.

Vaccine development

The immense occurrence of malaria disease in the developing countries makes the imperative need for vaccine development and deploying complimentary control and prevention strategies [92]. As an effective means of malaria control is currently lacking, due to drug and insecticide resistance, the development of an appropriate vaccine remains the vital means for malaria control and elimination [92,119]. The development of effective malaria vaccines has been a major goal of the malaria research community for many decades [120].

Due to lack of an efficient vaccine by now, mosquito control strategies involving insecticide-treated bed nets and application of insecticides and artemisinin combination therapies have been used. These control measures are considered to decrease the burden malaria in different areas. The most common advanced vaccine candidate is RTSS (RTS,S/AS01), that would improve the malaria interventions. It has been developed through a partnership between the PATH Malaria Vaccine Initiative (MVI) and GlaxoSmithKline Biologicals (GSK). RTSS trials, conducted in African children, demonstrated a vaccine efficacy for clinical malaria of 50% among children aged between 5 and 17 months old but only 30% in infants, the target population [121]. While RTS,S demonstrates that a malaria vaccine is possible, an ideal candidate to support global eradication efforts would need to have a higher efficacy [122]. Most importantly the candidate vaccine (RTS,S/AS) can bring clinical effectiveness in the 25-60% range in various malaria endemic areas [123]. But researchers recommend that RTS,S/AS01 could be an important addition to current malaria control in Africa [124].

In general, presently employed vaccines show a reasonably high rate of efficacy, with approximately 90% of efficacy [103]. With regard to a promising malaria vaccine agent, however, parts of the scientific community are in conformity that the high standards of quality will not be met. With respect to a promising malaria vaccine, it was commonly affirmed how innate immunity elicited through a vaccine could not be expected due to the lack of real innate immunity against the disease. Certainly, research findings only suggest cases of the before-quoted clinical immunity that decreases the burden of malaria [125]. Policies should support the linkage of IPTp and antenatal care clinics because utilization of antenatal care clinics increases uptake of IPTp [126].

In general, the new Technology Roadmap updated in 2012 outlines that by 2030, vaccines should be developed that provide at least 75% protective efficacy against clinical malaria, reduce transmission of the parasite, and can be deployed in mass campaigns [127].

Conclusions

Malaria control involves artemisinin based combination therapy (ACT) and long-lasting insecticidal nets (LLIN) supported by indoor residual spraying of insecticide (IRS), and intermittent preventive therapy in pregnant women. But, in the absence of any vaccine, and with the problems associated with drug resistance, prevention of malaria has to return to basic principles such as anti-mosquito measures and the use of mosquito nets over beds for protection. But shifting of vectors' behavior towards outdoor biting could be the challenge for long-lasting insecticidal nets and IRS based control strategies. In addition, significant gaps in supplies and equipments, poor community participation, as well as quality assurance and supportive supervision for malaria diagnosis were challenges for prompt diagnosis which is a challenge for accurate treatment. Attempts should be continued to channelize information regarding malaria transmission, importance of prompt diagnosis and effectively employing the significance of available control and prevention strategies. Frequent evaluation of the strengths as well as the weaknesses of the different control measures in estimating malaria incidence and time trends should be sustained in future in malaria transmission areas. In addition, further studies on the biting behavior, on new technologies for control, drug resistance on the currently used drugs and vaccine development issues should be continued. An increased and sustained commitment from all implementing and funding partners remains an urgent priority too.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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