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Malaria: A narrative review of historical efforts in prevention and control

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Abstract:

Malaria is an ancient disease that continues to exert a significant toll on the health of many populations worldwide. Since historic times, when its seasonality, recurrent fever and chills, were documented, various methods for its control have been implemented based on then-extant scientific knowledge, technological advancement and the understanding of its pathogenesis and epidemiology. As knowledge of the disease increased, approaches for its control were modified or improved to reduce disease burden and eliminate the disease. Today, our current knowledge of malaria has afforded newer approaches for prevention and control, including newer drugs and procedures to monitor emerging threats and hence more effective control mechanisms. In this narrative review, we consider a brief history of malaria, with insights into malaria pathogenesis and an evolution of prevention and control measures into the present day.

Keywords: Malaria prevention, malaria history, *Plasmodium*

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Paludisme: Revue narrative des efforts historiques de prévention et de contrôle

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Résumé:

Le paludisme est une maladie ancienne qui continue d'avoir un impact considérable sur la santé de nombreuses populations à travers le monde. Depuis l'Antiquité, date à laquelle sa saisonnalité, ses épisodes de fièvre récurrente et ses frissons ont été documentés, diverses méthodes de lutte contre le paludisme ont été mises en œuvre, s'appuyant sur les connaissances scientifiques de l'époque, les progrès technologiques et la compréhension de sa pathogénie et de son épidémiologie. À mesure que la connaissance de la maladie s'est approfondie, les approches

de lutte ont été modifiées et améliorées afin de réduire la charge de morbidité et d'éradiquer la maladie. Aujourd'hui, nos connaissances actuelles sur le paludisme ont permis de développer de nouvelles approches de prévention et de lutte, notamment de nouveaux médicaments et des procédures de surveillance des menaces émergentes, et donc des mécanismes de lutte plus efficaces. Dans cette revue narrative, nous présentons un bref historique du paludisme, en apportant un éclairage sur sa pathogénie et sur l'évolution des mesures de prévention et de lutte jusqu'à nos jours.

Mots-clés: Prévention du paludisme, historique du paludisme, *Plasmodium*

Introduction: A brief history of malaria

Malaria is an ancient disease with an early history as far back as 500 BC. The first reference to the disease mentioned its characteristic recurrent fever and chills, and was documented in the early Chaldean, Chinese, and Hindu writings (1). Ancient philosophers such as Hippocrates and Celsus alluded to malaria in their writings (2,3). Others mentioned its seasonality, the disease being more frequent during the late summer and early autumn (1). In the sacred Vedas of the Indians, it was referred to as the "king of diseases" and was associated with spleen enlargement, and its symptoms were attributed to supernatural forces (4,5). Malaria holds an important place in the annals of history, being infamous as the infectious disease that has had the most devastating impact on man. It is believed to have contributed to the fall and conquest of nations, as soldiers fell and were subdued, not just by the enemy's bullet, but by the scourge of the disease (6). As Brabin (7) noted, it attacked all combatants during World War I, causing epidemics and severe consequences for troops and civilians. In the Desert Mounted Corps, a British Army group composed of three divisions of military men, about 19,652 of 40,000 soldiers were ejected due to *Plasmodium falciparum* malaria (8). In addition, immigrant troops from Africa and India brought in a large pool of malaria parasites, serving as a mobile reservoir that further worsened the landscape of the malaria scourge during the war (7).

Plasmodium ovale and *P. vivax*, capable of causing malaria relapse, played important roles in the war scenes by triggering persistent difficult-to-treat infections, hence causing the evacuation of a large number of sick troops from combat zones (8). As soldiers in malaria-plagued war zones wore out, they were replaced by non-immune troops, with far-reaching consequences. Furthermore, malaria epidemics aboard voyage ships were of note during the war (9). This play-out of events affected military planning and war strategies, consequently factoring into war outcomes. Sometimes, military operations provided the conditions that fostered the advancement of the disease. For example, soldiers were often disposed to construct underground channels, an environment conducive to water-logging, and that provided the ambience required for mosquito breeding (8). Towards the end of the war in 1918, the concurrent outbreak of influenza and malaria resulted in over 1000 deaths, with a disease-to-combat casualty ratio of about 37 to 1 (7). The impact of malaria was also seen in World War II, Korean and Vietnam wars where malaria drug scarcity was a bottleneck.

Due to frequent military personnel encounters with the scourge of malaria (and infectious diseases in general), they are regularly involved in infectious disease research, as these diseases often play a role in determining the out-come of wars. In 1880, Charles Louis Alphonse Laveran, a French Army surgeon, discovered the parasite, as he examined the blood of a febrile soldier in Algeria (4). He described the parasite as transparent, often crescent-shaped, or ovoid, and having darkly stained pigment granules towards the center (10). He named this parasite *Oscillaria malariae* (11), now called *Plasmodium*. Further research led him to identify four distinct forms of the parasite, later recognized as the parasite in different developmental stages. His discovery was phenomenal in light of the pervasive knowledge of his day; firstly, that malaria was caused by foul smears, and then, the more scientific proposition of a so-called *Bacillus malariae* aetiology (11).

In 1897, seven years after Laveran's initial discovery, Sir Ronald Ross of Britain, another Army surgeon, discovered the parasite in the intestine of mosquitoes and subsequently demonstrated its lifecycle through a series of experiments involving avian-infecting species of *Plasmodium* (4). Ross received the Nobel Prize in medicine in 1902, while Laveran received it in 1907 for their discovery of the parasite and the vector that transmits it. Moreover, further details of the parasite lifecycle, particularly of the exoerythrocytic phase of infection, were elucidated by Shortt and Garnham in 1947, while the identification and characterization of the dormant hypnozoite form was made by Krotoski in 1982 (11–13). Today, we now know that human malaria is caused by six species of *Plasmodium,* namely, *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale curtisi*, *P. ovale wallikeri* and

P. knowlesi (14–16), and is transmitted by several species of the female *Anopheles* mosquito, notably by *Anopheles gambiae* and *Anopheles funestus* in West Africa.

Human malaria parasites:

Human malaria is caused by six species of *Plasmodium*. These parasites vary slightly in biochemical/molecular attributes, as well as the diseases they cause.

Plasmodium falciparum:

Plasmodium falciparum causes the most severe form of malaria. Following liver-stage infection, the parasites are released into the bloodstream, where they infect red blood cells (RBC) and produce high levels of blood-stage parasites (17). These parasites cause changes in the physiology of the red cells, modifying the red cell surface such that they stick to the wall of blood vessels, a phenomenon known as sequestration, and that contributes to disease pathology. Sequestration inhibits splenic clearance of the parasite, damages host cell endothelia and obstructs host microvasculature. These features are characteristic hallmarks of severe malaria caused by *P. falciparum*.

Plasmodium vivax:

Next to *P. falciparum*, *P. vivax* causes the highest number of malaria (18). It is the most widespread and significantly contributes to malaria morbidity, especially in Southeast Asia and South America, where it is prevalent. *Plasmodium vivax* has a dormant parasite stage, the hypnozoite, which can remain in the liver for months or years without causing symptomatic disease until it eventually re-enters the bloodstream to cause a relapse (19). *Plasmodium vivax* merozoites only infect reticulocytes, the juvenile form of the red blood cell. Furthermore, they require the Duffy antigen on the surface of red blood cells for invasion. This attribute is thought to contribute to a much lower prevalence of *P. vivax* in Africa, as majority of the population have no Duffy antigen on the red cell (20). *Plasmodium vivax* malaria is characterized by recurring fevers that occur every third day (approximately every 42-56 hours), called 'tertian fever'.

Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi:

Plasmodium ovale has traditionally been considered a single species and afterwards as members of the *ovale* subspecies; however, recent evidence has shown that these are two distinct species (21,22). Although both are identical in morphology and geographical distribution, they are genetically distinct (23,24). Both parasites are known to have the same course of infection: sporozoites can develop into dormant hypnozoites; they infect reticulocytes, and infected cells appear more prominent than usual (15,25). However, a study has highlighted slight differences in hypnozoite latency period in travelers' malaria (26), as well as higher thrombocytopenia in infection due to *Plasmodium ovale wallikeri* (27).

Plasmodium malariae:

Plasmodium malariae causes mild malaria symptoms, with recurrent fevers in a quartan manner, and tends to infect patients chronically (14). Chronic infection results from a slow parasite lifecycle (erythrocytic cycle every 72 hours) and result in lower parasitemia that the immune system can manage for long periods (15). Infection with *P. malariae* is associated with nephrotic syndrome with consequences for long-term kidney failure (28). Although, they have a limited geographical range than *P. falciparum* and *P. vivax*, *P. malariae* infection, transmission may persist undetected in unsuspecting geographical locations (28).

Plasmodium knowlesi:

Plasmodium knowlesi is a zoonotic malaria parasite that preferentially infects young red blood cells, but with time, can adapt to infect older cells (15). The disease presents with the classic symptoms of malaria, such as fever, chills and headache, and additional signs such as myalgia/arthralgia, nausea and vomiting, anorexia and jaundice (29). It is primarily a parasite of long-tailed and pig-tailed macaques, from which the parasite is transmitted to man; no human-human transmission has been recorded (15,16). Although, there is as yet no evidence of human-mosquito-human transmission of the parasite, studies have shown the biological possibility of this occurrence (30,31), and with increasing prevalence of Knowlesi malaria in parts of Asia, human-human transmission is feared to contribute to disease distribution (32).

Pathogenesis of malaria

The malaria lifecycle involves an alternation of parasite stages between the mosquito vector and humans (Fig 1). The different parasite developmental stages in humans involve the asexual sporozoite, merozoite, trophozoite, schizont and the gametocyte, while in the mosquito, the gametocyte, gametes, zygote, ookinete, oocyst and sporozoite are the different stages involved.

Pre-erythrocytic infection:

The lifecycle begins when an infected mosquito takes a human blood meal. As the infected mosquito takes the blood meal, it releases a hundred or more sporozoites into the blood stream (33). Blood feeding and sporozoite injection is facilitated by the mosquito saliva which contains several proteins, vasodilators, anticoagulants and immunomodulatory compounds, that prevent the otherwise formidable skin barrier from halting sporozoite entry and survival (34).

Our scientific understanding of the fate of injected sporozoites has improved greatly in the past few years, largely through studies on murine models of malaria. Approximately 50 % of injected sporozoites are arrested at the skin site of inoculation, where they exhibit a classical gliding locomotion with average speed decreasing over time (35). Of the remaining sporozoites, others are transported via the lymph to the skin-draining lymph nodes, where partial differentiation into parasite exoerythrocytic stage occur (35), while others penetrate blood vessel endothelia and are transported to the liver (36).

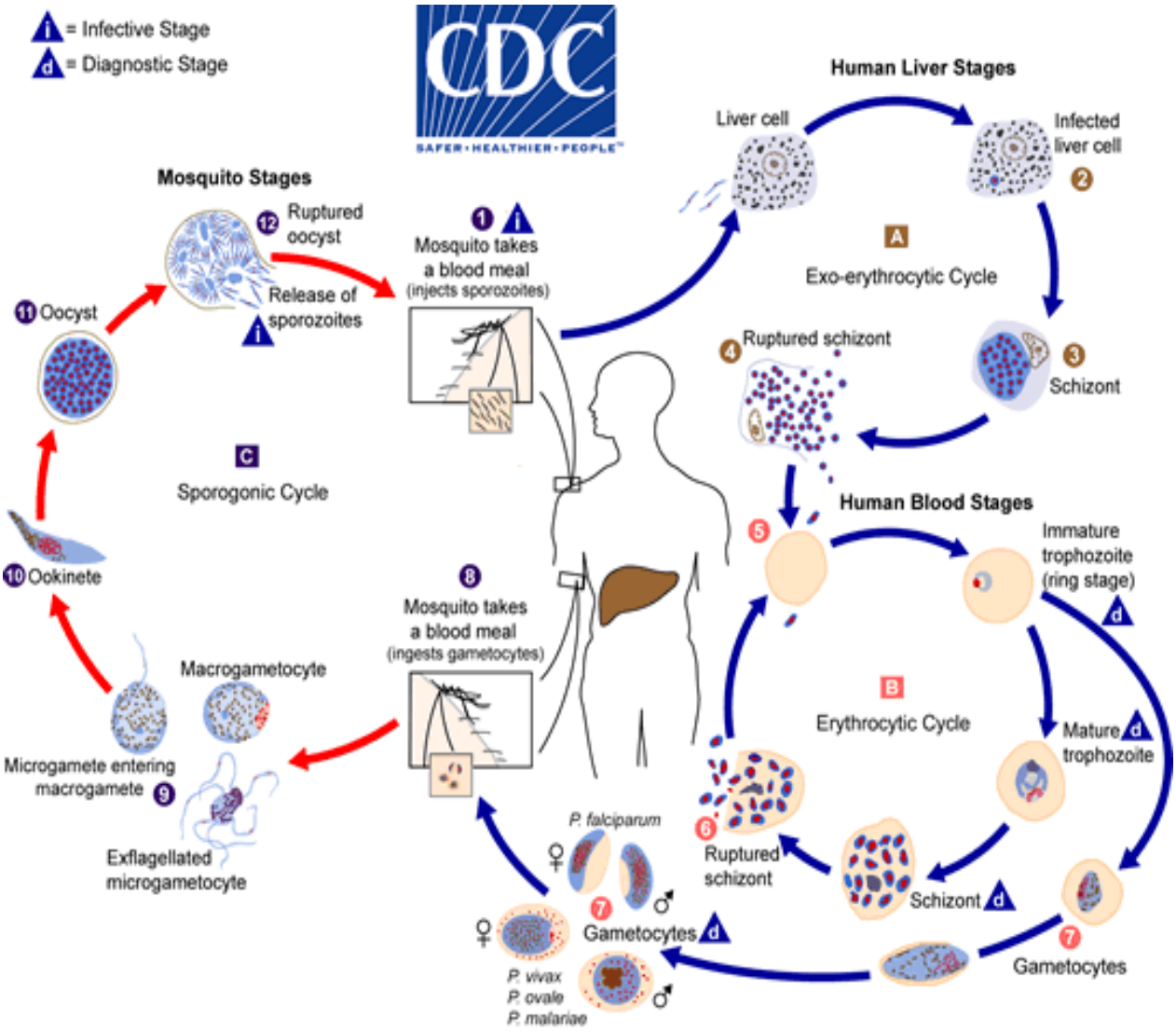

Fig 1: The Malaria Lifecycle. (Source: Center for Disease Control and Prevention)

In a recent study employing humanized mouse model of infection, *P. falciparum* sporozoite motility and penetration of blood vessels appear similar to those of the rodent parasites, *P. berhei* and *P. yoelii* (37). The study highlighted some interesting features of similarity at the initial phase of infection between the rodent- and human-infecting species of *Plasmodium*. In addition, parasite motility decreases upon close proximity and contact with blood vessels, a move thought to improve their interaction and possibly their penetration of blood vessels (38) for subsequent dissemination to the liver predilection site.

The migration from the loci of sporozoite inoculation to the liver is faced with several hurdles. First, sporozoites have to deal with the influx of immune cells, polymorphonuclear leukocytes, lymphocytes and monocytes due to mast cell degranulation (39). Phagocytic immune cells such as the macrophages, neutrophils and dendritic cells also play roles in interfering with sporozoites' migration. Likewise, immunoglobulins specific to the circumsporozoite protein (CSP) neutralize free sporozoites and impede their migration (40). Howbeit, the stealth mechanisms in *Plasmodium* prevent absolute neutralization by the effector activities of the immune system (36).

Moreover, as free sporozoites migrate to the liver, they bypass the immunologic activity of Kupffer cells using a mechanism known as *cell traversal*. Simply, the sporozoites enter a Kupffer cell at one end and exits at the other end, altering the plasma membrane integrity and destroying the cell in the process (41). As Kupffer cells line the sinusoidal covering of the liver, sporozoites have to do a lot of Kupffer cell traversing before eventually settling in a final host liver cell (34). In the hepatocyte, sporozoites are enclosed in a parasitophorous vacuole, where they multiply and are transformed into schizonts. For each infected hepatocyte, several thousands of merozoites are produced (15), and released as merosomes (41), a form of the parasite enclosed in host cell membrane. This enclosure in host cell membrane is thought to contribute to the ability of *Plasmodium* to evade the host immune system. As merosomes are released and escape the liver, they shed this enclosure and become free merozoites, ready to infect red blood cells.

Intraerythrocytic infection:

Invasion of erythrocytes by a merozoite is initiated by the merozoite surface proteins through direct interaction with the red blood cell (RBC) surface. The invasion is further facilitated by the merozoite's micronemes and rhoptries, organellar structures present in the merozoite, which also aid the formation of the parasitophorous vacuole where the parasite grows and multiplies (16). In addition, the parasite conditions the internal environment of the erythrocyte for its survival by exploiting RBC nutrients and exporting parasite-derived proteins that further drives the disease pathogenesis. RBC remodeling is anchored on parasite-induced protein targeting networks that sort and target proteins to specific subcellular locations in the host cell, including on the RBC membrane (42). This network includes *Maurer's clefts* and *J-dots,* membranous structures that are seen independent of the parasitophorous vacuole, and that contribute to protein transport to the RBC surface. In addition, the parasite degrades red cell haemoglobin within its digestive vacuole resulting in heme, a toxic by-product which is further metabolized into hemozoin (43). As RBC nutrients are utilized, the merozoite grows and develops into schizonts which are formed by multiple nuclear asexual divisions, thus producing 15-40 merozoites per infected red cell (16, 44).

This stage of the disease eventually produces the fevers, chills and rigors of clinical malaria as mature schizonts in multiple infected RBC synchronously rupture and release their constituent merozoites and pathogen-associated molecular patterns (PAMPs). The resulting sequelae often occur in varying degrees, dependent on the host immune response. The released merozoites are now ready to infect other red blood cells. Moreover, commitment to the production of sexual stage parasite occurs in some merozoites during blood stage infection. Simply, merozoites differentiate into gametocytes and are released as the schizont ruptures (45). This process in *P. falciparum* takes approximately 10-12 days during which the parasite undergoes different developmental stages in the spleen and bone marrow before the matured forms are released into blood circulation. These gametocytes circulate in the blood and are picked up by the mosquito during a blood meal.

Mosquito-stage infection:

Within the mosquito, gametocytes egress from infected red cells and develop into gametes. Exflagellation of male gametocytes results in eight microgametes whereas a female gametocyte develops to form one immotile macrogamete (45,46). The microgamete fertilizes the macrogamete, resulting in the production of a zygote, which then transforms into a motile ookinete. The ookinete penetrates the mosquito midgut wall by utilizing its lectin molecules and mosquito-derived sugars (40) and is afterward

transformed into an oocyst on the outer surface of the mosquito midgut. The oocyst generates thousands of sporozoites which penetrate the mosquito salivary gland, ready to be released into a human host during the mosquito's next blood meal.

Obstacles to malaria elimination as a public health problem:

The vaccine imbroglio:

The malaria parasite is complex, with a genome size of 23.3Megabases and over 5400 genes (47). This repertoire of genetic information (including several multigene families) informs the plethora of variant proteins/antigens expressed by the parasite during, and between each developmental stage. For example, the *var* family of genes encode up to 60 variants of a single protein, the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), in a single parasite, which contributes to antigenic variation and immune evasion (48).

This polymorphism in protein biology and attendant antigenic variation serves as a formidable obstacle to vaccine development. In addition, the variation in parasite gene expression between lifecycle stages contributes to the complexity. This complexity and dynamism in protein expression contributes to parasite complexity, phasic availability of antigens during infection, and provide stealthy cover from immune defense mechanisms (49). These complexities cause difficulty in mounting a sterilizing immunity against the parasite. The wide range of *Plasmodium* antigens exposed to the immune system, make it difficult to identify the best antigen vaccine candidates, and an immune system response directed at one stage of the parasite is rendered ineffective during another stage of the parasite (50).

Parasite drug resistance:

Plasmodium species resist antimalarials through changes to the genes encoding various transport proteins that transport various solute molecules within the parasite. Solute transport typically involves nutrients, metabolic by-products and xenobiotics, including substances that could potentially harm the parasite. Two key cellular compartments are target solute destination sites; the parasite digestive vacuole and the cytosol. The digestive vacuole is the primary site for haemoglobin digestion, and contains various hydrolytic enzymes of diverse classes that help accomplish hemoglobin digestion, heme detoxification and oxygen radical neuralization (43). Serving various purposes including the detoxification of harmful substances, the digestive vacuole is thus akin to the lysosome of other eukaryotic cells, where potentially toxic substances are shipped for processing (51).

PfMDR1 is an ATP-binding cassette transporter composed of 1,419 amino acids residues, with 12 putative transmembrane domains, present on the parasite's digestive vacuole (52). Its particular location on the lysosomal-type compartment of the digestive vacuole membrane makes it implicated in the transport of solutes, including antimalarial drugs (53). Although, the nature of single nucleotide polymorphisms (SNPs) in this gene will have differing effect on how antimalarials are transported, the general mechanism of action involves drug trafficking away from their target sites. This factor impacts on drug efficacy, offering the parasite resistance to the implicated drug.

There are five prevalent amino acid mutations in the *pfmdr1* gene, namely the N86Y and Y184F which according to epidemiological studies, are more prevalent in Asian and African parasites (52), and involves the substitution of asparagine for tyrosine in N86Y and tyrosine for phenylalanine in Y184F (51). The S1034C, N1042D and D1246Y mutations are more commonly found in South American parasites, and involve substitution of serine for cysteine, asparagine for aspartate, and aspartate for tyrosine at their respective codons (51). The N86Y and N1042D reduce parasite susceptibility to chloroquine and quinine respectively, and concomitantly increase susceptibility to lumefantrine and mefloquine, ACT partner drugs (53). Similarly, amodiaquine resistance is associated with 86Y, Y184 and 1246Y resistance alleles (54,55). Increased copy number of the gene is associated with mefloquine resistance and reduced lumefantrine susceptibility (56).

The PfCRT is composed of 424 amino acid residues arranged into 10 transmembrane domains. This transporter also sits on the parasite's digestive vacuole membrane, where it mediates drug trafficking from the parasite's intravacuolar compartment to the cytosol, potentially shuffling away drugs from their active site, for example shuffling chloroquine away from its heme target (57). Mutations in *Pfcrt* gene has been implicated in antimalarial drug resistance; the (*Pfcrt*-K76T) mutation, where lysine is substituted for threonine confers concomitant chloroquine and amodiaquine resistance (54,55); SVMNT allele for amodiaquine resistance; and *Pfcrt*-C101F for piperaquine resistance (58). The 7G8 isoform of the parasite contains five point mutations viz; C72S, K76T, A220S, N326D, and I356L, which are all revealed to line the central drug-binding cavity. Four of these mutations are required to confer chloroquine

resistance, although the K76T appears to be a key mutation (57), being conserved in chloroquine-resistant parasites, (59), and along with *pfmdr1* mutations, employed as a molecular marker in determining chloroquine resistance (60,61). Furthermore, levels of expression of the PfCRT determine chloroquine resistance, as low expression levels do not confer resistance to the drug.

PfCRT is opined to play roles in the trafficking of other metabolites; for example amino acids arising from haemoglobin breakdown, glutathione, iron, chloride and hydrogen ions, alkaloids, and acting as a non-specific cation channel (51,62). This transporter is therefore important to the normal physiological functioning of the parasite, being recently confirmed to play roles in the export of host-derived peptides of 4–11 residue length, with tendencies not congruent as a non-specific transporter of other metabolites and/or ions (63). In addition, other antimalarials such as primaquine, quinacrine, mefloquine, and low-weight peptides containing aromatic amino acids are able to competitively inhibit chloroquine from interaction with mutant PfCRT, indicating the role of this transporter in transporting additional antimalarial drugs and peptides outside the digestive vacuole (43).

Mutation in the *P. falciparum* Kelch 13 gene (*pfkelch13*) mediates resistance to artemisinin antimalarials, a discovery feared to sabotage the recent gains in malaria morbidity and mortality worldwide. *PfKelch13* has a single exon, and is located on chromosome 13 of *P. falciparum* (64). The gene encodes a protein of 726 amino acid residues, which is structurally configured into three protein domains: a sequence specific to *Plasmodium*; a BTB or POZ domain (a recognized signature for protein-protein interaction, also present in other proteins); and six repeats of the kelch motif, called the beta-propeller domain (65). Artemisinin resistance occurs due to mutations in this beta-propeller domain of kelch 13 (66). Over 100 of these mutations have been identified, with majority of the significant mutations occurring in Asia. C580Y, R539T, I543, and Y493H, are the most frequent of the mutations (67). Drug resistance (if not checked) will increase morbidity and mortality of the disease, serving as obstacles to malaria elimination/eradication.

Asymptomatic malaria reservoir pool:

Nigeria continues to bear a significant toll of the worldwide malaria burden. In 2021, Nigeria accounted for 27% of all malaria cases, the highest of any country in the world (68). Aju-Ameh (60) presents a unique perspective on asymptomatic malaria as a major challenge to malaria elimination. This author described a study in which 272 humans and 214 mosquitoes were investigated for the malaria parasite. This study revealed that humans had more parasite biomass (36.8%) compared to engorged anthropophagic female *Anopheles* mosquitoes (0.5%). This finding illustrates a higher prevalence of *Plasmodium*-infected humans than mosquitoes, and this is believed to be "the existing phenomenon in most scenarios" (69). These human parasite reservoirs are a potential source of continuous parasite transmission within the population.

As gametocytes are the parasite forms infective to mosquitoes, the presence of mature gametocyte in blood is crucial for a sustained parasite transmission (70). Moreover, establishing and quantifying gametocyte presence in blood is important to monitor transmission patterns and the potential infectiousness of asymptomatic individuals (71). Detection may be achieved by microscopy. However, very low gametocyte densities will require more sensitive approaches for their detection (72), especially in low transmission settings where gametocyte detection by microscopy is elusive. However, failure to detect gametocytes by microscopy or molecular methods does not exclude the possibility of malaria transmission, provided that other parasites forms are present. This is true because all malaria have the capacity to produce gametocytes (71). Evidently, in endemic settings, asymptomatic infections usually persist through the dry season, perpetuating disease transmission into the wet season (70,73, 74). Generally, the higher the circulating gametocyte numbers, the higher the infectiousness of an individual. And, although, higher gametocyte densities tends to higher infectiousness, submicroscopic gametocyte levels still efficiently transmits parasites to mosquitoes (74,75).

Deletions in *P. falciparum* Histidine-Rich Protein 2 and Protein 3 Genes:

The majority of rapid malaria testing for *P. falciparum* leverages the detection of histidine-rich protein 2 (68), a biomolecule produced in prolific amounts during asexual stage growth, with highest numbers occurring during the ring stage, and reduced accumulation during trophozoite and schizont stages of development (76). Its implementation in malaria rapid diagnostic testing has transformed the malaria diagnosis landscape, allowing for a more rapid diagnosis in community surveys and in malaria-endemic regions with a poor health-care infrastructure (77).

The occurrence of *P. falciparum* HRP-2 gene deletions was first observed in 2010 in

Peru, where samples positive for microscopy but negative by malaria rapid diagnostic test (mRDT) were scrutinized (78). In the study by Gamboa et al., in 2010 (79), 41% of retrospectively tested samples lacked the HRP-2 gene, and 21.6% of the samples lacked the HRP-3 gene, a closely related gene to the former, that produces a protein of similar structure and shared epitopes (79). The deletions have since then been detected in other regions such as in Ghana (80), Ethiopia (81), Nigeria (82), and in other regions of the world (83–85).

Parasites that do not express the HRP-2 gene or having HRP-2/3 gene deletions undermine the effectiveness of the HRP-2 based rapid testing, and interfere with prompt diagnosis and treatment, which are essential elements in the malaria response and elimination race. As HRP-3 can still be detected in HRP-based mRDT assays, this protein provides some usefulness in testing. However, concomitant deletion of both genes in parasite strains worsens case detection and paralyzes the usefulness of rapid testing employing the histidine-rich proteins.

Climate change and vector expansion:

Climate change and global warming is believed to be a driving factor in vector expansion to regions they are traditionally not present. For malaria, this is true for *Anopheles stephensi*, originally native to the Indian subcontinent, parts of the Middle East and south Asia regions, but now found in Africa. *Anopheles stephensi*, a malaria vector primarily found in parts of Southeast Asia, the Arabian Peninsula and the Middle East has recently arrived in Africa, reversing previous gains in selected regions and threatening to worsen the malaria crisis in new parts.

The first report of *A. stephensi* in Africa was in Djibouti in 2012, where the vector triggered an epidemic of *P. falciparum* (86). Before the vector's invasion of Djibouti, malaria was at the verge of elimination in the country, with only 27 cases reported in 2012. However, with the two epidemics of malaria in the country, over 3000 cases were recorded between 2013 and 2014; in the early 2013 epidemic, 1228 cases were reported, and in a second more severe epidemic spanning from late 2013 to early 2014, over 2017 cases were reported (86). Since then, malaria cases have increased in the region (Fig 2), with over 73000 cases reported in 2020 (87), as well as recorded yearly deaths (68). Since 2012 when *A. stephensi* entered Africa, it has spread to other countries, notably Ethiopia, Sudan and Somalia (88–90), and more recently Nigeria (91) and Kenya (92).

In Ethiopia, invasion of the vector has been linked to at least one outbreak of the disease (93), and reports of insecticide resistance (pyrethroids, organophosphates and carbamates) in all regions (68,94,95). Although it is generally unclear and somewhat variable what the overall role of *A. stephensi* is to malaria transmission in some of these regions, the Ethiopia epidemic, and the identification of circumsporozoite proteins in female *A. stephensi* mosquitoes through vector surveillance studies have indicated blood feeding on humans and some role in malaria transmission (86,88,95,96). Furthermore, it is feared that due to the unique invasive properties of this vector and the rapid urbanization in Africa cities, the recent gains in malaria control efforts could be sabotaged (97–99).

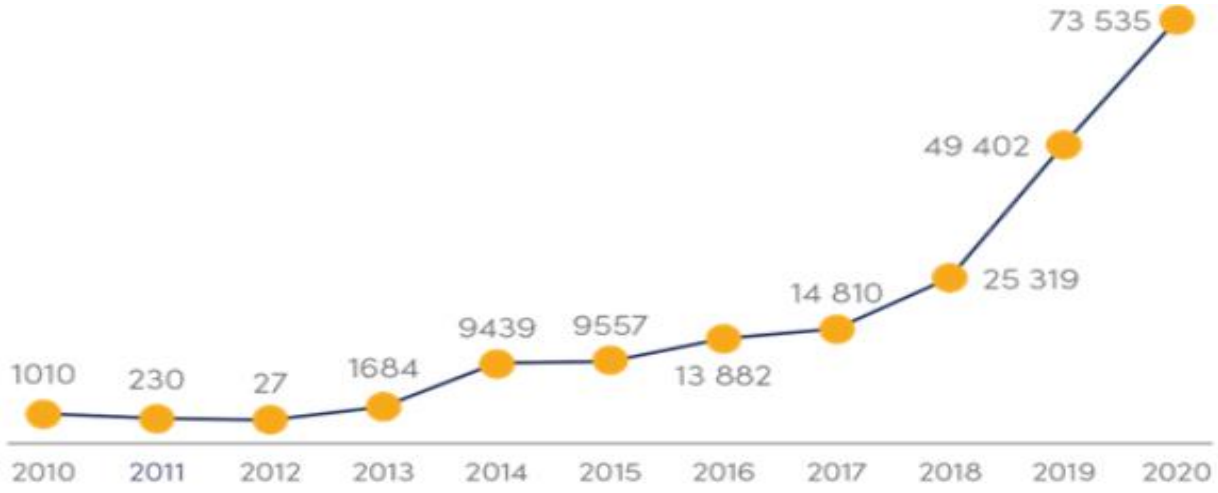

Fig 2: Impact of *Anopheles stephensi*'s invasion of Djibouti: From near elimination in 2012 to geometric increase in reported malaria through subsequent years [Source: WHO (116)]

Malaria control: Global targets and current efforts

Historical background of malaria control:

From the earliest times, malaria has been associated with stagnant water in swampy environments. In fact, the name "malaria" (*malaria*: Bad air) is the result of such association, when the Italians attributed the disease to the ill-smelling vapours from swamps (3). Although such attribution lacked precision, it reveals the appreciation of stagnant water as a factor in the cause of seasonal febrile illnesses, a distinctive feature of malaria. Ancient practices therefore included to a large degree, the control of malaria by draining/eliminating water from swamps, marshes, ponds or other body of stagnant water (2,100). This practice also occurred during warfare when soldiers fell to malaria (8), and still remains, as health education programmes often advice to clear and remove stagnant water around living premises, since these water enclosure serve as breeding sites for mosquito vectors.

As the etiology and lifecycle of the parasite were discovered in late 19th century, subsequent efforts in malaria control involved the use of larva-eliminating strategies and quinine administration in the early 20th Century, although quinine itself had been discovered earlier and used in the general treatment of intermittent fevers (4). The use of anti-larva strategies involved the larvicide Paris Green (copper acetoarsenite) and larvivorous fish (101).

In the 1950s, the WHO initiated the Global Malaria Elimination Programme (GMEP), which was intended to eradicate malaria globally (102). The initiative was based upon the discovery and the effectiveness of dichlorodiphenyltrichlorethane (DDT), an insecticide that found wide spread use during the World War II. However, the GMEP initiative failed to achieve its ultimate goal, although substantial malaria elimination was recorded in many countries. It came to an end in 1969, with the realization that sub-Saharan Africa, the seat of the malaria plague was not responsive to a large-scale eradication program such as GMEP (103). Moreover, due to a highly rigid approach, the use of a single elimination tool, and inadequate foresight and planning, the GMEP failed to deliver on its goal (102).

The next programme targeted towards malaria was the Roll Back Malaria (RBM) campaign, initiated in 1998 at the debut of Gro Brundtland's term as the Director-General of the World Health Organization (104). It was a joint effort of the WHO, United Nations International Children's Emergency Fund (UNICEF), the United Nations Development Programme (UNDP) and the World Bank (105), born in the face of the high burden of malaria in sub-Sahara Africa, a region that then accounted for 90 % of the global malaria mortality. The initiative had a goal to reduce malaria morbidity and mortality by half in 2010 (106), through resource mobilzation and concerted partner efforts (103). The campaign failed for a number of reasons; leader ship, inadequate funding and drug resistance, amongst others (105,107–109).

Current goals/objectives of the WHO and associated World Organizations:

When the RBM campaign came to an end, 10 years after it began, the key UN agencies involved converged to discuss and implement a wider and more robust strategy for malaria elimination, the Global Malaria Action Plan (GMAP) (110). The GMAP was a recommendation from the RMB board, and was developed based on agreement between all participating bodies, and the collective input of international institutions and experts (111). Key intervention strategies included prophylactic treatment for pregnant women, use of ACT, use of insecticide treated nets, and indoor insecticide spraying (110).

In 2015 during the 68th World Health Assembly (Geneva), key stakeholders endorsed the Global Technical Strategy for Malaria 2016–2030 (GTS), the current strategy that outlines current milestones and goals for malaria control. These goals, with an overarching aim to reduce disease burden and eliminate malaria, are closely linked to specific goals of the United Nation's Sustainable Development Goals.

World Health Organization Global Technical Strategy (GTS) for Malaria:

The Global Technical Strategy (GTS) of the WHO (112) for malaria is anchored on five principles targeted at reducing disease burden and ultimately eliminating and eradicating the disease. The first strategy focuses on the use of combined intervention approaches that are adapted to the local context; the second is focused on leadership and community participation; the third is surveillance, monitoring and evaluation; the fourth is equity of access to health services, particularly for the most vulnerable; the fifth is innovation in intervention tools and approaches. These principles are intended to guide implementation of the strategy to achieve its vision, goals and milestones. The vision is a world free of malaria.

Table 1: Goals, Milestones and Targets of the World Health Organization Global Technical Strategy

Goals	**Milestones**		**Targets**
	2020	**2025**	**2030**
To reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
To reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
To eliminate malaria in countries where it was transmitted in 2015	At least 10 countries	At least 25 countries	At least 35 countries
To prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

The goals, milestones and targets are highlighted as follows; (1) To reduce malaria mortality rates globally compared with 2015. The specific milestones are to reduce malaria mortality by at least 40% by 2020, and by at least 75% by 2025. The 2030 target is to reduce the mortality by at least 90%; (2) To reduce malaria case incidence globally compared with 2015. The specific milestones are to reduce malaria case incidence by at least 40% by 2020, and by at least 75% by 2025. The 2030 target is to reduce mortality by at least 90%; (3) To eliminate malaria from countries in which malaria was transmitted in 2015. The specific milestones are to eliminate malaria in at least 10 countries by 2020, and at least 20 countries by 2025. The 2030 target is to eliminate the disease in at least 25 countries; and (4) To prevent re-establishment of malaria in all countries that are malaria-free. The specific milestones and 2030 target are to prevent re-establishment of malaria in all malaria-free countries. Within the context of the WHO's goals, elimination is defined as the interruption of the local transmission of a specified malaria parasite in a defined geographical area because of deliberate activities. The goals and targets of the GTS are summarized in Table 1.

United Nation's Sustainable Development Goals:

The Sustainable Development Goals are a shared scheme of the United Nations that is geared towards development and cuts across various strata, including education, environment and ecosystems, economic development and gender equality. Included in this multifaceted scheme is also the healthcare infrastructure (113). The SDGs are composed of 17 goals, 169 targets and 248 indicators; Goal 3, target 3.3 specifically addresses the scourge of malaria and other infectious diseases. It aims by 2030 to *"…end the epidemics of AIDS, tuberculosis, malaria, neglected tropical disease and combat hepatitis, water-borne diseases, and other communicable diseases."* (113).

Ending the malaria epidemic is also indirectly targeted by other goals of the SDGs; for example, goals 1, 2, 6, 9 address poverty, hunger, clean water and sanitation, and climate change respectively. These also address the scourge of malaria. Concerted efforts by partners and agencies will help achieve this feat.

Current efforts in achieving global targets:

Surveillance and monitoring:

Surveillance for vector distribution, drug efficacy and parasite resistance patterns are key approaches in driving the current global targets. As the malaria parasite and their vectors keep evolving, studies on their distribution and biological characteristics will keep the scientific and global malaria community abreast of the newest trends and effective strategies in intervention programs. For WHO, vector surveillance should entail the continued assessment of vector species present in particular geographical locations, their abundance and seasonality. For example, surveillance studies helped identify *Anopheles stephensi* in Africa and particularly in Nigeria (91). *Anopheles stephensi* is an efficient malaria vector traditionally native to regions of South Asia and the Arabian Peninsula, but now spreading in parts of Africa (99,114). In addition, relevant vector binomics such as host preference, place and time of bite, indoor and outdoor biting preferences, and susceptibility to currently used insecticides are monitored (112).

Regular monitoring such as this is necessary to keep abreast of the dynamics of vector distribution and their potential to transmit dis-

ease. In the face of environmental changes, such as global warming, and rapid urbanization, the landscape of malaria epidemiology is likewise changing, and hence the need for continuous monitoring. The likelihood of renewed malaria transmission in "malaria-free" regions is now feared as a subtle possibility. For example, the US, which has not recorded any indigenous malaria transmission in the last two decades recently experienced incidence of malaria (115), thus reemphasizing the need for a continuous monitoring even in regions that have eliminated the disease.

The WHO in 2022 launched a strategic plan to address the menace of antimalarial drug resistance in Africa (68,116). This strategy is composed of three objectives: first, to facilitate the detection of antimalarial drug resistance thereby ensuring a timely response; second, to slow down the emergence of resistance to artemisinin and artemisinin combination therapy (ACT) partner drugs; and third, to reduce the evolution and spread of drug-resistant parasites where resistance has been confirmed (116). The overall goal is to minimize the threat and impact of antimalarial drug resistance due to *P. falciparum* in Africa. Further, four pillars are outlined in the strategy as the pivot for implementation of the objectives: Pillar I seeks to strengthen the surveillance of antimalarial drug efficacy and resistance; pillar II seeks to limit drug pressure through judicious use of malaria diagnostics and therapeutics; pillar III undertakes to limit the spread of antimalarial drug-resistant parasites; and pillar IV looks to stimulate research and innovation into the effective utilization of existing tools in the fight against resistance, as well as to develop novel tools.

Efforts in the surveillance of antimalarial drug resistance are often carried out through population-wide screening or as part of clinical trials. Nyunt *et al*., (2015), showed the presence of resistance in Myanmar, a malaria endemic area in the Greater Mekong subregion of Southeast Asia (117). The study revealed the diversity of *P. falciparum* antimalarial drug resistance genes among local residents in the study region. Mutations in *K13*, *pfarps10*, *pffd*, and *pfmdr2* were identified in the study. Further, mutations in the propeller region of K13 (C580Y) were associated with artemisinin resistance and delayed parasite clearance lasting more than 72 hours after drug administration. Similarly, the V127M, D195Y and T484I mutations were found in the *pfarps10*, *pffd*, and *pfmdr2* genes respectively. In other studies, mutations in *pfcrt* and *pfmdr1* genes were found to be associated with chloroquine resistance in malaria-endemic regions (59,118). In Northern Nigeria, polymorphisms in *pfmdr1* gene were associated with reduced sensitivity to the partner drug lumefantrine, a component of a key ACT drug adopted for use (119). This occurrence was corroborated in Southwest Nigeria, giving hints of parasite drug resistance due to single nucleotide polymorphisms (SNPs) in the *pfmdr1* gene (120).

Prompt diagnosis and treatment:

The WHO GTS (112) advises diagnosis of all suspected malaria cases before administering treatment. Diagnosis through quality-assured microscopy or rapid testing is advised to confirm malaria and thus reduce the over-use of ACTs and the possibility of parasite drug resistance. This practice will especially be useful in malaria endemic settings where a clinical presentation of fever is almost always presumed to be malaria.

Furthermore, prompt and effective treatment of confirmed cases will reduce morbidity and prevent disease progression. *P. vivax* and *P. ovale* spp. confirmed uncomplicated cases should receive a 14-day course of primaquine in addition to ACT, provided they are not pregnant women and are not glucose-6-phosphate dehydrogenase (G6PD) deficient. Parenteral administration of artesunate or artemether should be done in complicated malaria cases, followed by an oral course of ACT. In all treatment cases, oral based monotherapy is discouraged. Intermittent preventive treatment (IPT) of malaria is recommended for pregnant women and infants as these groups are especially vulnerable to malaria. Chemoprophylaxis is likewise recommended for travelers who visit areas of malaria transmission.

Research and development:

Research and development are ongoing for several innovative applications in malaria prophylaxis, diagnosis, and treatment. These include procedures that detect G6PD deficiency to guide primaquine-administered radical cure, vaccines for the most vulnerable, HRP-2 RDT alternatives, and new drugs, among others. In October 2021, the WHO approved use of the RTS,S malaria vaccine for children in moderate to high malaria transmission areas (121). The RTS,S malaria vaccine is an effort of 30 years of research and development by GlaxoSmithKline, supported by various partners. The vaccine roll out is approved for children from 5 months of age, to be received in four doses (122). In addition, the R21/Matrix-M malaria vaccine with over 75% efficacy was recently approved for use in Nigeria (123).

Hemozoin-based assays for diagnosis of malaria are underway with several field tests

carried out (124,125), although none has reached full scale implementation. Similarly, other applications such as saliva and urine-based specimens are currently being explored for the non-invasive diagnosis of malaria (126,127).

New bioactive agents for the treatment of malaria are also in development to cushion the effect of widespread resistance to currently available drugs. Some of these combinations have been dubbed 'Next-generation antimalarials', and include novel products exploring new mechanisms of anti-plasmodial action, and others to be used in combination with current partner drugs. The most currently advanced Next-generation antimalarial agent is the Ganaplacide-lumefantrine combination, which was found to be effective and well tolerated in adult and adolescent patients with uncomplicated *P. falciparum*, following a phase 2 trial (128). In addition, Cipargamin is a phase 2 clinical trial drug that disrupts parasite sodium homeostasis by interfering with the *P. falciparum* ATPase4 (129).

Another Next-generation agent is the M5717-pyronaridine combination which explores the anti-hemozoin activity of pyronaridine, and protein synthesis inhibitory activity of M5717 to achieve anti-plasmodial activity. While pyronaridine (Pyramax) is currently approved for use in an antimalarial regimen, M5717 is a novel agent that targets elongation factor 2 in the protein synthesis pathway of the parasite (130). The M5717-pyronaridine combination is nearing phase 2 clinical trial. Furthermore, adenosine sulfamates, a novel class of nucleoside analogs that inhibit the tyrosine tRNA synthase of the parasite are in preclinical development (131,132). Concerted efforts by the research community, donors and partner agencies will be needed to accelerate research and development towards achieving the 2030 goals of the WHO and associated world organizations.

Contributions of authors:

AEA, FSA and OOA conceptualized the study, AEA reviewed the literature, AVO reviewed the draft, FSA supervised and reviewed the final draft. All authors approved the manuscript submitted for publication.

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