UNMASKING THE INDIAN BURDEN OF MALARIA: A REVIEW ON COMPREHENSIVE APPROACH TO ELIMINATE PROTOZOA

Abstract

The military hospital in Constantine, where Laveran discovered the malaria parasite in 1880. Since then, the eradication process has been in operation. There were many developments, from quinine to vaccines, but malaria symptoms still exist, including fever, chills, headache, muscle aches, and fatigue. It can lead to organ failure, seizures, coma, and even death in severe cases. Therefore, depth study must require. We aimed to investigate the impact of malaria control programs on the prevalence of Malaria in endemic regions. The systematic review and cross-sectional study will provide valuable information on the effectiveness of different malaria control strategies and the factors influencing the success of such programs. The study's findings may lead to the development more effective and sustainable malaria control programs in endemic regions. It was also observed that the treatment for Malaria involves a combination of antimalarial drugs. However, drug resistance has become a significant problem in some parts of the world, making treatment more difficult and increasing the risk of death. In addition, enzyme deficiency and abnormal genetic expression are attributed to rising Malaria.

Keywords: Malaria, Acute kidney failure, Seizure, Drug resistance, herp-2/herp-3

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I. INTRODUCTION

The history of malaria outbreaks is believed to go back to the beginnings of civilization. It is the most widespread disease due to which many people have lost lives and is even thought to have been the cause of major military defeats and the disappearance of some nations. Early Chinese medical records from 2700 BC and the Ebers Papyrus, written 1200 years later, provide the earliest descriptions of malaria. Hippocrates, who lived in the fourth century BC, described this illness that finally disregarded its demonic roots and connected it to the evaporation from wetlands, which, when breathed in, led to the infection. This idea persisted until Laveran identified the disease's origin in 1880. In the blood of malaria victims, Laveran, a French military surgeon, initially observed parasites. For this discovery, he was awarded the Nobel Prize in 1907. The most common disease in Africa, according to Cartwright and Biddis, is malaria. A tiny protozoon that belongs to the Plasmodium species group and has multiple subspecies is the primary cause of malaria.

The Plasmodium parasite, which threatens human life, spreads to humans through female Anopheles mosquito bites. Malaria's clinical manifestations might be anything from asymptomatic to severe and life-threatening(Rahman and Ul, 2019). Today's emergence of malaria is observed due to mutation in parasitic genes, abnormality in enzymes, and drug resistance. These became the talk of the town, and most scientists were trying to find alternative treatments for treating malaria. The most typical signs and symptoms include fever, headache, and flu-like symptoms such as nausea, vomiting, and muscular aches. In extreme circumstances, the patient may experience problems such as cerebral Malaria, anaemia, kidney failure, respiratory distress, and in the worst cases, death. Therefore, the plan strongly emphasises interventions such as indoor residual spraying (IRS), insecticide-treated bed nets (ITN), and early diagnosis and treatment of malaria cases. Malaria is the most serious and harmful of all parasitic human diseases. Additionally, Malaria during pregnancy is linked to anaemia, low birth weight, maternal and foetal deaths, and patients with HIV/AIDS are particularly at risk. Other vulnerable groups include migrants, mobile communities, and travellers who visit areas with high malaria transmission rates and who have not yet partially recovered from the disease after prolonged exposure to it or are not taking chemopreventive medications. Currently, four types of treatmentare recommended for Malaria:ITN, Larvicides, small molecules, vaccines, and naturally obtained drugs. Bed nets are readily available, a physical barrier between men and parasites. Utilising bed nets treated with pesticidesas a vector control measure(Singhal et al., 2022). For more than 20 years, the impact of pyrethroid resistance on managing Malaria has been a major issue. The evidence of control failure caused by physiological resistance against ITNs is varied, despite the rapid and predicted growth of resistance in response to the widespread deployment of ITNs. Numerous laboratory and semi-field studies show that ITNs have a less immediate impact on resistant mosquito populations' death and blood feeding than susceptible populations(Talipouo et al., 2019). The use of larvicidesis as older as civilisation. Larvicides either may come from natural or synthetic sources. Additionally, Plants, bacteria, algae, lichen, and fungi are frequently sought-after sources of larvicides (Milugo et al., 2021).There were many antimalarial studies have been carried out using isolated compounds of plants such as Quinine from *Cinchona officinalis*[2], (2,4-dihydroxy phenyl)-3-[8-hydroxy-2-methyl-2-(4-methyl-3- pentenyl)-2H-1-benzopyran-5-yl]-1-propanone from *Artocarpus altilis*[3], Naphthoquinone from*Daldiniaconcentrica*[4], Kozupeptins A and B from *Paracamarosporium sp*.[5], Diterpenoids from *Andrographis paniculata*[6],

Strasseriolidesfrom the Fungus *Strasseriageniculata* [7], Norcaesalpin D from *Caesalpinia bonducella*[8], Xanthone from *Andrographis paniculata*[9], Conessine from*Holarrhenaantidysenterica*[10], Aspidoscarpine from*Aspidospermaolivaceum*[11], Gymnemagenol from *Gymnemasylvestre*[12], Cedrol from *Cyperus rotundus*[13], Guaianolide sesquiterpene lactones from *Artemisia afra*[14], Cassane, and Norcassane from *Caesalpinia crista*[15], Jacaranone from *Pentacaliadesiderabilis* [16], Dehydrobrachylaenolide from *Dicomaanomala*[17], Halogenated Compounds from *Halimeda macroloba* Seaweed[18], Aristolochic acids isolated from *Aristolochia indica* Linn[19], Atalaphillinine from Citrus, Glycosmis, or Severinia plants[20], 2β, 3β, 19α-trihydroxy-urs-12-en-28-oic acid from *Kigelia Africana* [21], Sesquiterpene artemisinin from *Artemisia annua* L [22].Conversely, Larvicides are increasingly a preferred substitute due to mosquitoes' extensive tolerance to them and their detrimental impact on non-target creatures and the environment(Santhoshkumar et al., 2011b). Small-molecule drugs include endoperoxides, 4-aminoquinolines, and amino alcohols (Plouffe et al., 2016). Uncovered chemicals consistently exhibited weak transmission-blocking efficacy at the nanomolar level and cross-reactivity with asexual blood and liver stages. Vaccines are antigenic preparation containing weak and inactivated microorganisms, including RTS, s/as01 vaccine, r21, viral-vectored vaccine, celtos, whole sporozoite vaccines, pfspz with chemoprophylaxis, radiation attenuated sporozoites, genetically-attenuated parasites, immune responses help apparent plasmodium infection in the liver to prevent the onset of blood-stage Malaria, the possibility of developing a clinically applicable, highly effective, conventional subunit vaccine against Malaria appears less likely. Although live-attenuated vaccination strategies show the most potential for eliciting protective immune responses(Marques-Da-silva et al., 2020)and naturally obtained plant-based phytochemicals alkaloids, including terpenoids, indole, bisindole, quinolone, and isoquinoline alkaloids, were identified with promising antimalarial activity (Oladeji et al., 2020). However, the malaria problem has not entirely been resolved in the nation. Numerous factors contributed to this, such as the quick changes in metropolitan areas' lifestyles and the unexpected, rapid influx of people. Additionally, bed nets' effectiveness is hindered by several factors, including vector resistance, drug resistance, poor efficacy, and water harvesting. Our study aimed to thoroughly evaluate the literature on the effect of malaria control programmes on malaria incidence in endemic regions. Therefore, we highlighted neglected malaria causes, their assessments, and recommendations for complete recovery from protozoal transmission and related complications.

II. THE LIFE CYCLE OF MALARIA

The life cycle of *Plasmodium* parasites involves asexual as well as sexualreplication that is linked to an obligatehost change from a human intermediatehost to a female mosquito of the genus *Anopheles* as the finalhost.Plasmodium parasites must infect and inhabit multiple cell types during this complex life cycle to ensure developmentalstage progression and progeny production.The erythrocyticschizogony, which occurs within the erythrocytes ofthe human host, involves a sophisticated reorganization of theterminally differentiated and metabolically reduced host cell inthe process of securing nutrient supply from haemoglobin digestionas well as blood serum uptake, removal of toxic waste,protection against the host immune response, and life cycleprogression.During schizogony, *P. falciparum* establishes the Maurer'sclefts. This secretory organelle resides outside the parasite'scellular boundaries within the erythrocyte cytoplasm to facilitate host-parasite interaction and sequestration to avoid splenicclearance of the infected erythrocyte.Seclusion is eitherachieved via

cytoadherence of the infected erythrocyte to variousreceptors on the surface of vascular endothelial cells in the postcapillary venules of different organs or via resetting infected erythrocytes with uninfected erythrocytes.Thecytoadherence of *P. falciparum*-parasitized erythrocytes is establishedby members of the diverse *var* multigene family encodingseveral different versions of *P. falciparum* erythrocyte membraneprotein 1 (PfEMP1), which are exclusively expressed in *P. falciparum*and presented on knob-like protrusions on the erythrocyteplasma membrane.

III. THE BURDEN OF MALARIA IN INDIAN STATES

According to the latest National Vector Borne Disease Control Program (NVBDCP) report, around 3,38494malaria cases in 2019;1,86532 malaria cases in 2020; 1,61753 malaria cases in 2021; 1,73975 malaria cases in 2022;20384 malaria cases were reported till march, 2023in India. The highest burden of the disease is ina few central and north-eastern states. Odisha, Chhattisgarh, Mizoram, AndhraPradesh, Tripura,West Bengal, Bihar, and Jharkhand reported the highest malaria cases in 2023. The NVBDCP has implemented several disease control measures, including surveillance, prevention, and treatment activities. They have also encouraged using insecticide-treated bed nets and indoor residual spraying of insecticides to control mosquito vectors(National Vector Born Control Programme, 2017).

Slno	States/UTs.	2019		2020		2021		2022		Till March 2023	
		Malaria Cases	Deaths	Malaria cases	Deaths	Malaria cases	Deaths	Malaria cases	Deaths	Malaria cases	Deaths
1	AndhraPradesh	3104	0	2027	0	1315	0	2019	0	467	0
2	ArunachalPradesh	139	0	33	0	8	0	17	0	0	0
3	Assam	1459	4	484	2	162	0	280	0	20	0
4	Bihar	1608	0	518	0	647	0	539	0	159	0
5	Chhattisgarh	60458	31	36667	34	29733	38	30028	11	7403	0
6	Goa	272	0	102	0	90	0	2	0	0	0
7	Gujarat	13883	1	4771	1	4921	0	4766	0	191	0
8	Haryana	1497	0	111	0	54	0	50	0	0	0
9	HimachalPradesh	109	0	34	0	15	0	10	0	0	0
10	Jharkhand	37133	2	16653	8	14198	0	19129	4	2153	0
11	Karnataka	3499	0	1701	1	913	2	279	0	17	0
12	Kerala	656	0	268	1	309	1	439	0	61	0
13	MadhyaPradesh	14147	3	6760	1	3181	2	3719	0	315	0
14	Maharashtra	8866	7	15215	12	19303	14	15437	25	1487	0

15	Manipur	16	0	36	2	19	0	14	0	3	0
16	Meghalaya	2615	4	2018	4	491	3	463	8	45	0
17	Mizoram	8543	8	7781	6	8018	10	10222	10	1111	0
18	Nagaland	20	0	12	0	8	0	8	0	1	0
19	Odisha	39556	9	41739	9	25503	13	23770	5	4534	0
20	Punjab	1139	0	109	0	71	0	109	0	0	0
21	Rajasthan	3421	1	1276	0	925	0	1026	0	17	0
22	Sikkim	7	0	4	0	4	0	6	0	0	0
23	TamilNadu	2088	0	891	0	772	0	344	0	59	0
24	Telangana	1711	0	870	0	874	0	611	0	67	0
25	Tripura	12437	1	3395	2	10136	4	12771	2	990	0
26	Uttar Pradesh	92732	0	28668	0	10792	0	7039	0	177	0
27	Uttarakhand	296	0	15	0	13	0	19	0	1	0
28	WestBengal	25928	6	14049	7	28987	3	40563	3	1101	0
29	AndamanAndNicobar Islands	202	0	85	2	27	0	46	0	5	0
30	Chandigarh	22	0	7	0	6	0	1	0	0	0
31	Delhi	713	0	135	1	167	0	173	0	0	0
32	JammuAndKashmir	105	0	37	0	31	0	37	0	0	0
33	Ladakh			0	0	0	0	0	0	0	0
34	Lakshadweep	11	0	6	0	1	0	0	0	0	0
35	Puducherry	21	0	15	0	5	0	0	0	0	0
36	The Dadra and NagarHaveliandDaman and Diu	81		40	0	54	0	39	0	0	0
	INDIA	338494	77	186532	93	161753	90	173975	68	20384	0

IV. TRANSMISSION OF MALARIA

The primary etiological factor in malaria deaths is *Plasmodium falciparum* (Pf). Pf is an obligate intracellular parasite of disease-causing erythrocytes and hepatocytes. These lead to numerous disorders that might result in mortality from infection, includingCerebral Malaria and severe anaemia. In erythrocytes, Pf continually replicates during 48 hours, causing exponential growth and a rapid spread of the disease. Pf is the most significant infectious disease affecting children. Due to this, fast diagnostic procedures based on the detection of hrp2 are unable to detect the parasites. In addition, the primary treatment for Pf infections, Artemisinin, is now partially resistant tomutations in *pfkelch13*(Fahad et al., 2021).Unfortunately, their extensive and occasionally ineffective usage has supported the emergence and spread of Pf parasites resistant to drugs. As a result, multidrug resistance (MDR) exists inMalaria again. However, slower parasite clearance rates in treated patients result from the emergence of Artemisinin resistance (Duffey et al., 2021).

The most prevalent human malaria parasite, *Plasmodium vivax* (Pv), puts 2.5 billion people at risk of contracting the disease. The Duffy antigen is required for Pv to infect red blood cells. People who do not express the Duffy antigen are regarded as resistant to Pv infection. As a result, the prevalence of Duffy's negativity is considered on the Pv global map as a proxy for the population immune to disease. PvMalaria has traditionally been considered benign; after an acute infection, a nonimmune person with high Pv relapse periodicity can experience recurrent malaria episodes on average once a month for more than a year. The cumulative risk of anaemia is increased by repeated malaria cases and consequent parasite-induced hemolysis, especially in young and malnourished children. As haemoglobin levels drop, the danger of death increases. Concomitant diseases like pneumonia and diarrhoea make the situation even worse. Recurrent Pv malaria during pregnancy is linked to miscarriage, early delivery, stillbirth, and low birth weight (Id et al., 2019). Radical cure treatment is the therapeutic protocol that aims to eradicate Pv in blood and liver stages. This therapy combines an 8-aminoquinoline, the only hypnozoiticidal medication class currently available, with a schizonticidal drug, frequently chloroquine (CQ) or Artemisinin-based combination therapy (ACT). The world health organisation (WHO) suggests giving PQ at a total dose of 3.5 mg/kg (210 mg for adults) or 7 mg/kg (420 mg for adults) for temperate strains. Two significant issues complicate PQ management. First, poor adherence is caused by the total dose being provided over a lengthy 7–14-day period, or even eight–weeks. The range of PQ treatment non-adherence is 2 to 40%. Lack of an immediate benefit, a poor awareness of the long-term advantages for the person and the community, and the misconception that vivax malaria is a benign illness are other reasons that contribute to non-adherence. Providers and patients are concerned about potential adverse effects, especially the risk of severe hemolysis in people with underlying glucose 6-phosphate dehydrogenase (G6PD) deficiency(Rahi and Sharma, 2022).

Stevens first described the *Plasmodium ovale* malaria parasite in 1922. OvaleMalaria, which is rare, has a mild clinical presentation and is easily treated with chloroquine-based conventional antimalarial medication. Therefore, it has received little attention since then(Kotepui et al., 2020). However, according to the researcher, 5.3% of *P. ovale* patients suffered severe sequelae, including hyperbilirubinemia, pulmonary oedema, shock, considerable bleeding, and decreased awareness, according to the most recent study on severe *P. ovale* malaria in travellers and migrants. Additionally, a separate set of primers (np-2002

primers) were used to detect *P. ovale* in some of these samples. These primers were created to overcome the presence of polymorphisms in the *P. ovals'*ssrRNA gene that would have reduced the effectiveness of the detection process. According to recent sequence research, the *Plasmodium ovale*Curtisi and *Plasmodium ovale*wallikeri are the two nonrecombining species that comprise most of the P. ovale spp.

Patients with *P. Malariae* infection may experience multiple convulsions, acute renal injury, and Malaria in the brain. Patients with *P. Malariae* infection most frequently experience severe anaemia, lung involvement, and renal impairment sufferers of *P. Malariae*(Singh et al., 2022). Pixel export signal, signal peptide, transmembrane domains, and a variable region are features of proteins that are likely exported from the parasite to the surface of infected red blood cells in the proteins produced by fam-l and fam-m. Most fam-l and fam-m genes also occur as doublets and face the telomeres. Additionally, a trait not previously observed in subtelomeric gene families in other plasmodium species is the ability of the proteins produced by the fam-l and fam-m genes to form heterodimers(Kapishnikov et al., 2019).

V. THE REASON BEHIND MALARIA

1. **Failure of RDT Test and Deletion of hrp2/ hrp3 Gene:** Rapid diagnostic tests (RDT) are crucial for managing malaria cases. Since they were first created in the 1990s, RDT usage has increased significantly. RDTs are employed in 90 countries with high malaria incidence in the public healthcare system. However, there have been reports of deletions of pfhrp2 and pfhrp3 in populations from Peru, Mali, India, and one clinical case from Brazil, among other probable reasons for erroneous RDT unfavourable results (Jejaw Zeleke et al., 2022).

   A single subtelomeric copy of the gene encoding the protein Hrp2 can be found on chromosome 8 of the Pfgenome. Pf only makes this protein; its amino acid sequence contains 34% histidine, 37% alanine, and 10% aspartic acid. Pfhrp2 is a water-soluble, 60–105 kDa, a surface-associated protein synthesised and maintained throughout the asexual life cycle (the gene has a 1073 pb). The parasite discharges this protein into the cytoplasm of red blood cells (RBCs), and infected people also have it circulating in their peripheral blood. Hrp2 is one of the RBC cytosolic components released into the bloodstream once parasites burst from the host cell. HRP2 can be as high as 100 g/ml in plasma. Since its discovery, it has been implicated in a wide range of processes, including the crystallisation of hemozoin, the production of actin, the suppression of t-cells, the binding of glycosaminoglycans, and pro-coagulation. Pfhrp-2, in contrast, is located in the parasite cytoplasm or digesting vacuole and is essential to Pfmetabolism. Additionally, this protein actively promotes the polymerisation of the toxic heme group, produced when the host's haemoglobin breaks down, into the malaria pigment hemozoin, which is no longer dangerous(Poti et al., 2020).

   The histidine-3-rich protein (hrp3), also known as the tiny histidine-rich protein, is encoded by the pfhrp-3 gene, which is present in the non-telomeric region of chromosome 13. 30-35 kDa polypeptide Pfhrp3 contains 29% alanine and 30% histidine. Two sections in the core protein-coding region contain tandem repeats, and these two regions are separated by a 72-nucleotide stretch devoid of repeats. What function this

protein plays in the parasite's survival is unclear. Pfhrp-3 and pfhrp-2 are structurally and functionally very similar. Exon 1 of both contains a peptide that serves as a signal, and exon 2 encodes histidine-rich amino acid sequences ranging from 75 to 90 nucleotides(Jejaw Zeleke et al., 2022).

2. **A suitable environment for Protozoa:** In India, there are more than 400 tiny rivers and eight big rivers. The disease primarily affects rural and tribal populations in the nation because there are many locations where water stagnates during the rainy season, including ponds, ditches, marshy areas, seepage water that serves as a temporary mosquito breeding ground, as well as some permanent water bodies like rivers, river beds, pools, rice fields, lakes, and agricultural channels, except for Himalayan regions where drinking water is produced from harvested rainwater. The potential for malaria parasite growth in rainwater collected and held for many days. India features a variety of climates, including dry and wet, high and low altitudes, plains, and hills. Many people dieyearly from poor access to clean drinking water, but other areas of India lose people to floods and their associated consequences. It was seen that rainfall was harvested in hilly locations. This water source is the cause of many parasites that live in water, particularly anopheles mosquitoes. Additionally, this increases the public's exposure to Malaria. Indian railway and irrigation system development was linked to the spread of Malaria. Many breeding sites for malaria vectors were created during the construction of railway embankments, and workers from various sections of the nation likely brought different parasite strains to the locations where they worked. A few homes are also crucial in providing mosquitoes a comfortable resting place. Most structures in rural regions are thatched or made of mud, which the mosquitoes prefer since it allows for the right temperature and humidity. Homes were typically constructed near ponds and lakes, where mosquito breeding was prolific, and hosts were readily available for the insects consuming blood. These were the leading causes of the rise in malaria cases then. In India, the tribal tribes that live in remote, forested areas endure a disproportionately large burden of Malaria. They cannot protect themselves from mosquito bites because they lack adequate housing.

3. **Parasite Resistance to Antimalarial Drugs:** The world health organisation (WHO) defines antimalarial drug resistance as the capacity of a parasite strain to persist and proliferate despite the administration and absorption of medication given in doses equal to or higher than those typically advised but within the subject's tolerance, provided drug exposure at the site of action is sufficient. Due to the selection of parasites with genetic mutations or gene amplifications that limit susceptibility, antimalarial resistance develops (Belete, 2020).Antimalarials with an artemisinin basis are the cornerstone of effective pharmacological therapy. However, eliminating Malaria is a race against time due to the risk of losing its effectiveness. In 2013, artesunate-sulfadoxine-pyrimethamine (ASP) was replaced with artemether-lumefantrine (al) due to the discovery of highly resistant parasite isolates against sulfadoxine-pyrimethamine (SP) in India(Hemming-Schroeder et al., 2018). Recent research has indicated that SP resistance may be increasing. Except in India's north-eastern states, SP is the companion medicine in the widely used ACT AS-SP. As a result of the accumulation of resistance mutations, the durability of the ACT AS-SP in India is uncertain. The first report of chloroquine-resistant Pv came from Papua New Guinea in 1989. In regions like Indonesia and Oceania, considered the epicentres of chloroquine resistance, high-grade chloroquine-resistant Pv is standard. Combining

4. chloroquine and primaquine can prevent acute sickness and hypnozoite relapses. Primaquine is effective against blood and liver stages and against strains resistant to chloroquine. Acute lung injury, pulmonary oedema, splenic rupture, acute renal failure, severe anaemia, severe thrombocytopenia, with or without bleeding from various parts of the body, severe hepatic dysfunction, and status epilepticus are all possible outcomes of severe Pv infections(Forte et al., 2021).

Antimalarial drug	**Protozoa**	**Mechanism**	**Site of action**	**Mechanism of resistance**	**Citation**
Chloroquine, Amodiaquine, Piperaquine, Mefloquine, quinine, quinidine	Plasmodium spp.	It accumulates in the digestive vacuoles of the parasite and inhibits the polymerization of toxic heme molecules in the infected blood cells from the haemoglobin breakdown; the accumulation of thisheme molecule causes damage to the parasite and leads to its death.	Digestive vacuoles	Mutations in the gene encoding the P. Falciparum chloroquine resistance transporter (pfcrt). Mutations in other genes, such as the multidrug resistance gene 1 (mdr1)	(Silva et al., 2020), (Li et al., 2020), (Imwong et al., 2020).
Proguanil, pyrimethamine	Plasmodium spp.	The metabolite cycloguanil inhibits the enzyme dihydrofolate reductase, disrupting the parasite's ability to replicate and survive.	Cytosol	Genetic mutation in the parasite's dihydrofolate reductase enzyme.	(Hemming-Schroeder et al., 2018)
Primaquine, Tafenoquine	Plasmodium vivax, plasmodium ovale	It interferes with the metabolism of the malarial parasite, and its active metabolite	Hepatocyte (hypnozoites)	Mutations in the parasite's genes involved in drug metabolism and	(Llanos-Cuentas et al., 2022)

		generates oxidative species causing oxidative damage and destruction of the parasite's cellular components.		detoxification, such as the cytochrome P450 enzymes	
Sulfadoxine		It acts as a competitive inhibitor of the dihydropteroate synthase enzyme, thereby preventing folate production and inhibiting the parasite's growth and replication.	Cytosol	Genetic mutations in the dihydropteroate synthase (DHPS) enzyme of the parasite	(Hemming-Schroeder et al., 2018)
Dapsone	Plasmodium spp.	Inhibition of dihydropteroate synthase alters folate metabolism and impairs the parasite's ability to synthesize DNA and essential cellular components.	Cytosol	Point mutations in the dihydropteroate synthase (DHPS) Enzyme	(Bucher et al., 1997)
Atovaquone	Plasmodium spp.	Inhibition of the mitochondrial electron transport chain of the malaria parasite.	Mitochondria	The development of mutations in the parasite's cytochrome b gene reduces the drug's binding affinity and effectiveness.	(Rocamora et al., 2021)
Artesunate, Artemisinin	Plasmodium spp.	It converts into an	Endoplasmi	Mutations in the	(Saito et al., 2020)

		active metabolite within the parasite, which interacts with the heme and leads to the generation of reactive oxygen species, which causes damage to the parasite's proteins, membranes and other cellular components as well as disruption of calcium homeostasis, thereby causing the death of the parasite.	c reticulum	parasite's kelch13 gene and altered drug uptake and metabolism	
Lumifrantine	Plasmodium spp.	It interferes with the function of the parasite's mitochondria, leading to disruption of ATP synthesis and subsequent inhibition of protein synthesis and parasite growth.	Mitochondria	Mutations in the P. Falciparum multidrug resistance 1 (pfmdr1) gene	(Skyler et al., 2017), (Ecker et al., 2012)
Pyronaridine	Plasmodium falciparum and Plasmodium vivax	It inhibits the heme detoxification process in the malaria parasite. In addition, Pyronaridine interacts with heme released during haemoglobin digestion by the parasite and prevents		The exact mechanisms of resistance are not well-defined but may involve mutations in the parasite's drug target or alterations in	(Li et al., 2020)

		its conversion into hemozoin, a non-toxic crystalline form. As a result, the accumulation of toxic heme molecules within the parasite leads to its death.		drug transport or metabolism.	
Doxycycline	Plasmodium spp.	It disrupts protein synthesis in Plasmodium Parasites, inhibiting their growth and replication.	Ribosome	Mutation in the protozoan ribosomal subunits alters the drug's binding affinity.	(Lago et al., 2020)
Clindamycin	Plasmodium spp.	It specifically acts on the mitochondrial protein synthesis machinery of the parasite, leading to impaired protein synthesis within the organelle and subsequent parasite death.	Ribosome	Alterations in the drug's target site (ribosomal subunit) or the acquisition of enzymes that modify or inactivate the drug.	(“Current World Literature,” 2003)

5. **Enzyme Deficiency:** G6PD is a hereditary, x-linked enzymatic disease caused by single nucleotide polymorphismsthat impair the regular operation of the G6PD enzyme. Glucose-6-phosphate dehydrogenase is an enzyme that works in the pentose monophosphate pathway. Red blood cells may prematurely oxidise due to a deficiency of the G6PD enzyme.Lack of this enzyme results in hemolysis, which causes oxidative damage to red blood cells brought on by free radicals. This affects 400 million people worldwide. There are 13 exons and 12 introns in the gene on the x chromosome that codes for the G6PD protein. Approximately 160 highly polymorphic DNA-level variations in this gene may be connected to G6PD deficiency(Lo et al., 2019). Somedrugs, such as primaquine, dapsone, sulfonamides, quinolones, chloramphenicol, nitrofurantoin (antibiotics), and phenazopyridine (analgesics), have been described as the hemolytic trigger that causes a

6. hemolytic crisis in G6PD-deficient individuals(Vanaerschot et al., 2020).Antimalarial medications known as 8-aminoquinolines, such as primaquine and tafenoquine, can severely hemolysis those deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). In malaria-endemic regions, females with intermediate G6PD activity (70% enzymatic activity) should be avoided (Commons et al., 2020). However, the requirement for a quantitative test currently prevents widespread diagnosis of G6PD deficiency at the more conservative threshold required for prescribing Tafenoquine(Llanos-Cuentas et al., 2022).

7. Vector Resistance: In India, pyrethroids, the family of insecticides used on all long-lasting insecticidal nets, are particularly resistant to the anopheles mosquito. As a result, vector control is a necessary component of any effort to combat the disease conveyed by Anopheles mosquitoes. The main strategies for managing resistance are (i) Annual rotation of insecticides with various modes of action, (ii) Combining pyrethroid-based ITN and IRS with non-pyrethroids, (iii) Mosaic spraying of two different insecticide classes in various locations, and (iv) combining various insecticide classes into a single product(Matowo et al., 2020a). In addition, the world's commitment to eradicating Malaria by 2030 necessitates immediate action, including developing combined and efficient control products like organochlorine (DDT) and organophosphate (malathion) and synthetic pyrethroids; impregnated bednets are treated with deltamethrin and alpha-cypermethrin. Following the worldwide plan for insecticide resistance management (IRM), several Asian nations are implementing an IRM approach against malaria vectors, which includes management strategies for choosing insecticides, utilising a rotation system during field interventions, routinely monitoring, and integrating(Edwards et al., 2019).

The cornerstones of India's and other nations' vector control methods against Malaria are ITN and IRS(Milugo et al., 2021). The IRS targets indoor resting (endophilic) mosquitoes, and the ITN only offers protection from mosquito bites at night when a person sleeps beneath the net. There is a warning for more zoophilic, oesophageal, and exophilic vectors because both vector control methods only affect anthropophilic, endophytic mosquitoes. In India, outdoor biting during the early evening hours when people are unprotected by a bednet and residual spray can encourage persistent/residual Malaria. Additionally, mosquito behaviour changes over time due to evolutionary processes such as behavioural plasticity, protective behaviour, and behavioristic resistance. Studies have shown that when vectors rest in cattle sheds, their activity switches from indoor to outdoor resting. Like early biting, blood meal feeding before people sleep under the ITNs has been seen to avoid interaction with IRS. It is crucial to acknowledge the difficulty posed by the spread of malaria vectors to new regions(Milugo et al., 2021).

Mosquito exposure to public health insecticides is mainly blamed for insecticide resistance in malaria vectors. However, intense selection pressure is also exerted by agricultural pesticides, which helps explain why some vector species have developed resistance. This is due to the shared chemical properties, concurrent applications, and agricultural use of these chemicals without restriction. Higher insecticide tolerance in malaria vectors has also been linked to water exposure of

mosquito larvae to sub-lethal levels of pesticides, herbicides, and other pollutants. (Matowo et al., 2020b).

This earlier investigation also identified two promising substances, Imidacloprid and chlorpyrifos emulsifiable concentrate, for farm pest control and cereal preservation during storage. The WHO pesticide evaluation programmeendorsed the organophosphate chlorpyrifos for controlling immature mosquitoes and assessed it for net impregnation. In addition, Imidacloprid (neonicotinoids), a stimulator of the nicotinic acetylcholine receptor, is sometimes employed in combination with the widely-used pyrethroids. In mosquitoes, metabolic resistance is one of the primary mechanisms.It has been connected to the widespread application of pesticides in rice crops that get irrigation, facilitating the overproduction of detoxifying enzymes. Four CYP6P3 and one CYP325 cytochrome P450, two delta class GSTs, one peroxiredoxin, and two cuticular precursor genes were found to be overexpressed in adult mosquitoes, and this overexpression was reported to be influenced by the presence of xenobiotics and agricultural pesticides in the agroecological sites(Tangena et al., 2020).

8. Protozoal Manifestation of the Human

- Unrousable coma or cerebral Malaria is the most distinctive symptom of severe falciparum malaria. The main mechanisms of cerebral Malaria include the accumulation of immune cells and platelets, the sequestration of parasitised red blood cells in brain capillaries, the production of cytokines, and the release of microparticles. This leads to endothelial blood-brain barrier lesions, which cause brain injuries like oedema, ischemia, and haemorrhages. Any age can experience this symmetrical, widespread encephalopathy. People with low immunity are more likely to develop cerebral Malaria, and treatment options, access to critical care, and the level of accompanying significant organ failure all affect how severe it gets. Nearly half of the patients with coma and other organ dysfunction, such as renal impairment, pulmonary oedema, jaundice, metabolic acidosis, or hypoglycemia, also have cerebral Malaria. Additionally, even thoughmost kids fully recover, cerebral Malaria in kids is linked to severe neurodevelopmental aftereffects, including stroke, cognitive decline, and an elevated risk of epilepsy.

- Prolonged, repetitive, focused, and refractory seizures are linked to cerebral Malaria, and 18–47% remain subclinical. Because phenobarbital and benzodiazepines continue to be the effective treatment for seizures, respiratory suppression is a frequent side effect of both drugs and ventilatory support is typically not accessible; managing episodes can be difficult. Most malarial locations require some level of toleration for continuous seizure activity to workwith cerebral malaria-associated attacks because intensive phenobarbital treatment carries a risk of respiratory failure and mortality (Birbeck et al., 2019). In addition, the seizures are usually generalised and may herald a coma's onset.

- Potential causes of lactic acidosis and hyperlactatemia in malaria patients are explored. Lactic acidosis may be caused by increased lactate production and decreased lactate removal (Possemiers et al., 2021). Numerous processes, such as the metabolism of intraerythrocytic Plasmodium parasites, aerobic glycolysis by

stimulated immune cells, and an increase in anaerobic glycolysis in hypoxic cells and tissues as a result of parasite sequestration and anaemia, all contribute to the increased lactate production. Hyperlactatemia may worsen if there is impaired liver and kidney lactate clearance brought on by underlying liver and kidney illness. Unless it is caused by severe anaemia alone, in which case the prognosis is better, metabolic acidosis is a worrisome symptom in adults and children with severe Malaria. Acidosis due to Malaria is dependent on lactate buildup. Other organic acids, mainly from the stomach, also play a crucial role.

- Acute kidney injury (AKI) is one of the main risk factors for severe Malaria. Reduced renal function is a vital sign of severity in younger children, whereas AKI affects older children and adults almost exclusively and necessitates renal replacement treatment. The fulminant form of AKI is associated with a poor prognosis and is typically accompanied by multiple significant organ failures. Following renal replacement therapy, ideally hemofiltration or hemodialysis, survivors fully regain their renal function. The histological features of acute tubular necrosis, interstitial nephritis, and glomerulonephritis in malaria-related AKI are less common(Kumar et al., 2018).

- One of the traits of malaria infection is intravascular hemolysis, especially of red blood cells (pRBCs) infected with Plasmodium. This hemolysis produces host- and parasite-derived compounds, cell-free heme, and other substances that may result in inflammatory reactionssuch as parasite sequestration, microvascular dysfunction, endothelial activation, extensive intravascular hemolysis, and hemodynamic instability, leading to the exacerbation of a potent systemic inflammatory response on the kidneys, is the most likely mechanism by which severe causes the development of AKI (Katsoulis et al., 2021)

VI. RECOMMENDATION

Malaria should then be brought to the public's attention so that ongoing public health initiatives aimed at the proper use of bed nets, drainage of standing water, and increased public awareness about lowering the risk of insect bites can potentially reduce the prevalence of malaria and improve children's health. In order to reduce the incidence of malaria, the population should also practise good hygiene, sanitise their environments, and use water purifiers and clean water storage. Managing water Achieving malaria eradication requires multisectoral collaboration and methods that link environmental science and malaria control, such as conducting locally pertinent ecological monitoring, incorporating landscape data into malaria surveillance systems, and developing environmental management strategies to lessen malaria burdens. Along with rural development, an intelligent urbanisation policy must be implemented nationwide. In comparison to other times and scenarios during the century, the higher magnitude of change in species prevalence predicted for the latter half of the twenty-first century under the high emission scenario, driven primarily by increasing and fluctuating temperature, along with more extended seasonal tropical rainfall accompanied by drier phases and the inherent influence of rapid land use change, may lead to the more significant increase in malaria burden. It is always appreciated when malaria eradication policies are created at the district level. The government should implement preventative measures through the health department as malaria cases increase.Changes to therapies or treatments will result

from this. There is a limited understanding of how people in developing regions interact on social media during outbreaks and what valuable insights this dataset could offer during public health crises, even though government agencies and healthcare institutions in developed areas increasingly rely on social media to build epidemic forecasts and outbreak response. Demand for bed nets treated with insecticides will rise. The general public is urged to use insecticide-treated bed nets, which also serve as a physical barrier between humans and animals or protozoa. A schedule for immunisations should be developed; few recently introduced vaccinations were used in preclinical or clinical settings. Based on the high safety and effectiveness evidence from a pilot programme initiated in Ghana, Kenya, and Malawi, the WHO advised the first-ever malaria vaccine, RTS, S/AS01, for at-risk children. It will be a historic development for malaria prevention—at least for P falciparum malaria and child health—if a malaria vaccine is added to the regular schedule of childhood vaccinations. Community-focused malaria interventions should be suggested everywhere to ensure and increase access to the currently available tools among hard-to-reach communities, such as persons living and working in remote woods and the minority Indigenous populations.

VII. CONCLUSION

This review adds the prevalence of malaria-causing protozoa, their genetic expression, and their resistance tomedication. Our study also includes the aetiology behind Malaria,such as HERP 2/3 gene deletion suitable environment and vector resistance. However, we failed to highlight the cause of herp2/3, responsible for Malaria. Despite the novel medication and existing combination,people still suffer from malaria-associated acute kidney disease, anaemia, metabolic acidosis, and delayed chronic kidney ailments. Based on the review, our study concludes that severe health complications could be observed if Malaria is not eradicated in the coming days. To achieve malaria eradication, several strategies need to be implemented. The first step is to strengthen health systems in endemic countries to ensure that malaria cases are accurately diagnosed and treated quickly. This requires training health workers and improving laboratory facilities to diagnose malaria cases accurately.Another strategy is to implement vector control measures such as using insecticide-treated bed nets and indoor residual spraying to reduce the number of Anopheles mosquitoes that transmit the Plasmodium parasite. These interventions are effective in reducing malaria transmission in many settings.In addition, there is a need for effective antimalarial drugs that can cure the disease and prevent its transmission. Developingnew antimalarial medicines and vaccines is crucial for the success of malaria eradication efforts.Finally, community engagement and participation are essential for the success of malaria eradication efforts. This involves educating communities about malaria prevention and control measures and involving them in the planning and implementationof malaria control activities. Malaria remains a significant global health challenge, affecting millions yearly, particularly in sub-Saharan Africa. While efforts to combat the disease have progressed in recent years, much work remains to be done to prevent and treat Malaria effectively. Developing new and improved prevention and treatment strategies, combined with efforts to improve access to resources and education, is essential for reducing the burden of Malaria and improving public health worldwide. Governments, organisations, and individuals must continue to work together and invest in malaria control and elimination efforts to ensure a healthier, more prosperous future for all.

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