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A REVIEW ON MALARIA, CONTROL&CHALLENGE STRATEGIES

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ABSTRACT

In India accounts for about 70% of WHO's Southeast Asian malaria. More than 2 million cases, approx 1,000 deaths are reported annually from malaria, due to the recognition of many ecotypes paradigms of malaria, the risk of malaria transmission within the state is heterogeneous and variable.This latest report draws on data from 87 countries and territories with ongoing malaria transmission. The high-exposure population of 4,444 is a population living in forest areas such as Orissa, Jharkhand, Madhya Pradesh, Chhattisgarh, and northeastern states, and accounts for most of the morbidity and mortality of malaria. World Health Organization (WHO) reported that 229 million cases and 409 thousand deaths from malaria occurred in 2019. The pattern of clinical manifestations of severe malaria has also changed, with multiple organ failure more common in falciparum malaria, but there are reports of vivax malaria with severe symptoms.The reported estimated morbidity-mortality gap, it is necessary to estimate actual malaria. Artemisinin-based combination therapies (ACTs), are critical tools in reducing the global burden of malaria, Only 45% (99/221) of articles with therapeutic efficacy as a primary outcome and performing molecular correction reported corrected efficacy outcomes calculated in a way consistent with WHO recommendations. The World Health Organization carries out a malaria control program on a global scale, focusing on local strengthening of primary health care, early diagnosis of the disease, timely treatment, and disease prevention. Globally, the burden of malaria is lower than ten years ago. However, in the last few years, there has been an increase in the number of malaria cases around the world. In this review, discuss about the host immune response in malaria, analyzing the latest studies on the roles of pro- and anti-inflammatory cytokines. To achieve sustainable control over malaria, healthcare professionals will need a combination of new approaches and tools, and research will play a critical role in development of various novel strategies.

Keywords: - Malaria, Plasmodium Falciparum, Plasmodium vivax, WHO Resistance, Quinine,

1.INTRODUCTION

The term protozoal infectionsprings from the Italian malariameans ‘bad air’. Protozoal infection remains a heavy parasitic infection with high mortality rates **[1]**. Protozoal infection poses an excellent threat to public health, and concerning 50% ofworld population is in danger of plagued by malaria. Among the four Plasmodium species that cause malaria, Plasmodium falciparum is that the most dangerous and causes severe malaria **[2]**.Malaria could be a devastating parasitic infectious disease, particularly in desert African, components of Asia, and South America. Even ifmany efforts undertaken, nowadays, it is each of the foremost causes of morbidity and mortality, in the main in pregnant women and children. Consistent withthe World Health Organization (WHO) report in 2018, there have been 228 million protozoal infection cases and 405000 deaths within the world. The world’s population is in danger of malaria disease, most cases (93%), and deaths (94%) according in Africa. Concerninga hundred twenty five

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million pregnancies are at risk of malaria every year, and 272,000 youngsters aged lower than five years die because of malaria **[3]**. On thirtyGregorian calendar month 2021, the planet Health Organization declared that the People's Republic of China (PR China) had been certified protozoal infection-free **[4]**. When a field mission in PR China 2021 by freelance certification panel. This award of malaria-free certification could be a major milestone each for the planet history in malaria obliteration programmed and for the Chinese public health history. Protozoal infection is one in allthe highest3 infectious unwellnesss in terms of disease burden and impacts on the world population. Consistent withthe planetprotozoal infection Report, 229 million individuals had malaria and 409,000 people died of it in 2019**[5]**. On twenty one April, WHO printeda replacement report highlight successes and lessons learned among the "E-2020" cluster of protozoal infection-eliminating countries? Despite the challenges expose by the COVID-19 pandemic, varietyof those countries according zero endemic malaria cases in 2020, whereas others createdspectacular progress in their journey to changing into malaria-free. Before World protozoal infection Day, country leaders, frontline medical experts and international partners came alongin a very virtual forum continuedtwentyoneApril to share experiences and reflections on efforts to succeed in the target of zero malaria **[6]**.

1. ANTIMALARIAL DRUGS

Medicines have two important roles in the fight against malaria. First, rapid and effective treatment of malaria aims to prevent progression to severe disease and limit the growth of gametocytes, thereby preventing transmission to mosquitoes **[7]**. Second, drugs can be used to prevent malaria in endemic populations, including different strategies for chemoprevention, intermittent prophylaxis, and mass drug use**[8]**. Antimalarials are used to treat and prevent malaria infections. Most antimalarial drugs target the red blood cell stage of the malaria infection, which is the stage where the infection causes symptomatic disease. The level of pre-erythrocytic (liver stage) activity of most antimalarial drugs was not well characterized that emerged in Wuhan, China, in late 2019. It is a highly contagious disease spread with a global mean mortality rate of 4.6% **[9]**. This is due to the inhibitory effect of these two drugs on other coronaviruses, such as SARSCoV1 **[10,11]**. However, the results are contradictory **[12,13]**.

Currently available antimalarials are grouped into three main groups: quinoline derivatives, antifolates and artemisinin derivatives. Quinoline is the most widely used antimalarial agent to control malaria. Quinine, an alkaloid isolated from the bark of the Cinchona tree, was the first antimalarial agent used to manage the disease in the 17th century. Quinine is still used against severe malaria, often in combination with other antimalarial agentsto reduce treatment time and minimize side effects **[14, 15]**.

Chloroquine and quinine are the most studied antimalarials because of their ease of preparation, good pharmacokinetic properties, and low toxicity and side effects**[2]**. Although promising structural analogues such as isoquine have received much attention, the limited number of systematic synthetic methods to diversify the 4-aminoquinoline may have hindered the development of new drugs **[1]**.

2. DRUG REPORTED WITH HIGH EFFICACY

Artemisinin and its derivatives**,** Amodiaquine**,** Piperaquine**,** Lumefantrine**,** Lumefantrine**,** Tafenoquine **[16]**.The current literatures evident that molecules containing urea and thiourea pharmacophoresare potent inhibitors of human DNA-topoisomerase II and active against various cancer cells **[17,18,19]**.

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3.CLASSIFICATION OF ANTIMALARIAL DRUGS [20]

S. No.	Drug Name	Mechanism of Action	Use
1.	Chloroquine	Accumulate in the digestive vacuole of parasite inhibition of heme detoxification	Treatment in falciparaum infections where chloroquine remainsenstive
2.	Amodiaquine	Accumulate in the digestive vacuole of parasite inhibition of heme detoxification	Treatment of non-severe falciparum infections where chloroquine resistance has emerged
3.	Quinine	Accumulate in the digestive vacuole of parasiteinhibition of heme detoxification	Treatment of severe malaria and multidrug resistance falciparauminfections ,Treatment of malaria during pregnancy in the first trimester
4.	Mefloquine	Accumulate in the digestive vacuole of parasiteinhibition of heme detoxification	Treatment of non-severfalciparumwherechlorquineresistancehasemereged Chemoprophylaxis in regionwherechlorquine resistance
5.	Atovaquone	Targets the cytochrome, located in the inner mitrochondrial membrane of the parasite, inhibition of the respiratory reaction of parasite	Treatment of multidrug resistance falciparaum infections
6.	Sulfadoxine, Sulfene	Inhibit the dihydropteorate synthetase enzyme, inhibition of folate biosynthesis	Treatment of non-sever falciparum in combination with pyrimethamine
7.	Artimisinin	Inhibition of protein synthesis pathway	Combination with qunine increase efficacy of treatment where qunine resistance has emerged

5. LIFE CYCLE OF MALARIA PARASITES

The life cycle of the malaria parasite is extremely complex and requires the expression of specific proteins for the survival of invertebrate and vertebrate hosts. These proteins are required for both intracellular and extracellular survival, the entry of many cell types, and the avoidance of host immune responses. When injected into a human host, the sporophytes of falciparum P. and malariae P. cause immediate schizophrenia, while P. ovale. and vivax P. sporozoites can cause immediate schizophrenia or lead to delayed schizophrenia as they pass through the mentioned hypnozoite phase. The life cycle of the malaria parasite is shown in Figure 1 and can be divided into several stages, starting with the invasion of the flagellate into the bloodstream **[21]**.

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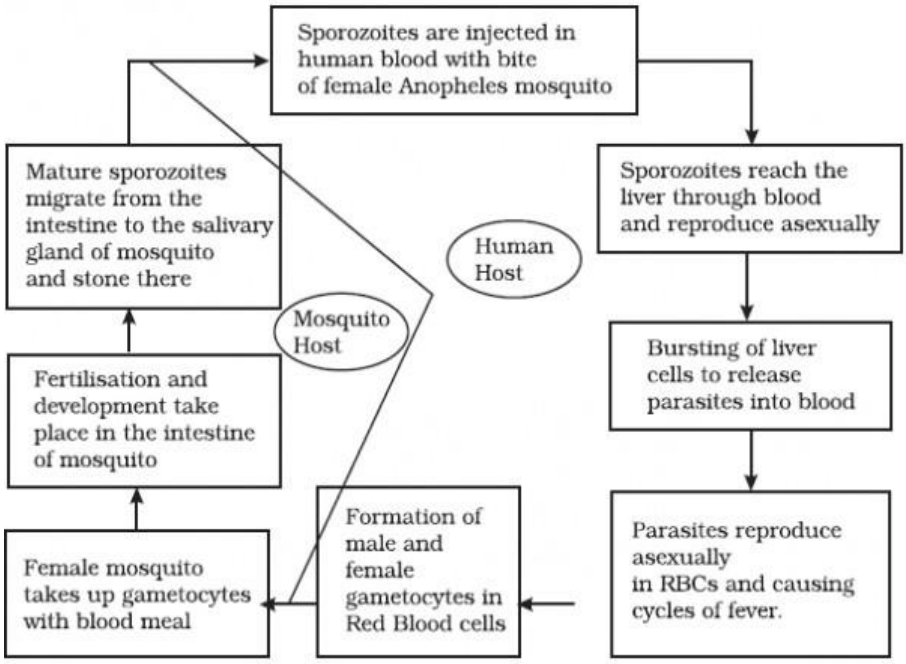

Fig.1 Life cycle of the malaria parasite

6. DEGRADATION OF HEMOGLOBIN BY PROTEASE

In *P. falciparum* food vacuole several aspartic proteases (plasmepsin I, II, III, IV) and cysteine proteases (falcipain-1, falcipain-2/, falcipain-3) have been isolated which used for degradation of hemoglobin as displayed in Figure.2**[22,23]**.

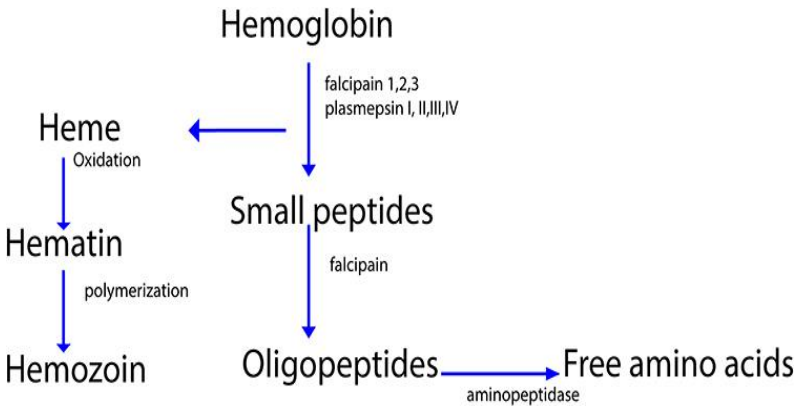

Fig.2 Degradation of hemoglobin

7. PREPATENT PERIOD

7.1 Pre-erythrocytic schizogony

The flagellates transmitted from the salivary glands of Anopheles mosquitoes are injected into the human host along with anticoagulant-containing saliva to ensure a regular blood meal. The flagellates are thought to rapidly migrate away from the injection site, but a recent study using a rodent parasite (Plasmodium yoelii) as a model system

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indicates that, at least in this case, most of the infectious flagellate remains there. Injections formany hours, with only a slow release into the circulation **[24]**.

7.2 Exo-erythrocytic schizogony

Once in human blood, falciparum P. days and undergoes a process of clonal multiplication known as extracellular schizophrenia. Sporozoites reach the liver and infiltrate the hepatocytes (hepatocytes), where they remain 9 to 16**[25]**. The receptors on the spore bodies responsible for entry into hepatocytes are mainly the thrombospondin regions on peripheral proteins and on thrombospondin-binding adhesion proteins. These domains bind specifically to heparan sulfate proteoglycans on hepatocytes **[26]**. Each sporozoite produces tens of thousands of merozoites inside hepatocytes, and each merozoite can invade a red blood cell (RBC) when it is released from the liver **[27]**. Days Arrival The time required to complete the tissue phase varies depending on the infecting species; (8–25 falciparum P.days for, 8–27 vivax P.days P.days for, 9-17 oval P.days and 15-30 P. malariae), and this period is called prenatal period.6.3

7.3 Erythrocytic schizogony

Merozoites enter erythrocytes by a complex process of infiltration, which can be divided into 4 stages: (a) initial recognition and reversible attachment of the merozoite to the erythrocyte membrane; (b) reorientation and junction formation between the merozoite terminal end (irreversible binding) and the release of substances from the rhombic and microneme organelles, leading to the formation of vacuoles parasitic cells on shore; (c) migration of the junction and infiltration of the erythrocyte membrane around the merozoite accompanied by removal of the merozoite's surface layer; and (d) closure of the parasitic vacuole and erythrocyte membrane upon completion of merozoite infiltration**[28]**. In this repeated infiltrate-nucleus-release-invasion-release-invasion cycle that continues, approximately 48 cases of infection with P. falciparum P., ovale P. and vivax P. h in and 72 infected with P. malariae. It happens quite synchronously and the merozoite is released at about the same time of day. The content of infected red blood cells released during lysis stimulates the production of tumor necrosis factor and other cytokines responsible for the characteristic clinical manifestations of the disease **[28,29]**.

Several specific ligand-receptor interactions have been identified to be involved in entry **[29,30]**.Sequencing of the P. falciparum genome, completed in 2002, indicates that several molecules involved in invasion are members of larger gene families **[31,32]**. 175 (EBA175) is an Erythrocyte falciparum P.A. binding antigenfound on human erythrocytes during invasion primary glycoprotein-binding protein **[28]**. After entry, the main parasite ligand called falciparum P.1 (PfEMP1), encoded by a multigene family called erythrocyte membrane proteins var, is expressed on the surface of infected GR **[33,34**]. PfEMP1 has a central role in falciparum P. Pathogenesis and multiple host receptors can be recognized simultaneously by multiple adhesion regions located in the extracellular region of PfEMP1 **[35,36]**. A small percentage of merozoites in red blood cells eventually differentiate to produce microscopic cells and macrospores (male and female respectively), which are no longer active in the human body. These gametocytes are essential for the transmission of the disease to the new host of the female Anopheles mosquito. Normally, several different cycles of asexual erythrocytosis occur prior to the production of gametes. In falciparum P.days. Gametocytes appear on the fifth day of the main attack in h and gametocyte division takes place from 10 to 12 days, erythrocyte schizonts take 48 days vivax P. and ovale P. after the attack.Primary attack due to infection, then becomes more; they occur in anything from 5 to 23 P. malariae**[37]**.

7.4 Sexual phase in the mosquito

A mosquito that feeds on the blood of an infected individual may ingest these gametocytes during its mid-phase, where the macrospores form macrospores and the amplification of these gametes. Microcells give rise to microcells. These gametes fuse, undergo fertilization, and form a zygote. This turns into the oocyte, which penetrates the cell wall in the mid-stage and develops into the oocyte**[38]**. The spores in the oocyte produce many spores and when the follicle ruptures they migrate to the salivary glands for further transmission to other hosts during the month. When an infected mosquito bites a susceptible host, the following and subsequent days, the mosquito remains infectious for 1 to 2 days. This form of the parasite is found in the salivary glands after the onset of the 10-18 Plasmodium life cycle **[39]**.

8. RESISTANCE OF ANTIMALARIAL DRUG

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If we lose artemisinin due to drug resistance, we could face incurable malaria **[41]**. In this review, the emergence of current antimalarial drug resistance is considered in two parts: and second, the follow-up screening process, where the survival advantage in the presence of antimalarial drugs is considered. Antimalarial treatment leads to a preferred in vivo efficacy that can exceed 50% in non-immune patients, resulting in RMPs of approximately 10 per clonal cycle **[42]**. The antimalarial converts this positive value to a negative value, resulting in RMPs of 10-1 to 10-4 per cycle. These negative PMRs are also known as parasite killing rates or parasite reduction rates **[43]**, all of which transmit and propagate resistance **[41]**.

8.1 Resistance on genetic basis

Genetic events that confer resistance to antimalarials (while preserving parasite viability) are sspontaneous and rare and are considered to be independent of the drug used. These are mutations or copy number changes of genes that encode or involve parasite targets of drugs or flow/flowpumps that affect visceral drug concentrations. A single genetic event may be sufficient, or several unrelated events may be necessary (nosebleeds). Since the probability of occurrence of polygenic resistance is the product of the probabilities of the individual components, it is a significantly rarer event. P. Southeast Asian falciparum parasites have been shown to have an increasing tendency to develop resistance **[44]**. Resistance to chloroquine in P. falciparum may be polygenic and was initially attributed to mutations in the transporter coding gene (PfCRT) **[45]**. Resistance to atovaquone results from point mutations in the gene, which encodes cytochrome b. Atovaquone is only deployed as a fixed conjugate with proguanil (chloroguanide). In this combination, it is proguanil acting on the mitochondrial membrane, rather than cycloguanil, a metabolite of proguanil that inhibits dhfr, which appears to be the key factor. It is not known whether resistance develops to proguanil action in mitochondria**[46]**. Although the target of artemisinins has recently been identified (PfATPase6) **[47]**. Response to antimalarial regimens in settings with less frequent transmission was poorer in pregnant women than in nonpregnant women of the same age in the same location **[48]**. Treatment failure leads to the development of drug resistance. The placenta can contain a large number of parasites, thereby increasing the probability of selection. These parasites often have a unique surface antigen phenotype (they bind to chondroitin sulfate A and hyaluronic acid), suggesting that the expression of a single gene is conserved **[49]**.

8.2Pregnancy

After the development of infection in a pregnant woman who has never had malaria during pregnancy (usually a prigravide in an endemic area), the infecting parasites are unlikely to be picked up by the reaction.Immune response to surface-expressed antigens, and therefore if resistance to mutant occurs, it does not need to be present in a variant subpopulation to ensure its survival. There are even data that suggest that pregnant women are more attractive to mosquitoes **[50]**. Pregnant women are widely recommended for malaria prophylaxis, but the only drugs that are considered safe are chloroquine, which is not effective against P. falciparum almost everywhere, and proguanil, the drug. Resistance, and reduced biotransformation to the active metabolite of the antifol, cycloguanil. . Prophylaxis for pregnant women has given way to putative intermittent therapy (IPT) with SP, in which a single therapeutic dose is administered two or three times during pregnancy, despite MS becoming resistant to medicine. Antimalarial resistance is selected using drug concentrations sufficient to inhibit the multiplication of susceptible, but not resistant, parasites. The parasite is present in the blood, so the concentrations of the free (unbound) drug achieved in the plasma are most therapeutically relevant. Several behavioral, pharmacological and pharmacokinetic factors influence the likelihood that the parasite will encounter subtherapeutic levels of antimalarials. Some antimalarials (particularly lumefantrine, halofantrine, atovaquone and to a lesser extent mefloquine) are lipophilic, hydrophobic, and quite variable in absorption (individual variability in bioavailability. change up to 20 times) **[51,52]**. There are also large inter-individual differences in the volume of distribution. Together, they cause significant inter-individual variation in blood concentration profiles **[53]**.

9.COMBINATION OF DRUG

The theory behind combination drug therapy for tuberculosis, leprosy, and HIV infection is well known and now generally accepted for malaria **[54,55]**. If two drugs are used with different modes of action, and thus different

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mechanisms of resistance, then the probability that the parasite develops resistance to the two drugs is a product of the individual parasite probability.Theiroddity **[56,57]**.Combined artemisinin derivatives are particularly effective due to their very high killing rates (10,000-fold parasite reduction/cycle), no side effects, and no significant resistance **[43]**.

9.SYMPTOMS AND DIAGNOSIS

Accumulation and sequestration of parasite-infected red blood cells in various organs such as heart, brain, lung, kidney, subcutaneous tissue and placenta is a telltale sign of falciparum P. Accumulation Aggregation results from interactions between parasite-derived proteins, present on the surface of infected erythrocytes, and certain host molecules expressed on the surface of uninfected erythrocytes, endothelial cells.And in some cases placental cells in cerebral malaria [58]. A (CSA) in placental infection and the intercellular adhesion molecule. In malaria-specific manifestations, several parasite adhesion receptors have been identified, such as hyaluronic acid and chondroitin sulfate [59, 60]. Malaria is particularly dangerous for pregnant women and young children and in endemic countries malaria is an important determinant of perinatal mortality [61]. Parasite retention in the placenta is a key feature of P. falciparum infection. during pregnancy and is associated with serious adverse outcomes for both mother and child, such as preterm birth, low birth weight, and increased neonatal mortality [62] PfEMP1, a CSA ligand, is the target primary targets of protective immune-related antibodies and falciparum P. isolates whose sequences in the placenta are primarily associated with CSA [63]. Rapid diagnostic tests “dipsticks”, which easily detect malaria antigen in blood strips in minutes, are easy to perform and do not require trained personnel or special equipment. Ideally, blood should be drawn at the patient's temperature as that is when the greatest number of parasites can be found. Viscous drops have been used in routine diagnostics and have been used sparingly as a parasite for 200 years [64]. In many parts of the world, falciparum P. became resistant to Fansida and chloroquine, the two most commonly used and affordable antimalarials [65,66]. To overcome this problem and prolong the useful life of current drugs, combination therapy is increasingly used. Artemisinin, obtained from the plant Artemisia annua, is an extremely effective antimalarial drug, and this drug, or its derivatives such as artesunate or artemether, is used mainly in combination with several other drugs.Such as Fansidar and mefloquine [67,67,68]. Recent reports have described the development of advanced malaria vaccines and several malaria vaccines during clinical development [69,70]. Several major international initiatives have been launched to combat malaria [71]. These include the WHO Malaria Recurrence programme, the Multilateral Malaria Initiative [72], the Malaria Drugs Joint Venture, the Malaria Vaccine Initiative and the Global Fund to Fight AIDS, Tuberculosis and malaria, supporting the implementation of prevention and treatment programmes. There are a number of ways to reduce the transmission of malaria, but there is currently no way to completely stop it. Therefore, new methods are urgently needed [73]. Recently, important technical advances, including modification of the mosquito germ line, characterization of specific tissue promoters, and identification of impact molecules that impede parasite growth, has resulted in the production of transgenic mosquitoes incapable of spreading the malaria parasite [74].Although the transgenic potential of mosquito vectors has been thoroughly studied in the laboratory, more research is needed to develop release and survival strategies of these modified mosquito populations in the field. . In a recent study, it was reported that when feeding on Plasmodium-infected blood, malaria-resistant transgenic mosquitoes had a significant fitness advantage over wild-type mosquitoes [75].

11. COMPLICATIONS IN PATIENTS WITH SEVERE MALARIA

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Patients with severe malaria should be treated in an ICU. Should clinical deterioration to severe malaria occur, it usually develops 3–7 days after fever onset, although there have been rare reports of non-immune patients dying within 24 hours of developing symptoms.

11.1 Neurologic complications

Cerebral malaria is the most common clinical presentation and cause of death in adults with severe malaria. The strict definition of cerebral malaria requires the hypoglycemia, bacterial meningitis and viral encephalitis) ruled out **[76]**.

11.2 Pulmonary complications Presence of the parasite P. falciparum and the patient's inability to wake up with a Glasgow score of 9 or less, and other causes (eg: Acute lung injury usually occurs several days after illness onset Disease can progress rapidly, even after an initial response to treating malaria and eliminating parasites Pulmonary edema is usually noncardiac and can progress to acute respiratory distress syndrome (ARDS) with increased blood pressure Pulmonary capillary permeability **[77]** ARDS is defined as acute lung injury and blood pressure oxygen/inspiratory oxygen fraction of 200 mmHg or less **[78]**.

11.3 Renal complications Acute renal failure is usually oliguric (<400 ml/day) or anuric (<50 ml/day), rarely nonoliguric, and may require temporary dialysis **[78]**. Urine sediment is usually unremarkable. In severe cases, acute tubular necrosis may develop secondary to renal ischemia **[79]**.

12. MONITORING TREATMENT

Blood samples were examined for malaria using thick and thin blood slides stained with Field and Giemsa stains, respectively, and examined by light microscopy using a 100 × objective. Examination of 15 Plasmodium falciparum 10 × µ1 blood was considered equivalent to 5 by counting 1000 red blood cells and expressing the number of parasite cells as a percentage. For the purposes of this study, red blood cells.Optimum dipstick testing was performed according to the manufacturer's instructions (Flow Inc, Portland, OR, USA) on all samples on the same day or after storage at 4°C. Accuracy of results Parasites and test strip readings were confirmed by a second examiner **[80,81]**.Patients with blood containing the parasite Plasmodium falciparum were hospitalized for treatment and daily blood samples were obtained for blood parasite monitoring according to standard DHT practice. Optimal test strips were performed on the same samples until the blood became negative on the microscope**[82]**.

13. FORCASTING STUDIES[83]

In 1911, Christopher's developed a malaria early warning system in Punjab based on rainfall, the number of fever deaths and the price of wheat. Since this initial system, researchers and practitioners have continued to search for factors that determine the spatial and temporal variability of malaria in order to improve disease burden prediction systems. . Malaria forecasting is now done in many countries and often uses data on environmental risk factors, such as climate conditions, to predict incidence rates for a particular geographic area.Over a period of time **[84]**.

13.1 Forecasting method

- GLM
- ARIMA
- Grey methods
- Smoothing methods
- Neural networks
- Mathematical models
- Visual methods

13.2 Forecasting data

Predictive methods include statistical modeling, mathematical modeling, and machine learning methods. Statistical methods include generalized linear models, Automatic Regressive Integrated Moving Average (ARIMA) **[85]**and HoltWinters models **[86]**. Mathematical models based on an extension of the RossMacDonald transmission model of susceptibility to infection **[87]**. Other authors have predicted malaria incidence using neural networks, a machine learning technique. Number, incidence, or prevalence of malaria according to linear, Poisson, or logistic regression. All but one regression model includes climate-related variables such as precipitation, temperature, vegetation and/or relative humidity **[88]**. In general, meteorological variables have been altered to account for the delayed effects of weather on malaria infections. Two studies explored the impact of including covariates as higher-order polynomials. Several studies have used a generalized linear modeling approach to time series analysis by including prior (later) malaria incidence as a self-healing covariate in the model. Some models include terms for seasons or years to account for seasonal and annual variations. Seven studies (24%) used forecasting methods based on the ARIMA

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model with some including the seasonal component (SARIMA) **[89]**. Although not explicitly stated, many studies have used the transfer function model, also known as ARIMAX. Typically, these ARIMA-based models incorporate different weather series as covariates, although one study also included malaria burden data in neighboring districts. According to Briet, studies (14%) in China used Gray's method to predict malaria, none of which incorporated predictors other than malaria incidence **[90]**. Two studies (7%) used mathematical models **[91,92,93,94]**.The Gaudart group incorporated the vector component into the SIRtype model and used data from a cohort of children, remote sensing data, literature, and expert opinions of entomologists and parasitologists **[95,96]**. The study used the infection-recovery exposure susceptibility (VSEIRS) model, although they incorporate two different susceptibility recovery pathways based on different time periods (according to season and year), mimicking different transmission intensities. They found that rainfall had a significant effect on the annual variability of malaria epidemics, and that including rainfall as a predictor improved the accuracy of the forecasts. The parameters of their model are based on the literature as well as the laboratory results. We identified three studies (10%) that used neural networks in their analyses, and each study used different inputs and a unique network structure. Two of the studies used meteorological variables to predict malaria incidence, also including evapotranspiration and sunshine hours to predict malaria incidence **[97,98,99]**.

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