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Burden of Malaria - A Journey Revisited

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Abstract **Review Article**

Malaria has been one of humanity's oldest and deadliest diseases. Despite gains over the first 15 years of this millennium, malaria control has stagnated in the last several years, with resurgence and rising morbidity in several highly endemic countries exacerbated by service disruptions due to the COVID-19 pandemic. Malaria imposes great socio-economic burden on humanity, and with six other diseases (diarrhea, HIV/AIDS, tuberculosis, measles, hepatitis B and pneumonia), accounts for 85% of global infectious disease burden. Malaria is caused by the bite of an infected, female, *Anopheline* mosquito. Mosquito is at the root of several vector borne diseases including malaria. The mechanism of spread of malaria in the human body has been well studied. Symptoms show up based on the type of organism involved in infection. Eradication of malaria and related diseases depends on eradication of the mosquito. Treatment options involve drugs, natural and synthetic, of which chloroquine occupies the prime position. The good news is that new vaccines may be approved more quickly than RTS,S, both because the malaria vaccine approval process has been streamlined and because of the success in deploying Covid-19 vaccines so quickly. This first vaccine against malaria is a breakthrough, but not the only breakthrough we need. While we should celebrate this milestone, the time to advance next-generation vaccines is now.

Keywords: Malaria, Disease, Tuberculosis, Measles, Diarrhea, Anopheline Mosquito, Pandemic.

INTRODUCTION

Malaria has been one of mankind's most dreaded, crippling and, at times, lethal diseases. The history of malaria is as old as mankind itself [1]. It is very common to tropical and subtropical regions, being less common in countries with snow bound areas, desert climates and very cold climatic conditions [2]. More than 500 million people have died on account of malaria and an even greater number have suffered ill-health from the disease in the last 100-150 years or so [2]. About 20 million people suffer from this disease annually, in India alone[3] , although exact figures cannot be given or documented because most patients opt for treatment in private/ corporate hospitals in cities and lesser number go to Government hospitals, most notably in rural and semi-urban areas. As a result, many clinically treated cases are not documented clearly. As of now, year-wise and country-wise statistics are not available but even vague approximations of casualties make malaria dwarf all other diseases. Besides causing harm to the health of the person and his family, malaria severely reduces the work capability and efficiency of persons thereby doing great damage to society in economic terms. The losses suffered by countries during malaria epidemics in socio-economic terms are unestimable [1]. In modern times, malaria affects several countries of Latin America, Africa and Asia. Malaria imposes great socio-economic burden on humanity, and with six other diseases (diarrhea, HIV/AIDS, tuberculosis, measles, hepatitis B and pneumonia), accounts for 85% of global infectious disease burden [16, 17, 19-21].

As per WHO data, the African Region shares the highest global malaria burden. In 2020, 95% of malaria cases and 96% of malaria deaths were reported from this region. 80% of all malaria deaths in the region were of children below 5 years of age. Four African countries accounted for just over half of all malaria deaths worldwide: Nigeria (31.9%), the Democratic Republic of the Congo (13.2%), United Republic of Tanzania (4.1%) and Mozambique (3.8%).However, there are some countries who have been able to successfully eradicate Malaria. The WHO has granted malaria-free certification to 40 countries and territories

globally. Between 2020 and 2022 a total of 12 countries were certified malaria free by WHO. These countries are United Arab Emirates, Morocco, Turkmenistan, Armenia, Argentina, Kyrgyzstan, Uzbekistan, Paraguay, Sri Lanka, Algeria, China and El Salvador. In India, no state so far has been able to completely eliminate Malaria. In 2019, India accounted for 88 per cent of malaria cases and 86 percent of deaths due to malaria in the WHO South-East Asia region. It is also the only country outside Africa which is among the 11 'high burden to high impact' countries. India is now on the road to reach zero malaria cases by the year 2030. It is a signatory to the National Framework for Malaria Elimination (NFME) and has been making efforts to achieve the goal. By taking adequate measures, India was able to reduce the number of malaria cases by 60 per cent as compared to 2017 and recorded 46 per cent reduction as compared to 2018. Odisha is one of the states that is moving closer to achieving the malaria free goal. The state government had announced last year that it recorded a 90 per cent reduction in malaria cases in the last three years.

MALARIA IN JAMMU AND KASHMIR

In Jammu and Kashmir, Malaria was recorded to be the most prevalent Vector Borne Disease in the region with 5833 positive cases from last 14 years from 2005–2018. However, mortality due to this disease has not been recorded from the region uptill now. Highest number of cases were recorded during 2011(1091 cases) and since then, malaria has followed a steep declining trend in the region [18]. This decline in malarial incidences is attributed to the constant efforts made by the health department. The massive awareness campaigns launched by the administration over the years remained result oriented due to which Jammu and Kashmir is set to be malaria free in the coming couple of years while no positive case of the epidemic has been reported so far this year. Official sources in the Health and medical Education Department said that aggressive awareness campaigns by the Department and the awareness about cleanliness among the people, resulted in making Jammu and Kashmir malaria free very soon. In 2011, 1091 cases of malaria were registered in Jammu and Kashmir including 1046 cases of *Plasmodium vivax* (PV) and 46 cases of *Plasmodium falciparum*.

CAUSES

Malaria is caused by the bite of a female *Anopheles* mosquito on human beings [4]. There are several species of mosquitos known today, over 3000 of them, and the *Anopheles* mosquito is one of them. Incidentally, the male *Anopheles* mosquitos do not show any tendency to feed on vertebrates / human blood. The female *Anopheles* mosquito is a nocturnal feeder, i.e., bites only during night times [4]. Flying at one mile per hour, it senses exhaled carbon dioxide or heat/ infrared radiation reflected from the skin of the person to zoom in on its target i.e., you and me [4]. The female mosquito does this because she feeds on the protein found in the blood to survive and to develop her eggs. The other species, '*Aedes aegypti'* and '*Aedes albopicto'* mosquitos, are day feeders causing other choicest ailments like Dengue Fever and Chikugunya whereas Yellow Fever, Japanese Encephalitis etc. are caused by the '*Culex'* mosquito.

SPREAD OF THE DISEASE

The name 'malaria' is derived from the Latin name 'malaria' meaning bad or foul air. During winter season, the mosquito populations grow in huge numbers as the weather, especially in tropical countries, is very favourable for the growth of mosquitos. The winter season comes immediately after the rainy season when large quantities of water ponds are formed due to stagnant waters leading to accumulation of dirt, filth and microorganisms in them. These ponds often produce a foul/ peculiarly-unpleasant-smelling air. The female mosquitos, especially the *Anopheline* type, find these ponds/water bodies suitable breeding grounds for laying down their eggs. It is while incubating on these eggs that the protozoal microorganisms in water ponds/bodies, especially of the type '*Plasmodium'*, enter into the bodies of the *Anopheline* mosquitos. Once entered into the body of the *Anopheles* mosquito, the protozoal microorganisms are stored in the stomach/belly of the mosquito from where they migrate into the salivary glands [5, 20-22].

The body of the mosquito seems to offer excellent resting place for these microorganisms. When the female *Anopheline* mosquito bites a human being, the organisms are transferred from the mosquito to the human being. Malaria is thus caused by the protozoal microorganism '*Plasmodium*' and mosquito is only an insect vector carrying the organism from the water pond to human body. Alternatively, malaria may also be caused by the bite of a healthy *Anopheline* mosquito on a malaria infected human being and then a second bite by the freshly infected *Anopheline* mosquito on another healthy human being.

This discovery [6] was made by Major Ronald Ross in Aug 1897 when he was posted as a British Army Surgeon at Secunderabad Cantonment in the then 'Hyderabad Deccan' part of India, under a treaty signed between the British Indian Government and the then Nizam (i.e., ruler of the erstwhile Hyderabad State of India). For this discovery, Ross was honoured6 with the coveted Nobel Prize in Physiology or Medicine for the year 1902. It is believed that '*Plasmodium'* organisms do not survive in the bodies of other animals/creatures like chicken, goats, dogs, cats or even flies etc. and so the latter cannot act as carriers/vectors of this disease. Even if water contaminated with '*Plasmodium*' from a pond or even if water from a container in which malarious mosquitos have died is drunk by a healthy human being, malaria does not occur. Malaria is caused by the bite of a mosquito and mosquito alone, wherein

it transfers '*Plasmodium*' from its salivary glands into the blood of a human victim man, woman, child, adult or Senior Citizen. By logic, this also implies, malaria to be a non-contagious disease.

LIFE CYCLE OF MALARIAL PARASITE

A parasite is a species responsible for causing a particular type of disease or ailment or a biological condition. (Literally, a parasite means an unwanted guest who creates trouble for its host). Malarial parasites i.e. the *Plasmodium* group have a very complex life cycle and can exist in many different forms like sporozoite, schizont, merozoite, trophozoite and gametocyte. These forms vary in terms of the structure of their cell's constitution and different stages of evolution. When a human being is bitten by an '*Anopheles*' mosquito, the parasite is introduced in its sporozoite form. The latter rapidly invades the liver where it matures first into a schizont form and then into a merozoite. The merozoite form of the parasite leaves the liver and then invades red blood cells (Erythrocytes). Within erythrocytes, the merozoite is sequentially transformed into a trophozoite, then into a schizont and finally back to a merozoite which ruptures out of the erythrocyte to inoculate other erythrocytes. Within the erythrocyte, some merozoites also develop into gametocytes which are taken up by mosquitos, whereby they are matured back into infective sporozoites–thereby initiating the infective process, in a cyclical form, all over again [7]. This circuitous life cycle, shown in Figure 1, drawn below, is used very advantageously for targeting the disease using a variety of anti-malarial drugs.

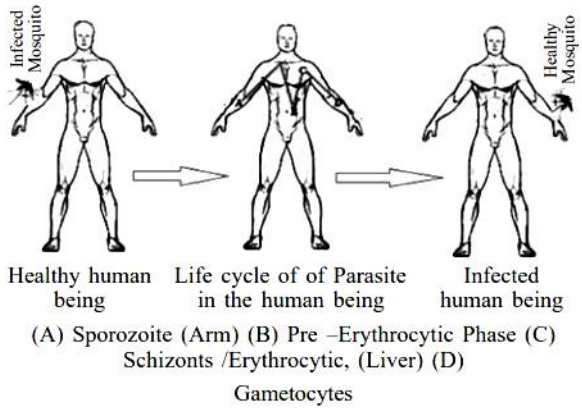

Fig 1: Life Cycle of Malarial Parasite

TYPES OF ORGANISMS

The organisms [1] normally responsible for malaria belong to the genus '*Plasmodium'* which belongs to the class of protozoa known as 'sporozoa'. Of these, there are four different species [1] which are believed to be responsible for human malaria. These are *Plasmodium malariae*, the parasite of quartan malaria; *Plasmodium vivax*, the parasite of benign, tertian malaria; *Plasmodium falciparum*, the parasite of malignant or sub-tertian malaria and *Plasmodium ovale*– the parasite that causes a mild type of tertian malaria. The feverish effects caused by various species of *Plasmodium* in human body are shown below:

- *Plasmodium vivax*: Widely distributed throughout the world; New generation of merozoites formed every 48 hours; Fever comes every third day in the patient.
- *Plasmodium ovale*: Found in West Africa and South America; New generation of merozoites formed every 48 hours; Fever comes every third day in the patient.
- *Plasmodium malariae*: Found in tropics and temperate zones; New generation of merozoites formed every 72 hours; Fever comes every fourth day.
- *Plasmodium falciparum*: Found in tropics including India; Very dangerous; shows lot of resistance to several conventional drugs; Fever comes every day.

PREVENTION AND TREATMENT OF MALARIA

Despite gains over the first 15 years of this millennium, malaria control has stagnated in the last several years, with resurgence and rising morbidity in several highly endemic countries exacerbated by service disruptions due to the COVID-19 pandemic. In 2020, malaria was estimated to have resulted in 627,000 deaths and 241 million cases, with 77% of deaths in children <5 years of age [22]. Overall, 90% of malaria cases and deaths are reported in Africa, and six countries namely Nigeria, DRC, Uganda, Mozambique, Angola, and Burkina Faso and account for 55% of all cases globally. It is obvious from the discussion given above that the great Mosquito is central to the cause and spread of malaria. You eliminate mosquito and you have eliminated malaria. However, this is more easily said than done. It is an irony of life that even the largest of animals like the gigantic Dinosaurs have vanished from the surface of the earth but not the tiny mosquito as shown by Steven Spielberg in the famous Hollywood feature film Jurassic Park [8]. Nevertheless, several mosquito eradication or control programmes have been undertaken by Governments all over the world. Removal of stagnant water ponds or water bodies coupled with effective mosquito control measures using insecticides like DDT etc., have been central to these programmes. Furthermore, use of mosquito nets, several commercially available antimosquito / mosquito-repellent creams, antimosquito smoke coils/agarbathis etc., at individual levels, have been adopted for effective prevention of mosquito bites. If, inspite of all these measures, a malarious mosquito were to bite a human target making him/her malaria infected, a choice of drugs, synthetic and natural, are available now both for prophylaxis and treatment. Among the synthetic drugs, 'Chloroquine', which should have been called "Chloro Queen," occupies the prime position as anti–malarial drug or the largest used drug compared to any antimicrobial drug known to man today. It may be mentioned here that Opium/ Morphine has been recognised for centuries as the 'Queen of

Drugs' in view of its beneficial analgesic and narcotic activities. Nevertheless, chloroquine outdoes morphine in terms of its ability to save millions of lives over decades, tonnage and manufacturing challenges. Several other synthetic antimalarial drugs such as Amidoquin, Hydroxychloroquine etc. are structural modifications derived from a crucial intermediate used in chloroquine manufacture. Developed during the Second World War, chloroquine is a generic name as the drug contains [9] in its chemical constitution a chlorine substituent attached to a quinoline ring. Chloroquine has the advantages of being less toxic compared to other anti-malarials, it is longer lasting and has the ease of administration. Today, India is a world leader in the manufacture, formulation and distribution of chloroquine despite the fact that chloroquine manufacture involves costly raw materials, sophisticated technology, rigorous quality control and serious environmental problems.

The synthetic antimalarials led by its prime candidate chloroquine did great service to mankind, over a period of decades, in the treatment of malaria even outdoing the natural drugs like Quinine and Quinidine. The latter are plant products, alkaloidal in character and isolated, in relatively smaller quantities, from the bark of the Cinchona plant after a long and tedious extraction process. Prolonged use of synthetic antimalarials leads to resistance among most of the malaria types, especially the one caused by species *Plasmodium falciparum*. The latter was not only highly resistant strain of malaria but even proved to be lethal. Based on a request (around 1967-68) by Vietcong leaders during the Vietnam War, the Chinese authorities set out11, as a Secret Project, for a natural cure for malaria. It may be stated here that Vietnam is a country, under the Mekong Delta, full of bushes and stagnant waters with a huge spread of mosquitos carrying *Plasmodium falciparum* causing great fatalities among its soldiers at that time. Extensive and intensive studies were carried out by Chinese Scientists, led by Mrs. YouYou Tu [11], under a programme code-named "Project 523", to find a traditional natural herbal cure for malaria culminating in the discovery of Artemisinin (or Quinghaosu) in 1986. The latter is an active principle/chemical compound, a sesquiterpene lactone in chemical constitution, isolated from the plant 'sweet worm wood' belonging to the family *Artemisia annua*, called Quinghao in Chinese. Other semi-synthetic derivatives such as Dihydroartemisinin, Artemether etc. were also found to be antimalarials active against *Plasmodium falciparum*. Dihydroartemisinin, obtained by the simple sodium borohydride reduction of the lactonic carbonyl group in artemisinin, was found to be ten times more active than artemisinin and also the bioactive metabolite. For her outstanding, dedicated and committed work, Mrs. YouYou Tu was honoured with many Chinese and international awards including the most coveted Nobel Prize (getting ½ the prize money on sharing basis) for Physiology or Medicine in 2015 [11][12]. Again, as in the case of any drug (natural or synthetic), resistance comes in sooner or later and so Artemisinin-based Combination Therapies (ACTs) are recommended for malaria treatment. Low bioavailabilities, poor pharmacokinetic properties and high cost are some of the disadvantages of artemisinins. (The present cost of Artemisinin is around Rs. 9000/- per 100 mg bottle).

The main interventions used for prevention of malaria include vector control with long lasting insecticidal bednets (LLINs) and indoor residual spraying of insecticides (IRS). However, *Anopheles* vector resistance to pyrethroids, the main insecticide used in LLINs, has become widespread, and insecticide resistance also increasingly threatens the utility of IRS. In addition to vector controls, prompt treatment of malaria with artemisinin-based combination therapy (ACTs) is recommended in all settings where falciparum malaria is endemic. ACTs have played a crucial role in controlling malaria over the past 20 years, with artemether-lumefantrine being the most widely used ACT in Africa. However, artemisinin-resistant *Plasmodium falciparum* parasites have spread in Southeast Asia3, resulting in reduced treatment efficacy of some ACTs. More alarmingly, recent reports from Rwanda and Northern Uganda suggest the emergence of artemisinin-resistant parasites in Africa. Loss of artemesinin activity would threaten the activity of partner drugs such as lumefantrine; loss of both components of ACTs could have devastating consequences across the continent [23-25].

VACCINE DEVELOPMENT

There is an old adage which says 'Prevention is better than Cure' and vaccines justify this saying most admirably. Vaccines are Medical Agents which have served mankind as one of the most effective means of preventing the spread of infectious diseases, most notably Smallpox, Polio, Measles and several others, thereby saving millions of lives. Vaccination involves inoculating/injecting the highly weakened/partially dead form of the pathogen so that the body quickly develops an ability (called immune response) to fight the organism and retains the structure of the pathogen in its memory for long time to come. In the case of malaria too, attempts have been made to develop a suitable vaccine. Considerable success has been achieved with the development [13] of a vaccine called RTS, S known by its trade name Mosquirix. The latter has been found to fight against *Plasmodium falciparum*, which, of late, is very predominant in the countries of Sub-Saharan Africa especially afflicting children below 5 years. Developed over a period of 10 to 12 years by GlaxoSmithKline (GSK) Laboratories [13], Belgium, on a No-Profit-No-Loss basis with a generous financial support from PATH Foundation and Melinda & Gates Foundation (both based at Seattle, Washington, USA), the vaccine is administered to children in 4 doses, first three smaller and the fourth

one in booster form. The R stands for Repeat region of *Plasmodium falciparum* circumsporozoite protein (CSP), T stands for T-cell epitopes of CSP, S for hepatitis B Surface antigen and free 'S' protein assembling to RTS, S. Approved by European Medicines Agency (EMA) in 2015 and launched by WHO under a UN subsidy programme, the vaccine has an efficacy of only ~ 50% at best [14]. This low efficacy is because Malaria is a complex disease with the parasite passing through multiple life stages/forms present in different body parts. Nevertheless, vaccine RTS, S or Mosquirix is in use because the benefits outweigh the risks. Further work on malaria vaccines is in progress [15]. The newly approved RTS,S vaccine has been tested and proved safe in hundreds of thousands of children, but very rare negative side effects may become apparent in a wider rollout. It is moderately effective, which is amazing, but not as good as it could be. Multiple booster doses may be required; the malaria parasite may evolve to evade it.

CONCLUSION

In May 2015, the World Health Assembly endorsed the Global Technical Strategy (GTS) for Malaria Elimination 2016-2030, which lays down clear global goals, milestones and targets till 2030. In accordance with the GTS, the Government of India launched the National Framework for Malaria Elimination 2016-2030 in February 2016 and the National Strategic Plan for Malaria Elimination 2017-2022 in July 2017 with WHO support. India has a vision of a malaria free country by 2027 and elimination by 2030. WHO supported the country to accelerate malaria elimination activities in the states as per NSP 2017-2022. WHO's High Burden to High Impact (HBHI) strategy has been initiated in four high endemic states i.e. West Bengal, Jharkhand, Chhattisgarh and Madhya Pradesh in July 2019.

Conflict of Interest: Authors declare that there is no conflict of interest.

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