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An overview of natural history of the human malaria

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Abstract
Malaria has troubled humans for thousands of years. Disease resembling malaria has been described for more than 5000 years. Malaria is currently endemic in more than 100 tropical and subtropical countries. The etymology of malaria is derived from *mal aria* means bad air in medieval Italian. This is because ancient Romans thought that malaria came from fumes in the swamps. Over 25 distinct species of *Plasmodium* are identified for transmission of malaria in primates but only four species of *Plasmodium* are responsible for human malaria *viz. Plasmodium falciparum, Plasmodium ovale, Plasmodium malariae* and *Plasmodium vivax*. Sometimes humans may infect with *Plasmodium knowlesi* (also called traveler's malaria or monkey malaria) that normally infect animals. *Plasmodium knowlesi* is prevalent in Southeast Asia, especially Malaysia. Out of which malaria due to *Plasmodium falciparum* (also called cerebral malaria) is prevalent in tropical and subtropical countries and is most fatal. By study natural history of human malaria we can learn that, work of some pioneers help the human race to survive this deadly disease in therapeutic way otherwise nature would had given natural selective protection to humans by providing some genetic alterations and current world scenario would be different.

Keywords: Malaria, *Anopheles*, vector, protozoa, *Plasmodium*, parasites

1. Introduction
Malaria is probably one of the most common, lethal and famous vector borne diseases of the world causing more than one million deaths and 200 millions infections each year. Malaria is currently endemic in more than 100 tropical and subtropical countries. The etymology of malaria is derived from *mal aria* means bad air in medieval Italian. This is because ancient Romans thought that malaria came from fumes in the swamps. Over 25 distinct species of *Plasmodium* are identified for transmission of malaria in primates but only four species of *Plasmodium* are responsible for human malaria *viz. Plasmodium falciparum, Plasmodium ovale, Plasmodium malariae* and *Plasmodium vivax*. Sometimes humans may infect with *Plasmodium knowlesi* (also called traveler's malaria or monkey malaria) that normally infect animals. *Plasmodium knowlesi* is prevalent in Southeast Asia, especially Malaysia. Out of which malaria due to *Plasmodium falciparum* (also called cerebral malaria) is prevalent in tropical and subtropical countries and is most fatal because it multiply quickly in blood cells. *Plasmodium vivax* is the most common species worldwide. *Plasmodium ovale* occurs mainly in West Africa and Western pacific islands. *Plasmodium malariae* occurs worldwide. *Plasmodium ovale* and *Plasmodium vivax* can remain dormant in liver and relapses by hypnozoites may appear after months and even years after exposure. There are 41 *Anopheles* species that transmit malaria, which bites mainly at dawn and dusk. Primary malaria vector species from Africa are *Anopheles gambiae* and *Anopheles funestus*. In most parts of the world except Africa, the anthropophilic index of the malaria vector is less than 50% or less but in Africa, this index is more than 80%. Only the female *Anopheles* feed on blood and are vector of malaria parasites. Humans and female *Anopheles* mosquitoes are two hosts of malaria parasite. Malaria has incubation period not less than seven days. The antigen based rapid diagnostic tests (RDTs) and Giemsa staining are two preferred diagnostic technique used for malaria. Young children, pregnant women, elder people and peoples with compromised immunity are at more risk to this disease. Malaria have several clinical symptoms such as fever, chills, headache, muscle aching, weakness, vomiting, diarrhea, cough, abdominal pain *etc*. more severe conditions give symptoms such as jaundice, anemia, organ failure, followed

by coma and death [1, 3].

The life cycle of *Plasmodium* is very complicated and begins with an infective stage, where sporozoites are injected into humans by *Anopheles* and ultimately invade hepatocytes where they undergo exoerythrocytic schizogony (first phase of asexual reproduction) and produce merozoites. These merozoites enter blood and undergo erythrocytic schizogony (second phase of asexual reproduction) resulting in the production of more merozoites. This process is repeated indefinitely which cause malaria. After this young merozoites develop into male and female gametocytes and taken up by female *Anopheles*. In *Anopheles* these gametocytes mature into male and female gametes and fertilize and produce a motile zygote called ookinete (sporogony). Ookinete penetrates the gut wall and became oocyst that further produce sporozoites that migrate to salivary glands of *Anopheles* and are injected to humans, when the *Anopheles* bites them. The first evidence of malaria parasite was found in mosquitoes preserved in amber from the Cenozoic era that are approximately 30 million years old. Human malaria originated in Africa around 10000 years ago with start of agriculture revolution. Molecular studies suggest that malaria parasites came to human from the great apes through bites of vector mosquitoes [1].

1.1 History of Malaria: Malaria has troubled humans for thousands of years. Disease resembling malaria has been described for more than 5000 years. In 2700 BCE, tertian and quartan fever due to malaria was described in Nei Ching (The Canon of Medicine). The father of medicine Hippocrates noted the symptoms of malaria like disease in 4th century. He also linked malaria to appearance of Sirius the Dog Star. In Susruta (Sanskrit medical literature), the description of malaria like symptoms are given. Vedic literature (1500-800 BCE) called malaria the 'king of diseases'. Malaria is not seen in the books of Mayans or Aztecs. Alexander Great may have died of malaria. Romans attributed malaria disease to the swamps. 'Roman fever' was actually malaria that infected the Roman Empire. Malaria was prevalent in ancient Egypt around 800 BCE and it is confirmed using DNA-based methods. The ancient Greek historian Herodotus wrote that, the builders of the Egyptian pyramids were given large amount of garlic to protect them from malaria. Greek poet Homer (750 BCE) mentioned malaria in 'The Lliad' and Aristophanes (445-385 BCE) mentioned malaria in 'The Wasps'. Pharaoh Sneferu, who reigned Egypt from 2613-2589 BCE, used bed nets for mosquito bite prevention. Cleopatra VII, the last Pharaoh of Egypt also used mosquito nets for sleeping [2, 3].

1.2 Evolution of Malaria: In the last 150 million years of malaria parasite evolution, many lineages of malaria parasites evolved and radiated. They parasite most groups of land vertebrates including reptiles, birds and mammals. Molecular evidence suggests that malaria parasitic ancestor was a chloroplast containing free living protozoan which later adapted to gut living in aquatic invertebrates. This organism probably had obligate sexual reproduction. At later stage, these pre malaria parasites became asexual and intracellular and evolved schizogony. Schizogony proliferate their reproductive potential. This schizogony cycle in the RBCs of humans and other vertebrates cause malaria. Following this period, certain lineages of the ancestral malaria parasites evolved two host life cycle with blood feeding habits [4].

Human biting preferences of malaria vectors was probably coevolved with agrarian revolution in Africa, where low density and hunting life cycle shifted to high density communal living in settlements. This new man made environment increases the small water collections close to human dwellings. This new situation drives malaria vectors to feed primarily on human blood rather than other mammals and breed close to human dwellings. After originated in Africa, malaria spread to Mesopotamia, the Indian Peninsula and South East Asia between 10000-5000 years ago. It reached India around 3000 years ago. Around 2500-2000 years ago, it reached Mediterranean shores and around 1000-500 years ago, it reached Northern Europe. At the end of 15th century, it reached the New World and in mid 18th century, it spreads across North America. In America it was introduced by African slaves. Finally in 19th century, it became pandemic and over one half of the world population became at risk of this disease [1].

1.3 Discovery of Malaria: In 1718, Italian physician Francisco Torti coined the term malaria (bad air) on old belief that it is associated with swamp air. Charles Louis Alphonse Laveran, a French army surgeon was the first to report parasite in the malaria patient blood in 1880. Laveran examined blood samples of 192 malaria patients and saw pigment containing crescents in 148 patients. For this, he was awarded with Nobel Prize in 1907. Camilio Golgi, an Italian physiologist describes two forms of diseases, one with tertian fever and another with quartan fever. He also found that malaria fever is due to rupture and release of merozoites into the blood. For this, he was awarded with Nobel Prize in 1906. In 1890, Giovanni Battista Grassi and Raimondo Filetti, first coined two malaria parasite *Plasmodium vivax* and *Plasmodium malariae* that infect humans. Later in 1897, William H. Welch coined another human malaria parasite *Plasmodium falciparum*. Further in 1922, John William Watson Stephens coined the fourth human malaria parasite, *Plasmodium ovale*. In 1897, Ronald Ross discovered that mosquitoes are the vector of malaria parasites. He also describes the complex life cycle of human malaria parasite. He published his observations in the "British Medical Journal". Ross does his experiments on *Plasmodium relictum* (malaria parasite of sparrows and crows). For this, he was awarded with Nobel Prize in 1902 [1, 5].

1.4 Prevention and Cure of Malaria: Use of Cinchona (also called fever tree or Peruvian tree or Cardinal tree or Jesuit tree) bark for malaria treatment is 200 years old. Linnaeus named the Cinchona tree in 1742, after the countess 'Chinchon' accidentally omitting the "h" in her name. Spanish missionaries first used Cinchona bark powder for fever treatment. It was also used by the Quechua Indian of Peru to treat severe chills. Jesuit missionaries take Cinchona bark to Europe. Cinchona bark contains quinine (plant alkaloids) which has anti malarial properties. French Chemist Joseph Pelletier and Jean Biename Caventou isolated quinine from Cinchona bark in 1820. Quinine remains an important and effective malaria treatment worldwide except few observations of quinine resistance. In the 2nd century, Chinese identified sweet wormwood (*Artemisia annua*) plant as an effective treatment of malaria. This remedy was lost and rediscovered later as artemisinin drug by Chinese

pharmacologist Tu Youyow in 1972. For this he was awarded with Nobel Prize in 2015. Today artemisinin (Qinghaosu) and other artemether group of drugs are main defense against drug resistance malaria. Yet there is no reported case of resistance to artemisinin. Another substitute of quinine was Plasmochin (1926) followed by Atabrine (1932). Plasmochine and Atabrine were banned due to its toxicity and side effects such as yellowish skin, psychotic reactions *etc*. Later anti malarial drug Resochin (Chloroquine) was discovered in 1930 by Johann Hans Andersag. Chloroquine resistant *Plasmodium falciparum* and *Plasmodium vivax* were reported later. Sontochin (3-methyl chloroquine) was introduced as Chloroquine alternate later in 1934. Further Proguanil (pyrimidine derivatives) discovered during World War II and Mefloquine (4-quinoline methanol) discovered after World War II [2, 6].

DDT and Pyrethrum are most famous preventive measures used against malaria in history. Othmar Zeidler synthesized DDT (Dichloro Diphenyl Trichloroethan) in 1874 and later Paul Muller discovered its insecticidal properties in 1939. For this Muller was awarded with Nobel Prize in 1948. However DDT was banned in United States in 1972 due to its carcinogenic effects and threats to wildlife. Pyrethrum is another natural insecticide derived from flowering plant *Chrysanthemum cinerariaefolium*. It attacks the nervous system of insects. In 17th century, clinical indications of malaria were dark pigmentation of a postmortem spleen and brain. Malaria infected half million men of U. S. troops in the South Pacific during World War II and killed 60000 American soldiers. The US Public Health Service (USPHS) was first to combat malaria outbreak within United States. Later CDC (Centers for Disease Control and Prevention), was founded in United States in 1946 and dedicated itself for eradication of malaria in United States. CDC eradicated the malaria by 1951 by the mass campaign that removes mosquito breeding sites and large scale insecticide spraying. By inspiring with CDC, WHO (World Health Organization) began a program in 1955 to globally eradicate malaria. Eradication planning was divided in four successive steps: preparation, attack, consolidation and maintenance. Some countries like India got benefited by this campaign, while African countries remain unaffected. Complications such as drug resistance strains of malaria parasites and harmful effects of DDT make the campaign unfeasible. WHO abandoned this program in 1969 and change this mission to control the malaria rather than its eradication [4].

1.5 Resistance to Malaria: "Malaria hypothesis" was proposed by J.B.S. Haldane in 1948. He proposed that certain genetic polymorphism have been naturally selected to high frequencies to protect against malaria in areas where it is endemic. Malaria hypothesis is supported by several genetic disorders such as thalassemia, G6PD deficiency, sickle cell anemia, RBC Duffy negativity, ovalocytosis *etc*. These all genetic disorders provide resistance with different extent to African population from *Plasmodium falciparum* infection, where it is endemic and prevalent [2].

2. Conclusions

Loss of one species is beneficial for another species. Although the life cycle of malaria parasite is very complex, yet it is evolved and radiated very successfully. It is really an evolutionary masterpiece. Its survival is possible due to its strong association with most successfully evolved arthropod, the mosquitoes. It is their luck that they chose to live in the most perfect host, the mosquitoes. It seems that, mosquitoes gave boon to malaria parasite to protect and nourish them. Malaria parasite co evolved with their vectors. With evolution of hematophagy in vector mosquitoes, their spread became possible to land vertebrates. With increasing population of humans, there was an easy source of available blood for the vector mosquitoes, which help them to select human blood over other land vertebrates. Blood provide rich source of food for malaria parasite. Temperature is the limiting factor for survival and reproduction of vector mosquitoes, so malaria became more fatal in tropical and subtropical countries due to more vectors populations, especially in African countries, who suffered most from this deadly disease. Agriculture practices, communal living, small water collections, domestication *etc.* drives the vector mosquitoes towards anthropophily rather than zoophily. However in 20th century, the mortality due to malaria is reduced due to improved living conditions, awareness, therapeutic drugs and vector control measures. By study natural history of human malaria we can learn that, work of some pioneers help the human race to survive this deadly disease in therapeutic way otherwise nature would had given natural selective protection to humans by providing some genetic alterations and current world scenario would be different.

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