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# Mitigating Climate Change on Malaria by Biotechnological Applications

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## ABSTRACT

Climate change is progressing globally and is likely to affect the human health in various ways. Transmission of vector borne diseases like malaria, which is endemic in most parts of India, is likely to be affected by climate variability. Temperature affects the developmental period related to different stages of mosquitoes' life cycle like blood feeding rates, gonotrophic cycle and longevity. Increase in temperature increases the probability of transmission by reducing the time of gonotrophic cycle, increasing the rate of blood meal digestion and greater frequency of feeding the host. Various reports on the impact of climate change on malaria in India on climate change and its impact on incidence of malaria, regarding impact of climate change on malaria in India with emphasis on selected sites, have shown marked impact and likelihood of increased incidence of malaria and development of new endemic regions. Its hence important to develop newer strategies and Biotechnology, which can play a vital role in combating malaria by intervening at diagnostic, prophylactic, therapeutic and preventive levels by interfering in malarial transmission by vector mosquitoes. Applications to malaria control can be in the form of (a) newer drug development, (b) vector incapacitation-transgenic mosquitoes, (c) vaccine development-identification and manufacture, (d) differential diagnosis- speciation and drug sensitivity of malaria parasites. Biotechnology and improved surveillance of malarial infection is the key in mitigating the effect of climate change on incidence of malaria.

**KEY WORDS:** biotechnology, climate change, control, malaria, surveillance, transgenic

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## INTRODUCTION:

The changing climate is a globally established and progressive threat to the planet, its inhabitants and the mankind. During the last 100 yrs, human activities related to burning of fossil fuel, deforestation and agriculture have led to 35% increase in CO<sub>2</sub> levels in the earth's atmosphere leading to increased trapping of heat culminating in global warming. This process is in continuance with a projected average global temperature rise of 1.8° to 4.0° C by the year 2100, depending upon increase in anthropogenic green house gas (GHG) concentration and measures to limit them. As per IPCC fourth assessment report, eleven of the last twelve years (1995 to 2006) rank among the twelve warmest years in the instrumental record of global surface temperature<sup>[1]</sup> (IPCC, 2007). The IPCC

reported global rise of sea level 1.8 mm per year from 1961 to 2003 and projected the total rise of 3 to 6cm by the year 2100. These climatic changes will cause disruption of ecosystem to support human health and livelihood causing the impact on health system leading to increase in health related risk like Malaria, Cholera, strokes etc.

Taking an account of global climate change and its impact on health, W.H.O in October, 2007<sup>[2]</sup> declared the theme “Protecting health from climate change” for World Health Day, 2008. One of the potential health consequences is a change in distribution patterns of vector-borne diseases like malaria, which is associated with one of four species of parasite and transmitted by a mosquito vector. Climatic conditions and temperature in particular, directly influence mosquito development, feeding-frequency and longevity of the mosquito, as well as the time in which the parasite develops inside the mosquito and other environmental factors such as vegetation and breeding sites.

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### ***Malaria- A Global Scenario:***

Malaria is one of the most severe public health problems worldwide and according to WHO estimates about 300 to 500 million suffer globally from malaria and about 2.7 million die because of it and its complications. According to the WHO's world health report on malaria, 2011<sup>[3]</sup> and the Global action Plan, 3.3 billion people (half the world's population) live in areas at risk of malaria transmission in 106 countries and territories. In 2010, malaria caused an estimated 219 million clinical episodes, and 660,000 deaths. An estimated 91% of deaths in 2010 were in the African Region, followed by 6% in the South-East Asian Region and 3% in the Eastern Mediterranean Region (3%).

### ***Malaria in India:***

Malaria is endemic in almost all part of India except elevations above 1800 meters<sup>[4]</sup> and some coastal areas. Out of the four species of malarial-parasite: *Plasmodium*, three species are responsible for malaria in India .*P.Vivax*, *P.falciparum* and *P.malariae* out of which *P.vivax* is responsible for about 50%,*P.falciparum* 40 %-50%.and *P.malariae* in small numbers. Six species of *Anophele* mosquito, the vector, are responsible for malaria transmission in India. According to the World Malaria Report<sup>[5]</sup>, 22% of India's population live in high transmission , 67% live in low transmission areas and 11% live in malaria-free areas. In 2013, 0.88 million cases have been recorded with *P. falciparum* causing 53% and *P. vivax* causing 47% of the infections and the incidence of malaria in India accounted for 58% of cases in the South East Asia Region of WHO. According to the estimates to assess India's actual malaria death burden, the total annual number of cases in India may be about 9.7 million, with about 30,014 – 48,660 deaths.<sup>[6] [7]</sup>

### ***Climate Change: Indian Scenario***

The latest climate change scenarios and projections for India, based on Regional Climate Modeling (RCM) system, known as PRECIS applied for India using IPCC scenarios A2 and B2 shows an annual mean surface temperature rise by the end of century, ranging from 3 to 5°C under A2 scenario and 2.5 to 4°C under B2 scenario, with warming more pronounced in the northern parts of India<sup>[8]</sup>. A 20% rise in all India summer monsoon rainfall and further rise

in rainfall is projected over all states except Punjab, Rajasthan, and Tamil Nadu, which show a slight decrease. More extremes in maximum and minimum temperatures are also expected and similarly extreme precipitation may also result, particularly over the west coast of India and west central India<sup>[9]</sup>.The disruption in rainfall patterns and temperature can be expected to lead to an increased burden of vector-borne diseases. However, the capacity to cope with potentially increasing levels of these risks and diseases is limited, particularly in developing countries like India.

### ***Climate Change and Malaria in Asia and India:***

Spatial and temporal distribution of vector-borne diseases like malaria, dengue and chikungunya are likely to be affected the most as the mosquitoes which transmit the diseases are cold blooded. Their life cycle and development of pathogen in their body are likely to be affected at varying temperature and relative humidity. Studies undertaken in India with A2 scenario on malaria reveal that the transmission window in Punjab, Haryana, Jammu & Kashmir and northeastern states are likely to extend temporarily by 2–3 months and in Orissa, Andhra Pradesh and Tamil Nadu there may be reduction in transmission windows.<sup>[10][11]</sup>

The Climate change phenomenon in India may lead to increased incidence of malaria in winter season. The summer season may also become warmer and may show some decrease in the incidence of disease, if the duration of temperature above 40 ° C increases. However, the rain fall and monsoon season may possibly be erratic and the incidence of malaria may increase or decrease depending upon the rain fall and humidity. Looking at the global scenario, the incidence of malaria may increase in colder areas where at present it is less prominent due to rise in the temperature and the climate being more conducive for the malaria parasite and vector. So, newer areas may show upsurge of malaria cases and become endemic due to global warming while some of the warmer areas may show reduced incidence of the disease depending upon the rise in temperature and efficacy of mitigation strategies of climate change.<sup>[12]</sup>

### ***Impact of climate change on Vector Borne diseases:***

The climate change may have important and far reaching effects on infectious diseases especially the vector borne diseases which are transmitted by

poikilothermic arthropods like mosquitoes. The vector borne disease transmission depends greatly on survival and reproduction rate of the vector, time of year and level of activity especially the biting rate and the rate of development and reproduction of parasite in the vector. The vectors, pathogens and parasites reproduce and survive within certain optimal climatic conditions and any change in these conditions can modify greatly the properties of disease transmission. The most influential climatic factors include temperature, precipitation and relative humidity and they play important role by acting on vectors as well as parasites and pathogens.

### ***Interplay between climate change, Malaria parasite and vector:***

Temperature affects the developmental period related to different stages of mosquitoes life cycle like blood feeding rates, gonotrophic cycle and longevity. Increase in temperature increases the probability of transmission by reducing the time of gonotrophic cycle and increasing the rate of blood meal digestion and greater frequency of feeding the host. The development rate of mosquito larvae is temperature dependent: below 16°C development of *An. gambiae* mosquitoes stops and below 14°C they die. In cold temperatures the larvae develop very slowly and in many cases they may be eaten by predators and may never live to transmit the disease. Once larvae emerge to become adults, the rate at which they feed on man is dependent upon the ambient temperature. At 17°C the female mosquitoes (*An. gambiae*) feed on humans every 4 days while at 25°C they take blood meals from humans every 2 days. Rainfall increases the breeding habitats for mosquitoes leading to increased population sizes and the rate of malaria transmission.

The rate of development of the malaria parasite in female mosquitoes is very sensitive to ambient temperature. The rate of the parasite development in the female mosquito has an exponential relationship to temperature. This means that very small increase in external temperature will reduce the time it takes for the parasite to mature several fold. At optimum temperature of 28°C an *Anopheline* mosquito egg takes ten days to reach the adult age. The duration gets prolonged at lower temperature while duration is decreased at increase temperature however at more than 40 °C the mortality occurs in the mosquitoes.<sup>[13]</sup> The sporogony of malarial parasite is greatly affected by change in climate as the mosquitoes are cold blooded arthropods. The best condition for development of malarial parasite is

between 20 to 30 °C and a relative humidity of 60%. The minimum temperature for the development of *P.vivax* ranges from 14.5 to 16.5 °C, while for *P.falciparum* it ranges from 16.5 to 19 °C. At 20 °C *P.falciparum* takes 22 to 23 days whereas at 25 °C it takes only 12 to 14 days to complete the sporogony cycle. *P.vivax* requires 16 to 17 days to complete the sporogony at 20 °C, whereas it is reduced to 9 to 10 days at 25 °C.

### **BIOTECHNOLOGY & MALARIA:**

Biotechnology employs powerful but simple procedures to identify, isolate, purify and study the regulation of genes and their products.<sup>[14]</sup> The use of monoclonal antibody and genetic engineering technologies could provide the essential tools to help overcome the difficulties encountered in development of vaccines for protozoan and helminth parasites of livestock<sup>[15]</sup>. The difficulties encountered are due to the inability to identify antigens which induce protective immune responses and in obtaining sufficient quantities of vaccine trials.<sup>[16]</sup> Application of biotechnology to researches in parasitology provides promising avenues for significant breakthroughs in vaccine production and can play a role in controlling malaria in the following ways.

#### ***A. Diagnostic Tools:***

Prompt and accurate diagnosis is critical to the effective management of malaria. Malaria diagnosis involves identifying malaria parasites or antigens/products in patient blood. In the laboratory, malaria is diagnosed using different techniques, e.g. conventional microscopic diagnosis by staining thin and thick peripheral blood smears, other concentration techniques, e.g. quantitative buffy coat (QBC) method, rapid diagnostic tests.

1) *Rapid diagnostic tests (RDTs)*: Since the World Health Organization (WHO) recognized the urgent need for new, simple, quick, accurate, and cost-effective diagnostic tests for determining the presence of malaria parasites, to overcome the deficiencies of light microscopy, numerous new malaria-diagnostic techniques have been developed. RDTs are all based on the same principle and detect malaria antigen in blood flowing along a membrane containing specific anti-malaria antibodies; they do not require laboratory equipment. Most products target a *P. falciparum*-specific protein, e.g. histidine-rich protein II (HRP-II) or lactate dehydrogenase (LDH). Some tests detect *P. falciparum* specific and pan-specific antigens

(aldolase or pan-malaria pLDH), and distinguish non-*P. falciparum* infections from mixed malaria infections

2) *LAMP Loop-Mediated Isothermal Amplification technique*: The LAMP technique is claimed to be a simple and inexpensive molecular malaria-diagnostic test that detects the conserved 18S ribosome RNA gene of *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. LAMP is more reliable and useful for routine screening for malaria parasites in regions where malaria is endemic. LAMP appears to be easy, sensitive, quick and lower in cost than PCR.

3) *Microarrays*: Microarrays may play an important role in the future diagnosis of infectious diseases. The principle of the microarrays technique parallels traditional Southern hybridization. This diagnostic technique, however, is still in the early stages of development.

4) *FCM assay*: Flow cytometry has reportedly been used for malaria diagnosis, the principle of this technique is based on detection of hemozoin, which is produced when the intra-erythrocytic malaria parasites can be detected by depolarization of laser light, as cells pass through a flow-cytometer channel. This method may provide a sensitivity of 49-98%, and a specificity of 82-97%, for malarial diagnosis and is potentially useful for diagnosing clinically unsuspected malaria.

5) *Automated blood cell counters (ACC)*: An ACC is a practical tool for malaria diagnosis, which uses a Cell-Dyn® 3500 apparatus to detect malaria pigment (haemozoin) in monocytes, and showed a sensitivity of 95% and specificity of 88%, compared with the gold-standard blood smear.

6) *Mass spectro-photometry*: A novel method for in vitro detection of malaria parasites, with a sensitivity of 10 parasites/μl of blood, has been reported recently. It comprises a protocol for cleanup of whole blood samples, followed by direct ultraviolet laser desorption mass spectrometry (LDMS). For malaria diagnosis, the principle of LDMS is to identify a specific biomarker in clinical samples. In malaria, haeme from haemozoin is the parasite-specific biomarker of interest.

8) *Nanotechnology*: A pioneering mobile device using cutting-edge nanotechnology to rapidly detect malaria infection and drug resistance could revolutionize how the disease is diagnosed and treated. The device -- the size and shape of a mobile phone -- will use a range of latest proven nanotechnologies to rapidly analyze the parasite DNA from a blood sample. It will then provide a

malaria diagnosis and comprehensive screening for drug susceptibility in less than 20 minutes, while the patient waits. With immediately available information about the species of parasite and its potential for drug resistance, a course of treatment personally tailored to counter resistance can be given. The handheld device will take a finger prick of blood, extract the malarial DNA and then detect and sequence the specific mutations linked to drug resistance, using a nanowire biosensor. The chip electrically detects the DNA sequences and converts them directly into binary code, the universal language of computers. The binary code can then be readily analyzed and even shared, via wireless or mobile networks, with scientists for real-time monitoring of disease patterns.<sup>[17]</sup>

### **B. Drugs:**

Artemisinin comes in a few derivatives, including the oil soluble artemether, which has been found to induce through the release of free radicals that serve to damage the malaria organism. The malaria parasite accumulates iron by infecting iron-rich red blood cell. Excessive iron that is spilled onto the surrounding tissues will activate the artemisinin and the combined drugs to generate a burst of free radicals that attack the iron rich cells, killing the parasite in the process.

In principle, combination drug therapy should greatly alleviate this problem. Also, the pathway of converting Artemisinic acid, [the precursor of artemisinin] to artemisinin is being incorporated into microorganisms & microbial strains for commercial production of the precursor through fermentation.

### **C. Control of insect populations:**

Vector control is an important component in the prevention and control of VBDs, especially for transmission control. The theme for the World Health Day, 2014 is Vector-Borne Diseases, so the World Health Organization has strategized for the sustainable and cost-effective application of vector control interventions. Reduction of vector insect populations will reduce disease transmission. This can be accomplished in various ways, for instance, with insecticides like permethrin<sup>[18]</sup>, by managing the environment (elimination of breeding sites) or by interfering with reproduction (sterile-insect releases). Recent technological advances suggest an alternative approach, namely genetic modification of the

competence of the vector arthropod to transmit pathogens (vectorial competence).

- 1) *Sterile-insect technique (SIT)*: Insect populations can be controlled by the release of large numbers of sterile males. Thus, if a female mates with a male that has no sperm or whose sperm was rendered unviable, this female will have fewer or no progeny. When many sterile males are released, the local population tends to decline or become extinct.
- 2) *Larvicides*: Trypsin-modulating oostatic factor (TMOF), a mosquito decapeptide, terminates trypsin biosynthesis in the mosquito gut. The hormone is secreted from the ovary, circulates in the hemolymph, binds to a gut receptor and stops trypsin biosynthesis by exerting a translational control on trypsin mRNA. Because of the unique primary amino acid sequence of the hormone and its stable three-dimensional conformation, TMOF is not degraded by gut proteolytic enzymes. Using this unique property, hormone fed to different species of mosquito larvae stops food digestion and causes larval mortality. Cloning and expressing the hormone on the coat protein of tobacco mosaic virus (TMV) in *Chlorella* sp. and *Saccharomyces cerevisiae* cells and feeding the recombinant cells to mosquito larvae caused larval mortality.<sup>[19]</sup>

#### **D. Genetically modified mosquitoes:**

1) *Genetic manipulation of mosquito vectorial competence [Transgenesis]*: One option to interfere with parasite transmission is to genetically modify the mosquito for midgut expression of effector genes, whose products inhibit parasite development. Successful development of the technology described above (transgenesis, promoter characterization and effector-gene identification), permitted the creation of genetically modified mosquitoes impaired in their ability to transmit the malaria parasite tested for the first time by genetically engineering *Anopheles stephensi* for midgut expression of the salivary gland and midgut peptide 1 (SM1). This peptide binds to a putative ookinete receptor on the luminal surface of the midgut epithelium and strongly inhibits ookinete midgut invasion. The genetically modified (GM) mosquitoes are substantially impaired in their ability to transmit the parasite.

The identification of efficient anti-Plasmodium effector genes is an essential prerequisite

for the generation of a refractory mosquito. Mosquito transgenesis has the advantage of having no off-target effects because transgene expression is restricted to the engineered mosquito. The anti-Plasmodium effector genes can be engineered to express in specific tissues (midgut, fat body, and salivary glands), only in females, and in a blood-induced manner. Although it has been shown that a mostly refractory mosquito can be produced in the laboratory, challenges remain for translating these findings to field applications. A method to drive effector genes into mosquitoes in the field still needs to be devised. The MEDEA and homingnuclease (HEG) approaches are among the most promising ones. Additional issues that need to be considered are the multiplicity of *Anopheles* vector species (each needs to be separately engineered), the reproductive barriers within a given species (cryptic species), mass production and sex selection of transgenic mosquitoes (females cannot be mass-released in the field), the large size of the constructs expressing multiple effector genes, and the possible loss of trans gene expression over time

2. *Paratransgenesis*: An alternate approach to spread effector genes through mosquito populations is to introduce effector genes into bacteria that inhabit the mosquito gut, rather than introducing them into the mosquitoes themselves. This approach (known as paratransgenesis) can be used for reducing the capacity of mosquitoes to vector malaria parasites. When *E. coli* displaying the inhibitory SM1 peptide<sup>[18]</sup> or PLA2 on its surface was fed to *An. stephensi* followed by an infectious blood meal, significantly fewer *P. berghei* parasites developed as compared to control mosquitoes fed on wild-type bacteria. Paratransgenesis refers to an alternative approach for delivery of effector molecules via the genetic modification of mosquito symbionts. Advantages of paratransgenesis are the simplicity of genetic modification of bacteria, the ease of growing the genetically modified bacteria in large scale, the fact that it bypasses genetic barriers of reproductively isolated mosquito populations, and effectiveness does not appear to be influenced by mosquito species.

#### **E. Genetic manipulation of mosquito-pathogenic fungi and viruses [Entomopathogenic fungi & viruses]:**

Insect fungal pathogens, *Metarhizium robertsii* and *Beauveria bassiana* are natural killers of insects including mosquitoes. Several studies have highlighted the promising use of insect fungal pathogens for controlling adult malaria

mosquitoes and reducing malaria transmission rates. Recently, *M. robertsii* was genetically engineered to deliver anti-Plasmodium peptides or proteins into the mosquito hemocoel for killing sporozoites or preventing sporozoite invasion of mosquito salivary glands.

#### A. Vaccines:

High genetic diversity, variability of potential target molecules (e.g., *Plasmodium var*:genes), and intracellular sequestration are strategies frequently used by pathogens that allow them to elude immune attack. According to the WHO, the hope is that an effective vaccine will be available within the next 7–15 years. Types of malaria vaccines—Early malaria vaccine development efforts focused on the parasite's pre-erythrocytic stage—the period during which the organism, in the form of a sporozoite, enters a person's blood stream and heads for the liver, where it matures and begins a prolific multiplication process. Today, vaccine developers are trying to develop three types of vaccines:

1) *Pre-erythrocytic vaccine*: Pre-erythrocytic vaccine candidates aim to protect against the early stage of malaria infection—the stage at which the parasite enters or matures in an infected person's liver cells. These vaccines would elicit an immune response that would either prevent infection or attack the infected liver cell if infection does occur. These candidates include (a) Recombinant or genetically engineered proteins or antigens from the surface of the parasite or from the infected liver cell; (b) DNA vaccines that contain the genetic information for producing the vaccine antigen in the vaccine recipient; (c) Live, attenuated vaccines that consist of a weakened form of the whole parasite (the sporozoite) as the vaccine's main component.

2) *Blood-stage vaccine candidates*: Blood-stage vaccine candidates target the malaria parasite at its most destructive stage—the rapid replication of the organism in human red blood cells. Blood-stage vaccines do not aim to block all infection. They are expected to decrease the number of parasites in the blood, and in so doing, reduce the severity of disease. Evidence suggests that people who have survived regular exposure to malaria develop natural immunity over time. The goal of a vaccine that contains antigens or proteins from the surface of the blood-stage parasite (the merozoite) would be to allow the body to develop that natural immunity with much less risk of getting ill.

3) *Transmission-blocking vaccine* : Transmission-blocking vaccine candidates seek to interrupt the life cycle of the parasite by inducing antibodies that prevent the parasite from maturing in the mosquito after it takes a blood meal from a vaccinated person. These vaccines would not prevent a person from getting malaria, nor would they lessen the symptoms of disease. They would, however, limit the spread of infection by preventing mosquitoes that fed on an infected person from spreading malaria to new hosts. A successful transmission-blocking vaccine would be expected to reduce deaths and illness related to malaria in at-risk communities. A more effective malaria vaccine should generate both strong antibody and potent T-cell immune responses<sup>[21]</sup>

#### IV. BETTER MALARIA SURVEILLANCE:

Looking at impact of climatic variability on the disease, better malarial surveillance is required in future, for which WHO has promoted Malaria Early Warning Systems (MEWS)<sup>[22]</sup> as a way of improving how decision-makers manage epidemics, by giving them more time to plan and respond. Therefore it is the right time to redress the balance and position MEWS as a standard approach for national surveillance in order to predict epidemics of Malaria in different regions in future.

The latest contributions of biotechnology in the diagnostic tests are the Rapid Diagnostic Tests[RDTs]which detect malaria antigen in the blood containing specific anti-malaria antibodies and target a *Plasmodium*-specific protein like histidine-rich protein II(HRP-II),LAMP technique, Flow cytometry and Nanotechnological biosensors.

Role of biotechnology in the treatment of malaria is through the drug, Artemisinin Combined therapy,in which 2 or 3 antimalarial drugs are administered, each with a distinct mechanism of action against the parasite. Interfering with reproduction (sterile-insect releases) or introducing algae with genes incorporated to produce trypsin-modulating-oostatic-factor which inhibit the trypsin formation in the gut of the larvae in the breeding places of the larvae which act as larvicides. A novel method discovered is to make the vector incompetent to host the parasite. The SM1 peptide strongly inhibited parasite development and transmission when administered to mosquitoes. Entomopathogenic fungi attacks both the vector and the parasite, and reduces the transmission of the disease. For the prevention of this disease, there are 3 main types of vaccines being developed also.

Biotechnology has brought about a faster means of discovering new facts in the scientific world and has its role in all the various aspects of science. It is “Biotechnology”, the manipulation of living organisms and their bio-chemical structures, which is helping in the diagnostic techniques, treatment and prevention of malaria which plays a key role in combating the effects of climate change on it. So Biotechnology is indeed our last and best line of defence against the changed pattern of diseases emerging due to global warming.

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