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Defeating Malaria with Preventative Treatment of Disease and Deterrent Measures against Anopheline Vectors (Diptera: Culicidae).

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Review Article

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ABSTRACT

Malaria is a major public health issue in many regions of the world and is transmitted to the human by the bite of the infected Anopheles mosquitoes. It is a major health problem that particularly causes considerable morbidity and mortality in humans. Symptoms of malaria are nighttime fevers, chills, body aches, headaches, nausea, vomiting and general uneasiness that can range from mild to severe condition. This article provides information on the risks, symptoms and treatment of disease, and general preventative measures against mosquitoes. The risk of disease increases during wet seasons when accumulated water causes mosquitoes to breed. Blocking the transmission of the parasite from patient to patient is a key to the malaria eradication. The mosquitoes which drive parasite transmission are key targets for interventions of adopting vector control measures. One important control strategy against this mosquito borne malaria disease is the mosquito control, which aims to reduce human-mosquito contact. Different control measures can be used routinely against mosquitoes and their larvae including chemical (insecticide), biological (larvivorous fish or pathogenic fungi), environmental (land filling or drainage) and personal protection (mosquito repellents formulated as pills, coils, ointments, lotions, and sprays; and insecticide-treated or untreated bed nets). For adults' vector control, certain tools such as indoor spraying and space spraying, both alone and in combination, are the key factors. This information generated will ensure the sustainability of the vector control strategy to avoid increased malaria threatens.

INTRODUCTION

Malaria is a mosquito borne disease and presents health threat to the many peoples of the world. Mosquitoes transmitting parasite infection is caused by the bite of female Anopheles vectors. Malaria is an acute and sometime chronic infectious disease due to the presence of protozoan parasites within the red blood cells. The blood of a human infected with malaria infects the mosquito and the cycle continues. Malaria occurs more frequently during warm and humid seasons, and transmission is more intense in urban areas, including downtown business areas. The risk is higher for those peoples staying in places with nearby stagnant water reservoirs, and having no mosquito protection, but transmission can occur in any urban setting. Tropical areas are more vulnerable to parasitic diseases and the risk of contracting arthropod-borne illnesses is increased due to climate change and intensifying globalization [1-3]. Worldwide, mosquitoes transmit diseases to more than 700 million peoples annually and are responsible for 1 death for every 17 peoples currently alive. Malaria results from an infection by a protozoan carried by *Anopheles* species. About 2.5 billion people are at risk, more than 500 million peoples become seriously ill with malaria every year, and more than one million peoples die due to malaria [4].

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The Mosquito Enemy

Several Anopheles species are responsible for transmission of malaria. Throughout the world, each species of Anopheles is peculiar to a localized area. Of the 460 Anopheles species, approximately 100 can transmit malaria parasites. The *Anopheles stephensi* Liston (Diptera: Culicidae) and *A. subpictus* Grassi are commonly found during survey work in the region. The *A. stephensi* is a sub-tropical species distributed throughout the Middle East and South Asia and is also a major vector in urban areas in India, Pakistan and Iran accounting for several malaria cases annually [5]. This species has a unique characteristic of breeding proficiently in underground water tanks prevalent in villages and urban areas [6]. The *A. subpictus* is another species that is widely distributed in oriental regions and is a prolific breeder during the rainy season. Sibling species of *A. subpictus* (fresh water form) has been incriminated and established as a primary vector of malaria in some regions and is a well-established secondary vector of malaria in other locations [7].

The Malaria Parasite

Different species of the causative organism of genus Plasmodium can cause different degrees of illness. The malaria organism is a protozoan that is a microscopic, single-celled animal, not to be confused with a bacterium, which belongs to the plant kingdom. The parasite has a complex life cycle, reproducing first in the liver, then in the red blood cells and finally in the mosquito. During these three cycles the parasite transforms itself and emerges each time with new physical and biochemical characteristics. Mosquitoes prey on a variety of hosts such as humans, monkeys, lizards and birds carrying species of malaria parasites which in turn infect only specific hosts. Of the approximately 50 different species of malaria parasites sharing the genetic name Plasmodium, only 5 infect humans; *Plasmodium falciparum*, the killer; *Plasmodium vivax*; *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. Among those, *P. falciparum* is the most common species identified followed by *P. vivax* and *P. falciparum* traditionally accounts for the majority of deaths. The *P. vivax* is one of two forms of relapsing malaria to infect humans and is the most prevalent species. It has the ability to become dormant in the liver (hypnozoite) and can be reactivated after months or even years leading to an attack of blood stage malaria despite the absence of a mosquito bite. In the blood of an infected patient a minority of parasites form gametocytes- the sexual form of the parasite. It is these gametocytes, taken up in the mosquito's blood meal, that infect the mosquito and thus continue the parasite's life cycle [8-9].

The Life Cycle of the Malaria Parasite

During the humans feeding (between dusk and dawn- midnight to 4 am is the peak time), females Anopheles introduce a hollow stylet containing a duct which is connected to the salivary glands. Trough this duct females inject a few drops of saliva to act as a local anesthetic so that a person do not feel the bite. Simultaneously with saliva females introduce into bloodstream hundreds of motile sporozoites. The malaria organisms (sporozoites) injected into the body by the bite of the infected mosquito remain in the bloodstream for only a short period usually less than one hour. They disappear from the circulation and establish themselves in the cells of the liver, where they commence cycles of reproduction, a process lasting from six to twelve days. During this time, each sporozoite grows through repeated divisions of the nucleus into one large cell named schizont, now containing thousands of tiny new parasites. The increased pressure causes the schizont to burst and release these newly formed parasites called merozoites, which leave the liver and enter the red blood cells where they initiate cycles of reproduction [10].

Common Symptoms of Malaria

Typically, malaria can develop as quickly as seven days after a person is bitten by an infected mosquito. Normally, the time between being infected and when symptoms start (incubation period) is seven to 18 days, depending on the specific parasite with which a person is infected. However, in some cases it can take up to a year for symptoms to develop. The initial symptoms of malaria are flu-like and include a high temperature (fever), headache, sweats, chills and vomiting. These symptoms are often mild and can sometimes be difficult to identify as malaria. With some types of malaria, the fever occurs in four to eight hour cycles. During these cycles, a person feels cold at first with shivering that lasts for up to an hour. Then fever is developed that lasts for two to six hours, accompanied by severe sweating. Other symptoms of malaria can include muscle pains, diarrhea and generally feeling sick If a person becomes infected with the most serious type of malaria, caused by the *P. falciparum* parasite, there is a risk to quickly develop severe and life-threatening complications such as breathing problems and organ failure if not treated promptly.

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Preventative Treatment of Malaria

There are medicinal programs that may help to avoid malaria (in addition to taking measures to repel mosquitoes), however, there is no one method that can protect completely against the risks of contracting malaria. There are 2 types of anti-malarial drugs used to suppress the clinical symptoms of malaria, but they will not prevent the establishment of a malaria infection. If anti-malarial drugs are true prophylactics (to guard before) they would prevent malaria infection by killing the parasites (sporozoites) at the moment they are introduced into bloodstream by the bite of the Anopheles. Instead, anti-malarial medications act by eliminating the parasites during their multiplication phase in the liver stage or their replication phase in the red blood cells. In offering guidance on the choice of anti-malarial drugs, the main concern is to provide protection against *P. falciparum,* which is the most dangerous form of the illness. The majority of available anti-malarials target the blood stage in the parasite life cycle, since this leads to the clinical symptoms of malaria. Current treatment requires a 3-day administration once or twice daily. Ideally, a drug is needed that requires just a single oral administration, thereby improving compliance and allowing the healthcare worker to directly observe treatment. This is especially important when treatment follow-up is difficult as is the case in many malaria endemic countries. The dosage of Chloroquine (taken weekly) is the recommended prophylaxis treatment. This treatment should be started one week prior to possible disease exposure. Prophylaxis is recommended for peoples traveling to remote areas of the country, high outbreak areas and especially along the state borders [11].

It is imperative that always take the medication at regular intervals throughout the stay in a malarious region, and it should be continued to do so for 1-4 weeks after leaving the area. Taking the full course of suppressants is essential even for a short stay because one single bite of vector is sufficient to infect a person. Always take the suppressant with plenty of water to reduce stomach discomfort which may occur occasionally. Since an adequate concentration of the drug in the blood is reached a few hours after ingestion, a person may start the medication on the day of departure. However, it would be ideal to take a complete supply of medication to avoid any problems in getting the anti-malarial drugs that are prescribed by the family Physician.

General Preventative Measures against Mosquitoes

Several strategies and approaches are available for preventing mosquito bites to prevent malaria infection, including repellents and these approaches should be considered by those living in affected areas and by travelling to areas where there is high risk of infection.

Electronic mosquito repellents

Electronic mosquito repellents are designed to repel female mosquitoes by emitting high-pitched sounds almost inaudible to the human ear. These are claimed by their manufacturers to be effective in repelling mosquitoes and preventing disease [12]. Electronic mosquito repellents are marketed in response to a huge demand from the public for convenient, safe and effective anti-mosquito products. Female Anopheles mosquitoes transmit malaria by sucking blood from humans, and these small hand-held, battery-powered repellents are intended to repel them by emitting a high frequency buzz almost inaudible to the human ear. They can be used both indoors and outdoors, and are claimed to repel mosquitoes within a range of up to 2.5 meters [13]. Some of the electronic repellents seem to be based on known aspects of mosquito behavior, while others have no scientific data to substantiate their claims. Manufacturers have put forward at least two reasons to explain the alleged repellent action of sound against mosquitoes. One reason is that the flight sound of males repels females once they have been inseminated; hence, what ever mimics the male's flight sound may repel females. Another reason is that mosquitoes avoid the ultrasonic cries of bats [14]. However, research has shown that male mosquitoes are actually the ones attracted by the female flight sound and females normally have a very weak sensitivity for sound compared with the males [15].

Mechanical Protection from Vectors

Mechanical forms of protection are still the most effective means of preventing the spread of malaria. Ensure that the window and door screens of room are fit tightly and free of holes. At the same time check the screens to be sure the mesh is small enough to prohibit the entrance of any mosquitoes. In malarious areas, un-screened bedrooms require use of mosquito bed nets except in buildings with sealed windows and central air conditioning. There are several good reasons for using bed net in addition to preventive medication: 1) Because it provides protection when the Anopheles mosquito is most active, and

chances of infection are reduced. Some Malariologists estimate that with proper use of bed nets malaria cases could be reduced by two-thirds. 2) It offers protection from other diseases transmitted by mosquitoes, such as flariasis, which is known for massive swelling of the limbs. 3) It also protects against ticks, beetles, flies, spiders and other insects which may enter to bed.

Mosquito Repellent

Apply mosquito repellent available in sprays, lotions and towelettes to all exposed areas of skin as well as clothes, avoiding eyes and mouth. Since repellent gradually evaporates and some will be lost through perspiration, swimming and active exercise, re-apply after every few hours for continuous protection according to the manufacturer's directions. Periodic outbreaks of malaria have occurred in some tourist locations, thus, if traveling in a high-risk area, applying repellent from dusk to dawn is necessary. Apply a repellent containing the insecticide DEET (concentration 30 to 35%) or picaridin (concentration 20% or greater for tropical travelers). The repellent should be applied to all exposed non-sensitive areas of the body and their frequent application ensures continuous protection. The time of day and type of insects to be avoided determine when the repellent should be applied. Mosquitoes that transmit malaria (Anopheles mosquitoes) are night biters. Thus, if traveling in a malarious area, be especially vigilant in applying repellent from dusk to dawn. Mosquitoes that transmit dengue (Aedes mosquitoes) are day biters, and travelers need to be especially vigilant applying repellent during daytime hours when in areas of dengue risk. Peak biting times are usually during the early morning hours and again from late afternoon to dusk.

Wearing of Protective Clothing

Wearing of clothing that exposes as little skin as possible is a good practicable measure. Beginning from the sunset wear long-sleeved shirts and long pants in light colors such as beige or yellow. Avoid wearing of dark clothing that attracts mosquitoes, as does the scent of perfume or after-shave lotion. Treat outer clothing with permethrin (or other pyrethroid) when traveling in an area of high risk for malaria or other mosquito-borne or other vector-borne diseases. If a person is not sleeping in a sealed room or in air-conditioned room, always sleep under a permethrin-impregnated bed net when at risk. Regularly, check the net for rips and tears, and keep it tucked in around the bed at all times. Ensure that all open windows have insect screens. Use an aerosol insecticide before going to bed and a vaporizer device throughout the night. Outdoors, a smoldering pyrethroid coil can be used to reduce flying insects.

Insecticides Killing Mosquitoes

Insecticides are currently most practical in controlling mosquito vector, and therefore cannot be overlooked. Insecticides kill mosquitoes instantly by acting on the central nervous system. Therefore, monitoring of insecticide resistance at regular intervals is necessary so that an effective management strategy can be designed. The effective resistance management mainly depends upon early detection of the status of resistance. The susceptibility studies of malaria vectors *A. stephensi* and *A. subpictus* collected from various locations have been conducted by adulticide bioassay of DDT, malathion and deltamethrin, and larvicide bioassay of fenthion, temephos, chlorpyriphos and malathion using diagnostic doses. Both species from all locations exhibited variable resistance to DDT and malathion from majority of locations. Adults of both the species are susceptible to deltamethrin. Larvae of both the Anopheline species showed some evidence of resistance to chlorpyriphos followed by fenthion whereas susceptible to temephos and malathion. Revealing the mechanism of resistance is equally important to that of monitoring resistance in mosquito vectors. Variation in insecticide resistance mainly depends upon the type of insecticide and frequency of use. Excessive and unwanted usage of insecticides not only increases vector resistance, but also results in cross resistance to other insecticides. Although various mechanisms of insecticide resistance in insects such as metabolic resistance (i.e. esterases, monooxigenase or glutathione-s-transferase), resistance due to reduced penetration and behavioral resistance are reported in several vectors, generally it is governed by either involvement of metabolic mechanisms or alterations at target sites. Since there are limited numbers of insecticides available for vector control, an approach focused on the rotational use of insecticides or a mosaic strategy can be adopted to delay development of resistance in malaria vectors as studied in a field trials to manage multi-insecticide resistant. Also, emphasis needs to be given to other eco-friendly methods of vector control, such as biocontrol with larvivorous fish, and biolarvicides especially *Bacillus thuringiensis* should be included in the integrated vector management program [16]. Among the pesticides tested, insecticides are found most promising and show the most potent activities. For protection against mosquitoes, bed nets and clothing may be soaked in or sprayed with permethrin. Permethrin is an insecticide licensed for use on clothing; when applied

according to directions, it can be effective on clothing for several months and on bed nets for half a year. Permethrin physically binds to the fabric, which then can be repeatedly washed without loss of effects; this also prevents absorption through skin. In some countries, deltamethrin liquid is available to find these products locally. Treat outer clothing with permethrin (or other Pyrethroid) when traveling in a high disease risk area.

Essential Oils Killing Mosquitoes

Essential oils play an important role in controlling several mosquito species. In general, essential oils from plants have been considered important natural resources to act as insecticides. Efficacy of various essential oils has been screened against mosquito vectors for their larvicidal and knockdown effects. Of these, 8 oils viz., calamus oil, cinnamon oil, citronella oil, clove oil, eucalyptus oil, lemon oil, mentha oil and orange oil have been screened further against *A. stephensi* for their larvicial and knockdown effects at different concentrations. Mentha oil proved the most promising against *A. stephensi* recording LC_{50} and LC_{90} values of 39.74 and 115.67 ppm, respectively, for larvicidal activity [17]. For evaluation of larvicidal potential against *A. stephensi,* the ethanolic, methanolic and dichloromethane leaves extracts of three different plants have been used in dose-dependent experiments in two media, while the antioxidant enzymes activities investigated using four different methods viz., superoxide dismutase, peroxidase, ascorbate and catalase. The comparative performance of ethanolic extracts (65-90%) has been found better than the methanolic extract (70-87%) and dichloromethane extract (60-70%). Among the three plants extracts tested in two media, *Stevia rebaudiana* exhibited higher larvicidal activity with LC_{50} (24 h) in methanolic extract than *Parthenium hysterophorous* and *Ginkgo biloba*. The *G. biloba* and *P. hysterophorous* exhibited the strongest anti-oxidative enzymes activity, and *S. rebaudiana* found less active and no significant difference observed [18]. These plants can be further used for vector control alternative to synthetic insecticide due to eco-friendly and diseases control activities.

The new strategies for malaria prevention and control are emphasizing 'integrated vector management' (IVM). This approach reinforces linkages between health and environment, optimizing the benefits to both sides. Integrated vector management strategies are designed to achieve the greatest disease-control benefit in the most cost-effective manner, while minimizing negative impacts on ecosystems and adverse side-effects on public health. The application of these methods as an integrated control system could be adjusted to environmental conditions for rapid and effective vector and disease controls.

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