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Strategies for Malaria Prevention and Control

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Received: Sept 20, 2022 Accepted: Oct 9, 2022

INTRODUCTION

Globally, a handful of malaria vaccine publications have endeavoured to provide a detailed image of all clinical trials that have occurred in the past. Now, it is challenging to sum up, all projects in a single rave as the field has expanded at an unprecedented rate. WHO has compiled a "rainbow table" spreadsheet, an inclusive publicly available collation regarding global malaria vaccine projects published in the past years (Schwartz et al. 2012).

Malaria is a life-threatening disease affecting young children and pregnant women caused by parasites of the *Plasmodium* genus. With about half of the world's population on the verge of infection, it poses a significant health hazard. It is transmitted to the host when pathogen-ridden mosquitoes bite them. People from third-world countries are at a greater risk of getting the infection and are more susceptible to death, especially children below five years of age residing in sub-Saharan Africa (Laurens 2018).

The need to develop a vaccine against malaria has been stressed from the documentation of the parasite in 1897. In 1897, Ronald Ross discovered the mosquito (vectors) that transmit the disease. Moreover, the parasite can only be transmitted by the female *Anopheles* mosquito. The appearance of resistant parasites and vectors has triggered to focus on other control achievements, including a vaccine. (Mahmoudi and Keshavarz 2018). Malarial immunity through vaccination was established more than 30 years ago when individuals were immunized via continual bites of *Plasmodium falciparum*-infected mosquitoes, but irradiated mosquitoes still hold metabolic activity. (Arama et al. 2014). After being neglected for decades, attempts to cope with malaria have increased significantly with the international community's funding. An increase in funding has boosted the status of proceedings comprising control of malaria, such as the acquisition and dispersal of artemisinin-based combination therapy (ACT), the anti-malarial drug group of choice and insecticide-treated bed nets (ITNs) along with other mosquito vector control plans. These medications have been temporarily associated with the decline in the incidence of malaria of more than 50% in certain zones of Africa. Regrettably, the poor healthcare infrastructure of many malaria-endemic countries hinders the implementation of ACTs and ITNs. Moreover, it has been observed that the microorganism is developing resistance to anti-malarial drugs and rapidly spreading it. Even now, the opposition has been set in Asia to the artemisinin derivatives. So, an effective vaccine is needed to control, eliminate, or even eradicate malaria (Crompton et al. 2010).

Only two species of *Plasmodium* are in the run for vaccine development out of five species that cause malaria in humans. More than 90% of malaria-related deaths are attributed to *Plasmodium (P.) falciparum*, and there is a similar ascendency of *P. falciparum* projects in the malaria vaccine landscape (Schwartz et al. 2012). Unfortunately, to develop a fruitful vaccine for *falciparum* malaria, there are certain complications, such as the extreme intricacy of malarial parasite life, intricate and diverse parasite genomes, immune dodging, and the complex nature of the infectious cycle of the parasites (Mahmoudi and Keshavarz 2018).

Vaccines are at the top of the list in promoting both individual and public health, among all the highly effective tools. Vaccination against infectious diseases has made the most significant contributions to global public health compared to all other human interventions. Presently, no licensed or registered vaccine exists for malaria. Some experts deemed it necessary to eliminate malaria. The WHO published strategic goals to accredit malaria vaccines encountering *P. falciparum* and *P. vivax* with no less than 75% protective efficacy against clinical malaria and reducing spread to enable elimination (Laurens 2018).

There are quite a few malaria vaccine candidates who have undergone different phases of clinical trials; however, until now, there was not a good candidate with practical usefulness. Currently, the contenders are directed against those stages of the pathogen life cycle, which comprises humans and mosquitoes for a malaria vaccine. Still, up until now, for potential vaccine development, only some proteins have been considered (Crompton et al. 2010).

Citation: Hayder H, Uzair M, Ahmad S, Ashraf U, Huzaifa A, Mehmood MS, Mughal MAS and Saleem F, 2023. Strategies for malaria prevention and control. In: Aguilar-Marcelino L, Younus M, Khan A, Saeed NM and Abbas RZ (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 3, pp: 157-163. https://doi.org/10.47278/book.oht/2023.91

Table 1: Discoveries regarding malaria by various scientists in the history (Cox et al. 2020)

Sr.no	Year	Discovery	Scientists
1	1880	Discovered parasites in blood as well as sexual stages of malaria in bloods were discovered	Alphonse laveran and William MacCallum
2	1897	Different phases of transformation cycle in culicine mosquitoes and birds infected with *Plasmodium relictum* were found.	Ronald Ross
3	1898	It was described after certain experiments and observations that plasmodium is spread by mosquitoes that act as their vectors	Giovanni Battista Grassi, Amico Bignami, Giuseppe Bastianelli
4	1948	It was reported and described that agents (parasite) responsible for malaria are grown in liver or hepatic system before they gain entry into the blood vessels	Henry
5	1982	The last stage in the life cycle that is the presence of inactive stages in the liver was completely described	Wojciech Krotoski

Malaria History

Malaria is an old Infectious disease. According to all proofs and experiments, malaria was first documented in China in about 2700 BC, in clay tablets in Mesopotamia in 2000 BC, in Egypt in 1570 and in Hindi textbooks in the sixth century. These historical records are kept with so many caries and precautions. Still, these are very important for studies when we move into the following centuries, and we get firm knowledge through these records. Greeks that contain Homer in 850 BC, Agrigentum having state Empidocal in 550 BC, and Hippocrates in 400 BC was well known in the documentary and different aspects of poor health, including fever and spleen enlargement, were observed in the people that were resident of dirty areas. Antoni van Leeuwenhoek found bacteria in the year 1676, and the formation of the germ theory of diseases by Louis Pasteur and Koch during 1878-1879 also made help in the discovery of malaria at an intensive degree (Cox et al. 2020). The general history of malaria was described in 1849 (Poser Charles and George 1999). In 1970, widespread resistance was developed to malaria, and there was no treatment for malaria (Butler et al. 2010). Malarial disease always has been a public problem. It impacts death and infection rates in underdeveloped countries. After that, a noticeable decrease in malarial cases was seen between 2000 to 2010, but it has always remained a challenge (Corine et al. 2020). Table 1 highlighted the various discoveries in the history regarding malaria.

Malaria Status in Pakistan

In Pakistan, each year, 3.5 million confirmed cases of malaria are reported. Between 2015 to 2018 there is regular increase in malaria cases. According to WHO, in 2017 and 2018, 60% of the people in Pakistan lived in the malaria-endemic region (Ali et al. 2010). Out of six countries in the Eastern Mediterranean region, Pakistan has the highest ratio of malaria transmission. The prevalence of malarial infection is different in different provinces and varies in different cities due to climate changes. The province wise prevalence of malarial infection in Pakistan in 2017 was 1.1% in Punjab, 26.5% in Sindh, 20.5% in Baluchistan, and 30% in Khyber Pakhtunkhwa (Ali et al. 2010).

Strategies about Prevention of Malaria

With the advancement in technology, various techniques have been developed to control malaria. Vector control and community mobilization are the effective methods which are described below;

Vector Control

The term "vector control" refers to a set of actions taken against a disease vector with the goal of protecting recognized disease transmission hotspots while limiting the disease vector's capacity to spread the disease. The capability of populations of local vector, or more specifically, the size of the population of the vector, human biting behaviours, and duration relative to the sporogony period determines the susceptibility to malaria. Climate, regional ecology, humans, and vector activity significantly impact each of these variables. To be as effective as possible, vector control strategies must be tailored to the local environment. The goal of vector control during an elimination phase is to lower the populations of local vector having capacity below the very critical level required to uphold transmission (Gueye et al. 2016).

Main Methods for Vector Control

Insecticide-treated Mosquito nets (ITNs)

Long-lasting insecticidal nets (LLINs), which have insecticide lasting up to 3 years, and conventionally treated nets, which have insecticide lasting up to 12 months, are both ITNs. WHO directed all health ministries as well as donor organizations to increase ITN distribution, focusing on populations of young children and expectant mothers since they are at high risk (WHO 2007). With periodic mass distribution campaigns, most national malaria control programs currently use ITN distribution to provide universal coverage.

Larval Source Management (LSM)

LSM is the control of aquatic/watery habitats that may serve as breeding grounds for the mosquito to halt the maturation

of immature stages. It is still neglected as a malaria control tool in Africa despite being one of the oldest weapons in the fight against the disease (Fillinger and Lindsay 2011). LSM got increasing attention as a result of the recent realization that outdoor biting plays a role in the transmission of malaria and offers benefits of lowering outdoor as well as indoor mosquito populations (Gies et al. 2009).

LSM can be Further Classified as

a. Habitat Modification

Landscaping, land reclamation, surface water drainage, and filling are all examples of permanent changes to land and water. It can be completed with basic tools and supplies in remote locations (Fillinger and Lindsay 2011; Tusting et al. 2013).

b. Larviciding

Mosquitoes can regularly be controlled by spraying biological insecticides or chemicals on water bodies. It works better in locations with few, stable, and easily identifiable habitats. The anopheline mosquito larvae control and the decreased numbers of adult mosquitoes have been demonstrated to be effective with microbial larvicides. They do not affect other aquatic species, which gives them a safety edge over chemical larvicides (Tusting et al. 2013).

c. Biological Control

Watery ecosystems are being invaded by natural enemies (e.g., invertebrates, parasites, predatory fish, and disease organisms) (Fillinger and Lindsay 2011; Tusting et al. 2013). To make this strategy work, a lot of resources, and better organization from professionals is needed.

d. Habitat Manipulation

By manipulating water levels, for example, actions like flushing, clearing drains, exposing, or shading, habitats are frequently taken to the sun. Habitat manipulation is more suited in environments with scarce resources, like habitat modification (Tusting et al. 2013).

Indoor Residual Spraying (IRS)

The main Global Malaria Eradication Campaign strategy is IRS. It contributed to the complete eradication of malaria in certain countries and considerably reduced its impact in others (WHO 2015, Global technical strategy for malaria 2016–2030). In 2015, the IRS provided protection to almost 106 million individuals. Its recent growth into areas with high transmission has prompted concerns about its long-term viability as it has traditionally concentrated on areas of low or seasonal transmission (WHO 2015, Global technical strategy for malaria 2016–2030). Several nations have employed IRS to eradicate malaria and manage epidemics.

Methods Under Development

Mass Drug Administration (MDA)

Using the curative drug dose to treat the whole population in a certain area without checking for infection and irrespective of the appearance of signs and symptoms is known as mass drug administration. Since the early 1930s, it has been used to manage malaria and in the 1950s (Poirot 2010), WHO promoted its elimination and eradication. MDA with antimalarials has proven to be effective when used in conjunction with other malaria prevention strategies. For instance, MDA with sulphadoxine-pyrimethamine and IRS achieved significant malaria control levels during the Garki Project in Northern Nigeria in 1969 (Molineaux and Gramiccia 1980). Primaquine and chloroquine were administered to almost 70% of the population of Nicaragua, preventing 9200 instances of malaria (Garfield and Vermund 1983).

According to current research, ivermectin mass medication administration is working well in controlling malaria, especially for residual malaria. An endectocide that has been approved for use in humans is ivermectin. It is a semi-synthetic derivative of Streptomyces avermectin fermentation products. Over one billion treatments have been administered for neglected tropical diseases such as lymphatic filariasis (Chaccour et al. 2013; Chaccour et al. 2015), onchocerciasis, and strongyloidiasis over the previous 25 years. The drug makes blood deadly to malaria mosquitoes after being ingested for around six days while it is still in the bloodstream. As a result, following a single conventional oral dose, fewer Anopheles mosquitoes survive to bite a person who has had ivermectin treatment (Chaccour et al. 2013; Chaccour et al. 2015).

House Improvement (HI)

Houses are the primary transmission habitat in many endemic regions (Huho 2013; Bayoh 2014; Barreaux 2017). In the past, it was believed that better housing was a factor in the malarial eradication in the USA and the decrease in disease incidence in Europe (Zhao 2016). Modern homes typically give protection against malaria that is comparable to ITNs and are preferable to older homes constructed of natural materials that have numerous openings for mosquitoes to enter. Comparing contemporary housing to traditional housing, data from demographic, health, and indicator surveys of malaria carried out in the 21 SSA nations between 2008-2015 demonstrate a decrease in malaria prevalence (Tusting 2015).

Swarm Sprays

The sites of mating swarms appear to be linked to swarm indicators on the ground (i.e., wood piles, walls, or the boundaries between grass and footpaths) which are consistent throughout the seasons (Diabaté et al. 2011).

Sugar Feeding

A novel vector control method, called attractive toxic sugar bait (ATSB), kills both female and male mosquitoes as they search for vital sources of sugar in the open air (Beier 2012). The ATSB method employs a fruit or floral aroma to draw mosquitoes in, a sugar solution to stimulate eating, and an oral toxin to kill the insects. The mosquitoes that consume the toxic ATSB solutions are destroyed. Either plants will be sprayed with the ATSB solutions, or they will be suspended in straightforward bait stations. Given its simplicity in terms of technology and operation, safety for the environment, and affordability, this intervention is great for reducing malaria in low- to middle-income nations. Spinosad and boric acid are the typical insecticides used by ATSBs; however, ivermectin has lately emerged as a viable option (Müller et al. 2010; Beier 2012).

Community Mobilization

All malaria preventive efforts must succeed in part due to community mobilization and methods for behaviour modification. This might take the shape of community-based initiatives, media, information, education, and communication (IEC) items used in public health communication. Communities can gain a better understanding of the disease by utilizing influential members of the community and teaching them about the advantages and proper application of malaria preventive methods. Misconceptions concerning the spread of malaria should be dispelled, as should the need for prevention and quick diagnosis and treatment when one suspects the disease (Ingabire et al. 2014).

Malaria Vaccine Development

Pre-erythrocytic Stage Vaccine (Live attenuated liver stage)

Live attenuated vaccine is still the most critical choice because it offers long-term sterile immunity to malaria transmission. The attenuation of irradiated sporozoites depends upon the random mutations that block the liver stage development. Therefore, immune individuals support attenuated heterogeneous populations, but the genetically dissipated sporozoites limit this study solely for experimental purposes (Silvie et al. 2002). Despite all limitations, sporozoites have proved helpful in providing long-term sterile immunity (Morrot and Zavala 2004). In humans and mice, experimental sporozoites have been shown to provide immunity against malaria transmission at the liver stage (Nussenzweig et al. 1967; Hoffman et al. 2002).

Moreover, genetically attenuated parasites (GAPs) are formed by transfection of the asexual blood stage. Therefore, it causes consistent and continual production of genetically stable attenuated sporozoites. Complete cessation of the hepatic stage demonstrates the production of GAPs even with weak preventive measures. Recently, a gene named USI3 has been identified in the parasite *Plasmodium berghei*. It is known that deletion in this gene results in the loss of a parasite's ability to mature in merozoites. Animals that were attenuated with the three consecutive doses of the removed USI3 gene demonstrated that animals had sterile immunity even for a more extended period. This experiment must be translated for *P. falciparum* (Mueller et al. 2005).

Blood Stage Vaccine

Immunity develops against individuals over time by naturally exposing people to the pathogenic agent, but sterile immunity can only be induced artificially. Over time, as children become sexually mature, they have also obtained the degree of semi-immunity that protects them against serious infections, but not against all infections. In passive transfer studies at the early stage, it came to know that when immunoglobin from semi-immune individuals acts against the blood stage, it cures the clinical complications in a person with no or low immunity (Cohen et al. 1961). It is also seen that children who live in endemic areas develop a degree of immunity against cerebral malaria in only one or two episodes that protect them against severe disease. Antigens that are present on the surface of infected RBCs and merozoites are erythrocytic malarial vaccine candidates which include merozoite surface proteins 1, 2 and 3 (MSP1, MSP2, MSP3); apical membrane antigen (AMA1); glutamate-rich protein (GLURP); ring-infected erythrocyte surface antigen (RESA); serine -repeat antigen and erythrocyte-binding antigen (Gupta et al. 1999).

Some studies in Gambia have shown that the protective effect of antibodies in a genetically diversified field of MSP3 is even stronger than in target-conserved areas (Polley et al. 2007). A vaccine trial was held in Papua New Guinea using a mixture of RESA protein, MSP1, and MSP2, which showed an increased number of infections from non-vaccine type parasites with MSP2 compared to those who received a controlled vaccine (Genton et al. 2002).

Merozoite Vaccine

The merozoite antibody-mediated vaccine can be obtained by targeting any of the merozoite surface proteins (MSP), peripheral surface proteins, and, to a lesser extent, secretory

organelle proteins (Siddiqui et al. 1987). In the recent advanced studies, clinical trials of first surface protein like MSP1 having AS02 adjuvant were recommended with 42k Da carboxyl protein fragment (Stoute et al. 2006). MSP1 is a major pleomorphic protein in two allelic forms; both are still being studied preclinically (Woehlbier et al. 2006). Recently, MSP3 phase 1 clinical trials, B and T cell epitopes along with aluminum adjuvant, showed high antibody levels in vaccinated organisms. When transferred to the mouse model, it was seen that antigen-specific antibodies could inhibit parasite growth in vitro along with clear parasitemia and monocytes (Druilhe et al. 2005). These are the evaluation in the efficacy trial and showed that the choice of functional antigen should not depend on the genes but should be based on the functional assay (Dorfman et al. 2005). A rodent malaria model system, explain why the antibody response is short-lived and it is because the parasites induce the deletion of antigen-specific memory B cells (Wykes et al. 2005).

Subunit Vaccine

The live attenuated or killed vaccine is not feasible in many diseases. In a subunit vaccine, an antigen or part of an antigen is identified from a pathogen that induces immunity against the whole pathogen on vaccination. The hepatitis B vaccine is an effective protein subunit vaccine. This vaccine was designed to give the maximum humoral immune response. Proteins have a significant variation in their immunogenicity. So, the protein subunit vaccine does not apply to many diseases (Courouce et al. 1981).

The latest generation of subunit vaccination is DNA-based (Ulmer et al. 1993: Li et al. 1993). The DNA sequence from *P. falciparum* was inserted into various recombinant DNA viruses forming recombinant viral vaccines or inserted into plasmid DNA molecules forming DNA vaccines (Schneider et al. 1998; Wang et al. 1998). DNA vaccines are taken up by the expressed host protein and form T cell epitopes that join with the HLA molecule which is prime naïve to T-cells and form the memory T-cells (Gurunathan et al. 2000). Viral vaccines also work similarly, but viruses infect the cells and express T-cells antigens before the start of infection (Miyahira et al. 1998). DNA or Viral vaccines induce a high T-cell response but not a good antibody response (Paoletti 1996; Gurunathan et al. 2000).

Whole Sporozoite Vaccines (WSV)

The work on WSV has been a challenge since the 1970s. It was thought that the idea of WSV was impractical because of the synthesis of irradiated sporozoite (Smith et al. 1991). In 2010, a company named Sanaria worked on harvesting PfSPZ from the salivary gland of a mosquito infected by laboratory parasites, followed by preservation, vialing, and cryopreservation in liquid nitrogen (Hoffman et al. 2010). The efficacy of WSV in humans is seen to be dependent on the dose (Seder et al. 2013; Mordmuller et al. 2017; Sissoko et al. 2017). The level and duration of protection in homologous or heterologous sporozoite in malaria-naive adults depend upon the dose and regime with either PfSPZ-CVac or PfSPZ vaccine that has achieved a high level of immunity (Epstein et al. 2011; Ishizuka et al. 2016; Epstein et al. 2017).

Placental Malarial Vaccine

The placental malaria vaccine targets the chondroitin sulfate A (CSA) that binds the parasites and sequesters them in the placenta. Other pre-erythrocytic and erythrocytic stage vaccines that protect the general population against malaria can also protect pregnant women. Naturally, antibodies to the CSA are present to protect against malaria after several pregnancies, as in endemic areas, mothers are resistant to placental malaria (Fried et al. 1998). Placental parasites express the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) which is the member of VAR2CSA that bind to the CSA binding site (Salanti et al. 2003). The antibodies induced by the VAR2CSA prohibit parasite binding to CSA (Fried and Duffy 2015). VAR2CSA is a complex target with an extracellular domain >300kd, six BDL domains, and some interdomain regions. Recently, in field cases, seven to eight BDL domains have been found (Doritchamou et al. 2019).

Conclusion

Malaria still poses a threat to public health, especially in Sub-Saharan Africa, where it is a major cause of morbidity and mortality, particularly among children. Significant strides have been made in reducing malaria-related morbidity and mortality over the past 10 years. The vector control strategy still needs to be rapidly developed to realise its full potential. ITNs and IRS are the main malaria prevention and control methods because of their proven efficacy in lowering disease load. However, setting goals for eradicating malaria in numerous nations is justified by scaling up the combination of vector control measures. The development of novel vector control techniques is essential for the eradication of malaria, however many of these techniques have limitations, particularly in terms of lowering the disease burden, necessitating more research. The cost is the biggest obstacle that makes IVM a missed prospect in many endemic nations. Antimalarial use for high-risk groups, including children and pregnant women, lowers the disease burden in endemic nations. NGOs, governments, scientists, and research institutions must work together to develop improved malaria prevention strategies. This would end the disease's needless deaths of children under five by 2030, as the Sustainable Development Goals mandated.

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