Malaria Vaccine: A Future Hope to Curtail the Global Malaria Burden

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ABSTRACT

It has been estimated that nearly half of the world's population is at the risk of contracting malaria with sub Saharan Africa being the most risky area. The existing frontline malaria control interventions are not only expensive but also become ineffective owing to the emergence of insecticide and drug resistance. It calls for an innovative approach in terms of potential and reliable vaccine as an additional tool. Over centuries, the public health experts have been actively engaged to formulate a safe, affordable and potential malaria vaccine and accordingly a notable achievement has also been attained. However, many challenges are required to be flagged immediately and effectively to devise an ideal prophylactic malaria vaccine. Therefore, the global community has to remain waiting quite a few more years to build a wannabe malaria-free world in the near future.

Keywords: Malaria, malaria elimination, malaria eradication, malaria parasite, vaccine

Review Article

INTRODUCTION

Malaria is one of the most common mosquito-borne diseases in the tropical and subtropical countries.[1] It is a disease of poverty inflicting a serious negative impact on health and socioeconomic development in the poorest countries of the world that cannot afford to succeed.[2] The recent World Health Organization (WHO) Malaria Report 2011[3] estimates that 3.3 billion people were at the risk of malaria in 2010, although of all geographical regions, populations living in sub-Saharan Africa (SSA) have the highest risk of acquiring malaria; among 216 million episodes of malaria in 2010, which approximately 81%, or 174 million cases, were reported from the African Region. There were an estimated 655,000 of malaria deaths in 2010, of which 91% were from Africa. Despite the availability of effective interventions, malaria still remains to be one of the most important causes of maternal and childhood morbidity and mortality.[4]

MALARIA PARASITES: THE SILENT KILLERS

Malaria parasites comprise a diverse group of protozoans that infect reptiles, mammals and birds and that are transmitted

through the bite of different families of blood-feeding insect vectors.[5,6] They encompass two closely related genera, *Plasmodium* and *Haemoproteus*,[5] which contain about 170 and 150 morphologically distinct species, respectively.[6] Human beings may be infected by the five species of *Plasmodium,* however both *Plasmodium falciparum* and *Plasmodium vivax* can cause severe disease, but *P. falciparum* has been the focus of most vaccine-related research. *Plasmodium ovale* and *Plasmodium malariae* are rarely considered as vaccine targets, whereas *Plasmodium knowlesi*, a primate malarial parasite that was used in the early blood-stage vaccine studies,[7,8] has only recently emerged as the cause of a naturally acquired infection in humans.[9]

P. falciparum causes the most severe infections and nearly all malaria-related deaths[10] and *P. vivax*, which accounts for 70 million to 80 million malaria infections each year in Asia, Oceania and south America but which is rare in most of Africa.[11] The extensive diversity of malarial surface antigens is one of the main reasons why clinical immunity develops only after repeated infections with the same species over several years.[10]

THE COMPLEX LIFE CYCLE OF *PLASMODIUM* PARASITE

The life cycle of parasites is extremely complex [Figure 1] and comprises morphologically and antigenically distinct stages that are targeted by stage-specific immunity.[12] A malarial infection

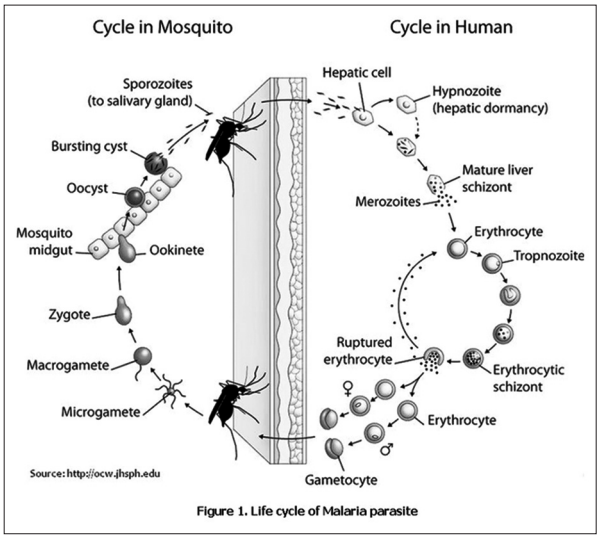

Figure 1: Life cycle of malaria parasite

starts when the sporozoite stage of the unicellular protozoan *Plasmodium* is introduced by the female *Anopheles* mosquito in a vertebrate organism during a blood-feed. Some sporozoites find their way to the liver and infect hepatocytes. Inside the hepatocyte the parasite transforms itself and proliferates massively into the merozoite stage that will infect erythrocytes. Subsequent cyclic erythrocytic stages are responsible for the symptoms, complications and fatality associated with malaria.[13]

After a few cycles of asexual stages, some of the infected erythrocytes differentiate into gametocytes and once ingested by the mosquito through a blood meal, it undergoes fertilization generating an oocyst. The sporozoites, produced in the oocyst, migrate to the mosquito salivary glands and are then ready to be introduced into the next vertebrate host.[13] Notably, two of the human malaria parasite species, *P. vivax* and *P. ovale*, produce dormant liver stages, known as hypnozoites, that are the sources of relapses weeks or months after the primary infection.[12]

EXISTING MAJOR MALARIA INTERVENTIONS

Vector control is remains considered to be a cornerstone in malaria control. In the recent past, a few countries have attained malaria elimination by employing exiting front-line vector control interventions such as indoor residual spraying (IRS) and long lasting insecticide-treated nets (LLITNs) and active case management.[14] However malaria continues as a leading public health problem in the developing economies and remain as a serious threat to humankind due to the emergence of drug resistance, unaffordable potent antimalarials, fragile health care facilities and the absence of reliable vaccine.[14,15]

Large number of malaria deaths could be reduced further by increasing coverage with existing control tools, but it is generally recognized that this would not be sufficient to achieve the high level of control that would be needed to make elimination a credible objective.[16] Furthermore, the limited successes that have been achieved in high transmission areas in SSA are threatened by the potential spread of artemisinin-resistant strains of *P. falciparum* from Southeast Asia[17] and by the spread of strains of *Anopheles gambiae* that are highly resistant to pyrethroids.[18] Therefore

additional tools will be required to achieve effective malaria control in these high-transmission areas.[16]

In this context, malaria vaccine could be a one of the most cost-effective as well as reliable complementary tool to reduce/contain the prevailing global malaria burden. A malaria vaccine for mass immunization delivered cheaply and widely can provide a long lasting protection and a massive effect on global public health. However, such a vaccine does not currently exist. Nevertheless, history teaches that complacency and an over-reliance on a small number of tools such as insecticide-treated nets (ITNs), IRS and Artemisinin (ART) to combat malaria are dangerous. There is therefore still a pressing need for a vaccine to complement other control and potential elimination tools.[19]

Globally, over the past several decades numerous stringent efforts have been made in order to develop effective and affordable preventive malaria vaccines. However the past decade is an important milestone in the malaria/global public health history, since there is a collective global-partnership and commitment among the international donors, public-private venture, research institutions, pharmaceutical industries and malariologist to address this age-old curse of poverty/humanity by stimulating the significant malaria vaccine research and development targeting various stages of the malaria parasites. As a result, world-wide there are several clinical trials are underway and the preliminary results are relatively encouraging and hopeful. In this context, the present scrutiny becomes more significant and pertains. It is an attempt to identify the existing barriers and how the global public health experts can explore and address the existing major challenges and issues to minimize the global malaria burden ultimate eradication by administering the safe, reliable, effective and affordable vaccines.

METHODS

In order to collect appropriate research materials for the present scrutiny, a detailed search on Scopus, Medline, Google Scholar and Academic Search Premier Databases has been carried out for the time period 1990-2011. A Boolean search strategy was adopted and the key words entered for search are "malaria vaccine," "malaria control and prevention," "malaria interventions" malaria vaccine trials" and "malaria control challenges and issues" in differing orders, in order to extract studies. Only articles, notes and reviews were chosen and their bibliographic details (authors, title, full source, document type and addresses) were downloaded to a file for this narrative review.

Malaria vaccines: A hope for the future

Malaria vaccines could be one of the most cost-effective interventions to reduce the enormous burden of disease in the poorest countries of the world.[20] Malaria vaccine development has been fuelled by new technology enabling the sequencing of the *P. falciparum, P. vivax* and *A. gambiae* genomes and the development of experimentally relevant animal models, combined with significant increases in financial resources from funders such as the Bill and Melinda Gates Foundation, the European Union, the US National Institutes of Allergy and Infectious Diseases and the US Agency for International Development.[21] Efforts to develop a vaccine have a winding and rather chequered history, but during the past decade a concerted international effort is now finally coming to fruition. It has resulted in accelerated clinical development of malaria vaccines targeting various stages of the malaria parasite life cycle.[22]

Significance of malaria vaccine

In the recent past, vaccines against infectious diseases have proved to be very effective. Likewise, malaria vaccines are being developed to achieve both protection of the vaccinated individual and the reduction of malaria transmission through the community.[23] Malarial vaccine development is hope for successful control of malaria. Several malarial vaccine candidates have been recently identified and the genetic manipulation of these candidates is becoming more efficient with the advancement of new biotechnologies.[24] Currently, there are 38 *P. falciparum* and two *P. vivax* candidate malaria vaccines or vaccine components in advanced preclinical or clinical development as listed by the WHO Malaria Vaccine Rainbow Tables.[21]

Potential targets of malaria vaccines

Malaria vaccine candidates are categorized according to the *Plasmodium* life cycle stage at which the targeted antigen is expressed.[21] Four stages of the malaria parasite's life cycle have been the

targets of vaccine development efforts [Figure 2]: The stage that is inoculated by the mosquito into the human host (sporozoite); the liver stage before the parasite invades the human red blood cells (RBCs) (pre-erythrocytic [PE] stage); the stage when the parasite is invading or growing in the RBCs (merozoite, erythrocytic stage); and the stage when the gametocytes, after being ingested by a mosquito, leave the RBCs and fuse to form a zygote which then continues the infection in the mosquito vector (gametocyte stage).[25]

Types of malaria vaccine

PE stage vaccine

A great deal of effort has focused on vaccines targeting the asexual blood stage, because this approach can directly reduce morbidity and mortality associated with malarial disease in humans.[26] Among the four stages the first two stages are often grouped as "PE stages", the sporozoites being inoculated by the mosquito into the human blood stream; and the parasites developing inside human liver cells.[25] PE stages vaccine usually aim to completely prevent infection,[27] it would be ideal for travelers because it would prevent the advent of clinical disease if completely efficacious. A partially efficacious PE vaccine would be expected to reduce the incidence of new blood stage infections. This in itself may reduce the incidence of morbid episodes.[28]

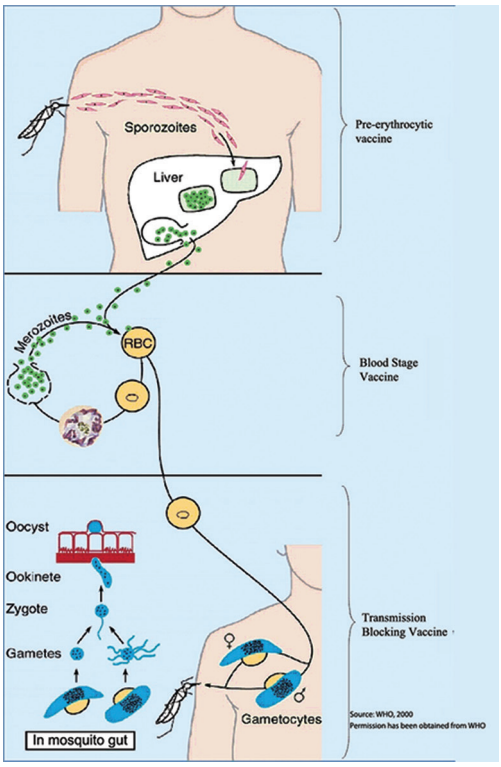

Figure 2: Potential targets of malaria vaccine development

Implications of PE stage vaccine

The sporozoite stage of *P. falciparum* is one of the potential targets of malaria vaccine. If immune mechanisms can prevent sporozoites from entering or developing within hepatocytes, the release of merozoites from the liver and the resulting clinical malaria will thereby be averted. Thus an effective sporozoite vaccine should stimulate the production of serum antibodies capable of neutralizing sporozoites before they can invade hepatocytes. Ideally such a vaccine would also be recognized by T cells, thus generating immunological memory capable of boosting the antibody response upon subsequent exposures to sporozoites.[29] In addition, an ideal vaccine should sensitize cytotoxic T cells and cytokine-producing T cell subsets as these T cells interfere with the exoerythrocytic cycle of parasite development.[30]

Anti-asexual blood stage (erythrocytic) vaccine

Vaccines targeting the blood stages of malaria are intended to reduce morbidity and mortality and are being developed in hopes of creating a multistage multiantigen vaccine.[31] It reduces malaria related morbidity and mortality among the most susceptible groups (i.e., children <5 years old and pregnant women) living in areas where malaria is endemic.[32] Erythrocytic vaccine strategies aim to elicit antibodies that will inactivate merozoites and/or target malarial antigens expressed on the RBC surface, thus inducing antibody-dependent cellular cytotoxicity and complement lysis; they also are intended to elicit T-cell responses that will inhibit the development of the parasite in RBCs. This type of vaccine would mostly serve as a disease-reduction vaccine in endemic countries by decreasing the exponential multiplication of merozoites.[28]

Implications of anti-asexual blood stage vaccine

Natural immunity against malaria which should have been acquired over time, because of multiple infective bites is lost due to the absence of continued exposure. The goal of blood stage malaria vaccines is to protect against disease and death, which can be achieved through acquisition of such immunity.[33] A blood stage vaccine to *P. falciparum* malaria would offer enormous

benefit to the public health, particularly for the expectant mother, infants and children living in endemic areas.[34]

Transmission blocking vaccines

TBVs could block transmission of malaria from mosquitoes to humans would offer another important tool in the fight against malaria.[35] A successful TBV employing the Anopheline midgut alanyl aminopeptidase N 1 antigen would break the transmission cycle effectively, using the human body to create antibodies against antigens present on the sexual stages of the parasites, which develop in the mosquito midgut and thus block their development in the vector mosquito.[23] Ultimately it breaks the complex cycle of malaria transmission and helps to tackle the malaria community's long-term goal of eradication.[35]

Implications of TBVs

In most malaria-endemic locations, TBV coverage, even if partial, would reduce disease and death due to malaria. In areas of relatively low transmission, as in most endemic locations outside tropical Africa and also possibly in parts of tropical Africa itself, malarial would be reduced probably in direct proportion to the effective coverage with TBVs. In many situations of low malaria endemicity, transmission could be stopped by TBVs.[23]

In some more highly endemic areas; the deployment of TBVs in conjunction with more traditional measures like ITNs and IRS could bring the end of malaria transmission within reach. Even incomplete TBV coverage would slow the build-up of malaria epidemics and reduce their size very substantially in many situations.[36] As malarial infections are transmitted mainly within a few hundreds of meters from an infectious human source, TBVs used within a community would protect the immediate neighborhood of the vaccinated individuals.[37] The inclusion of a TBV would also greatly prolong the useful life of vaccines against other stages by preventing the spread of parasites that become resistant to these vaccines.[20]

Malaria vaccine clinical trials

Evaluation of vaccine candidates in clinical trials is a cornerstone in the selection process of product development. Generally, <10% of preclinical vaccine projects progress to Phase III clinical evaluation.[38] Downstream, selection of vaccine candidates is based on safety and immunogenicity profiles (Phase I). Vaccine efficacy can be tested by experimental infections in humans (Phase IIa) or by naturally acquired infections in malaria endemic areas at a small (Phase IIb) or larger scale (Phase III).[39] Clinical development is also time consuming and costly.[21]

Prior clinical trials

The RTS, S" also called "RTS, S/AS" is a vaccine that targets the circumsporozoite protein and when given with an adjuvant system (AS01 or AS02) has consistently shown protection against *P. falciparum* malaria in children and infants in phase 2 trials.[40-45] But the vaccine have had an acceptable side-effect profile and was immunogenic in children who were 6 weeks of age or older. In addition, the vaccine could be administered safely with other childhood vaccines,[40,46] and provided protection against severe malaria.[41]

The on-going major clinical trial

Phase III safety and efficacy trial of the RTS, S malaria vaccine candidate

RTS, S is the most clinically advanced malaria vaccine candidate in the world today. In clinical trials, it is the first to demonstrate that it could help protect young children and infants in malaria-endemic areas against infection and clinical disease caused by *P. falciparum*, the most deadly species among the malarial parasites.[41,42] The launch of the Phase III efficacy trial of the RTS, S malaria vaccine candidate marked an important milestone after more than 20 years of research and development. The trial started in May 2009 and is now underway at 11 sites in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania). Together, the 11 sites completed enrolment in January 2011, with the participation of 15,460 infants and young children, making this the largest malaria vaccine trial to date.[47]

The trial initial results show that the RTS, S/AS01 vaccine has reduced the occurrence of malaria by half in children of 5-17 months of age in the 12 months after vaccination and that the vaccine is potent enough to cause a significant effect on the burden of malaria in young African children. But additional information on vaccine efficacy among young infants and the duration of protection are critical to determine how this vaccine could be used most effectively to control malaria.[48]

A similar analysis is required to be conducted in the infant group within the end of 2012. An additional data set, which will include information about the vaccine's longer-term protective ability for both groups of children, should be available by the end of 2014 which can provide evidence for national and international public health organizations to evaluate the vaccine candidate's full potential for use.[47] If the required regulatory and public health information, including safety and efficacy data from the Phase III program, is deemed satisfactory, the WHO has indicated that a policy recommendation for the RTS, S malaria vaccine candidate is possible as early as 2015, paving the way for decision making by African nations regarding large-scale implementation of the vaccine through their national immunization programs.[47]

Daunting challenges and thorny issues

A safe and effective malaria vaccine can contribute greatly to control and prevention of disease. Although a review of global activity in malaria vaccine development does reflect significant activity, its progress has remained slow. Pursuing the current research and development strategies may not result in the availability of a vaccine with the characteristics suitable to impact significantly on disease morbidity in developing countries. Therefore, it is critical that the main challenges to malaria vaccine development be unambiguously identified and collectively addressed.[49]

Unique features of malaria parasites

Human being a relationship with parasites has been a long one on the evolutionary scale. The methods adopted by parasites to thrive and colonize living organisms are truly fascinating. Along with basic features such as fecundity and resistant cyst structures, the parasites exhibit a fine-tuning of modifications in response to attack by the host immune system. While the host fights the parasites through its armory of immune as well as certain behavioral responses, the parasites appear to use the host immune responses towards quorum sensing, limiting their own number, however surviving.[13]

Antigenic diversity and immune evasion of malaria parasite

Parasite diversity is a cornerstone of host-parasite relationships, which become more complex with increasing numbers of participating actors. For example, if a host species interacts with many parasite species, its immune system is likely affected by more natural selection pressures than if it interacts with just a few parasite species.[50] Understanding the population structure of the malaria parasite and how it is genetically distinct in different regions, may open up new avenues to area-specific control measures.[51]

A few hundred species have been described by examination of different morphological traits of these microscopic organisms. However, recent studies based on parasite identification by means of deoxyribonucleic acid sequence differences have revealed a much higher diversity of malaria parasites. Thus, only in birds, this group could include up to 10,000 distinct species.[52] Early optimism for vaccines, particularly for sporozoite vaccines, was tempered as the problems caused by genetic (hence, antigenic) variability of the parasite and the difficulty of generating high levels of durable immunity emerged.[53] Against a parasite with more than 5200 genes, the inadequacy of definitive knowledge regarding the nature of protective immunity and absence of reliable surrogates of protection are among the key challenges to a rational evaluation and prioritization of candidate vaccines.[49]

Need better understanding on host specificity

Determination of host specificity or host range of human malaria parasites is of great importance not only for further understanding the parasite biology but also for better malaria control. Surveys of malaria parasites in great apes are thus required. Besides, the investigation of malaria infection in great apes should be helpful for the primates' health and biodiversity conservation efforts.[54]

Require better understanding

An understanding of the biology and epidemiology of malaria transmission is critical to the deployment of malaria TBVs. Because malaria depends for its transmission upon contact between a human population and appropriate species of *Anopheles* mosquito, malaria transmission is strictly limited to within certain distances of the aqueous breeding sites of these mosquitoes.[37] Pre-clinical assessment of the whole organism PE vaccine strategies is important for translation to clinical trials in humans. Prioritizing the most potent and safe strategy is important to build on the momentum for arrested *Plasmodium* liver stages as anti-malarial vaccines.[55]

Mathematical models

A potential limitation of current malaria challenge models involving sporozoite infection relates to the uncontrolled number of sporozoites inoculated by biting mosquitoes. This number is generally thought to vary up to a maximum of several thousand sporozoites.[56-60] Use of a well-defined number of inoculated sporozoites will strengthen the power of the model, as the dose probably influences the prepatent period.[61,62]

Low commercial interest

None of the three types of malaria vaccines is yet made available. At present, industry's greatest interest is in liver stage vaccines, with a secondary interest in blood stage vaccines. Both of these and especially the liver stage vaccines are of interest for travelers and military and have, therefore, attracted some industrial involvement in their development. There is, however, little commercial interest in a TBV whose relevance is to poor countries where malaria is endemic. Thus, while a TBV would-be of great public benefit, it lacks industrial support and requires a home in the public sector that can champion its development.[20]

However, for the malaria parasite, the stages that cause disease are different from the stages that transmit the parasites from the mosquito vector to the human host and vice versa. Accordingly, vaccines are being developed against the different parasite stages to achieve these different effects.[23] One of the main problems confronting malaria vaccine development in general is the relatively low level of commercial interest. This is because the potential market with endemic malaria is mainly in the poorest countries who despite their medical need, do not have the economic means to support large-scale purchase and distribution.[23]

Requisite of second-generation vaccines

The development of an effective malaria vaccine has taken many decades, but there is now a good chance that the first malaria vaccine will be licensed within the next few years. However, this vaccine (RTS, S) will not be fully effective and more efficacious and second-generation vaccines will be needed. Good progress is being made in the development of potential vaccines directed at each of the three main stages of the parasite's life cycle, with a variety of different approaches, but many challenges remain unsolved, e.g., overcoming the problem of polymorphism in many key parasite antigens.[16]

Ideal vaccine: The mystery needs to explore

Vector-control programs have proved to be incapable of eradicating malaria from the tropics and so preventive strategies must focus on individual protection. Despite major efforts over the past 50 years to develop a malaria vaccine, no product has been licensed yet to release.[55] An effective malaria vaccine would improve the prospects for eradicating malaria.[63] Vaccines that interrupt the transmission of malaria are emphasized in discussions of eradication,[64] but the ideal malaria vaccine would provide a direct clinical benefit. Due to the complex life cycle and high antigenic diversity of the malaria parasite, a multistage vaccine may be necessary for optimal protection against the disease.[26]

PE vaccines may primarily be used for travelers from nonendemic areas to prevent blood stage infection. Asexual blood stage vaccines will primarily be targeted at young children in endemic areas to control parasitemia, resulting in reduction of morbidity and mortality. A long-term goal may be a multi-antigen, multi-stage vaccine that inhibits PE stages, asexual parasite growth and mosquito stage development.[39] Recently, hope has been renewed by the construction of several potential new PE, asexual stage and transmission-blocking vaccines, as well as new formulations and adjuvants for sporozoite vaccines.[27]

The history clearly show that malaria has eradicated as well as eliminated in the high-income countries by employing the aggressive prevention and control measures with more effective monitoring and evaluation strategies. Similarly, in the past decade, malaria incidence has fallen by at least 50% in one-third of the countries where the disease is endemic. However, the existing malaria control tools are insufficient to achieve eradication ultimately elimination in many countries. Indeed, malaria vaccines are widely considered a necessary component and an appropriate strategy to eliminate or eradication of malaria. However, it is likely that vaccines will need to be used in conjunction with other methods such as long lasting insecticide nets, IRS and ART rather than replacing them completely.[25] Besides, presently we have minimized the global malaria burden considerably, by inducting the low-cost interventions like ITNs due to the stringent effort and commitment of the public health professionals, international donors, public and private partnership. However, the recent decline of

the malaria burden within and between the countries is not uniform. The specific reason and the role of correlated compounding factors stay unidentified and imprecise that needs to be recognized by the global public health experts instantly.[2]

CONCLUSIONS

Over the past several decades, the experience and lessons teach us that although the existing conventional vector control interventions are competent to minimize the malaria burden considerably, they remain unproductive to eradicate malaria. In this context, introduction of malaria vaccine could be one of the most sustainable and cost-effective approach in the malaria prevention and control strategy. At the moment, than ever before we do have much substantial knowledge and better understanding on life-cycle of malaria parasites, disease transmission dynamics and immunogenicity of the host. Besides, the recent revolution in the biotechnology advancements, modern paraphernalia, world-wide partnership and stringent commitments has fuelled for the development of propholytic malaria vaccines.

The present scrutiny results clearly suggest that certainly we have attained a sustainable progress to devise the ideal malaria candidate vaccine and the recent clinical trial results are quite encouraging and optimistic. However, there are numerous challenges lying ahead on the road to attain the safe, effective, tolerable and affordable malaria vaccine that need to be addressed effectively and immediately. I strongly believe that although we are moving in the right direction steadily and slowly by administering ideal protective malaria vaccines, the global community have to wait quite a few more years to build a long-term ambitious goal of malaria-free world.

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