

RTS,S malaria vaccine development: progress and considerations for postapproval introduction

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Abstract: Though the burden of malaria has decreased in the last decade in some sub-Saharan African countries, it is still high in others, and there is no malaria vaccine in use. The development of malaria vaccines in combination with current control programs could be effective in reducing the malaria burden. In this paper, we review and discuss the progress made in the RTS,S malaria vaccine development and considerations for its postapproval process. We conclude that the development of malaria vaccines has been a long process confronted with challenges of funding, difficulty in identifying malaria antigens that correlate with protection, and development of adjuvant systems among others. The scientific approval of the vaccine by the European Medicines Agency in July 2015 and subsequent recommendations for pilot implementation studies by the World Health Organization made history as the first human parasite vaccine. It is also a major public health achievement as the vaccine has the potential to prevent thousands of malaria cases. However, there are implementation challenges such as cold chain systems, community acceptance, and monitoring of adverse events post-licensure that need to be carefully addressed.

Keywords: malaria, vaccines, challenges, introduction, Africa, implementation considerations

Introduction

Malaria caused by *Plasmodium* species leads to ~600,000 deaths worldwide each year. Approximately, 90% of these deaths occur in sub-Saharan Africa mainly among children less than 5 years of age.¹ Majority of malaria deaths in sub-Saharan Africa is attributed mainly to *Plasmodium falciparum*.

Tools currently used to reduce the burden of malaria in sub-Saharan Africa include insecticide-treated nets, indoor residual spraying, prompt treatment with efficacious artemisinin combination drugs, and preventive measures such as intermittent preventive treatment in pregnancy and seasonal malaria chemotherapy among children.

Between 2000 and 2013, malaria burden has decreased significantly in some sub-Saharan African countries.²⁻⁴ In spite of significant achievements, some countries in Africa still show stable (moderate-to-high) malaria transmission and are without any substantial reduction in malaria disease.¹ The mutating nature of the *Plasmodium* species makes it necessary to control malaria with all effective methods simultaneously. Recently, parasite resistance to artemisinin has been detected in some countries in Southeast Asia.⁵ This could possibly spread to other regions of the world. Although it is capital-intensive to use all effective control measures, the investments are likely to

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eventually impact significantly on malaria burden. In total, the yearly cost of malaria to sub-Saharan Africa is approximately US\$12 billion, and it is projected that this may slow up economic growth by up to 1.3% every year.⁶ This suggests that it would be beneficial to use all the available effective methods to drastically reduce the incidence of malaria in a very short time if Africa is to develop.

Vaccines have been shown to significantly reduce the burden of several viral and bacterial diseases. Malaria vaccines could therefore be effective in reducing malaria incidence. So far, the RTS,S malaria vaccine is the only approved vaccine against malaria under the trade name of Mosquirix (Glaxosmithkline plc, Brentwood, UK).⁷ In this paper, we discuss the progress and potential implementation challenges of the RTS,S malaria vaccine.

RTS,S malaria vaccine development

Malaria vaccine development has been ongoing since the 1960s.⁸ In general, the vaccine development process begins with target antigen discovery through basic science research. Potential vaccine candidates identified then go through pre-clinical research in animal models. These are followed by Phases I–III clinical trials in humans to determine the safety, immunogenicity, and efficacy of the vaccine candidate prior to submission for regulatory approval. The majority of potential candidates fall off the development pathway due to a lack of convincing data to move on to the next stage. The search for the RTS,S malaria vaccine has also followed the same process.

Malaria parasite target stage for RTS,S malaria vaccine development

Malaria vaccine candidate discovery targets the various antigens that are expressed along the life cycle of the malaria parasites; this can be described in three stages: the pre-erythrocytic stage, the blood stage, and the transmission stage. The target for the RTS,S malaria vaccine is at the pre-erythrocytic stage, when the malaria parasite enters and replicates in the liver after an individual is bitten by an infected mosquito.⁹ Specifically, the vaccine targets amino acids 207–395 of the circumsporozoite protein from the NF54 strain of *P. falciparum*.¹⁰ Similar to other pre-erythrocytic vaccine candidates (eg, ChAd63/MVA ME-TRAP¹¹), the RTS,S aims at preventing the liver invasion or preventing further development of malaria parasites in the liver. Other vaccines target the blood stage of malaria parasite, when the parasites infect and replicate in red blood cells leading to clinical symptoms. Blood-stage vaccine candidates (eg, AMA1/AS01B,¹² JAI-VAC-1¹³) aim at limiting the multiplica-

tion of malaria parasites in red blood cells, and thus prevent disease severity. Transmission-blocking vaccines (eg, PfSPZ vaccine¹⁴) interrupt parasite development in the guts of mosquitoes by introducing antibodies during a blood meal from a vaccinated individual. Transmission-blocking vaccines will not prevent diseases in humans but will prevent the spread of the disease and provide “herd immunity”.

Combining two or more vaccines with different parasite stage targets may provide a synergy leading to an improvement in vaccine efficacy.¹⁵ For example, a combined pre-erythrocytic and blood-stage vaccine that targets sporozoites evading the liver and merozoites invading the red blood cells may demonstrate a higher vaccine efficacy than what is observed using a single-stage vaccine.

The RTS,S malaria vaccine clinical trials

As at July 2015, there were ~22 preclinical malaria vaccine trials and 42 clinical trials being conducted across the world as per the WHO Rainbow Table of malaria vaccines under development.^{7,16} The RTS,S vaccine – the leading vaccine on this table – was developed by a collaboration established between Glaxosmithkline (GSK) and the Walter Reed Army Institute of Research in 1987. The vaccine had undergone several preclinical and early phase clinical trials in nonendemic countries and further human challenge trials in endemic regions.^{17,18} The key proof of concept in children was conducted in Mozambique¹⁹ in 2004, paving the way for subsequent Phase II and III trials in 2007 and 2009, respectively.²⁰ The Phase III trials were conducted at eleven sites in seven African countries with different malaria transmission intensities and patterns.⁹ The sites involved were in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania. The clinical trial participants were children aged 5–17 months and those aged 6–12 weeks at the time of the first vaccination.⁹ The trial was conducted under the leadership of a Clinical Trial Partnership Committee of eminent scientists in African research centers and their partners, the manufacturing company GSK, and the sponsor PATH Malaria Vaccine Initiative.

Efficacy of RTS,S malaria vaccine

Phase I/II trials of RTS,S vaccine among young children demonstrated encouraging results. In Mozambique, the efficacy of RTS,S with a less immunogenic adjuvant (AS02) was 65.9% (95% confidence interval [CI]: 42.6–79.8, $P < 0.0001$) after 6 months of follow-up²¹ and 33% (95% CI: 4.3–56.9, $P = 0.076$) after 14 months of follow-up of the same cohort.^{22,23} In Phase II trials among infants, the efficacy against first

malaria episode of RTS,S with a more immunogenic antigen (AS01) was similar when the vaccine was administered using two different schedules (0-, 1-, 2-month group, 61.6% [95% CI: 35.6–77.1], $P < 0.001$; 0-, 1-, 7-month group, 63.8% [40.4–78.0], $P < 0.001$, according-to-protocol cohort).²⁴ Other Phase II trials had different estimates of vaccine efficacy depending on the population studied, adjuvant system of the vaccine, and methods of assessing clinical malaria.²⁵ However, the efficacy estimates in these Phase II trials provided some expected vaccine efficacy in Phase III trials.

In Phase III trials,⁹ the efficacy of three doses of RTS,S vaccine administered at 0-, 1-, 2-month schedule followed by a fourth dose administered at 18 months was 36.3% (95% CI: 31.8–40.5) after an average of 48 months of follow-up among children aged 5–17 months at first vaccination and was 25.9% (95% CI: 19.9–31.5) among infants aged 6–12 weeks at first vaccination who were followed up for an average of 38 months. There was evidence of waning of vaccine efficacy over time in both age groups. Without a fourth dose, the vaccine efficacy was much lower. However, in the same Phase III trials, the vaccine prevented ~1,774 cases of clinical malaria per every 1,000 children aged 5–17 months vaccinated and followed up over the same period. The vaccine prevented 983 cases of clinical malaria among 1,000 infants aged 6–12 weeks at first vaccination and followed up for approximately an average of 38 months. Further studies have been conducted to determine the efficacy of the RTS,S malaria vaccine against the diverse strains of malaria parasite (characterized by different circumsporozoite protein alleles) that cause clinical malaria. After 1 year of follow-up of children aged 5–17 months, the RTS,S vaccine was slightly more efficacious (50.3% [95% CI: 34.6–62.3]) against clinical malaria caused by parasites of similar RTS,S vaccine construct than malaria caused by parasites of dissimilar RTS,S vaccine construct (33.4% [95% CI: 29.3–37.2]). Among children aged 6–12 weeks, there was no difference in the vaccine efficacy against any specific parasites causing clinical malaria.²⁶ The vaccine efficacy against diverse malaria parasite types suggests that the vaccine could provide cross protection among children in areas where there is clinical malaria infection from different strains of parasites. It also suggests that a multivalent vaccine construct could provide a higher vaccine efficacy as alluded to by Plowe.²⁷

Safety of RTS,S malaria vaccine

In general, the RTS,S malaria vaccine has been found to be safe. In a pooled assessment of safety data of the RTS,S

in Phase II trials, there was a higher frequency of upper respiratory tract infections, as well as rash and diaper rashes among RTS,S vaccinated infants that were mild to moderate in intensity and unrelated to the vaccinations.²⁸ This was not found in subsequent Phase III studies. The incidence of postvaccination febrile convulsion was similar in both vaccine and control groups.²⁹ Meningitis was more common among children who received the RTS,S vaccine but was not associated with vaccinations.³⁰

Regulatory and policy review of RTS,S malaria vaccine

The RTS,S malaria vaccine has recently received a scientific approval by the Committee for Medicinal Products for Human Use of European Medicines Agency (EMA) after data submission in June 2014.⁷ This approval makes history as the first malaria vaccine and the first human parasite vaccine. The approval is the first step in the regulatory process toward making the RTS,S vaccine available as an additional tool to existing ones currently recommended for malaria prevention and treatment.

Additionally, the approval from the Committee for Medicinal Products for Human Use of EMA also allows GSK to submit marketing authorization applications to National Regulatory Authorities in sub-Saharan Africa. Though the efficacy of the RTS,S malaria vaccine is partial, vaccines with partial efficacy can have a public health impact, particularly in areas with high incidence of disease. For instance, partially efficacious vaccines have been registered for use by regulatory agencies in the past and have shown public health impact. Such vaccines include those against rotavirus disease³¹ and pneumococcal pneumonia.³² The RTS,S malaria vaccine is therefore likely to be considered for registration by African regulatory agencies after a careful risk–benefit analysis.

For countries' public health agencies and their global health partners to consider implementation of new health interventions and products, a policy recommendation is required from the World Health Organization (WHO). In the case of RTS,S malaria vaccine, the WHO review was planned to occur after the EMA scientific opinion.³³ In the last quarter of 2015, a meeting of WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) was organized to review all efficacy and safety data of RTS,S vaccine. Based on the advice of SAGE/MPAC, WHO recommended the vaccine for pilot implementation studies in 3–5 sub-Saharan African countries to evaluate practical challenges of administering

three doses of the vaccine to children 5–9 months with a fourth dose between 15 and 18 months.³⁴

Challenges of RTS,S malaria vaccine development

Identification of target antigens and adjuvant system

Malaria vaccine development has been rather slow and challenging. The complex life cycles of malaria parasites make targeting a specific antigen difficult. There is also inadequate understanding of clear biological mechanisms leading to the malaria disease and few adjuvant systems required for boosting the immunogenic effects of the vaccine candidate.³⁵ However, current rapid advances in biotechnology such as genomics, proteomics, and bioinformatics are likely to improve timely identification of target antigens and their role in malaria disease progression. The use of viral vectors and recombinant DNA systems is gaining prominence in malaria vaccinology. For instance, hepatitis B virus and chimpanzee adenovirus have been used as vectors in constructing pre-erythrocytic⁹ and blood-stage malaria vaccine candidates.³⁶

RTS,S malaria vaccine is a recombinant yeast-expressed subunit vaccine that uses the hepatitis B surface antigen as a matrix carrier for epitopes derived from the circumsporozoite protein of *P. falciparum*.³⁷ Its adjuvant system has undergone various changes in the preclinical stages^{37,38} until a more immunogenic variant (AS01E) was identified that induces both cellular and humoral immunity.^{39,40} The current adjuvant system of RTS,S malaria vaccine is an encouraging step for new and more immunogenic systems for future vaccine candidates. New malaria vaccines and their adjuvant systems will have to adhere to WHO's guidelines that ensure quality, safety, and efficacy of the vaccine candidates.^{41,42}

Cost of RTS,S malaria vaccine development

The process of malaria vaccine development involves huge costs, thus making it challenging for scientists to seek funds for it or unattractive for profit-making pharmaceutical companies to invest in it. The manufacturers of the RTS,S malaria vaccine intend to invest over US\$600 million until the vaccine development is completed.⁷ The company's investment was supported by that of PATH Malaria Vaccine Initiative with more than US\$200 million in grants from the Bill and Melinda Gates Foundation.⁷

Development of second-generation vaccines will need to show noninferior or superior vaccine efficacy estimates in comparison to the first-generation vaccine. Small differences

in the assumed vaccine efficacy between the first- and second-generation vaccines will require large sample sizes and expensive clinical trials,⁴³ especially as the first-generation vaccine is expected to further reduce the cases of malaria in Africa.⁹ Cheaper innovative approaches will need to be established. For example, controlled human malaria infection models seek to reduce the cost and time for conducting Phase II trials to assess the safety, immunogenicity, and efficacy of potential vaccine candidates by using a few healthy adults. They are immunized with the potential vaccine candidate and then challenged by infected mosquito bites or by intravenous inoculation with cryopreserved sporozoites.^{44,45} Another example of a cheap innovative approach is the use of algae chloroplast to produce subunits of *P. falciparum* surface proteins 25 and 28 to develop a malaria transmission-blocking vaccine candidate.⁴⁶

Human and infrastructural demands for the RTS,S malaria vaccine development in Africa

Phase II/III malaria vaccine trials are mainly conducted in targeted populations in sub-Saharan Africa, not only where the burden of malaria is high enough to adequately evaluate the vaccine but also where existing health infrastructure is weak.^{47,48} This provides a challenge for sponsors of the clinical trials to set up systems to meet the requirement of their protocols and international standards of clinical trials. In preparation for the RTS,S malaria vaccine trials in Africa, a conscious effort was made to set up clinical trial infrastructure including human and logistical capacity according to International Conference on Harmonization Good Clinical Practice standards. To standardize study procedures, key protocols were established to define severe malaria⁴⁹ and malaria parasitemia.⁵⁰ The sponsors of the trial had committed over US\$300 million for this process. Additionally, the Malaria Clinical Trial Alliance of INDEPTH Network received a grant to support infrastructural development and clinical trial staff training.⁵¹ Similar initiatives such as the African Malaria Network⁵² and the Malaria Vectored Vaccine Consortium⁵³ have been established to test other malaria vaccine candidates. The capacity built in the last decade needs to be maintained to ensure sustainability for future trials of new malaria vaccine candidates despite the challenge of competing needs of African government funds and inadequate international funding for research.⁵⁴ There is also the need to build capacity for malaria vaccine discovery and preclinical studies in Africa, as has been done for the clinical phases of malaria vaccine development.

Another key infrastructure required for the RTS,S trials was a stable population to ensure efficient follow-up of enrolled trial participants. WHO recommends long-term (at least 2 years) follow-up in Phase III trials of pre-erythrocytic and blood-stage malaria vaccines to assess potential waning of vaccine efficacy and rebound effect.⁴² Such clinical trials therefore stand the risk of participant loss to follow-up as a result of factors that include movement out of the study area, death, consent withdrawal, or due to collective factors such as natural disasters, disease outbreaks, or civil wars. Frequent blood draws during the trials may also affect the trial participants' compliance to study procedures.⁵⁵ To minimize loss to follow-up, study participants need to clearly understand the study procedures during the consenting stages. Additionally, community engagement activities involving opinion leaders and community members need to be continuous throughout the study.⁵⁶ Participant loss to follow-up could also be minimized by careful selection of clinical trial sites with stable populations and robust address systems, as existing in the health and demographic surveillance systems of INDEPTH Network member sites that help to track trial participants.⁵⁷ In the RTS,S vaccine trials, children were followed up for several months in Phase II trials^{24,40} and for ~32 months in Phase III trials.²⁰

The just ended Phase III malaria vaccine trials recruited a large number of study participants – ~15,000 infants and younger children.⁹ It is likely that clinical trials of second-generation vaccines will require a larger sample size.⁴³ The need for large sample sizes requires multicenter trials with their attendant challenges, including trial coordination. For instance, multicenter trials require different ethical committees and regulatory authorities to approve the trial. This could delay the commencement of trials since the ethics committees and regulatory authorities do provide a very wide range of comments and suggestions that require substantial amounts of time to address and synchronize across the study sites prior to approval of the trial protocol. To avoid these bottlenecks in the short term, ethics committees and regulatory authorities in Africa may have to consider joint clinical trial protocol reviews. Ultimately, harmonizing ethical committees and regulatory authorities in Africa is worth considering.

Preparations for Phase IV malaria vaccine trials

Postapproval Phase IV studies will be required to identify rare adverse events that were not identified in Phase III studies. Phase IV studies are large studies and potentially include monitoring over 10,000 participants through an

efficient pharmacovigilance system. However, the pharmacovigilance system in sub-Saharan Africa where malaria vaccines will mainly be used is weak.⁵⁸ Several efforts have been made in establishing such systems in Africa. This includes the WHO collaborating centers of excellence in pharmacovigilance in some countries such as Ghana⁵⁸ and efforts by the INDEPTH Network, a nongovernmental organization made up of research institutions with health and demographic surveillance systems.⁵⁹ The key challenge in Phase IV studies is the lack of baseline disease profiles of rare diseases due to inadequate diagnostic tools in many health facilities in sub-Saharan Africa. As a result, Phase IV malaria vaccine studies to be carried out in sub-Saharan Africa would require further assessments of some rare diseases reported to be associated with vaccines such as intussusception⁶⁰ and Kawasaki Syndrome.⁶¹ Phase IV studies are currently being planned by GSK for the vaccine in sub-Saharan African countries. The study intends to enroll several thousands of children to allow identification of potential rare adverse events.⁶²

Considerations for RTS,S malaria vaccine introduction

Temperature requirements for malaria vaccines

Maintenance of an efficient cold chain system at specified temperatures will be required for storage and deployment of malaria vaccines from the manufacturers to the beneficiaries. Currently, the RTS,S malaria vaccine is expected to be stored at a temperature of 2–8°C²⁰ similar to other pediatric vaccines. Other malaria vaccine candidates under development are stored and transported at much colder temperatures.¹⁴ Insufficient cold chain infrastructure coupled with power supply problems will be challenges for rolling out the RTS,S malaria vaccine since the quality of the vaccine would be compromised outside the manufacturers' indicated storage temperature range. The existing cold chain system for the expanded program on immunization will have to be expanded to accommodate the malaria vaccines. The expansion requires commitment from governments of sub-Saharan countries and their development partners.

There is also a need to develop malaria vaccines that will not require expensive cold chain systems as is being developed for other vaccines. For instance, a cluster-randomized study conducted in Chad found tetanus toxoid vaccine to be safe and immunogenic at temperatures as high as 40°C for less than 30 days.⁶³

Packaging of the RTS,S malaria vaccine

Packaging of potential malaria vaccines will need to be considered in the manufacturing process to conform to WHO's preferred packaging profile through volume and weight reduction and use of sustainable disposal materials.^{7,64} It is expected that the RTS,S malaria vaccine will be packaged in smaller vaccine packs that will require minimal space for transportation from the manufacturing plant to the community level and reduce cost.

Community acceptance of RTS,S malaria vaccine

Introduction of new public health programs have sometimes been met with challenges leading to poor acceptability at the community level. Examples of such programmatic challenges were experienced during the introduction of polio vaccines in northern Nigeria⁶⁵ and antihelminthic drug treatment in Ghana.⁶⁶ These were poorly received as a result of inadequate community engagement, poor community understanding of the intervention, and sometimes mistrust. Introduction of a malaria vaccine may face similar challenges if appropriate community engagement processes are not properly instituted. However, the burden of malaria is very well known to the community members and there is a critical community demand for a malaria vaccine.^{67,68} This demand for a vaccine is likely to make community acceptance of a new vaccine easier. On the other hand, the high demand for a malaria vaccine may make community members perceive a partially efficacious malaria vaccine as a magic bullet for malaria control that could lead to a reduction in the use of other malaria control interventions such as bednets.⁶⁹ To understand community perceptions regarding the possible challenges of implementing a partially effective malaria vaccine, some exploratory studies were conducted at the time the Phase III RTS,S malaria vaccines trials were ongoing. These studies found that community members understand the concept of partially effective vaccines and are unlikely to switch their health practices to new interventions when they are introduced.^{69,70} This potential switch needs to be evaluated in Phase IV studies and as part of malaria control programs.

Cost of vaccine deployment and funding

The cost of the RTS,S malaria vaccine is currently unknown. Estimated cost of RTS,S malaria vaccine in six African countries has been estimated to be in the range US\$23.11–28.28 per fully vaccinated child based on an assumed unit cost of

a vaccine vial of US\$5.00 and country level indicators on Expanded Programme of Immunization.⁷¹

WHO pilot implementation studies

The WHO recommended large “pilot implementation studies” to assess the feasibility of administering four doses of the malaria vaccine in the context of the current immunization programs.³⁴ Some of the issues to be considered in the pilot studies are as described earlier. In addition, the pilot studies will also evaluate the impact of RTS,S malaria vaccine on infant and child mortality. However, there is an urgent need to ensure that these pilot studies are implemented without delay to enhance early use of the vaccine if its pilot introduction is feasible in the real-life setting.

Conclusion

We conclude that the development of the RTS,S malaria vaccine has been a long process confronted with challenges of funding, difficulty in identifying malaria antigens that correlate with protection, and development of adjuvant systems among others. The registration of GSK's RTS,S malaria vaccine by the EMA in July 2015 makes history as the first human parasite vaccine and a major public health achievement, as the vaccine has the potential to prevent thousands of malaria cases. However, as identified by the WHO's SAGE/MPAC, there are implementation challenges that need to be carefully addressed in the areas of cold chain systems, community acceptance, and monitoring of adverse events post-licensure to ensure a successful rollout of the new vaccine and subsequent ones.

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Author contributions

All authors contributed substantially to the conception of this work, drafting the article, and revising it critically for important intellectual content, and approved the final version to be published. All authors have agreed to be accountable for all aspects of the work and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

The authors' institution, Kintampo Health Research Centre, received grants to conduct Phase II/III trials of RTSS malaria

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