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Review Article

THE RTS,S/AS MALARIA VACCINE CANDIDATE: A STATUS REVIEW

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ABSTRACT

The RTS,S/AS malaria vaccine candidate is currently the most advanced in development. It is based on the circumsporozoite protein (CSP) combined with hepatitis B surface antigen. The vaccine is designed to prevent the malaria parasite from infecting the liver where it can mature, multiply, and re-enter the bloodstream, where it infects red blood cells and leads to symptomatic disease. This review documents the development process of the RTS,S/AS malaria vaccine candidate, from preclinical and early clinical trials to the recently concluded Phase III clinical trials. The final results demonstrated that vaccination with the 3-dose primary series reduced clinical malaria cases by 28% in young children and 18% in infants. A booster dose of RTS, S/AS, administered 18 months after the primary series, reduced the number of cases of clinical malaria in young children (aged 5-17 months at first vaccination) by 36% and in infants (aged 6-12 weeks at first vaccination) by 26%. Administration of the booster dose provided longer term protection against clinical malaria in both groups, with 1774 and 983 cases of malaria averted per 1000 children vaccinated in the older (age 5-17 months) and infant (6-12 weeks) age groups, respectively. The vaccine efficacy waned over time following the booster dose and further studies are ongoing to assess long term efficacy and the need for additional doses. The safety profile of the vaccine was acceptable. The vaccine has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures, especially in areas of high transmission.

KEY WORDS: RTS,S/AS malaria vaccine candidate, Malaria, circumsporozoite protein, *Plasmodium* parasite, vaccine efficacy

INTRODUCTION

Malaria, caused by the *Plasmodium* parasite, remains a global public health problem in the tropical world. An estimated 3.2 billion people are at risk and 198 million cases of malaria infection occur globally. The disease led to 584,000 deaths in 2013[1]. With a worldwide reduction of malaria mortality rates by 47% between 2000 and 2013, the progress in malaria control using long-lasting insecticidal nets, indoor residual spraying and expanding access to the artemisinin-based combination therapies is

remarkable [1]. However, the recent spread of parasite resistance to artemisinins may result in reversion of the positive trend [2].

Although existing interventions have helped to reduce malaria deaths significantly over the past decade, a well-tolerated and effective vaccine with an acceptable safety profile could add an important complementary tool for malaria control efforts. To date, no vaccine against malaria has been licensed [3].

Of the five species of *Plasmodium* that are known to cause disease in humans, two have received attention for vaccine



development (*P.falciparum* and *P.vivax*). Over 90% of malaria-related deaths are caused by *Plasmodium falciparum* hence most of the vaccines in development target *P. falciparum* [4].

The field of malaria vaccine research has grown to such an extent that it is now very difficult to summarize all projects in a single review. This is due to the increase in funding over the last 10 years which has allowed over 40 vaccine projects to reach the clinical trial stage [5]. This article is a comprehensive review of the most advanced malaria vaccine candidate so far, the RTS,S/AS malaria candidate vaccine. The main objective of this review is to outline the RTS,S/AS vaccine development process from conception to the current stage. This information may be useful and informative to those working in this field.

RATIONALE FOR A MALARIA VACCINE

There is general agreement that malaria eradication is not possible with the currently available technologies. Development of a highly efficacious malaria vaccine which dramatically reduces transmission would be a transformative tool that could enable future eradication [5].

The Malaria Vaccine Technology Roadmap was launched in 2006 and updated in 2013. The document was the result of a collective effort by the malaria vaccine community, coordinated by the WHO Institute for Vaccine Research (IVR) and expressed the landmark goal for vaccine development; to develop and license a first-generation vaccine with 50% efficacy against severe disease and malaria-related mortality protecting for more than 12 months by the year 2015. Strategic goals to be realized by the year 2030 are; development of malaria vaccines with protective efficacy of at least 75 percent against clinical malaria suitable for administration to appropriate at-risk groups in malaria endemic areas and development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. Vaccines to reduce transmission should be suitable for administration in mass campaigns [5].

Many lines of evidence indicate that humans can be vaccinated against malaria. Individuals born in endemic areas who survive the first years of exposure continue to develop parasitaemia on natural exposure, but become resistant first to severe, life-threatening malaria and then to clinical disease. Frequent re-exposure is required to maintain this condition of immunity with infection (concomitant immunity) [6].

Compared with other infectious diseases of major global importance such as HIV and tuberculosis, malaria vaccine research is facilitated by the availability of a clinical challenge model and a high attack rate in endemic areas, enabling definitive assessment by human experimentation for vaccines that prevent infection [6].

The malaria parasite has a complex life cycle, in that different stages of the parasite can be found in the human host and in different organs of the body during infection. This exposes different sets of parasite antigens to the immune system. Therefore, a malaria vaccine requires a

polyvalent multicomponent vaccine with a combination of candidate antigens from different stages of the life cycle [7].

A lot of work has been done in the field of malaria vaccine research. Of all the malaria vaccine candidates in development, the most advanced is the RTS,S/AS malaria vaccine candidate which is currently in phase IV clinical trial [7]. A summary of the global malaria vaccine pipeline is shown in figure 1.

THE RTS,S/AS MALARIA VACCINE CANDIDATE DEVELOPMENT

The RTS,S/AS malaria vaccine candidate is the first and, to date, the only malaria vaccine candidate to have consistently shown efficacy in malaria-naïve and semi-immune adults as well as in young children and infants living in malaria-endemic regions [8-15]. The vaccine is designed to prevent the parasite from infecting the liver where it can mature, multiply, and re-enter the bloodstream, where it infects red blood cells and leads to disease symptoms [8-15].

The development of this vaccine was initiated in 1987 at GlaxoSmithKline (GSK), as part of an ongoing collaboration with the Walter Reed Army Institute of Research (WRAIR) which began in 1984 to develop malaria vaccines for people residing in malaria-endemic regions, military personnel and travelers. The initial concept underlying RTS,S/AS development was built on the body of knowledge that existed in the field at that time. Over the following years, refinements to the initial concept occurred as the scientific knowledge in the fields of immunology and vaccine development evolved.

One of the components of the vaccine, the RTS, S antigen, is based on a large segment of the *P. falciparum* circumsporozoite protein (CSP) - amino acids 207 to 395 of the CSP from the NF54 strain of *P. falciparum*, containing known B and T cell epitopes [16]. The CSP had been identified as a promising target of protective immune responses by Nussenzweig et al [17]. The RTS,S consists of two proteins, RTS and S, simultaneously expressed in genetically engineered *Saccharomyces cerevisiae* yeast cells [18]. RTS is a chimeric protein derived from the genetic fusion of the carboxy-terminal half of the CSP (designated RT) to the hepatitis B virus gene encoding the virus surface protein (designated S) [18]. Many observations in rodent models, supported by some human data, showed that CSP was a logical candidate for the development of a human malaria vaccine [18].

Novel adjuvant systems (AS) were developed at GSK and tested preclinically and clinically with the aim of selecting a well-tolerated, immunogenic and efficacious formulation for the RTS,S antigen [19]. The Adjuvant Systems eventually selected and used in most of the clinical studies described in this review, belong to the AS01 and AS02 families. Both include the immune response enhancers MPL14 and QS21, [20] and are formulated either as a liposome based adjuvant in the case of AS01, or an oil-in-water emulsion based adjuvant, for AS02. [21]

A schematic representation of the CSP and the RTS,S/AS malaria vaccine is shown in figure 2.

Laboratory Development and Preclinical Testing of RTS,S/AS Vaccine

In 1984, GSK and the Walter Reed Army Institute for Research (WRAIR) entered into a Collaborative Research and Development Agreement to produce a malaria vaccine using genetic engineering techniques and *Escherichia coli* expression systems developed at GSK [22]. While several plasmodial antigens were pursued, the major focus of this collaboration was the CSP of *P. falciparum* and, to a lesser extent, the CSP of *P. vivax*. Over the following decade, multiple constructs, primarily based on the use of the central repeat region of *P. falciparum* CSP, were generated, expressed in *E. coli* and produced for preclinical testing and when necessary, manufactured at Good Manufacturing Process (GMP) grade for clinical evaluation [22-23].

Nearly a dozen constructs were tested preclinically and as many as six different vaccines were tested in the clinic in Phase I, Phase I/IIa challenge studies and up to Phase IIb studies in malaria endemic regions [23-28]. A few vaccine candidates reached efficacy testing in the laboratory-based challenge model. However, while a few volunteers were protected, the marginal efficacy observed did not justify further development of any of the candidates. Likewise, the only candidate that was tested in Phase IIb studies in Kenyan and Thai adult volunteers failed to show efficacy in these field studies and was also abandoned. [23,24]. However, researchers had now the proof that protection against malaria infection could be induced albeit at a low level, by CS-based pre-erythrocytic recombinant or peptide vaccines and that the laboratory-based challenge model could be a useful tool to 'down select' poorly performing candidates. [28].

In the late 1970s and early 1980s GSK scientists were developing what would become the first ever registered recombinant DNA vaccine. The vaccine, Engerix-B™, targets the hepatitis B virus and is produced in *Saccharomyces cerevisiae* yeast cells genetically engineered to express the gene encoding the virus surface protein HBsAg (or S). The striking feature of this expression system is that the S protein produced in the yeast cells spontaneously assembled into multimeric virus-like particles (VLP) [29]. The expertise acquired during the development of the Engerix-B™ vaccine led GSK scientists working on the malaria project to use the hepatitis B surface antigen as carrier matrix for the repetitive epitope of the *P. falciparum* CSP by fusing the appropriate CSP genetic sequence to that of the hepatitis B virus surface protein and expressing the chimeric gene in *S. cerevisiae* cells. The resulting fusion protein, assembled into VLP, similar to those formed by the unfused viral surface protein [30]

This initial construct, R16-HBsAg, was based on the concept of inducing exclusively an antibody response against the *N*-Acetylneuraminic Acid Phosphatase (NANP) antigen. The construct therefore contained 16 NANP repeats fused to HBsAg. The vaccine proved poorly immunogenic in a Phase 1 trial [31] and was later abandoned in favor of a more promising construct that

contained in addition to the dominant (NANP)_n B cell epitope several T cell epitopes recently identified in the C-terminal non-repetitive region of the CSP.[32] The new vaccine was designated RTS,S to indicate the presence of the CSP repeat region (R), T-cell epitopes (T) fused to the hepatitis B virus surface antigen (S) and assembled with unfused copies of S antigen[32]

Early Clinical Trials

Following the unprecedented demonstration of efficacy in the laboratory-based challenge model in malaria naive adult volunteers in the United States and Belgium, field evaluation was initiated with a Phase 2b study conducted in adult men from The Gambia [33]. In that study, the safety and immunogenicity of the RTS,S/AS candidate vaccine was successfully demonstrated. A subsequent Phase 1b trial in Gambian adult men provided proof-of-efficacy of the candidate vaccine under natural exposure to the parasite. 3 doses of RTS,S/AS vaccine administered at months 0, 1, 5 conferred significant protection against infection over a 15 weeks surveillance period (34%; 95% CI: 8–53; $p = 0.014$). Although efficacy appeared to wane during the surveillance period, a booster dose at 19 months during the subsequent transmission season demonstrated 47% (95% CI: 4, 71; $p = 0.037$) efficacy over a 9 week surveillance period. Furthermore, efficacy of RTS,S/AS did not appear to be strain specific.[34] Long-term safety and persistence of anti-CS and anti-HBs antibodies of the RTS,S/AS vaccine candidate in this population was subsequently documented over a 5 year surveillance period.[35]

Phase II Clinical Trials in Pediatric Population

Based on the encouraging results obtained in phase 1, Phase 2a and Phase 2b studies in adult volunteers, pediatric development of the RTS,S/AS vaccine candidate was initiated under a, private/public partnership agreement between GSK and the PATH Malaria Vaccine Initiative (MVI).

The RTS,S/AS candidate vaccine was shown to be highly immunogenic for both the CSP and S antigens and to have a promising safety profile in children from Mozambique. [36,37] Proof-of-concept of efficacy in the pediatric population was demonstrated in a large, double-blind, controlled study enrolling 2,022 children aged 1 to 4 years from Mozambique. Following vaccination according to a 0, 1, 2-month schedule, efficacy against first clinical episodes was 29% (95% CI: 11, 45; $p = 0.004$) and against severe malaria 58% (95% CI: 16, 81; $p = 0.019$) over a 6 month surveillance period, and 35% (95% CI: 22, 47, $p < 0.001$) and 49% (95% CI: 12, 71, $p = 0.02$), respectively, over an 18 month surveillance period. [38]. Importantly, sustained clinical benefit against all clinical episodes of malaria [26% (95% CI: 12, 37) $p \leq 0.001$] together with prevention of severe malaria [38% (95% CI: 3, 61) $p = 0.045$] was demonstrated over 45 months of surveillance.[39] Furthermore, at month 45, the prevalence of *P. falciparum* parasites was 34% lower in recipients of RTS,S/ AS than of control vaccine (12% vs. 19%, $p = 0.004$).

Over the 45 month period of surveillance, RTS,S/AS had an acceptable safety profile, with significantly less serious adverse events and a trend towards reduced all-cause mortality compared to recipients of control vaccine. The promising results obtained in field studies in older children led to the assessment of the RTS,S/AS candidate vaccine in infants within the EPI age range. Following staggered administration of RTS,S/AS with EPI vaccines (diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b vaccine; DTPw/Hib) at 8, 12 and 16 weeks of age in infants from Mozambique, the safety profile of RTS,S/AS in terms of serious adverse events was indistinguishable to that of hepatitis B control vaccine. [39] In this study, vaccine efficacy against infection was demonstrated over 3 months' follow-up [66% (95% CI: 43, 80) $p < 0.001$].[39]

The encouraging efficacy, immunogenicity and safety data from the Phase 2 trials in the pediatric population led to the decision by the GSK/MVI partnership to progress the RTS,S/AS candidate vaccine to Phase 3 clinical trials

Phase III Clinical Trials

The Phase III efficacy and safety trial of RTS,S/AS started in May 2009 and was completed early 2014 at 11 sites in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania) with 15,459 infants and young children participating, making this the largest malaria vaccine trial in Africa to date. The study was a multicenter, double blind, randomized controlled trial in children aged 6 weeks to 17 months at the time of first vaccination.[40,41] It was conducted in diverse malaria transmission settings across Africa. From March 2009 through January 2011, 15,460 children were enrolled in two age categories — 6 to 12 weeks of age and 5 to 17 months of age — for vaccination with either RTS,S/AS or a non-malaria comparator vaccine. The study was designed collaboratively with the Clinical Trial Partnership Committee (CTPC) that brings together representatives of several leading African research institutes, academic partners from the EU and the USA, Path-MVI and GSK. . In accordance with National policies, the research teams at each study centre ensured that malaria control measures, including insecticide treated bed net use, were optimized. The primary end point of the analysis was vaccine efficacy against clinical malaria during the 12 months after vaccination in the first 6000 children 5 to 17 months of age at enrollment who received all three doses of vaccine according to protocol. After 250 children had an episode of severe malaria, vaccine efficacy against severe malaria was evaluated in both age categories.

The results showed that three doses of RTS, S/AS reduced clinical malaria by approximately half in children 5-17 months of age at first vaccination [40]. In the 14 months after the first dose of vaccine, the incidence of first episodes of clinical malaria in the first 6000 children in the older age category was 0.32 episodes per person-year in the RTS,S/AS group and 0.55 episodes per person-year in the control group, for an efficacy of 50.4% (95% confidence interval [CI], 45.8 to 54.6) in the intention-to-treat population and 55.8% (97.5% CI, 50.6 to 60.4) in the per-protocol population. Vaccine efficacy against severe malaria was 45.1% (95% CI, 23.8 to 60.5) in the intention-to-treat population and 47.3% (95% CI, 22.4 to 64.2) in the

per-protocol population. Vaccine efficacy against severe malaria in the combined age categories was 34.8% (95% CI, 16.2 to 49.2) in the per-protocol population during an average follow-up of 11 months. Serious adverse events occurred with a similar frequency in the two study groups. Among children in the older age category, the rate of generalized convulsive seizures after RTS,S/AS vaccination was 1.04 per 1000 doses (95% CI, 0.62 to 1.64).[40]

In infants 6-12 weeks of age at first vaccination with RTS,S/AS, clinical malaria was reduced by approximately one-third[41]. The incidence of the first or only episode of clinical malaria in the intention-to-treat population during the 14 months after the first dose of vaccine was 0.31 per person-year in the RTS,S/AS group and 0.40 per person-year in the control group, for a vaccine efficacy of 30.1% (95% confidence interval [CI], 23.6 to 36.1). Vaccine efficacy in the per protocol population was 31.3% (97.5% CI, 23.6 to 38.3). Vaccine efficacy against severe malaria was 26.0% (95% CI, -7.4 to 48.6) in the intention-to treat population and 36.6% (95% CI, 4.6 to 57.7) in the per-protocol population. Serious adverse events occurred with a similar frequency in the two study groups. One month after administration of the third dose of RTS,S/AS, 99.7% of children were positive for anti-circumsporozoite antibodies, with a geometric mean titer of 209 EU per milliliter (95% CI, 197 to 222)[41].

In a subsequent analysis after 18 months of follow up, children aged 5-17 months at first vaccination with RTS,S/AS experienced 46% fewer cases of clinical malaria, compared to children immunized with a comparator vaccine, vaccine efficacy 46% (95% CI 42% to 50%) [43] Infants aged 6-12 weeks at first vaccination with RTS,S/AS had 27% fewer cases of clinical malaria than infants in the control group, vaccine efficacy ,27% (95% CI 20% to 32%).

Vaccine efficacy against severe malaria, malaria hospitalization, and all-cause hospitalization was 34% (95% CI 15% to 48%), 41% (95% CI 30% to 50%), and 19% (95% CI 11% to 27%),

respectively. Post vaccination anti-circumsporozoite antibody geometric mean titer varied from 348 to 787 EU/ml across sites in children and from 117 to 335 EU/ml in infants (per protocol).

Vaccine efficacy waned over time in both age categories (Schoenfeld residuals $p < 0.001$). These results were achieved on top of existing malaria interventions, such as insecticide-treated bed nets, which were used by approximately 80% of the trial participants. [42]

The final study results, analyzed vaccine efficacy, immunogenicity, safety and impact of RTS,S/AS over a median of 38 (IQR 39–50) and 48 (IQR 34–41) months of follow-up (post dose 1) in infants and young children, respectively.

From March 27, 2009, until Jan 31, 2011, infants aged 6–12 weeks and children aged 5–17 months were recruited and randomly assigned (1:1:1) by block randomisation with minimisation by centre to one of three groups. One

group received RTS,S/AS at months 0, 1, and 2, followed by a booster dose at month 20 (R3R group); a second group received the RTS,S/AS primary vaccination series with meningococcal serogroup C conjugate vaccine (Menjugate®, Novartis, Basel, Switzerland) instead of an RTS,S/AS booster (R3C group); and the third group received only comparator vaccines: rabies vaccine (Verorab®, Sanofi Pasteur, Paris, France) for children and Menjugate® for young infants (C3C [control group]). Young infants received the study vaccine at the same time as the Expanded Program on Immunization vaccines

The final results showed that RTS,S/AS prevented a substantial number of cases of clinical malaria over a 3–4 year period in young infants and children when administered with or without a booster dose. Efficacy was enhanced by the administration of a booster dose in both age categories [43]. A total of 9585 episodes of clinical malaria that met the primary case definition in children occurred in the control group (C3C group), compared to 6616 episodes occurred in the R3R group (vaccine efficacy 36.3%, 95% CI 31.8–40.5) and 7396 occurred in the R3C group (28.3%, 23.3–32.9); compared with 171 children who experienced at least one episode of severe malaria in the C3C group, 116 children experienced at least one episode of severe malaria in the R3R group (32.2%, 13.7 to 46.9) and 169 in the R3C group (1.1%, –23.0 to 20.5). In young infants, compared with 6170 episodes of clinical malaria that met the primary case definition in the C3C group, 4993 episodes occurred in the R3R group (vaccine efficacy 25.9%, 95% CI 19.9–31.5) and 5444 occurred in the R3C group (18.3%, 11.7–24.4); and compared with 116 infants who experienced at least one episode of severe malaria in the C3C group, 96 infants experienced at least one episode of severe malaria in the R3R group (17.3%, 9.5% CI –9.4 to 37.5) and 104 in the R3C group (10.3%, –17.9 to 31.8). In children, 1774 cases of clinical malaria were averted per 1000 children (95% CI 1387–2186) in the R3R group and 1363 per 1000 children (995–1797) in the R3C group. The numbers of cases averted per 1000 young infants were 983 (95% CI 592–1337) in the R3R group and 558 (158–926) in the R3C group [43].

The frequency of severe adverse effects (SAEs) overall was balanced between groups. However, meningitis was reported as a SAE in 22 children: 11 in the R3R group, 10 in the R3C group, and 1 in the C3C group. The incidence of generalised convulsive seizures within 7 days of RTS,S/AS booster was 2.2 per 1000 doses in young infants and 2.5 per 1000 doses in children [44].

The RTS,S/AS vaccine continued to display an acceptable safety and tolerability profile during the entire phase III study period. In both age categories, adverse events after vaccination included local reactions (such as pain or swelling), which were observed more frequently after RTS,S/AS administration compared to the comparator vaccine [43]. In the younger age category (i.e. infants 6–12 weeks of age at first injection), injection site reactions were reported less frequently after RTS,S/AS administration compared to the standard vaccines routinely used in the African EPI [43].

The incidence of fever in the week after vaccination was higher in children who received the RTS,S/AS vaccine

than in those receiving the comparator vaccine [43]. In some children this resulted in febrile reactions that were accompanied by generalized convulsive seizures, but all those affected fully recovered within seven days. The rates of other serious adverse events seen in the trial (mainly medical events requiring hospitalization, regardless of whether they were considered to be caused by the study vaccine) were comparable between the trial's RTS,S/AS candidate vaccine recipients and those receiving a control vaccine, except for cases of meningitis, which were reported in low numbers, but more often in the RTS,S/AS group compared to the control [43]. The meningitis signal previously reported [42] remained in the older age category, including a small number of new cases reported after the booster dose. This could be a chance finding as comparisons were made across groups for many different diseases, and because some of these cases happened years after vaccination without any obvious relationship to vaccination [43].

LESSONS LEARNT FROM RTS,S/AS MALARIA VACCINE RESEARCH AND DEVELOPMENT

Several lessons have been learnt during the research and development of the RTS,S/AS malaria vaccine. First, the RTS,S-based vaccines have repeatedly shown efficacy to reduce morbidity in endemic areas. Second, the safety and immunogenicity in young children has not been worse than in adult populations. As far as adjuvants are concerned, oil in water emulsions (AS01, AS02) are more immunogenic than alhydrogel for recombinant monomeric protein vaccines. In general, there has been little clinically significant interference between the malarial antigen and EPI vaccine antigens.

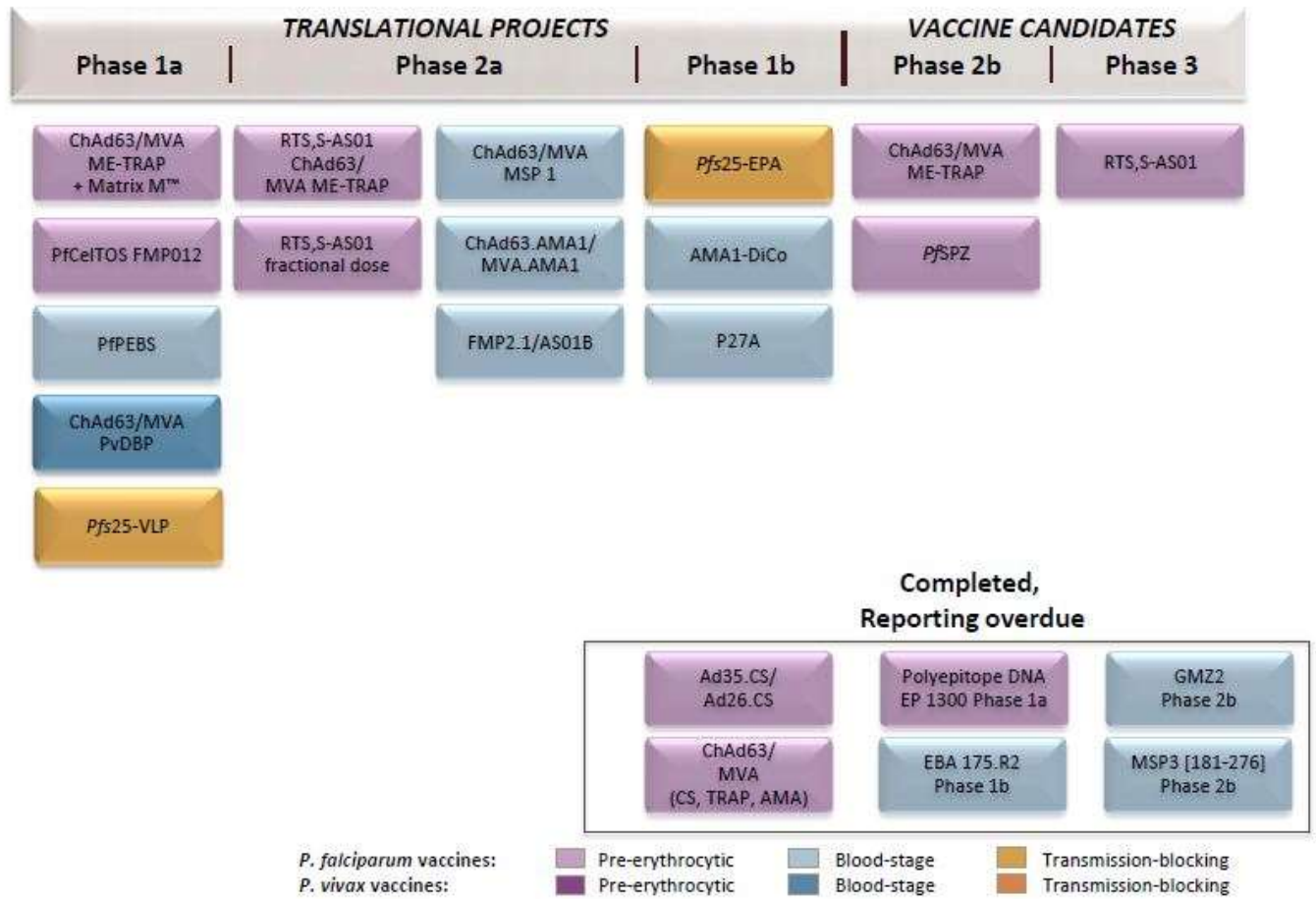
For assessment of vaccine efficacy in clinical malaria vaccine trials, observing the number of episodes of malaria is more useful and takes priority over time to first episode of malaria.

It is best practice that every Phase IIb/III vaccine trial design includes a commercialized vaccine that will benefit the control group as comparator and that any trial subject receives at least the standard package of preventive measures (LLIN and others) implemented in trial. Lastly, methodological and ethical issues would arise in testing of new malaria vaccines in the field if the RTS,S/AS malaria vaccine is licensed and becomes a standard preventive measure in a given setting.



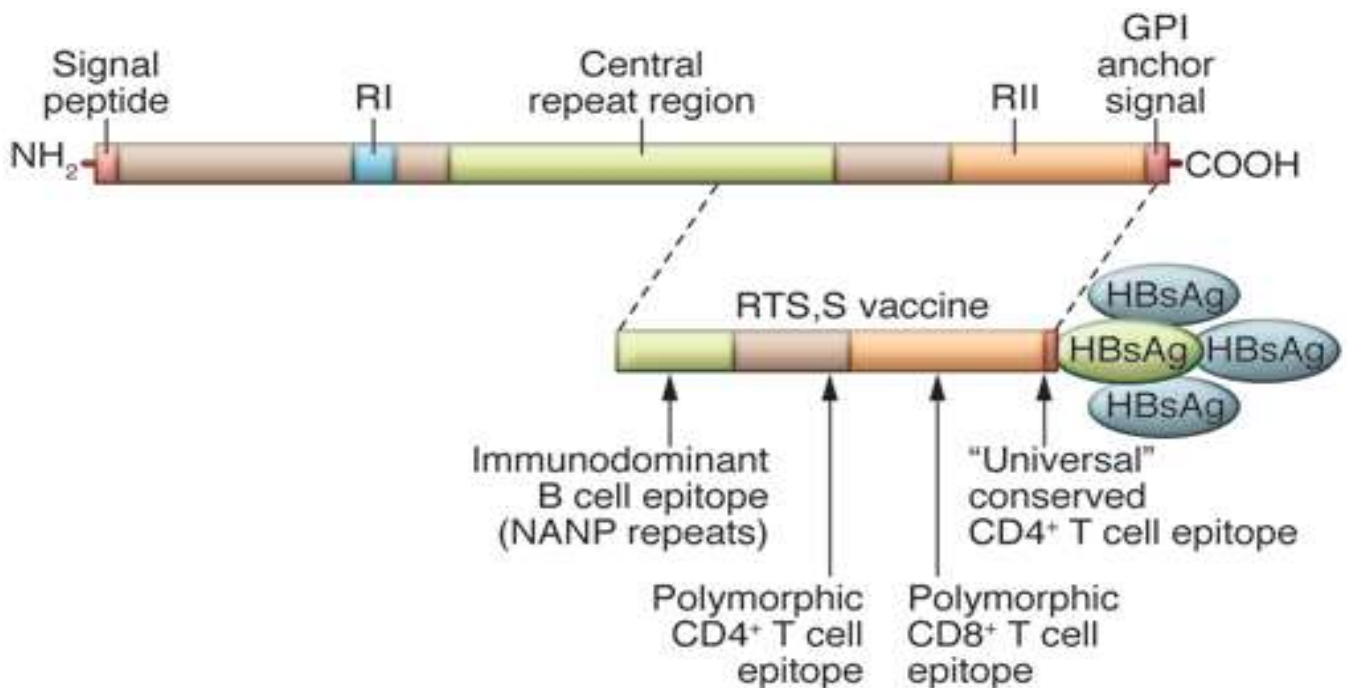
Figure 1: Global malaria vaccine pipeline

Global malaria vaccine pipeline



Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

Figure 2: Schematic representation of the CSP and the RTS,S vaccine



The CSP is the predominant surface antigen on sporozoites. CSP is composed of an N-terminal region that binds heparin sulfate proteoglycans (RI), a central region containing a four-amino-acid (NANP) repeat, and a GPI-anchored C-terminal region containing a thrombospondin-like domain (RII). The region of the CSP included in the RTS,S vaccine includes the last 16 NANP repeats and the entire flanking C-terminus. HBsAg particles serve as the matrix carrier for RTS,S, 25% of which is fused to the CSP segment. The central repeat region contains the immunodominant B cell epitope, which induces antibodies that block sporozoite infection of liver cells in vitro

Data source: Crompton PD, Pierce SK, Miller LH. Advances and challenges in malaria vaccine development. The Journal of clinical investigation. 2010 Dec 1;120(12):4168-78.

CONCLUSIONS AND RECOMENDATIONS

The RTS,S/AS vaccine prevented a substantial number of cases of clinical malaria over a 3–4 year period in young infants and children when administered with or without a booster dose. Efficacy was enhanced by the administration of a booster dose. Thus, the vaccine has the potential to make an impact on the malaria burden in sub-Saharan Africa and potentially an important social and economic impact on the sub-continent. The prospect of judiciously integrating a vaccine with the efficacy profile of RTS,S/AS to other malaria control measures certainly opens the door to the possibility of improved control of malaria in African children.

The challenge then will be to make the vaccine available, as soon as possible after its registration, to every infant and child who needs it in sub-Saharan Africa. For this to happen, vaccine demand must be forecasted in advance and manufacturing capacity must be adapted to the forecast. Mechanisms must be identified to make possible financing of vaccine procurement by supranational organizations and agencies, such as the Global Alliance for Vaccines and Immunization (GAVI), and UNICEF. The public health systems and infrastructures in the countries wishing to implement the vaccine must be adequately resourced to be

ready to integrate a new vaccine into their EPI schedule as well as to add new prevention methods to their malaria control programs

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) announced on July 24, 2015, that it has adopted a positive scientific opinion, under Article 58, for GSK’s malaria candidate vaccine Mosquirix®, also known as RTS,S/AS, in children aged 6 weeks to 17 months [44]. With this positive opinion, the WHO has indicated that a policy recommendation for RTS,S/AS is possible by the end of 2016, paving the way for decisions by African nations regarding implementation of the vaccine through their national immunisation programmes.[43]. WHO has established a Joint Technical Expert Group [45] with the intention that this group will provide advice to a joint committee of WHO’s Malaria Policy Advisory Committee and the Strategic Advisory Group of Experts committees, which will formulate WHO’s recommendations on the use of RTS,S/AS vaccine.

COMPETING INTERESTS

The authors declare that there are no competing interests regarding the publication of this paper.

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