RTS,S: Toward a first landmark on the Malaria Vaccine Technology Roadmap

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ABSTRACT

The Malaria Vaccine Technology Roadmap calls for a 2015 landmark goal of a first-generation malaria vaccine that has protective efficacy against severe disease and death, lasting longer than one year. This review focuses on product development efforts over the last five years of RTS,S, a pre-erythrocytic, recombinant subunit, adjuvanted, candidate malaria vaccine designed with this goal of a first-generation malaria vaccine in mind. RTS,S recently completed a successful pivotal Phase III safety, efficacy and immunogenicity study. Although vaccine efficacy was found to be modest, a substantial number of cases of clinical malaria were averted over a 3–4 years period, particularly in settings of significant disease burden. European regulators have subsequently adopted a positive opinion under the Article 58 procedure for an indication of active immunization of children aged 6 weeks up to 17 months against malaria caused by Plasmodium falciparum and against hepatitis B. Further evaluations of the benefit, risk, feasibility and cost-effectiveness of RTS,S are now anticipated through policy and financing reviews at the global and national levels.

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1. Introduction

RTS,S, a subunit malaria vaccine candidate, has now reached the scientific and regulatory milestone of a positive scientific opinion from European regulators for the prevention of malaria in young children in sub-Saharan Africa and continues to progress toward potentially being the first malaria vaccine deployed against a human parasite. RTS,S is comprised of a liposome-based adjuvant (AS01) and hepatitis B virus surface antigen (HBsAg) virus-like particles incorporating a portion of the Plasmodium falciparum-derived circumsporozoite protein (CSP) genetically fused to HBsAg. The indication is for active immunization of children aged 6 weeks up to 17 months against malaria caused by P. falciparum and against hepatitis B. If approved by national regulatory authorities and recommended by policy makers in countries of use, development of RTS,S will have taken more than 30 years (see Fig. 1). For a summary of the major milestones achieved during the first two dozen years of RTS,S development, the reader is referred to reviews published in 2010 [1,2]. The present review focuses on product development efforts and the associated scientific literature over the last half decade, particularly the Phase III program, the regulatory and anticipated policy and financing pathways, and the planned post-approval program/Phase IV studies.

But first, a recapitulation of the rationale for development of RTS,S in the context of the Malaria Vaccine Technology Roadmap developed by World Health Organization (WHO) in consultation with the Scientific & Public Health Malaria Community [3,4], is provided.

2. RTS,S and the Malaria Vaccine Technology Roadmap 2015 Landmark Goal

The Malaria Vaccine Technology Roadmap (MVTRM) was originally launched in 2006 and focused on the urgent need for vaccines to alleviate the ongoing severe disease and death due to malaria. As such, the priority for the global malaria vaccine development efforts was on P. falciparum, children under 5 years of age, and sub-Saharan Africa and other highly endemic regions. Largely driven by

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CSP, circumsporozoite protein; EMA, European Medicines Agency; GFATM, Global Fund to Fight Aids, Tuberculosis and Malaria; HBsAg, hepatitis B virus surface antigen; ITT, intention-to-treat; JTEG, Joint Technical Expert Group; MPAH, Malaria Policy Advisory Committee; MPL, monophosphoryl lipid A; MVTRM, Malaria Vaccine Technology Roadmap; PAP, post-approval program; SAGE, Strategic Advisory Group of Experts; TSP, Thrombospondin-like type I repeat domain; VE, vaccine efficacy; VIS, Vaccine Investment Strategy; WRAIR, Walter Reed Army Institute of Research; WHO, World Health Organization.

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the progress of early clinical development of RTS,S, the MVTRM set the following landmark goal: “By 2015, develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50 percent against severe disease and death and lasts longer than one year” [3].

The shared vision and strategic goals of the MVTRM were expanded in 2013 to include development of vaccines against Plasmodium vivax and development of malaria vaccines that reduce transmission of the parasite [4]. This expansion was driven by marked changes in malaria epidemiology associated with the scale-up of malaria control measures and the resultant reductions in malaria parasite transmission, a shift in peak age of clinical malaria to older age groups, and a decline in malaria-related deaths, coupled with substantial changes in the malaria research agenda. As the focus of the RTS,S development program was on the pediatric indication to prevent clinical malaria, the contribution of RTS,S to the strategic goal of developing vaccines that interrupt malaria parasite transmission (also known as VIMTs) has been largely unexplored to date, other than some recent preliminary findings that suggest that serum from RTS,S-vaccinated individuals does not inhibit sporogony in mosquitoes [5]. That said, the original 2015 landmark, which captures the goal of a first-generation malaria vaccine, remains unchanged in the updated MVTRM [4]. In that regard, on 23 July 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in accordance with the European Medicines Agency (EMA) Article 58 procedure, recommending the granting of a marketing authorization for RTS,S for an indication of active immunization of children aged 6 weeks up to 17 months against malaria caused by Plasmodium falciparum and against hepatitis B [6].

3. Circumsporozoite protein and RTS,S

The sporozoite plays a central role in the parasite life cycle, from the maturing Plasmodium oocyst in the midgut of the definitive host to initial infection of the intermediate host. In the case of P. falciparum, sporozoites are transmitted to the intermediate human host through the bites of the definitive female Anopheles mosquito hosts having parasite-infected salivary glands. Only a fraction of the sporozoites in the mosquito salivary glands are injected into the circulation and ultimately infect hepatocytes in susceptible humans. Because the parasite endures a significant numerical bottleneck as it is transmitted between hosts, it is thought the parasite is most vulnerable to immune attack as it cycles between the definitive and intermediate hosts [7]. That protective immunity able to block transmission of the parasite as it passes through these numerical bottlenecks is never acquired [8], despite repeated infections, provides an opportunity to induce novel immune responses through active immunization [9].

The circumsporozoite protein (CSP), which is the major surface protein of Plasmodium spp. sporozoites, forms a dense coat on the parasite’s surface and has been proposed to contribute to several critical roles as the parasites develops within the female mosquito and infects the mammalian host [10]. Although the primary amino acid sequences of CSPs differ between Plasmodium spp., the basic architectures are similar (Fig. 2): a N-terminus that encodes a signal peptide sequence, binds heparkin sulfate proteoglycans (Region I), and contains a conserved five amino acid (KLKQP) proteolytic cleavage site sequence and Pexel motifs [11]; a middle third that consists of tandem, species-specific amino acid repeats that are immunodominant C-cell epitopes recognized by the neutralizing antibodies [12] and contributes to sporozoite development in the mosquito [13]; and a C-terminus that contains a thrombospondin-like type I repeat domain (TSP) with cell adhesion properties (Region II), a canonical glycosylphosphatidylinositol ( GPI) anchor addition sequence, and three known T cell epitopes—a highly variable CD4⁺ T-cell epitope before the TSP, a highly variable CD8⁺ T-cell epitope within the TSP, and a “promiscuous” CD4⁺ T-cell epitope whose structure is conserved among all parasite isolates [14].

RTS,S contains 189 amino acids from CSP (NF54 199-387aa), including the last 18 NANP repeats and the C-terminus exclusive of the GPI anchor addition sequence. Approximately 25% of the Hepatitis B virus surface antigen (HBsAg) monomers in RTS,S particles are genetically fused to the truncated CSP and serve as protein carriers. Despite self-assembly into HBsAg virus-like particles, non-adjuvant RTS,S is weakly immunogenic and requires an adjuvant
Fig. 2. Graphical depiction of circumsporozoite (CSP) and RTS,S structures. CSP comprises an N-terminal region containing a signal peptide sequence and Region I that binds heparin sulfate proteoglycans and has embedded within it a conserved five amino acid (KLRKQ) proteolytic cleavage site sequence; a central region containing four-amino-acid (NANP)/NVPD) repeats; and a C-terminal region containing Region II [a thrombospondin (TSF)-like domain] and a canonical glycosylphosphatidylinositol (GPI) anchor addition sequence. The region of the CSP included in the RTS,S vaccine includes the last 18 NANP repeats and C-terminus exclusive of the GPI anchor addition sequence. Hepatitis B virus surface antigen (HBsAg) monomers self-assemble into virus-like particles and approximately 25% of the HBsAg monomers in RTS,S are genetically fused to the truncated CSP and serve as protein carriers. The CSP fragment in RTS,S contains three known T-cell epitopes: a highly variable CD4+ T-cell epitope before the TSF-like domain (TH2R), a highly variable CD8+ T-cell epitope within the TSF-like domain (TH3R), and a conserved “universal” CD4+ T cell epitope (CS.T3) at the C-terminus.

To improve the magnitude and duration of the immune responses to CSP [15]. The Adjuvant System selected [15], AS01, consists of two immunostimulants, 3-O-desacyl-4′-monophosphoryl lipid A (MPL) and QS-21 Stimulon® Adjuvant (QS-21), in a liposome formulation. Recent studies suggest that one mechanism of action of AS01 is to transiently stimulate the innate immune system and activate a high number of efficient antigen-presenting dendritic cells in the draining lymph nodes [16]. Also recently published are a repeated dose toxicity study after four administrations of RTS,S at two-week intervals in New Zealand white rabbits. As expected an acute inflammatory reaction was observed at the injection sites; however, all affected parameters returned to normal within 28 days after the last injection, indicating full recovery, and no local or systemic toxicities were observed [17].

In the context of RTS,S, the absence of the N-terminal region and the genetic diversity of CSP are worth noting. Immune responses to the CSP N-terminal region which contains two functional domains have been identified as potential targets for protective antibodies [18]. Whether antibodies specifically directed at the highly conserved Region I of CSP inhibit parasite binding and/or proteolytic cleavage, and more importantly confer protective immunity remains to be definitively established. Whereas the N-terminal region of the CSP appears to have limited genetic diversity, the central repeat and C-terminal regions are known to be naturally polymorphic, as recently confirmed in Mali [19] and Madhya Pradesh, India, where malaria is endemic in a population not previously exposed to RTS,S [20]. The validation of Region I as a target of protective immunity may become important in addressing any issues of genetic diversity associated with the more polymorphic C-terminal portion of CSP.

To evaluate CSP genetic diversity in populations administered RTS,S, an ancillary study to the pivotal Phase III trial of RTS,S (described below) was developed to genotype parasites from the vaccine trial [21]. Approximately 6,000 samples were drawn, representing both enrolled age categories, severe disease cases, first clinical episodes, and cross-sectional parasite-positive samples collected during study month 20. Parasite variants that infect vaccinated subjects will be evaluated for known T cell epitope (TH2R, TH3R, CS.T3) haplotypes, as well as differences in B cell epitope (NANP) repeat count distributions within the central repeat region of CSP. Whether administration of RTS,S is associated with a change in parasite genetic diversity (within and outside the csp locus) will be evaluated by enumerating the parasite genotypes to determine if the vaccine is limiting the complexity of infection (COI) instead of selecting for particular parasite variants in the RTS,S vaccinated population. The goal of this study is to determine if RTS,S selects specific parasite variants or alters the number of parasite types within a vaccinated subject, and to gain a better understanding of the mechanism of action of the RTS,S [21].

4. Phase III program

The cornerstone of the Phase III program was a pivotal efficacy and safety trial, MALARIA-055 (NCT00866619) [22,23], conducted by the RTS,S Clinical Trials Partnership at 11 clinical trial sites in seven African countries (one site in Burkina Faso, Gabon, Malawi and Mozambique; two sites in Ghana and Tanzania; and, three sites in Kenya). The trial started in May 2009, enrolled 15,459 infants and young children, concluded in January 2014, and the results summary through study end posted in January 2015 [23]. This double-blind, individually randomized, controlled, three-arm trial, in which participants received either three doses of RTS,S one month apart, followed by a booster dose 18 months later; three doses of RTS,S followed by a comparator (or ‘control’) vaccine at the time of booster vaccination; or only control vaccines throughout, had two age categories: young children aged 5–17 months and infants aged 6–12 weeks at the time of enrollment. The younger age category was aligned with the infant cohort targeted for co-administration with routine Expanded Program of Immunization oral polio and parenteral DTP-containing vaccines. The details of the trial, designed in consultation with appropriate regulatory authorities and the World Health Organization (WHO), have been published [24–27], as have some key learnings from community engagement during the conduct of the trial [28]. Other trials in the Phase III program were conducted to further assess RTS,S in co-administration with other routinely administered vaccines, to assess its safety and efficacy in HIV-infected infants and young children, and to document lot-to-lot consistency of vaccine manufacturing [29,30].

The pivotal Phase III trial was conducted in two phases: a double-blind phase from Month 0–32 [31–33]; and, an extension phase from Month 33 to study end [34]. The primary aim of the trial was to assess the efficacy of a three-dose primary vaccination course of RTS,S against clinical malaria over 12 months follow-up in two age categories (see above). Secondary aims were to describe the safety and immunogenicity of RTS,S, to evaluate the efficacy of the vaccine
candidate against other endpoints of public health importance (e.g., severe malaria and malaria hospitalization), and to evaluate a booster dose of RTS,S received at Month 20 with follow-up through a twelve-month period (Month 32). An additional analysis was conducted at the end of an extension of the follow-up period, including an evaluation of safety and efficacy against clinical malaria, severe malaria and prevalent parasitemia [34].

With respect to the primary aim in the per-protocol population of the pivotal Phase III trial, over the Month 2.5 to Month 14 follow-up period (i.e., 12 months post-dose 3), in the 5–17 months age category, the efficacy of RTS,S calculated by negative binomial regression model against first or only episode of malaria meeting the clinical malaria primary case definition was 55.8% (with 97.5% confidence interval ranging from 50.6% (lower limit) to 60.4% (upper limit), and p-value <0.0001) [23,31]. Over the Month 2.5 to Month 14 follow-up period, in the 6–12 weeks age category, the efficacy of RTS,S similarly calculated by negative binomial regression model against first or only episodes of malaria meeting the clinical malaria primary case definition was 31.3% (with 97.5% confidence intervals ranging from 23.6% (lower limit) to 38.3% (upper limit), and p-value <0.0001) [32].

With respect to the secondary aims of the pivotal Phase III trial prior to a booster (4th) dose of vaccine (Month 20), several results are worth noting: (1) vaccine efficacy and immunogenicity were lower in young infants than in children [32,33]; (2) vaccine efficacy waned over time in both age categories (Schoenfeld residuals p < 0.001) [31–33]; (3) despite modest and waning vaccine efficacy, the public health impact, reported as the number of cases of clinical malaria, severe malaria and all cause hospitalizations averted per 1000 persons vaccinated (ranging across sites from 37 to 2365, −1 to 49, and −3 to 131, respectively in the 5–17 month old age category (ITT), and from −10 to 1402, −3 to 37, and −153 to 145, respectively in the 6–12 week old age category (ITT)) was substantial, particularly, in the older age category and in the context of high disease burden—translated to the population at risk of malaria, cases averted or vaccine preventable disease incidence (VPDI) on this scale would have a major public health impact [33,35]; (4) increased risk for febrile convulsion within 7 days of administering RTS,S in children over 5 months of age at time of vaccination; and (5) meningitis was reported as a serious adverse event and the greater number of cases in the RTS,S group compared with the control vaccine group in the older age category reached statistical significance [33].

With respect to the final set of results, which included the efficacy of a 4th dose of RTS,S, and the efficacy, impact, immunogenicity, and safety of RTS,S from first vaccination to study end (SE) for a median follow-up of 38 months in the younger age category and 48 months in the older age category, several additional findings are noteworthy: (1) a 4th dose appeared to restore and maintain vaccine efficacy—VE (ITT) from Month 0 to SE was 36.3% (95% CI 31.8; 40.5) and 32.2% (95% CI 13.7; 46.9) against all episodes of clinical malaria and severe malaria, respectively, in the older age category, and 25.0% (95% CI 19.9; 31.5) and 17.3% (95% CI −9.4; 37.5) against clinical malaria and severe malaria, respectively, in the younger age category; (2) without a booster, VE (ITT) against clinical malaria continued to wane in both age categories and, in the older age category, severe malaria VE became non-significant over the entire study period (VE Month 0–SE = 1.1%, 95% CI −23.0; 20.5) and, in fact, the comparative incidence of severe malaria in the time period from Month 21 to SE was significantly higher [VE Month 21–SE = −41.0% (95% CI −98.5; −0.8); p = 0.04] than the control group; (3) despite waning efficacy, the number of cases of clinical malaria averted continued to accumulate in the older and younger age categories that were administered a 4th dose of RTS,S, reaching an average of 1774 and 980 per 1000 children vaccinated, respectively, with impact greater in sites with higher malaria burden (Fig. 3); (4) while administration of a booster dose of RTS,S led to an increase in anti-circumsporozoite geometric mean titers in both young infants and children, the titers after the booster was lower than concentrations after the primary course and the booster effect was only transitory; (5) the frequency of SAEs overall was balanced between groups; however, in the older age category meningitis was reported as an SAE during the entire study period in 11, 10 and one child in the four RTS,S dose, three RTS,S dose and control groups, respectively, while, in contrast, no imbalance in cases of meningitis was noted in the younger age category; and, (6) the incidence of generalized convulsive seizures within seven days of RTS,S booster was observed at a higher rate than controls in both the younger and older age categories (2.2 and 2.5/1000 doses, respectively) [34]. Based on the temporal association and biological plausibility, it was concluded that there was a reasonable possibility of causal relationship between RTS,S and the occurrence of febrile convulsions within 7 days post-vaccination [34].

A cautionary note: the detailed study analyses contain data from multiple protocol-specified and subsequent data analysis plan-specified time points, generating hundreds of comparisons and creating the opportunity for unexpected associations to emerge by chance. Similarly, the high standard of care provided to all trial participants may have limited the ability of this trial to detect an impact on more severe outcomes and mortality. With the former caveat in mind and despite a comprehensive analysis, no obvious explanation for the meningitis observation has been found, and while a temporal relationship to vaccination is lacking and the biological plausibility is low, a causal relationship cannot be confirmed or excluded at this point.

Beyond those highlighted above, additional results of extensive analyses of secondary, tertiary and exploratory aims of the trial, can be found in the published literature [31–34] and on the open access GSK clinical study register [23]. With respect to protective immune responses, much is still incompletely understood despite numerous recent analyses [36–40]. While antibody levels and to a lesser extent cell mediated immune responses, have been shown to associate with protection against malaria infection, a definitive correlate of protection remains elusive.

**Table 1** summarizes on-going clinical trials of RTS,S in support of the pediatric indication. A more comprehensive summary of list of trials conducted and results published since 2010 can be found in materials reviewed by WHO advisory bodies (see below) in 2013 [30].

### 5. Regulatory, policy, and financing pathway

As an initial step in the policy and regulatory process, GSK submitted a regulatory application to EMA in June 2014 [41]. The RTS,S regulatory application was reviewed under the Article 58 procedure, which allows the EMA to assess the quality, safety and efficacy of a product intended exclusively for use outside the European Union (EU) but which is manufactured in a EU member state, to address a disease recognized by the World Health Organization (WHO) as of major public health interest [42]. This assessment was done by the EMA in collaboration with the WHO and non-EU regulators, and requires products to meet the same standards as a vaccine intended for use in the EU. Under the Article 58 procedure, the CHMP performed a scientific evaluation of RTS,S and in July 2015 issued “a European scientific opinion”, adopting a positive opinion and recommending the granting of a marketing authorization for active immunization of children aged 6 weeks up to 17 months against malaria caused by *P. falciparum* and against hepatitis B, noting that use should be based on official recommendations considering *P. falciparum* malaria epidemiology in different geographical areas. It is important to emphasize that a positive
opinion is not licensure or registration in the EU, but provides a scientific opinion that African national regulatory authorities may use in their own regulatory review processes as they consider licensure and registration in their jurisdictions.

The positive opinion adopted by CHMP also plays a critical role in decision-making by WHO normative bodies. The technical group advising WHO on Phase 3 trials of malaria vaccines is the Joint Technical Expert Group (JTEG) on Malaria Vaccines, convened by the Immunization, Vaccines, and Biologicals Department (IVBD) and the Global Malaria Program (GMP) [43], and reporting jointly to the Strategic Advisory Group of Experts (SAGE) on immunization and the Malaria Policy Advisory Committee (MPAC) [42, 44]. Based on the positive opinion adopted by CHMP, JTEG’s evaluation of RTS,S will now be considered jointly by SAGE and MPAC who will advise WHO on recommendation(s) for use, anticipated in the last quarter of 2015 [44]. WHO will also consider RTS,S for prequalification (PQ), a process “intended to ensure that a specific vaccine from a specific manufacturer meets international standards of quality, safety and efficacy and is appropriate for the target population. Only WHO prequalified vaccines can be supplied to countries through UN agencies” [43].

Another critical step after WHO recommendation and PQ will be decisions by various international financing organizations and public–private partnerships, including Gavi—the Vaccine Alliance (Gavi), and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), to open country support windows for public financing.

In preparation for such a decision, Gavi included a malaria vaccine in a recent Vaccine Investment Strategy (VIS) review, an evidence-based prioritization process, undertaken once every five years, to identify new vaccines with high priority for inclusion in the Gavi portfolio [45]. Based on various analyses conducted as part of the VIS process, including a projection that RTS,S could potentially avert approximately 1 million future deaths in Africa over 15 years (Fig. 4) [46], and based on meeting certain pre-specified conditions [45], it is anticipated that the Gavi Secretariat will recommend to the Gavi Board the opening of a country support window, albeit highlighting the importance of coordinating the introduction of a vaccine as part of integrated malaria control programs and exploring opportunities for harmonized global procurement strategies with other international financing mechanisms (e.g., GFATM) [45].

Given that all clinical trial data from the field are from sub-Saharan Africa and given the scientific opinion adopted by CHMP, it is anticipated that any WHO recommendation, public financing, national regulatory authority review and national policy recommendations on introduction and use of the vaccine will be restricted to sub-Saharan Africa, consistent with the first landmark goal of the MVTRM.

6. Post-approval program/Phase IV studies

Post-approval studies play an important role in the introduction and scale-up of vaccines and are critical components of any vaccine
Table 1: Ongoing/planned RTS,S clinical and epidemiological studies.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Study and objectives</th>
<th>Location</th>
<th>Age at enrollment</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal Ph III efficacy and safety study extension</strong></td>
<td>Long-term efficacy, safety and immunogenicity of RTS,S/AS01 over an additional 3-year period. Primary endpoint: incidence of severe malaria. Secondary endpoints: clinical malaria, parasite prevalence and SAEs of special interest.</td>
<td>Tanzania, Kenya, Burkina Faso</td>
<td>5–17 months or 6–12 weeks</td>
<td>3600</td>
</tr>
<tr>
<td><strong>Co-administration Ph IIIb study (Measles, yellow fever and rubella vaccines)</strong></td>
<td>Non-inferiority of immune response and safety of the RTS,S/AS01 with or without co-administration of measles, yellow fever and rubella vaccines</td>
<td>To be determined</td>
<td>6 months</td>
<td>700</td>
</tr>
<tr>
<td><strong>Malaria Transmission Intensity study</strong></td>
<td>Annual cross-sectional surveys of <em>P. falciparum</em> parasitemia at peak of transmission in Ph III pivotal efficacy &amp; safety study catchment areas, during 4 years.</td>
<td>6 Sub-Saharan African countries; 8 research centers</td>
<td>6 months to 90 years</td>
<td>6400</td>
</tr>
<tr>
<td><strong>Ph III study on HepB Indication and EPI Integration</strong></td>
<td>Non-inferiority of Hepatitis B immune response. Co-administration with 10V S, pneumonia, non-inferiority of immune response Co-administration with rotavirus vaccine, non-inferiority of immune response.</td>
<td>Burkina Faso Ghana</td>
<td>8–12 weeks</td>
<td>705</td>
</tr>
<tr>
<td><strong>Ph II Schedule optimization study</strong></td>
<td>Exploration of various vaccination schedules around current EPI visits.</td>
<td>Malawi</td>
<td>≤7d–14w</td>
<td>480</td>
</tr>
</tbody>
</table>

$d =$ days, $w =$ weeks; $m =$ months, $y =$ years of age.

development program, as they address key questions that cannot be readily addressed in Phase III studies. For example, monitoring safety and determining effectiveness of vaccines in larger populations under more “real life” conditions are key data in refining the benefit-risk profile and optimizing the application of new vaccines. In the case of RTS,S, the post-approval program is being developed to meet regulatory commitments as part of the EMA Article 58 procedure. It can also be used to provide policy and decision-makers in-country, with additional information to assist in deciding on the use of a new tool in their national vaccine and malaria control programs.

As it relates to pharmacovigilance and impact, three studies are currently envisioned. An epidemiology study (EPI-MAL-002), to “set the baseline” for the incidence of pre-defined diseases that may be reported as adverse events following immunization and for malaria morbidity and mortality. This first phase will be
conducted in several countries, and will follow approximately 40,000 children for two years prior to the introduction of RTS,S in the study communities (this phase will start pre-approval). This study will be followed by a second phase to be conducted after national regulatory approval of RTS,S, such that RTS,S will be delivered using the immunization system already in place in the study area. The vaccination study (EPI-MAL-003) will enroll another approximately 45,000 children to determine the incidence of these same pre-defined diseases after immunization with RTS,S. To leverage and further enhance existing infrastructure, these two studies will be conducted at sites that already monitor the population in their catchment area through demographic surveys. A third study (EPI-MAL-005, a malarometric study), concurrent to the other two studies, will conduct cross-sectional surveys to collect data on the use and coverage of other malaria interventions and will track changes in disease burden during the period in which EPI-MAL-002 and EPI-MAL-003 are conducted.

In addition to these pharmacovigilance/malaria impact studies (baseline and vaccination phases) and concurrent malaria transmission intensity studies, the RTS,S post-approval program includes research in health economics and the piloting of communications materials to support possible introduction. Additional studies will be contemplated if deemed needed and feasible.

7. Conclusion

RTS,S, a candidate malaria vaccine, has now been successfully evaluated in a Phase III program conducted in eight African countries and undergone a stringent evaluation by a regulatory agency. Although vaccine efficacy may be modest, the number of cases averted in settings of significant disease burden, be it clinical malaria, severe malaria or malaria hospitalizations, on the scale seen in MALARIA-055 would have a major public health impact. But to do so will no doubt require that all available tools be brought to bear in an optimal way to prevent and treat malaria. In the end, the benefit, risk, feasibility and cost-effectiveness will be used to determine the impact of RTS,S. The former has initially been evaluated through EMA’s Article 58 procedure with a positive opinion for ages 6 weeks to 17 months, noting that subsequent evaluations are still needed by national regulatory authorities. The latter will now be evaluated through policy and financing reviews at the global and national levels.

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Fig. 4. Gavi projects that RTS,S could potentially avert around 1 million future deaths in Africa over 15 years (2015–2030) [46]. The point estimate of 1.1 million deaths averted (y-axis: cumulative deaths averted over a 15 year period) represents the midpoint of the Imperial College and Swiss Tropical Public Health model outputs for a scenario that includes a booster dose [44].


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