TANZANIA NATIONAL IMMUNIZATION TECHNICAL ADVISORY GROUP

INTRODUCTION OF MALARIA VACCINE **RTS,S/AS01** FOR USE AMONG CHILDREN IN TANZANIA POPULACE

Vaccine Policy/Strategy advice requested by the MoH

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EXECUTIVE SUMMARY

I. INTRODUCTION

a. Malaria

Malaria remains a primary cause of childhood illness and death in sub-Saharan Africa including Tanzania. More than 260 000 African children under the age of five die from malaria annually [1].In Tanzania, there were approximately 6 million cases of malaria and 2 460 deaths in 2020 [2].

The World Health Organization (WHO) is recommending widespread use of the RTS, S/AS01 (RTS, S) malaria vaccine among children in sub-Saharan Africa and in other regions with moderate to high *P. falciparum* malaria transmission. The recommendation is based on results from an ongoing pilot programme in Ghana, Kenya and Malawi that has reached more than 800 000 children since 2019.

WHO recommends that in the context of comprehensive malaria control the RTS, S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO. RTS, S/AS01 malaria vaccine should be provided in a schedule of 4 doses in children from 5 months of age for the reduction of malaria disease and burden.

b. General information on RTS,S AS/01 Vaccine

The RTS,S/AS01 malaria vaccine is a hybrid recombinant protein consisting of the PfCSP protein central NANP tandem repeat and C terminal regions fused to the N terminus of the S antigen of hepatitis B virus (HBsAg). The vaccine is formulated with the AS01 immunogenic Adjuvant System. The “R” stands for the central repeat region of the CS protein; the “T” stands for the T-cell epitope of the CS antigen; and first “S” for “Surface” portion which when co-expressed on yeast cells, displays both CS protein and S at their surfaces, while the next “S” stands for the hepatitis B surface antigen (a carrier matrix). The RTS fusion protein and free S protein assemble in RTS,S particles. AS01 includes the immune-enhancers monophosphoryl lipid A and QS21. Monophosphoryl lipid A consists of a chemically detoxified form of the parent lipopolysaccharide from the gram-negative bacterium*Salmonella minnesota*. QS21 is a natural saponin molecule purified from the bark of the South American tree, *Quillaja Saponaria* [3].

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[1] *https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk*

[2] *https://www.out.ac.tz/wp-content/uploads/2019/10/Malaria-Strategic-Plan-2015-2020-1.pdf*

[3] *Chatterjee D, Cockburn IA. The challenges of a circumsporozoite protein-based malaria vaccine. Expert Rev Vaccines. 2021 Feb;20(2):113-125. doi: 10.1080/14760584.2021.1874924.*

II. METHODOLOGY

a. Establishment of a working group

The Tanzania Immunization Technical Advisory Group (TITAG) held its meeting from 29th November to 8th December 2021 in Mwanza to address the policy question "***Should Malaria vaccines be introduced for use among targeted Tanzania populace?" "If so, what groups should be prioritized to receive the vaccines first?" and "What are the implications both technically and programmatic*" (Appendix I)** .To answer the research question posed by the Ministry of Health, the TITAG members used their three working groups. The first group was assigned to work on the disease burden, characteristics of the RTS, S/AS01 malaria vaccine, safety, efficacy and efficiency, the second group on the economical cost of introduction of vaccine and the third group on programmatic and delivery strategies.

Members used a scientific and systematic approach to review evidence with regard to the mentioned topic. Members used the programmatic perspective that was provided by the secretariat. To make the process effective, each member was assigned a section to work on and present. Communication between members was made through physical contacts and other means including phone calls, zoom, and emails to finalize the report. In a addition the team listened to a zoom presentation from one of the investigators for RTS, SA/S01 vaccine working at Ifakara Research institute. The presentation was followed by discussion.

b. Recommendation framework

The groups reviewed the epidemiology of Malaria and the potential use of RTS, S/AS01 malaria vaccine to control the disease.The members considered the burden of Malaria in the country especially among children, as well as cost-benefit criteria, and values and preferences, acceptability, feasibility, and equity for the vaccine use. The TITAG subgroup members used the GRADE approach to assess the certainty of evidence from low to high certainity.

c. Evidence search and assessment

Articles and studies were included if they provided data on vaccination with RTS, S/AS01 Malaria vaccine involved human subjects, reported primary data, included children at risk for Malaria infection, included data relevant to the efficacy and safety outcomes being measured, and included data for the specific vaccine formulation, dosage, and schedule being recommended

III. Presentation of the evidence

a. Vaccine and immunization characteristics

i. Safety

Candidate malaria vaccines have been developed targeting all the lifecycle stages in the mammalian host; however, the pre-erythrocytic stage has been the target of RTS,S.RTS,S/AS01 is a hybrid polypeptide consisting of a portion of the circumsporozoite protein (CS), a sporozoite surface antigen of the malaria parasite *P. falciparum* strain NF54, fused to the amino-terminal end of the hepatitis B virus S protein adjuvanted with AS01 Adjuvant System consists of a liquid suspension of liposomes with two

immunostimulant components: 3'-O-desacyl-4'-monophosphoryl lipid A (MPL) and Quillaja saponaria 21 (QS21). Adjuvanted vaccines have been in use in vaccine development for decades, and their safety profiles have been documented [4,5].

ii. Type, consequences and frequency of short- & long-term adverse events

Evaluation of safety data from clinical trials, have demonstrated a favourable safety profile for RTS,S/AS01 . The most important adverse events monitored during clinical trials are serious adverse events (fatal, life-threatenining, cause or prolong hospitalization, result in long-term disability or cuase congenital anomalies).

In a phase II open label trial to assess safety and immunogenicity of RTS,S/AS01 in infants 1-7 days of age when given with or without other EPI vaccines in Malawi , unsolicited AE were reported in 0-5% in subject in any RTS, S/AS01 group.Local AE (pain, redness and swelling) were similar across all groups at around 5%,7% and 4% of the participants respectively. General AE (drowsness, irritability and loss of appetite were also similar in RTS, S/AS01 and the control group[6].Fever was more reported in RTS,S/AS01 (15%) compared to the control groups.Generally, RTS,S/AS01 had a favourable safety profile, with no SAE attributed to it. Most AEs were non serious and resolved spontaneously.

In a phase 3 randomized controlled trial among children between 6-12 weeks and 5-17 months conducted study in 7 African countries including Tanzania population to assess the safety and efficacy of RTS,S/AS01 vaccine , in the older age category, serious adverse events (SAE) were reported in 1048 (17.6%) in the RTS,S/AS01 group and in 642 (21.6%) in the control group.In the younger age category, the corresponding rates were 569 of 4358 children (13.1%) in the RTS,S/AS01 group and in 293 of 2179 children (13.4%) in the control group. SAE which were causally related toRTS,S/AS01 vaccine were in 11 children in older group; 7 seizures, 3 pyrexia, 1 myositis, and 3 in the younger group ; 1 pyrexia, 1 febrile convulsion and 1 injection site reaction.

In the older age category, 56 of 5949 children (0.9%) died in the RTS, S/AS01 group and 28 of 2974 children (0.9%) in the control group.In the younger age category, 49 of 4358 children (1.1%; 95% CI, 0.8 to 1.5) died in the RTS,S/AS01 group and 18 of 2179 children (0.8%; 95% CI, 0.5 to 1.3) in the control group[7]. However, all fatalities were reported as not related to the vaccine.

There were relatively high reported frequency of meningitis in RTS,S/AS01 groups in all age categories compared to the control group with relative risk of 5.5 in the older age category and 4.0 in the younger age

4 Del Giudice G, Rappuoli R, Didierlaurent AM. Correlates of adjuvanticity: A review on adjuvants in licensed vaccines. InSeminars in immunology 2018 Oct 1 (Vol. 39, pp. 14-21). Academic Press.

5Stassijns J, Bollaerts K, Baay M, Verstraeten T. A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among children. Vaccine. 2016 Feb 3;34(6):714-22.

6 Witte et al., Safety and Immunogenicity of Seven Dosing Regimens of the Candidate RTS,S/AS01E Malaria Vaccine Integrated Within an Expanded Program on Immunization Regimen: A Phase II, Single-Center, Open, Controlled Trial in Infants in Malawi. Pediatr Infect Dis J. 2018 May;37(5):483-491. doi: 10.1097/INF.0000000000001937.

7 RTS,S Clinical Trials Partnership, et al., A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. N Engl J Med. 2012 Dec 13;367(24):2284-95. doi: 10.1056/NEJMoa1208394.

category. However, this disproportionate meningitis reporting was not observed in the pilot implementation phase[8] .

Another phase III RCT aiming to assess the safety of RTS,S/AS01 in HIV-infected children was conducted at two sites in western Kenya among children 6 weeks to 17 months with PCR confirmed HIV compared to rabies vaccine as comparator . Three doses were given at 0,1 and 2 months. AE were assessed 14 months after the first dose. SAE in RTS,S/AS01 recipients were 41 out of 99 (41·4%) and 37 of 101 (36.6%) in rabies-vaccine recipients. Most reported SAE weremainly pneumonia, febrile convulsions, and salmonella sepsis. Five of 99 RTS,S/AS01 recipients (5·1%,) and four of 101 rabies-vaccine recipients (4·0%) died, but no deaths were deemed related to vaccination[9]. Therefore, in this study, RTS,S/AS01 was well tolerated in HIV infected children.

In another phase III RCT to ssess Safety profile RTS,S/AS01 among children 6-12 weeks and 5-17months, children were randomized to receive 4 doses of RTS, S/AS01 (R3R) or non-malaria control vaccine (C3C), or 3 RTS,S/AS01 doses plus control (R3C). SAE incidence were 24.2% in all RTS, S/AS01 doses group, 25.3% in 3 RTS, S/AS01 doses and 1 comparator dose group and 28.4% among all 3 comparator dose group. Most frequently reported SAEs were cerebral malaria (9.9%–14.2%), pneumonia (6.8%–7.5%), febrile convulsions (5.3%–6.2%), gastroenteritis (5.0%–6.0%), and anemia (4.2%–6.6%) It was also observed thatthe incidence of febrile convulsions in children was higher during the first 2–3 days post-vaccination with RTS,S/AS01 than with control vaccine. Additionally, A statistically significant numerical imbalance was observed for meningitis cases in children (R3R: 11, R3C: 10, C3C: 1) but not in infants. Furthermore, cerebral malaria cases were more frequent in RTS,S/AS01-vaccinated children (R3R: 19, R3C: 24, C3C: 10) but not in infants. All-cause mortality was higher in RTS,S/AS01-vaccinated versus control in girls (2.4% vs 1.3%, all ages)

The most frequently reported fatal SAEs over the entire study period were Cerebral malaria (0.3%–0.4%), pneumonia (0.2%–0.5%), gastroenteritis (0.2%–0.5%), anemia (0.2%–0.4%), and convulsions (0.3%) in The 5–17 months age group, and pneumonia (0.4%–0.7%), gastroenteritis (0.5%–0.6%), anemia (0.1%–0.6%), malaria (0.2%– 0.4%), and sepsis (0.2%–0.3%) in the 6–12 weeks age group. It was reported that all fatalities were not related to vaccination[10].

In background paper by PAG that reviewed the safety profile, efficacy and programmatic feasibility of RTS,S/AS01 vaccine from pilot implementation data from Ghana, Malawi and Kenya, three safety signals that were identified in phase III clinical trial whereby there were higher cases of meningitis, cerebral malaria and increased all causes mortality among girls (rate ratio 10.5:1 ; 2.15:1 and 2.0 respectively)[11]. However, during sentinel hospital survaillance during piloting phase, the incidence rate ratio comparing rates of

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8 Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group (PAG). Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. September 2021

9 Otieno et al., Safety and immunogenicity of the RTS,S/AS01 malaria vaccine in infants and children identified as HIV-infected during a randomized trial in sub-Saharan Africa.Vaccine. 2020 Jan 22;38(4):897-906. doi: 10.1016/j.vaccine.2019.10.077.

10 Guerra Mendoza Y, et al., Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa. Hum Vaccin Immunother. 2019;15(10):2386-2398. doi: 10.1080/21645515.2019.1586040. Epub 2019 Apr 23. PMID: 31012786; PMCID: PMC6816384.

11 Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group (PAG). Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. September 2021

admission with meningitis in implementation and comparison areas, among vaccine-eligible children, was 0.81 (95%CI 0.43, 1.55). Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received RTS,S/AS01 vaccine, compared to 53% (2491/4672) of all other hospital admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 0.73 (95%CI 0.31,1.71). It was therefore concluded that no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis, and there were sufficient cases, and high coverage of the vaccine, to detect an excess of the magnitude observed in the Phase 3 trial.

The incidence rate ratio comparing rates of admission to hospital with cerebral malaria in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.77 (95% 0.44, 1.35). The incidence rate ratio for admission with other forms of severe malaria (excluding cerebral malaria) was 0.70 (0.54, 0.89), but there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (0.57, 1.56), and test of interaction (p-value 0.808). The incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the broader case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.96 (95%CI 0.61, 1.52). Therefore, they concluded that was no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria, and there were sufficient cases to detect an excess of the magnitude observed in the Phase 3 trial, if it was present.

The mortality ratio in the vaccine-eligible age group between implementing and comparison regions, was 0.93 (95%CI 0.84,1.03), a 7% reduction (95%CI -3%,16%). There was no evidence that the mortality ratio differed between girls and boys (p 0.343). The mortality ratio in girls was 0.98 and in boys 0.90, yielding a relative mortality ratio (girls:boys) of 1.08 (95%CI 0.92,1.28) which was not statistically significant refuting the findings from phase III trials. Details of relevant studies have been summarized in **Appendix II.**

Risk factors that can lead to adverse events

From the safety studies, there were no specific risk factors reported that were associated with adverse events.

- **Contraindications to vaccination**

No specific contraindication were identified from the safety studies.

iii. Efficacy and effectiveness

•Type-specific protection afforded

RTS,S induces protection with increased concentration of anti-CSP antibodies among vaccinees. Furthermore, RTS,S-specific anti-CSP T-cell immune responses are more frequently encountered among individuals who are protected post vaccination[12]. RTS,S vaccinees who developed immunity had increased levels of RTS,S-specific-induced anti-CSP antibody concentration as opposed to vaccinees who were not

12 Agnandji ST, et al. Clinical development of RTS,S/AS malaria vaccine: a systematic review of clinical Phase I-III trials.Future Microbiol. 2015;10(10):1553-78. doi: 10.2217/fmb.15.90. Epub 2015 Oct 6. Future Microbiol. 2015.

protected[13] [14]. RTS,S-induced CSP-specific IFN-γ CD4+ T cells, and IFN-γ CD8+ T cells are associated with protective immunity in malaria-naive adults that is further associated with the duration of protection[15] [16][17][18]. Noticeably, Anti-CSP antibody concentration has been associated with protection in both adults, children and infants[19,20,21]. Noticeably, based on modeling studies, it has been reported that vaccine-induced antibodies alone is responsible in preventing about 32% of malaria infections, increasing to 40% when CD4+ T-cell responses were further factored in the model [22].

• Critical determinants of the immune response

The target antigen of the RTS,S/AS01 vaccine is circumsporozoite protein, a surface protein expressed only in sporozoites, the invasive stage of the malaria parasite, which are transmitted by infected mosquito bites to human beings and develop to other stages in the liver [23]. The RTS,S/AS01 vaccine acts solely at the pre-erythrocytic stages. The anti-circumsporozoite protein antibodies and circumsporozoite protein-specific CD4-positive T cells are associated with protection from Plasmodium falciparum infection and clinical malaria[24, 25] .However, the duration of protection and determinants of immunogenicity after vaccination are unclear

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13 Stoute JA, Slaoui M, Heppner DG et al. A preliminary evaluation of a recombinant circumsporozoite protein vaccine against Plasmodium falciparum malaria. RTS,S Malaria Vaccine Evaluation Group. N. Engl. J. Med. 336(2), 86–91 (1997)

14 Kester KE, McKinney DA, Tornieporth N et al. Efficacy of recombinant circumsporozoite protein vaccine regimens against experimental Plasmodium falciparum malaria. J. Infect. Dis. 183(4), 640–647 (2001)

15 Lalvani A, Moris P, Voss G et al. Potent induction of focused Th1-type cellular and humoral immune responses by RTS,S/SBAS2, a recombinant Plasmodium falciparum malaria vaccine. J. Infect. Dis. 180(5), 1656–1664 (1999)

16 Kester KE, Cummings JF, Ofori-Anyinam O et al. Randomized, double-blind, Phase 2a trial of falciparum malaria vaccines RTS,S/AS01B and RTS,S/AS02A in malaria-naive adults: safety, efficacy, and immunologic associates of protection. J. Infect. Dis. 200(3), 337–346 (2009)

17 Stoute JA, Kester KE, Krzych U et al. Long-term efficacy and immune responses following immunization with the RTS,S malaria vaccine. J. Infect. Dis. 178(4), 1139–1144 (1998).

18 Sun P, Schwenk R, White K et al. Protective immunity induced with malaria vaccine, RTS,S, is linked to Plasmodium falciparum circumsporozoite protein-specific CD4+ and CD8+ T cells producing IFN-γ. J. Immunol. 171(12), 6961–6967 (2003)

19 Bojang KA, Milligan PJM, Pinder M et al. Efficacy of RTS,S/AS02 malaria vaccine against Plasmodium falciparum infection in semi-immune adult men in The Gambia: a randomised trial. Lancet 358(9297), 1927–1934 (2001)

20 Polhemus ME, Remich SA, Ogutu BR et al. Evaluation of RTS,S/AS02A and RTS,S/AS01B in adults in a high malaria transmission area. PLoS ONE 4(7), (2009)

21 Asante KP, Abdulla S, Agnandji S et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, Phase II trial. Lancet Infect. Dis. 11(10), 741–749 (2011)

22 White MT, Bejon P, Olotu A, et al. The relationship between RTS,S vaccine-induced antibodies, CD4(+) T cell responses and protection against Plasmodium falciparum infection. PloS One. 2013;8(4): e61395.

23 RTS,S Clinical Trials Partnership First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med. 2011; 365: 1863-1875

24 Kester KE Cummings JF Ofori-Anyinam O et al. Randomized, double-blind, phase 2a trial of falciparum malaria vaccines RTS,S/AS01B and RTS,S/AS02A in malaria-naive adults: safety, efficacy, and immunologic associates of protection. J Inf Dis. 2009; 200: 337-346

25 Olotu A Lusingu J Leach A et al. Efficacy of RTS,S/AS01E malaria vaccine and exploratory analysis on anticircumsporozoite antibody titres and protection in children aged 5–17 months in Kenya and Tanzania: a randomised controlled trial. Lancet Inf Dis. 2011; 11: 102-109

because of the lack of long-term follow-up in the phase 2 trials. In-depth analyses of the duration of protection is important for both the application of RTS,S/AS01 in Africa and for efforts to develop the next-generation of malaria vaccines based on circumsporozoite protein. The efficacy profile of RTS,S/AS01 can be informed by measurements of anti-circumsporozoite protein antibodies, enabling estimation of the duration of protection[26] [27]. It is estimated that an anti-circumsporozoite protein antibody titre of 121 EU/mL could prevent 50% of infections. Waning antibody titres predict the duration of efficacy against clinical malaria across different age categories and transmission intensities, and efficacy wanes more rapidly at higher transmission intensity. The immune responses induced by RTS,S/AS01 vaccination and by natural infection are distinct. In low transmission areas, efficacy against clinical malaria wanes because of the reduction in anti-circumsporozoite protein antibody titres. In high transmission areas, efficacy against clinical malaria wanes more rapidly because of both the reduction in antibody titres and the lesser blood-stage immunity in vaccinated participants compared with control individuals. Anti-CSP antibody titers wane during the follow-up periods with the efficacy against clinical malaria waning more rapidly at higher transmission due to reduction in anti-CSP antibody titers and lower blood-stage immunity in the vaccinated individuals vs. controls. These findings were attributed either to a probable inability of sporozoites to naturally boost vaccine-induced anti-CSP antibody responses or the polymorphic nature of the T-cell epitopes on the CSP. The anti-circumsporozoite protein antibody titres are a surrogate of protection for the magnitude and duration of RTS,S/AS01 efficacy. The relation between anti-circumsporozoite protein antibody titres and efficacy can be used to assess future iterations of RTS,S and second generation anti-circumsporozoite protein vaccines. Why antibody titres are not maintained is unknown, but could relate to the inability of sporozoites to naturally boost vaccine-induced antibody responses and the subsequent exposure to few sporozoites, or the polymorphic nature of the T-cell epitopes on the circumsporozoite protein[28].To improve the efficacy of malaria vaccines, it is suggested that addition of a conserved blood-stage vaccine component to RTS,S/AS01 as a multistage malaria vaccine is of paramount importance.

26 White MT Verity R Griffin JT Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. Lancet Infect Dis. 2015

27 RTS,S Clinical Trials Partnership Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015; 386: 31-45

28 Good MF Pombo D Quakyi IA et al. Human T-cell recognition of the circumsporozoite protein of Plasmodium falciparum: immunodominant T-cell domains map to the polymorphic regions of the molecule. Proc Natl Acad Sci USA. 1988; 85: 1199-1203

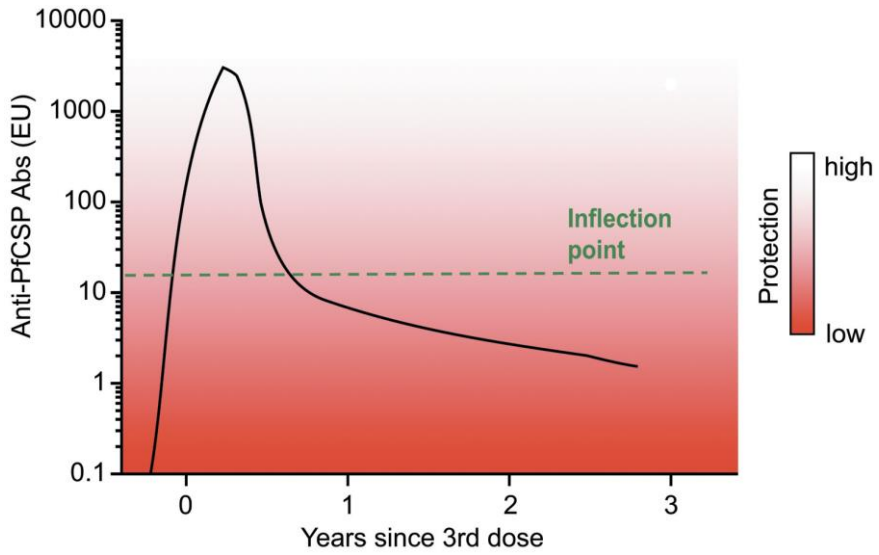

Figure 1*: Limited efficacy of RTS,S: After RTS,S vaccination anti-PfCSP titers undergo rapid decay with bi-phasic kinetics to levels below the threshold required for sustained protection, and this substantially reduces vaccine efficacy.*

- **Duration of protection & waning of immunity, if any**

Various phase IIa/IIb malaria clinical trials conducted in malaria endemic areas in Africa has shown that the vaccine is partially protective in adults, children and infants with. Furthermore, protection is only against *P. falciparum* malaria and wanes over time arguably the vaccination may therefore delay the acquisition of natural immunity to confer the needed protection.

The reported efficacy (VE) in adults was 34% and protection seemed to wane with an estimated efficacy during the first 9 weeks of follow-up being 71% (46-85) that decreased to 0% (-52 to 34) in the last 6 weeks[29]. In children, the vaccine efficacy for clinical episodes was 29.9% to and 57.7% for severe malaria[30] with another trial reporting an the overall adjusted VE of 56% and unadjusted VE of 49% against all episodes of malaria[31]. Reported VE among infants of 65.9% against clinical malaria[32] with vaccine efficacy ranging from 24.1% to 61.3% after 12 months from the third dose .These results were further confirmed in a phase III trial in sub-Saharan Africa in which 50.8% (ITT analysis) 55.8% (PP analysis) efficacy against

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29 Bojang KA, Milligan PJM, Pinder M et al. Efficacy of RTS,S/AS02 malaria vaccine against Plasmodium falciparum infection in semi-immune adult men in The Gambia: a randomised trial. Lancet 358(9297), 1927–1934 (2001)

30 Efficacy of the RTS,S/AS02A vaccine against Plasmodium falciparum infection and disease in young African children: randomised controlled trial.Alonso PL, Sacarlal J, Aponte JJ, Leach A, Macete E, Milman J, Mandomando I, Spiessens B, Guinovart C, Espasa M, Bassat Q, Aide P, Ofori-Anyinam O, Navia MM, Corachan S, Ceuppens M, Dubois MC, Demoitié MA, Dubovsky F, Menéndez C, Tornieporth N, Ballou WR, Thompson R, Cohen J Lancet. 2004 Oct 16-22; 364(9443):1411-20.

31 Bejon P, Lusingu J, Olotu A, Leach A, Lievens M, Vekemans J, Mshamu S, Lang T, Gould J, Dubois MC, Demoitié MA, Stallaert JF, Vansadia P, Carter T, Njuguna P, Awuondo KO, Malabeja A, Abdul O, Gesase S, Mturi N, Drakeley CJ, Savarese B, Villafana T, Ballou WR, Cohen J, Riley EM, Lemnge MM, Marsh K, von Seidlein L. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. N Engl J Med. 2008 Dec 11;359(24):2521-32. doi: 10.1056/NEJMoa0807381.

32 Aponte JJ, Aide P, Renom M, Mandomando I, Bassat Q, Sacarlal J, Manaca MN, Lafuente S, Barbosa A, Leach A, Lievens M, Vekemans J, Sigauque B, Dubois MC, Demoitié MA, Sillman M, Savarese B, McNeil JG, Macete E, Ballou WR, Cohen J, Alonso PLLancet. 2007 Nov 3; 370(9598):1543-51.

clinical malaria was observed over the first 12 mo of follow-up in children of 5–17 month with vaccine efficacy of 34.8% against severe malaria in the combined age categories during an average follow-up of 11 months [33].

In a Phase III clinical trial by the RTS,S Clinical Trials Partnership who reported in 2014 that was conducted at 11 centres in 7 sub-Saharan African countries with a wide range of transmission intensities, at total of 15,460 children aged 6-12 weeks and 5-17 months) were enrolled to evaluate efficacy and safety of RTS,S/AS01 when given according to a 0, 1, 2-month schedule. In addition, more than 4200 children (including children from both age groups) received a fourth dose, given 18 months after the third dose.

Results showed that in infants aged 6-12 weeks, the VE against first or only episode of clinical malaria over 12 months of follow-up (co-primary objective) was 31%. Other VE including against all episodes of clinical malaria, severe malaria and hospitilisation due to malaria over different follow-up periods in infants are presented in the table 1 below that has been adapted from the mosquirix-product-information.

Table 1 : Vaccine efficacy in all episodes of clinical malaria

	Vaccine efficacy against all episodes of clinical malaria (95% CI)	**Vaccine efficacy against severe malaria** (95% CI)	**Vaccine efficacy against hospitalisation caused by malaria** (95% CI)
Over 12 months follow-up from dose 3 (ATP* cohort, N = 6003)	33% (26; 39)	37% (5; 58)	32% (7; 50)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6003)	27% (20; 32)	15% (-20; 39)	17% (-7; 36)
3 doses only (ATP* cohort, N=5997)			
Over 30 months follow-up from dose 3	20% (13; 27)	11% (-22; 35)	10% (-15; 30)
Over 36 months follow-up from dose 3**	18% (11; 25)	13% (-17; 35)	13% (-9; 31)
3 doses + 4th dose (ATP* cohort, N=5997)			
Over 30 months follow-up from dose 3	28% (22; 34)	17% (-14; 40)	25% (3; 42)
Over 36 months follow-up from dose 3**	27% (21; 32)	21% (-7; 42)	27% (7; 43)

*According-to-protocol (ATP) cohort: all infants immunised according to schedule, N= total number in all 3 study groups

** The follow-up period from dose 3 to study end was not the same for all subjects because the study ended on a fixed date. The median length for this follow-up period is 36 months.

Results among children aged 5-17 months, the VE against first or only episode of clinical malaria over 12 months of follow-up (co-primary objective) was 56% (97.5% CI: 51; 60). Other VE including against all episodes of clinical malaria, severe malaria and hospitilisation due to malaria over different follow-up

33 Agnandji ST et al., First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children.RTS,S Clinical Trials Partnership Engl J Med. 2011 Nov 17; 365(20):1863-75.

periods, in children who received three doses only or three doses plus a fourth dose are shown in the table 2 below that has been adapted from mosquirix-product-information.

Table 2: Vaccine efficacy in all episodes of clinical malaria among children aged 5-17months

	Vaccine efficacy against clinical malaria (95% CI)	**Vaccine efficacy against severe malaria** (95% CI)	**Vaccine efficacy against hospitalisation caused by malaria** (95% CI)
Over 12 months follow-up from dose 3 (ATP* cohort, N=6880)	51% (47; 55)	45% (22; 60)	48% (35; 59)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6885)	46% (42; 49)	36% (15; 51)	42% (29; 52)
3 doses only (ATP* cohort, N=6918)			
Over 30 months follow-up from dose 3	34% (29; 39)	2% (-28; 25)	18% (1; 32)
Over 46 months follow-up from dose 3**	26% (21; 31)	-6% (-35; 17)	12% (-5; 26)
3 doses + 4th dose (ATP* cohort, N=6918)			
Over 30 months follow-up from dose 3	46% (42; 50)	32% (10; 50)	40% (26; 52)
Over 46 months follow-up from dose 3**	39% (34; 43)	29% (6; 46)	37% (24; 49)

*According-to-protocol (ATP) cohort: all children immunised according to schedule, N= total number in all 3 study groups

** The follow-up period from dose 3 to study end was not the same for all subjects because the study ended on a fixed date. The median length for this follow-up period is 46 months.

Further long-term follow-up was made whereby an extension for 3 additional calendar years in 3 out of the 11 centres in this phase efficacy study.Vaccine efficacy from the first vaccine dose given to the end of the

follow-up period (median duration of follow-up: 6.2 years in infants aged 6-12 weeks at first dose and 6.8 years in children aged 5-17 months at first dose) is shown in the table 3 below adapted from the mosquirix-product-information;

Table 3: Vaccine efficacy in all episodes of clinical malaria after long term follow up in children aged 5-17months

	Vaccine efficacy against clinical malaria (95% CI)	**Vaccine efficacy against severe malaria** (95% CI)
Infants aged 6-12 weeks at first dose (ITT cohort, N= 1905)		
3 doses only	13% (4; 21)	34% (9; 53)
3 doses + 4th dose	16% (7; 24)	31% (5; 50)
In children aged 5-17 months at first dose (ITT cohort, N= 2512).		
3 doses only	19% (11; 27)	10% (-18; 32)
3 doses + 4th dose	24% (16; 31)	37% (15; 53)

ITT: Intent-to-treat population
N= total number of subjects

The mosquirix-product-information is found at https://www.ema.europa.eu/en/documents/outside-eu-product-information/mosquirix-product-information_en.pdf (accessed on 03 Dec 2021). As describe above, the overall vaccine efficacity hence the corresponding protection offered by RTS,S wane over time in both age categories especially after the third dose as shown in tables 1-3 above and the figure 1 above that shows a limited efficacy overtime.Therefore, it is important that all other recommended malaria control measures are carried out[34].

- **Interference regarding protection or immunity with other vaccines?**

RTS,S can be given at the same time as other vaccines including diphtheria (D), tetanus (T), whole cell pertussis (Pw), acellular pertussis (Pa), hepatitis B (HepB), Haemophilus influenzae type b (Hib), oral polio (OPV), measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines (PCV) as there no reported interference regarding protection or immunity. However, It has been reported that co-administration of RTS,S with PCV increases the risk of fever within 7 days after vaccination [35, 36].

iv. Vaccine indirect effect

- Impact on resistance to antibiotics & antivirals

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[34] *https://www.who.int/immunization/sage/meetings/2015/october/3_Programmatic_options_RTSS.pdf and https://www.ema.europa.eu/en/documents/outside-eu-product-information/mosquirix-product-information_en.pdf (both accessed on 03 Dec 2021)*

[35] *Asante KP, Abdulla S, Agnandji S et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, Phase II trial.* ***Lancet Infect. Dis.*** *11(10), 741–749 (2011)*

[36] *https://www.who.int/immunization/sage/meetings/2015/october/3_Programmatic_options_RTSS.pdf and https://www.ema.europa.eu/en/documents/outside-eu-product-information/mosquirix-product-information_en.pdf (both accessed on 03 Dec 2021)].*

To our understanding, there is no evidence showing the impact of RTS,SAS01 vaccine on antibiotics and antivirals

- Herd immunity

To our understanding, there is no evidence showing the extent of herd immunity provided by RT,S/AS01 vaccine in the general population. The vaccine has not yet been deployed in routine vaccination.

- Potential negative population impact through change in age of infection for unprotected individuals or emergence of non-vaccine serotypes

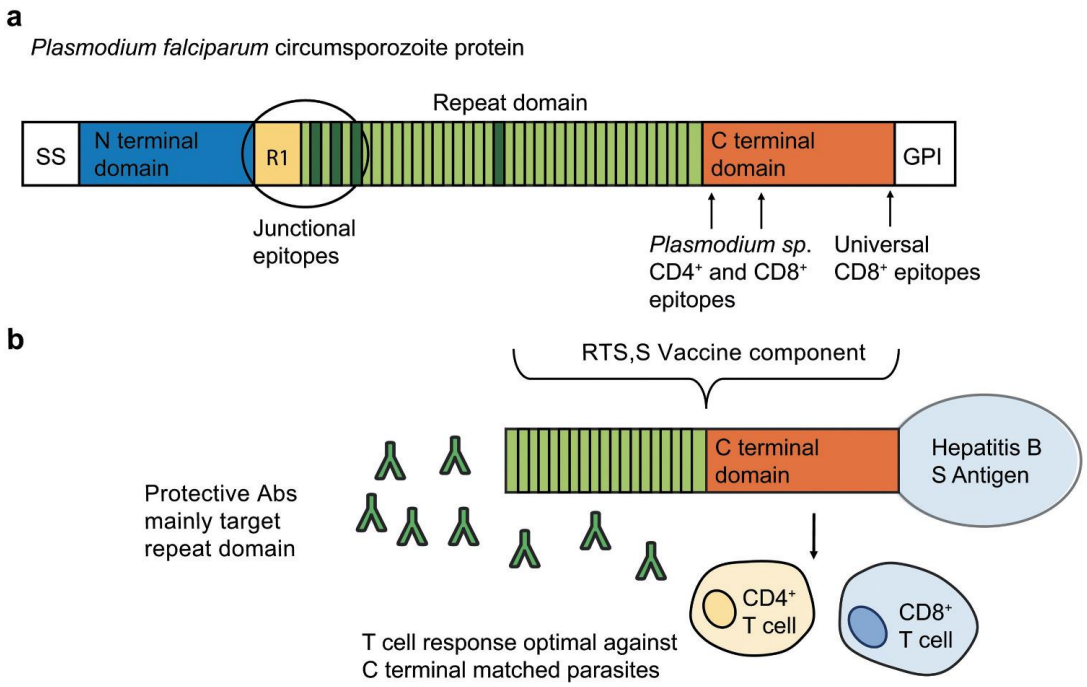
RTS,S/AS01 vaccine is proposed to be given in children 5-18 Months. However, immunity weans gradually up to 4-6 years after the booster dose. In recent years, there is changing in age burden of falciparum malaria in Sub-Sahara Africa with more burden shifting to school age children (5-9 years) compared to underfives[37]. With time,this may impact the effectiveness of malaria vaccine on morbidity and mortality in the population.

v. Vaccine characteristics

Structure of the RTS,S *P. falciparum* circumsporozoite protein-based malaria vaccine:

The RTS,S malaria vaccine is derived from *Plasmodium falciparum* circumsporozoite protein (PfCSP). The PfCSP contains three key domain, with the amino (N) and carboxy (C) terminus flanking the repeating units of Asparagine-Alanine-Asparagine-Proline (NANP) and Asparagine-Valine-Aspartic acid-Proline (NVDP) which are immunodominant in the humoral response (Figure 1a). The junctional amino acids located at theregion connecting N and the repeat region and downstream of the conserved region 1 (R1) have been found to be the epitopes of dual-binding antibodies with potent *Plasmodium* sporozoites (SPZ) neutralizing ability. The repeat region can induce infection blocking antibodies, while the C terminus is believed to induce T-cell responses which may be effective against homologous strains. There is also limited evidence for the induction of protective antibodies that target the C-terminal domain. RTS,S/AS01 is a pre-erythrocytic vaccine intended to limit the ability of *P. falciparum* to infect, mature and multiply in the liver by eliciting humoral and cellular immunity to the PfCSP, which is abundantly present at the surface of the sporozoite.

[37] *Griffin JT, Ferguson NM, Ghani AC. Estimates of the changing age-burden of Plasmodium falciparum malaria disease in sub-Saharan Africa. Nature communications. 2014 Feb 11;5(1):1-0.*



The RTS,S/AS01 malaria vaccine is a hybrid recombinant protein consisting of the PfCSP protein central NANP tandem repeat and C terminal regions fused to the N terminus of the S antigen of hepatitis B virus (HBsAg) (Figure 1b). The vaccine is formulated with the AS01 immunogenic Adjuvant System. The “R” stands for the central repeat region of the CS protein; the “T” stands for the T-cell epitope of the CS antigen; and first “S” for “Surface” portion which when co-expressed on yeast cells, displays both CS protein and S at their surfaces, while the next “S” stands for the hepatitis B surface antigen (a carrier matrix). The RTS fusion protein and free S protein assemble in RTS,S particles. AS01 includes the immune-enhancers monophosphoryl lipid A and QS21. Monophosphoryl lipid A consists of a chemically detoxified form of the parent lipopolysaccharide from the gram-negative bacterium*Salmonella minnesota*. QS21 is a natural saponin molecule purified from the bark of the South American tree, *Quillaja Saponaria*.

Vaccine presentation & formulation:

The RTS,S/AS01 malaria vaccine (recombinant, adjuvanted; Mosquirix™of GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart, Belgium) is presented in two vials, a powder and suspension for injection. The powder is white.The suspension is an opalescent, colourless to pale brownish liquid.

After reconstitution (mixing the powder and the suspension), 1 dose (0.5 ml) contains 25 micrograms of RTS,S adjuvanted with AS01$_E$. RTS is a portion of *P. falciparum* circumsporozoite protein fused with hepatitis B surface antigen (RTS), and combined with hepatitis B surface antigen (S)in the form of non-infectious virus-like particles (VLPs) produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology. AS01$_E$ adjuvant is composed of *Quillaja saponaria* Molina, fraction 21 (QS-21) (25 micrograms) and 3-O-desacyl-4’- monophosphoryl lipid A (MPL) (25 micrograms).

The excipients in the powder include sucrose, polysorbate 80, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate. The excipients in the suspension for injection include dioleoyl

phosphatidylcholine (DOPC), cholesterol, sodium chloride, disodium phosphateanhydrous, potassium dihydrogen phosphate and water for injections.

The powder contains 2 doses packaged in a vial (type I glass) with a stopper (bromobutyl rubber),aluminium seal with a flip-off polypropylene cap. The suspension is a 1 mL suspension for 2 doses in a vial (type I glass) with a stopper (chlorobutyl rubber), aluminium seal with a flip-off polypropylene cap.Mosquirix is available in a pack size of 50 vials (each for 2 doses) of powder plus 50 vials of suspension (each for 2 doses).

Mosquirix must be reconstituted prior to administration by withdrawing the entire contents of the vial containing the suspension into the syringe; adding the entire contents of the syringe into the vial containing the powder; and shaking gently until the powder is completely dissolved. The reconstituted vaccine is an opalescent, colourless to pale brownish liquid. The reconstituted vaccine has to be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, the vaccine does not have to be administered. After reconstitution, the vaccine should be used immediately; if this is not possible, the vaccine should be stored in a refrigerator (2°C to 8°C). If not used within 6 hours it should not be administered.

Each dose of 0.5 ml should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents. A new needle should be used to administer each individual dose of the vaccine.

Dosage & route of administration:

Vaccination in children from 6 weeks up to 17 months of age (at first dose): three doses, each of 0.5 ml, should be given at monthly intervals, and a fourth dose is recommended 18 months after the third dose. Mosquirix is for intramuscular injection only. The anterolateral thigh is the preferred site for injection in children younger than 5 months of age. The deltoid muscle is the preferred site for injection in children aged 5 months and older.The vaccine cannot be be administered intravascularly, intradermally or subcutaneously.

Administration schedule and possibility of co-administration with other vaccines:

If Mosquirix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. Mosquirix can be given concomitantly with any of the following monovalent or combination vaccines including diphtheria (D), tetanus (T), whole cell pertussis (Pw), acellular pertussis (Pa), hepatitis B (HepB), *Haemophilus influenzae* type b (Hib), oral polio (OPV), measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines (PCV). The co-administration of Mosquirix with PCV increases the risk of fever within 7 days post-vaccination. In a clinical study in infants aged 8-12 weeks, fever was reported more frequently in infants receiving PCV in co-administration with Mosquirix, DTPa/Hib and OPV simultaneously (26%), as compared to infants receiving only Mosquirix, DTPa/Hib and OPV (14%). The frequency of grade 3 fever on co-administration (defined as axillary temperature > 39.0°C) was ≤ 1%. Concomitant administration of rotavirus and pneumococcal conjugate vaccines with Mosquirix may reduce the antibody response to the circumsporozoite (CS) antigen of Mosquirix. The impact of this observation on

the level of protection induced by Mosquirix is currently unknown.Use with systemic immunosuppressive medications: In the absence of data it cannot be ruled out that efficacy is impaired in children receiving immunosuppressive treatment.

Flexibility of vaccination schedules:

The first dose can be given from the age of 6 weeks up to 17 months. The primary course consists of three doses of Mosquirix with an interval of one month between doses. After these first three doses, a fourth dose 18 months after the third dose is given. No flexibility to the indicated primary course and booster vaccination has been studied.

Cold chain & logistic requirements:

The vaccine shelf life is 3 years.The vaccine has to be stored in a refrigerator (2°C – 8°C) and should not be frozen. Store in the original package in order to protect from light. After reconstitution,chemical and physical in-use stability has been demonstrated for 6 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at 2°C to 8°C.

b. The disease

i. Burden of disease

Malaria is a life-threatening disease caused by Plasmodium parasites that are transmitted to people through the bites of infected female Anopheles mosquitoes called “malaria vectors”. Malaria is preventable and curable. Malaria prevalence was halved to 7.5% compared with 14.8% in 2015 [38]. Currently, northwest and southeast part of the country has the highest malaria burden while central corridor has the lowest malaria burden. Leading regions for malaria are Kigoma (24%), Geita (17%), Kagera and Mtwara (15%), Lindi, Tabora & Ruvuma (12%); meanwhile five regions (19%) have prevalence of <1%, these are Manyara, Arusha, Kilimanjaro, Njombe and Iringa. Malaria incidence per 1000 population reduced by almost 35% from 162 in 2015 to 106 in 2020. Hospital admissions due to Malaria decreased by 30% from 264,879 Cases in 2016 to 184,674 admissions in 2020 indicating a decrease of severe cases. Number of deaths resulting from Malaria has declined by 61% from 6,311 (2015) to 2,460 in (2020). Children under the age of five years and pregnant women are more vulnerable compared to other groups [39].

Malaria infection is generally higher in older children (5 years and above) population with marked heterogeneity across high-low burden disease areas.Overall malaria prevalence among school children aged between 5 and 19 years was 14.1% in Tanzania Mainland [40]. These children are asymptomatic and reservoir of malaria parasites posing threat of persistent malaria transmission in the community. Unfortunately, most of malaria interventions are channeled to more vulnerable groups (underfives and pregnant women) leaving the school going children group with no special interventions.

ii. Clinical characteristics of the disease

38 https://dhsprogram.com/pubs/pdf/MIS31/MIS31.pdf (accesed on 8th December 2021)
39 https://www.out.ac.tz/wp-content/uploads/2019/10/Malaria-Strategic-Plan-2015-2020-1.pdf
40 The 2019 School Malaria Parasitaemia and Nutrition Survey Report

Malaria is an acute febrile illness. In a non-immune individual, symptoms usually appear 10–15 days after the infective mosquito bite. The first symptoms are fever, headache and chills which may be mild and difficult to recognize as Malaria. If not treated within 24 hours, P. falciparum malaria can progress to severe illness, often leading to death [41]. Children with severe malaria frequently develop one or more of the following symptoms: severe anaemia, respiratory distress in relation to metabolic acidosis, or cerebral malaria. In adults,multi-organ failure is also frequent. In malaria endemic areas, people may develop partial immunity, allowing asymptomatic infections to occur. In Tanzania, the treatment of choice for uncomplicated malaria is Artemether-Lumefantrine (ALu). The alternative medicines for treatment of uncomplicated malaria are Dihydroartemisinin-Piperaquine (DPQ) and Artesunate-Amodiaquine (ASAQ). The treatment of choice for Severe Malaria is Artesunate Injectable, while Artemether Injectable is an alternative medicine [42].

iii. Use and cost of health care

Malaria increases work load and time of the health care providers leading to compromised quality of services, increased supplies needed for testing and treatment. Malaria undermines both economic, social development and also increases the burden on health services provisions. Studies have shown malaria reduces GDP growth by up to 1.3 percent[43]. Malaria is also a leading cause of workers and school's absenteeism[44].The median financial cost of treating one episode of severe malaria and uncomplicated malaria is $ 30.26 and $ 5.84 per respectively [45].

In 2020, there were approximately 6 million cases of malaria and 2460 deaths. This means that, per day, there were over 16,000 new cases and seven(7) deaths due to malaria in Tanzania [46]. In 17 regions with moderate to high malaria transmission, there were 5,559,696 cases of Malaria in 2020. Out of this, 2,559,696 (46%) of cases were underfives. There were 270,791 admissions, 116,440 (43%) of the admissions were underfives. Deaths due to malaria in the 17 moderate to high transmission regions were 2,365. Out of these, 1,206 (51%) of deaths were underfives [47]. Two point five days are lost on average per case of malaria. This means that, in 2020, there were 6.4 million lost days of productivity due to malaria for underfives in 17 moderate to high transmission regions, equivalent to 26,663 workers who did not go for work (calculation based on people working 240 days per year) [48]

iv. Alternative preventive and control measures

It envisions to make mainland Tanzania a society free from malaria by ensuring all Tanzanians have access to quality, effective, safe, and affordable malaria preventive and curative interventions through timely and sustainable collaborative efforts with partners, with emphasis on community ownership being the principal

41 National Malaria Strategic Plan 2021-2025
42 National Guidelines for Diagnosis, Treatment and Preventive Therapies 2020
43 https://www.who.int/publications/i/item/9789240015791
44 https://path.azureedge.net/media/documents/MCP_rbm_pi_rpt_6.pdf
45 https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-10-337 (accesed on 8th December 2021)
46 https://dhis.moh.go.tz/dhis-web-commons/security/login.action (accesed on 17th December 2021)
47 https://dhis.moh.go.tz/dhis-web-commons/security/login.action (accesed on 17th December 2021)
48 https://path.azureedge.net/media/documents/MCP_rbm_pi_rpt_6.pdf (accesed on 17th December 2021)

beneficiaries.The 2021-2025 Strategic plan consists of three (3) core and three (3) cross-cutting /supportive strategic interventions. The Core Strategic interventions are Integrated Malaria Vector Control (IMVC), Malaria Case Management (MCM) and Surveillance, Monitoring and Evaluation (SME). The cross-cutting strategic interventions are Commodities and Logistics Management, Social Behaviour Change and Advocacy (SBC&A) and Programme Management. The above strategies have significantly contributed to the reduction of malaria cases in Tanzannia. The intragrated malaria control include: the use of impregnated bed nets, indoor residual spray, destruction of mosquito bleeding sites, timely turning to health facitlities and use the use of at artemisinin commbination therapy[49]

Regional and international considerations

There have been several international and regional recommendations as follows:

To increase the health expenditure as a percentage of total government expenditure to 15% to which all SADC Member States were party. In Tanzania, the government contributes 7% of the resources in the implementation of MSP of 2021-25, this excludes human resources, infrastructure and salaries [50].

To scale up treatment of malaria through proven effective drug combination. This was agreed at the meeting held in October 2005 in Gaborone, Botswana. In Tanzania Artemether Lumefantrine is the medicine of choice for treatment of uncomplicated malaria. Dihydroartemisinin-piperaquine and Artesunate Amodiaquine are alternative medicines. To ensure safety and efficacy of medicines, the National Malaria Control Program in collaboration with research Institutions has put in place safety and efficacy monitoring of ACTs through annual Therapeutic Efficacy Studies [51].

To accelerate malaria prevention and control with the goal to eliminate malaria in Africa by 2030 using available control strategies. In Tanzania, Epidemiological stratification of malaria transmission risk was conducted sub nationally. Malaria stratification allows for allocation of interventions according to burden of disease. It has also allowed identification of Regions with very low transmission risk where implementation of Case Based Surveillance to support malaria elimination by 2025 [52].
High burden high impact initiatives.

The recently launched High Burden High Impact (HBHI) initiative emphasizes on the use of data to shift away from a “one size fits all” to a more tailored malaria control approach in order to accelerate progress towards malaria elimination goal by 2030. The initiative aims at reaffirming the global commitment to malaria control and accelerating strategic interventions in the countries with the highest burden to enhance progress towards the Global Technical Strategy goals. It calls for the efficient use and expansion of resources, particularly domestic financing. A more effective use of data and evidence will help guide the selection of

49 https://www.out.ac.tz/wp-content/uploads/2019/10/Malaria-Strategic-Plan-2015-2020-1.pdf (accesed on 17th December 2021)
50 https://www.sadc.int/news-events/news/sadc-secretariat-and-alma-discuss-interventions-eliminate-malaria/ (accessed on 21 December 2021)
51 http://www.dirco.gov.za/docs/2005/bots1013.htm (accessed on 21 December 2021)
52 https://www.out.ac.tz/wp-content/uploads/2019/10/Malaria-Strategic-Plan-2015-2020-1.pdf

appropriate mix of interventions for each setting; identify and strengthen the modes of delivery; intensify the use of those interventions; fast-track the introduction of new intervention [53].

- Disease potential for international spread & pandemic potential

Several factors and capacity constraints limit the ability of the region to achieve and sustain malaria elimination. These challenges include population mobility, border protocols, surveillance, quality assurance, knowledge management, and financing. Currently, Sub Sahara countries have introduced strategic framework for cross border collaboration (East Africa Community, Great Lakes Malaria Initiatives and SADC) This framework signed by member states guide implementation of interventions at border areas for the aim of controlling imported cases in the region [54] [55].

c. Economic and operational considerations

Malaria remains a major public health problem, with 228 million cases and more than 400,000 deaths worldwide in 2018. Most of this burden (about 94%) is concentrated in sub-Saharan Africa, and children under five years old are most vulnerable, contributing to 67% of all malaria deaths in 2018 [56]. As a result, the management of malaria puts substantial pressure on the health systems of Sub-Saharan African countries[57]. Intensive efforts to develop a vaccine to prevent clinical malaria in young children have taken place over the past decades with more than 30 candidate vaccines in different stages of evaluation. Currently, only the RTS,S candidate vaccine has been recommended by WHO for a pilot and implementation in selected sub-Saharan African countries with moderate-to-high malaria transmission intensity [58].

This part provide detailed information about the incremental costs of adding malaria vaccination to the Expanded Program on Immunization (EPI) based on micro-costing with resource utilization; production capacity, available supplies and competition dynamic in the market; vaccine affordability; social economic and social impact; and economic impact on the immunization programme.

i. Estimated Costs Implementation of RTS,S Malaria Vaccine in Tanzania

The cost analysis for introducing the RTS,S vaccine in the country is based on fixed and variable costs resulting from a fully vaccinated child (FVC) with four doses administration. The variable or recurrent costs depend on the actual number of vaccine doses delivered, whereas the fixed or non-recurrent costs include

53 https://www.who.int/publications/i/item/WHO-CDS-GMP-2018.25
54 https://twitter.com/ALMA_2030/status/1461438145157812224/photo/1
55 https://www.sadc.int/news-events/news/sadc-secretariat-and-alma-discuss-interventions-eliminate-malaria/
56Baral R, Levin A, Odero C, Pecenka C, Tabu C, Mwendo E, et al. (2021). Costs of continuing RTS,S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries. PLoS ONE 16(1): e0244995. https://doi. org/10.1371/journal.pone.0244995
57RTS, S Clinical Trial Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomized controlled trial. Lancet. 2015;386 (9988):31–45.
58 Bocoum FY, Nonvignon J., Sicuri E., et al. The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries. 2019, https://us.sagepub.com/en-us/nam/open-access-at-sage.

the costs of introducing the vaccination program and establishing a certain delivery capacity within which the costs do not depend on the number of doses delivered [59].
In addition, the calculation of costs for introduction and implementation of RTS,S vaccine is modeled based on administration of the recommended four doses of vaccine following the design and results of the Phase III trial. It is therefore assumed that the first three doses could be administered during the existing routine EPI visits. The administration of the fourth dose is supposed to follow 18 months after the third dose and assumed to require an additional visit and costs beyond the routine EPI window.Therefore, in this cost analysis, the main items in the cost estimations include: *purchase prices of the vaccine and vaccine supplies (syringes, cotton, alcohol, and safety boxes), wastage, cold chain storage/distribution, administration of the vaccine, management, training, and social mobilization*.

In addition, the computation of costs is being derived and categorized as: financial costs which include the value of resources purchased by the governments for the RTS,S/ AS01E introduction; resources such as vaccines, injection supplies, outreach allowances and per diems, and resources used in training and developing new communication materials[60]. Financial costs do not include costs of resources already paid for or owned by the government such as health workers' salaries. Second, economic costs which include all financial costs as well as the value of in-kind resources used for interventions (i.e., salaries of current health personnel, volunteer labor, donated supplies, and the opportunity cost of capital goods, where applicable). The value of donated goods and services is included in economic costs. The cost of vaccine procurement is included in the economic cost and not in financial costs in the baseline financial scenario, also any procurement-related add-on costs such as insurance, freight, etc. are included as financial costs.

Table 1 presents the incremental economic cost per fully vaccinated Child (FVC) (in USD 2015) based on the study conducted in five sub-Saharan African countries namely Burkina Faso, Ghana, Kenya, Mozambique and Tanzania.

59Bocoum FY, Nonvignon J., Sicuri E., et al. The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries. 2019, https://us.sagepub.com/en-us/nam/open-access-at-sage.
60Baral R, Levin A, Odero C, Pecenka C, Tabu C, Mwendo E, et al. (2021). Costs of continuing RTS,S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries. PLoS ONE 16(1): e0244995. https://doi.org/10.1371/journal.pone.0244995.

Table 4 : The incremental economic cost per fully vaccinated Child (FVC) (in USD 2015)

Cost Items	Burkina Faso		Ghana		Kenya		Mozambique		Tanzania	
	US$	% of Subtatol	US$	% of Subtatol	US$	% of Subtatol	US$	% of Subtatol	US$	% of Subtatol
Non-current Costs										
Cold room space/ equipment	0.28	14.50	0.38	23.30	0.91	4.90	0.51	14.70	0.52	53.10
Training	0.15	8.10	0.51	31.30	0.62	3.30	0.15	4.20	0.27	5.70
Social Mobilization	0.14	7.10	0.30	18.60	0.23	0.91	0.10	2.90	-	<0.1
Human Resource	1.73	89.40	0.60	37.10	14.14	75.80	3.13	90.70	3.08	64.90
Adjustment between levels	0.36	18.90	0.17	10.30	2.75	14.70	0.43	12.50	1.12	23.70
Subtotal	**1.96**	**100.00**	**1.62**	**100.00**	**18.65**	**100.00**	**3.46**	**100.00**	**4.74**	**100.00**
Recurrent cost/Vaccine related										
Vaccine	20.00	89.40	20.00	85.40	20.00	88.80	20.00	92.30	20.00	88.20
Vaccene Wastage	2.36	10.60	3.43	14.60	2.52	11.20	1.70	7.70	2.68	11.80
Air Freight	-	-	-	-	-	-	-	-	-	-
Subtotal	**22.36**	**100.00**	**23.43**	**100.00**	**22.53**	**100.00**	**21.70**	**100.00**	**22.68**	**100.00**
Recurrent cost Scenari 1b										
Labour	0.04	6.10	0.10	12.70	0.08	11.90	0.08	8.10	0.19	17.60
Supplies	0.61	93.90	0.69	87.30	0.60	88.10	0.97	91.90	0.90	82.40
Subtotal	**0.65**	**100.00**	**0.79**	**100.00**	**0.68**	**100.00**	**1.05**	**100.00**	**1.09**	**100.00**
Recurrent cost Scenari 2c										
Labour	0.16	19.30	0.32	22.10	0.19	23.90	0.29	21.20	-	-
Supplies	0.61	7.90	0.69	46.90	0.60	75.00	0.97	70.60	-	-
Fuel	0.07	72.80	0.47	31.70	0.01	1.10	0.11	8.20	-	-
Subtotal	**0.84**	**100.00**	**1.48**	**100.70**	**0.80**	**100.00**	**1.37**	**100.00**	**-**	**-**
Total Costs Scenario 1	**24.93**		**25.84**		**36.35**		**26.21**		**28.51**	
Total Costs Scenario 2	**25.12**		**26.53**		**36.48**		**26.53**		**-**	

Note: *Vaccine Price per dose is estimated USD 5.*

[b]Scenario 1: Four Vaccine administered at health facility

[c]*Scenario 2: Three doses administered at health facilities, 1 dose at outreach. Scenario 2 was not calculated for Tanzania as vaccinations are not administered in outreach setting.*

Source: *Bocoum FY. et al., (2019): The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries*

ii. Purchases Costs of Vaccine, Freight to the Country and Wastage

The data from Table 4 shows that, the purchase costs for the RTS,S vaccine, freight to the country and wastage ranges from USD 21.70 and USD 23.43 for the five Sub-Saharan African countries involves in the study. The purchases costs, freights and waste for Tanzania are estimated to be USD 22.68 including USD 5 purchase for a single dose of RTS,S vaccine making USD 20 for a FVC with four doses and USD 2.68 for wastage. In this case, wastage is assumed to be a composite of several variables including: vaccine loss along the line of cold chain supply/distribution/storage due, for example, to inadequate control of the temperature range and damage; vaccine wastage during reconstitution; and vaccine wastage in dose administration.

iii. Distribution and Storage (Cold Chain)

The costs for cold chain storage has been computed based on an injectable vaccine with the physical characteristics of the RTS,S candidate vaccine: a lyophilized vaccine to be injected after reconstitution with a liquid adjuvant, each requiring cold storage at 2^0C to 8^0C and two-vial package including the vaccine and adjuvant which makes a volume of 9.7 cm^3, containing two vaccine doses after reconstitution. The costs of cold chain distributions as summarized in Table 4 ranges from USD 0.28 as minimum cost to USD 0.91 as maximum costs in the five Sub-Saharan African countries involves in the study. The respective cost for Tanzania is USD 0.52 FVC.

iv. Training

Training is any important aspect when towards introduction of the malaria vaccine. The estimated costs for training comprises renting of space, daily allowance for the trainees, remuneration of the trainers, accommodation, food, and traveling costs for all. The costs estimated in the five Sub-Saharan African countries involved in the study as shown in Table 4 ranges from USD 0.15 as minimum cost to USD 0.62 as maximum. The cost for training of staff to administer the RTS,S Malaria vaccine for Tanzania is estimated to be USD 0.27 for FVC.

v. Social Mobilization

The costs associated with social mobilization campaigns include transportation, per diems for people contributing to the campaign and the costs of materials prepared and used in the campaign (such as T-shirts, leaflets, radio/TV communications). Table 4 shows that, the costs associated with these activities range from 0.00 to USD 0.30 for FVC for five Sub-Saharan African countries involved in the study. No cost was estimated to need for these activities for the case of Tanzania.

vi. Human Resources

The implementation of RTS,S Malaria vaccination will require additional human resources for management and administration at all levels for monitoring, evaluation, and quality control. The cost estimated for

additional human resources based data from Table 4 ranges from USD 0.6 as minimum to USD 14.14 as maximum for FVC in the five Sub-Saharan African countries. The estimated cost for human resources needs to implement the RTS,S Malaria vaccine in Tanzania is USD 3.08 for a FVC.

vii. Labour

The labour cost associated with implementation of the RTS,S Malaria vaccine in the five countries in the study as summarized in Table 4 ranges from USD 0.04 to 0.19 for a FVC. Among the five countries involved in the study, Tanzania seemed to with the highest labour cost of USD 0.19 for a FVC.

viii. Supplies

The cost for supplies of the RTS,S Malaria vaccine based on the information provided in Table 4 under scenario 1b, ranges from USD 0.60 to USD 0.97 in the five Sub-Saharan African countries involved in the study. The cost of supplies for Tanzania is estimated to be USD 0.90 for a FVC.

ix. Vaccine Administration

Vaccine administration is undertaken at the health facility level and it involves various types of resources such as consumables (vaccine supplies such as syringes, safety boxes, disinfectants, cotton pads, and recording tools), personnel, and capital costs for waste management. Two different scenarios are considered: 1) administration of all doses of the vaccine at the health facility and 2) administration of the first three doses at the health facility and the fourth in an existing outreach setting. Comparing the administration at the health facility, the outreach setting required additional resources for transportation, cold chain distribution, and storage space where the vaccine administration would take place.

The computation of cost estimates in both scenario was done based on adjustment between levels, by assuming that only 80% of the calculated costs for the health facilities were part of the actual total costs, so the amount indicated in the adjustment row is equal to a 20% reduction in fixed costs at the health facility level as shown in Table 4. In other words, the estimated total fixed cost per FVC is not the sum of the average fixed costs across levels (national, subnational, and health facility levels) because there were potential risks of ‘‘double counting’’ when summing up fixed costs across all levels, and this is likely to occur at the health facility level. For example, several health facilities from the same district may report the need for a new motorbike for vaccination outreach but this new resource would actually be shared across these facilities and managed directly at the district level.

The data presented in Table 4 shows that, the costs based on adjustment ranges from USD 0.17 to USD 2.75 as Maximum cost in the five countries involved in the study. The estimated cost for Tanzania based on this adjustment is USD 1.12 for FVC.

x. Estimated Incremental Economic Costs per FVC at Different Levels

Table 5: Incremental Economic Costs per full Vaccinated Child at Different levels (2015 USD)

Cost Items	Burkina Faso		Ghana		Kenya		Mozambique		Tanzania	
	USS	%	USS	%	USS	%	USS	%	USS	%
National	0.12	6.10	0.08	5.20	0.04	0.30	0.04	1.30	0.02	0.40
Regional	0.05	2.50	0.17	10.40			0.01	0.20	0.07	1.50
District	0.30	15.70	0.70	43.30	2.11	16.40	1.68	48.60	0.17	3.40
Facility (adjusted)"a"	1.47	75.70	0.67	41.10	10.99	83.61	1.73	50.00	4.50	94.60
Total	**1.94**	**100.00**	**1.62**	**100.00**	**13.14**	**100.00**	**3.46**	**100.10**	**4.76**	**100.00**

"a" Adjustment between levels, that is, it was assumed that only 80% of the calculated costs for the health facilities were part of the actual total costs, so the amount indicated in the adjustment row is deducted from the other rows to arrive at total costs

Source: *Bocoum FY. et al., (2019): The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries* [61]

Table 5 summarizes the estimate for incremental economic costs per FVC at different levels showing the total cost ranging from USD 1.62 as minimum to USD 13.14. The estimated cost for each level are as provided in Table 2. The total estimate incremental economic cost per FVC for Tanzania is USD 4.76.

xi. Total Cost Based on Scenario 1 to Implement for RTS,S Malaria Vaccine

Taking into consideration of all factors and attributes to implement the RTS,S Malaria vaccine based on the resent (2019) study conducted in five Sub-Saharan African Countries including Tanzania, the estimated total cost for FVC ranges from USD 24.93 to USD 36.35. The estimated respective cost for Tanzania is USD 28.51 for FVC under scenario 1.

xii. Further and Resent Cost Analysis Study

The resent study (2021) [62] conducted as pilot in three countries namely Malawi, Ghana, and Kenyaon cost analysis for implementation of RTS,S malaria vaccination shows that, if the vaccine price is USD5 per dose and assuming the vaccine is donor-funded, the estimated incremental financial costs range from USD1.70 (Kenya) to USD2.44 (Malawi) per dose, USD0.23 (Malawi) to USD0.71 (Kenya) per dose delivered (excluding procurement add-on costs), and USD11.50 (Ghana) to USD13.69 (Malawi) per FVC. The estimates of economic costs per dose are between three and five times higher than financial costs

61Bocoum FY. et al., (2019): The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries

62Baral R, Levin A, Odero C, Pecenka C, Tabu C, Mwendo E, et al. (2021). Costs of continuing RTS,S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries. PLoS ONE 16(1): e0244995. https://doi. org/10.1371/journal.pone.0244995.

on which the study estimated economic cost per FVC at USD 46.29 in Malawi, USD 47.87 in Ghana, and USD 60.12 in Kenya estimated with the assumption that, the cost to purchase the vaccine is USD 5.

Table 6 summarizes the outcome the pilot study through estimation of cost using to scenarios of vaccine implementation approaches: Scenario 1; continuing to vaccinate children within the Malaria Vaccine Implementation Programme (MVIP) areas after the pilot vaccination ends and Scenario 2; introduction of the vaccine in comparison areas while also continuing to vaccinate children within MVIP areas. The costs were assessed for each scenario, under alternative financial scenarios where each government pays 0%, or 100% of direct vaccine-related costs [63].

Table 6 : Unit costs of continuing to Vaccinate in Pilot Areas (in 2017 USD)

Metric	% Procurement Cost Paid by Government	Malawi		Ghana		Kenya	
		Finacial	Economic	Finacial	Economic	Finacial	Economic
Scerio 1: Continue Vaccination in MVIP Implementation Area Only							
Cost per dose	0%	2.44	8.24	2.28	8.73	1.78	8.46
	100%	4.30	NA	7.80	NA	7.98	NA
Cost of Derivery per dose	NA	0.24	0.33	0.90	1.66	0.71	1.19
Cost per FVC	0%	13.69	46.29	12.49	47.87	12.66	60.12
	100%	43.77	NA	42.66	NA	56.73	NA
Scenario 2: Continue Vaccination in MVIP Implementing and Expand to Comparizon Areas							
Cost per dose	0%	2.42	8.22	2.09	8.42	1.70	8.37
	100%	8.13	NA	5.05	NA	7.97	NA
Cost of Derivery per dose	NA	0.23	0.32	0.72	1.34	0.63	1.10
Cost per FVC	0%	13.58	46.14	11.50	46.22	12.09	59.47
	100%	45.63	NA	43.38	NA	56.64	NA

Source: PLOS ONE | https://doi.org/10.1371/journal.pone.0244995.t002 January 11, 2021

Under these alternative scenarios assuming that governments pay for 0% and 100% of vaccine cost as presented in Table 6, the financial cost per dose of vaccination estimate increases to USD2.44 and USD 4.30 in Malawi USD2.28 and USD8.73 in Ghana, and USD1.78 and USD8.78 in Kenya, respectively. The financial costs per FVC are USD 45.77 in Malawi, USD 42.66 in Ghana, and USD 56.73 in Kenya. The cost estimates are almost the same in scenario 2 although it seems to slight lower in scenario 2 because

63 *Baral R, Levin A, Odero C, Pecenka C, Tabu C, Mwendo E, et al. (2021). Costs of continuing RTS,S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries. PLoS ONE 16(1): e0244995. https://doi.org/10.1371/journal.pone.0244995.*

some of the initial setup costs especially related to the activities such as national level training and sensitization would have been undertaken under scenario 1.

Other studies by Galactionova and colleagues [64] estimated the cost of delivering RTS,S/AS01E in sub-Saharan Africa including Ghana and Kenya. They have reported the estimates of cost per FVC, for a 4-dose vaccine schedule, in Ghana at USD27.78 (financial) and USD30.46 (economic), and in Kenya at USD40.15 (financial) and USD49.80 (economic), in USD 2017 units. Further, their estimate of economic cost of vaccine delivery (net of vaccine and immunization supplies) was USD 0.91 in Ghana, and USD 2.43 in Kenya. Another recent study by Sicuri and colleagues [65] estimated the economic cost per FVC at USD 28.06 for Ghana and USD 40.41 for Kenya, in USD 2017 units. Their estimates of cost of delivery per dose were USD 0.22 in Ghana and USD 0.41 in Kenya.

The cost of delivery estimates presented by Baral R. and colleagues (2021), although not directly comparable, are within the range reported in the studies by Galactionova and colleaguesand Sicuri E. and colleagues (2017) whereby the estimate costs for delivery were (Ghana at USD0.72- USD0.90 (financial), USD1.34-USD1.66 (economic), and Kenya at USD0.63 - USD0.71 (financial), USD1.10-USD1.19 (economic).

xiii. Recommendations and Assumptions on Establishment of Costs Estimates for Introduction RTS,S Malaria Vaccine

a. Different Assumptions Used to Establish Cost Estimates

Based on these various studies conducted on Costs Estimates for Introduction RTS,S Malaria Vaccine, there are a few noteworthy key differences in assumptions and cost calculations approach across these studies that attribute to the differences in cost estimates. Galactionova and colleagues [51] used a generic set of activities, assumptions and inputs to estimate the costs, whereas Baral R. and colleagues[66], study projected the activities adapted from the country-specific malaria vaccine plans for the pilot and are country specific.The study identified spare capacity for vaccine storage in two of the three countries and therefore did not include any fixed costs associated with strengthening the cold chain in those settings reflecting the actual needs in country. This is contrast to the Sicuri et al.[10] which identify, and value incremental resource needs related to introduction of vaccine.

Although all studies used a base vaccine price of $5 per dose, the study by Sicuri et al.[10] assume the base price to include vaccine wastage as well as the procurement add-on costs, while the study by Baral R. and colleagues assumes both wastage and procurement add-on as an addition to the baseline vaccine price. Further, Sicuri et al [67] assumed full coverage of all children, while study by Baral R. and colleagues (2021) [53] assumes a different vaccine coverage rate based on the expectation from the EPI. Also vaccine drop-out rates substantially contribute to the cost per FVC. Although the actual coverage and wastage are not yet

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64 Galactionova K, Bertram M, Lauer J, Tediosi F. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data. Vaccine. 2015; 33:6710–6718. https://doi.org/10.1016/j.vaccine.2015.10.079 PMID: 26518406

65Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The costs of implementing vaccination with the RTS,S malaria vaccine in five Sub-Saharan African countries. Medical Decision Making Policy & Practice. 2019; 4:1–14. https://doi.org/10.1177/2381468319896280 PMID: 31903424

66 Baral R, et al. 2021, Correction: Costs of continuing RTS,S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0244995

67 Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The costs of implementing vaccination with the RTS,S malaria vaccine in five Sub-Saharan African countries. Medical Decision Making Policy & Practice. 2019; 4:1–14. https://doi.org/10.1177/2381468319896280 PMID: 31903424

known in the context of a 4-dose malaria vaccine studies estimate utilize anticipated coverage that varies by sub-regions/districts as estimated by the EPI representatives in respective countries [53].

b. Recommendations on Costs Estimates

It is estimated costs of RTS,S Malaria Vaccine per FVC in the five Sub- Saharan Countries Burkina Faso, Ghana, Kenya, Mozambique and Tanzania are 24.93, 25.84, 36.35, 26.21 and 28.51 respectively with the mean average cost of USD28.37 per FVC [55]. From another study, Baral R. and colleagues stimated economic cost per FVC at USD46.29 in Malawi, USD47.87 in Ghana, and USD60.12 in Kenya with mean average cost of USD 52.43 per FVC. Also, on the same study by Baral R. and colleagues (2021)1 considering different scenario, estimated cost per FVC to be USD45.77 in Malawi, USD42.66 in Ghana, and USD56.73 in Kenya with a mean cost of USD48.39 per FVC [53].

Another study by Sicuri and colleagues[68] estimated the economic cost per FVC at USD28.06 for Ghana and USD40.41 for Kenya, in USD 2017 with a mean average cost of USD34.24. In all studies, the cost to purchase the vaccine was assumption estimated at USD5. The mean average cost for the RTS,S Malaria Vaccine in consideration of the four resent studies is USD40.86 per FVC. If the RTS,S Malaria Vaccine is acquired through donor funding the estimated cost of FVC is USD13.69 for Malawi, USD12.49 for Ghana and USD12.66 for Kenya Baral R. and colleagues with mean average cost of USDS12.95 [53].

The estimated total cost for introduction and implementation of the RTS,S Malaria Vaccine depends on the estimated USD per FVC and the number of the target population at risk as provided in **Table 7.**

[68] *Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The costs of implementing vaccination with the RTS,S malaria vaccine in five Sub-Saharan African countries.* Medical Decision Making Policy & Practice. 2019; 4:1–14. https://doi.org/10.1177/2381468319896280 PMID: 31903424

Table 7: Target population for introduction of RTS, S/A0S1 malaria vaccinein Tanzania

S/N	Region	Burden Strata	Target (surving infants 2021)
1	Geita Region	High	118,442
2	Kagera Region	High	135,652
3	Katavi Region	High	40,407
4	Kigoma Region	High	116,704
5	Lindi Region	High	30,475
6	Mtwara Region	High	41,339
7	Ruvuma Region	High	50,974
	Subtotal		**533,993**
1	Mara Region	Moderate	113,480
2	Mbeya Region	Moderate	83,058
3	Morogoro Region	Moderate	88,977
4	Mwanza Region	Moderate	180,845
5	Pwani Region	Moderate	42,147
6	Rukwa Region	Moderate	46,377
7	Shinyanga Region	Moderate	72,579
8	Simiyu Region	Moderate	128,212
9	Tabora Region	Moderate	131,634
10	Tanga Region	Moderate	1,421,302
	Subtotal		**2,308,611**
	GRAND TOTAL		**2,842,604**

The total cost for introduction and implementation of RTS,S Malaria Vaccine in the Regions and population of high risk Malaria prevalence is **USD21,817,619**. If the intervention of RTS,S Malaria Vaccine has to be implemented in all regions and population with high and moderate risk of Malaria prevalence, the total cost is estimated to be **USD116,141,693**. These costs estimate are based on average costs established from different studies and the assumption that, the cost for the vaccine is paid by the Government at USD 5 per dose and USD 20 per FVC plus wastage and procurement add-on-costs.

If the RTS,S Malaria Vaccine is acquired through donor funded,the cost for the RTS,S Malaria Vaccine in the Regions and population of high risk Malaria prevalence is **USD 6,913,429.37** per FVC and **USD 36,811,722** per FVC in the Regions and population with high and moderate risk of Malaria prevalence.

xiv. Production Capacity and Available supplies

RTS,S developed by PATH Malaria Vaccine Initiative (MVI) and Glaxo Smith Kline (GSK) with support from the Bill and Melinda Gates Foundation is the most recently developed recombinant vaccine. In a bid to accommodate a larger group and guarantee a sustained availability for the general public, GSK applied for a marketing license with the European Medicines Agency (EMA) in July 2014. GSK treated the project as a non-profit initiative, with most funding coming from the Gates Foundation, a major contributor to malaria eradication [69].

On 24 July 2015, RTS,S received a positive opinion from the European Medicines Agency (EMA) on the proposal for the vaccine to be used to vaccinate children aged 6 weeks to 17 months outside the European Union. A pilot project for vaccination was launched on 23 April 2019, in Malawi, on 30 April 2019, in Ghana, and on 13 September 2019, in Kenya. In October 2021, the vaccine was endorsed by the World Health Organization for "broad use" in children, making it the first malaria vaccine to receive this recommendation. RTS,S/AS01 (RTS,S) is the world's first malaria vaccine shown to provide partial protection against malaria in young children. The vaccine is being provided to young children through national immunization programs in parts of three sub-Saharan African countries as part of a pilot introduction that began in 2019 [70].

In a position paper published on 29 January 2016, WHO officially adopted the joint recommendation of SAGE and MPAG; in doing so, the Organization recognized the public health potential of the RTS,S vaccine while also acknowledging the need for further evaluation before considering wide-scale deployment. There is currently no WHO policy recommendation for the large-scale use of the RTS,S malaria vaccine beyond the pilot programme. Given that the vaccine being not pre-qualified by WHO, then it will not be funded by GAVI and thus make countries to procure from their sources [71]. Many literature presented that GSK under the support from MVI is the only company that produce malaria vaccine that have been recommended by WHO to be used in the high and moderate malaria transmission areas.

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[69] Mosquirix: Opinion on medicine for use outside EU". European Medicines Agency (EMA). Archived from the original on 23 November 2019. Retrieved 22 November 2019

[70] Malaria vaccine becomes first to achieve WHO-specified 75% efficacy goal". EurekAlert!. 23 April 2021. Retrieved 24 April 2021.

[71] https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk

xv. Vaccine Affordability

The Immunization Program in Tanzania has been receiving implementation funds from GAVI since 2001. Prior to receiving GAVI funds, the immunization program received funding from both the central government and other partners DANIDA, WHO, UNICEF, DFID, Ireland Aid, JICA, GlaxoSmithKline and Rotary International. In 2002/03 the program continued to receive funds from the central government, GAVI/Vaccine Fund and other partners such as UNICEF, WHO, JICA, DANIDA, Ireland Aid, USAID and the Basket Fund. UNICEF, DANIDA and JICA support routine immunization activities whereas other partners WHO, UNICEF, DFID, and Rotary International support campaigns. GAVI also support Health System strengthening including the areas of Human resource acquisition, capacity building, storage and distribution of vaccines, cold chain equipment's supply and maintenance and other operational costs [72].

As the country now have moved to middle income countries, the country had to graduate from receiving GAVI support on immunization programme, however this is by phases from 2023 to 2043 where the country will be fully self-financing on immunization services. This implies that Government of Tanzania will need to invest more funds to support the immunization program, both for vaccines and injection supplies as well as immunization delivery costs [73]. As it is already known that the central government budget allocation in the vaccine and implementation is very minimal, an effective strategy is highly needed to address the financial incapability on the existing vaccines and the upcoming one for example a new malaria vaccine.

Despite the fact that Malaria Vaccine is expensive but the health benefits seems to outweigh the cost. The study done in 2015 indicated that in Tanzania a cost for malaria vaccine a full vaccinated child was 28.5 USD, however another study of 2019 in Malawi, Kenya, and Ghana has shown the increase cost of vaccinating child and the highest cost was around 60 USD per a child. However the vaccine had shown the efficacy of more than 36% against clinical disease in children aged 5–17 months over 4 years under a four-dose schedule. Moreover, in the high transmission sites the vaccine contributing most of the disease episodes, there was a significant public health impact, with between 1000 and 6000 cases estimated per 1000 population over 4 years of follow-up [74].

The recommendation is the Government through MOHCDGEC to develop the financial Sustainability plan for traditional vaccines including new one such as malaria vaccine.

xvi. Economic and Social Impact

The studies presents that the socio economic impact that faced communities that used malaria vaccines was the risk of mortality shifts to morbidity at around age five. This is due to protection duration and vaccine efficacy. However, modeling studies suggest that severe malaria is likely to occur at later ages in children

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[72] *Vaughan. K et al 2020. Immunization costs, from evidence to policy: Findings from a nationally representative costing study and policy translation effort in Tanzania. (http:// creativecommons.org/licenses/by/4.0/).*

73Manzi. F, et al 2019. The Costs of Different Vaccine Delivery Strategies to Reach Children Up to 18 Months in Rural and Urban Areas in Tanzania.

74Winskill P, Walker PGT, Griffin JT, et al. 2016 Modelling the cost effectiveness of introducing the RTS,S malaria vaccine relative to scaling up other malaria interventions in sub Saharan Africa. http://dx.doi.org/ 10.1136/bmjgh-2016- 000090.

received RTSS vaccine [75]. This place an emphasis on the need for long-term monitoring and evaluation of all setting that implementation would take place. This long-term monitoring is often resource consuming but critical in understanding the impact of interventions and shifting disease epidemiology over time [76]. Furthermore this transition in age for severe malaria needs to be explained to the communities, that it is not related to the vaccine deployment but rather a change in the disease prevalence, if not explained well, may affect the uptake of the vaccine over time.

In addition the impact of vaccine in the community projected using GDP per capital in the first year after beginning the vaccination program, and the results showed that projected GDP per capita would rise immediately in the intervention area compared with the same setting at baseline. This reflects the reduction in malaria episodes in children, which allows adults to spend more days at work instead of caring for sick children and thus produces an immediate increase in labor productivity. Apart from that, the vaccine would lead to fewer childhood malaria episodes which explain that households have to spend less on out-of-pocket expenses such as treatment and transport to a clinic and thus they could use more of their income to consumption of other goods and services, which tend to increase demand in the economy and further increase GDP [77].

Futher more, efficacy of RTS,S/AS01 vaccine is modest, however it provides significant public health benefit to the targeted population. The results from phase 3 showed that among children who received 4 doses of vaccine, 1744 clinical malaria cases were prevented for every 1000 children vaccinated. This benefit was mostly found in settings of intense malaria transmission.

xvii. Economic Impact on the Immunization Programme

- **Reduction in health care costs**

Based on literatures malaria vaccine implementation had an impact in health care cost especially for health system and society at large. Several studies were conducted in understanding economic impact of malaria vaccine, and It was found that the vaccine intervention can decrease health care cost in health system by reducing number of malaria cases for underfive who are costfully interm of monetory and social life[78]. Furthermore, the vaccine showed to decrease malaria childhood episodes which explain less households expenditure on out-of-pocket expenses for treatment of malaria cases and transport to clinic. Moreover addition of four doses of vaccine to these existing malaria interventions resulted in a 36.3% reduction in clinical malaria cases over 48 months of follow-up on average in children who received the first dose at age 5 to 17 months and 25.9% reduction over 38 months of follow-up on average in infants who received the first dose at age 6 to 12 weeks [79]. This has an implication on reduction of health care cost interm of hours of health care workers that would spent attending malaria cases, as well as other factors at health system level

75 Prof Brian M Greenwood. 2015. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. doi: 10.1016/S0140-6736(15)60721-8

76 van den Berg et al.2019. RTS,S malaria vaccine pilot studies: addressing the human realities in large-scale clinical trials. RTS,S malaria vaccine pilot studies: addressing the human realities in large-scale clinical trials | Trials | Full Text (biomedcentral.com)

77 Erez Yerushalmi et al. 2019. Exploring the Use of a General Equilibrium Method to Assess the Value of a Malaria Vaccine: An Application to Ghana https://journals.sagepub.com/doi/10.1177/2381468319894345.

78 Katya Galactionova et al 2016. Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa. http://creativecommons.org/licenses/by-nc-nd/4.0/

79 Christophe Sauboin, 2019. Economic Impact of Introducing the RTS,S Malaria Vaccine: Cost-Effectiveness and Budget Impact Analysis in 41 Countries

Table 8: Events and Diasability-Adjusted Life Years(DALY) Averted of infants or child RTS, S Vaccination accross all 41 countries

	Events Averted Over 15-Year Follow-up Period			Events Averted Over 15-Year Follow-up Period per 1,000 Vaccinees		
	Median	95% Confidence Interval		Median	95% Confidence Interval	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound
Child vaccination (doses at 6, 7.5, and 9 months with a fourth dose at 27 months)						
Number vaccinated	24,569,548					
Clinical malaria cases	16,764,732	14,236,975	19,382,566	682	579	789
Severe malaria cases	359,962	176,314	542,284	14.7	7.2	22.1
Malaria hospitalizations	192,213	95,727	288,158	7.8	3.9	11.7
Malaria deaths	112,881	55,011	170,306	4.6	2.2	6.9
DALYs averted (discounted)	3,385,585	2,170,699	4,792,303	138	88.3	195
Infant vaccination (doses at 6, 10, and 14 weeks with a fourth dose at 21 months)						
Number vaccinated	26,212,458					
Clinical malaria cases	15,980,852	13,399,059	18,656,822	610	511	712
Severe malaria cases	340,683	156,343	532,447	13	6	20.3
Malaria hospitalizations	181,187	83,983	282,447	6.9	3.2	10.8
Malaria deaths	106,965	48,940	167,302	4.1	1.9	6.4
DALYs averted (discounted)	3,158,769	1,917,650	4,610,007	121	73.2	176

- **Health gains (years of life saved, QALY gained, etc.)**

Vaccination of malaria vaccine have proven to avert deaths that would be caused by malaria for children who would be full vaccinated on three doses and fourth dose as booster. The study that was conducted in 41 countries indicated that cohort of children with four doses of the RTS,S vaccine candidate in addition to existing malaria interventions was projected to avert 16.8 million cases of malaria and almost 113,000 malaria deaths over the 15-year follow-up period, compared with no vaccination[80]. With a strategy of vaccinating infants, the estimated impact of adding vaccination to existing strategies would be 16 million cases of clinical malaria and 107,000 malaria deaths averted, compared with no vaccination[81]. Other studies have reported that the estimated incremental cost-eff ectiveness ratios (ICERs) for clinical cases and DALYs averted with both vaccination schedules compared with no vaccination are lowest at intermediate levels of PfPR2–10, but are generally less than $100 per DALY averted for a PfPR2-10 of more than 10% for a

[80] *Sauboin C, et al 2019. Economic Impact of Introducing the RTS,S Malaria Vaccine: Cost-Effectiveness and Budget Impact Analysis in 41 Countries. doi/pdf/10.1177/2381468319873324*

[81] *Sauboin C, et al 2019. Economic Impact of Introducing the RTS,S Malaria Vaccine: Cost-Effectiveness and Budget Impact Analysis in 41 Countries. doi/pdf/10.1177/2381468319873324*

vaccine price of $5 per dose [82].Further more another analysis that consider 43 countries indicated that vaccination is estimated to avert over 123 million malaria episodes and over half a million malaria related deaths within the first ten years. However countries with higher levels of by patent parasitemia in children between ages 2 and 10 (PfPR2–10) reported to benefit most from the vaccine introduction [83].

- **Cost effectiveness ratio of malaria vaccination programme**

An intervention is considered cost-effective if the incremental cost effectiveness ratio (ICER) per disability adjusted life years (DALYs) averted is less than three times the GDP per capita and is highly cost effective if the ICER per DALY averted is less than the per capita GDP [84]. Provided the assumption that a vaccine cost would range $5 per dose under a four-dose schedule, then per full vaccinated child the it would be more than USD 25 the vaccine was considered to be highly cost-effective (incremental cost-effectiveness ratio (ICER) of $44–$279 per disability-adjusted life year (DALY)) within same transmission level. In the study done in Malawi for example the vaccine's ICER shows that vaccinating infants with the RTS,S vaccine is very cost-effective, and when a societal perspective was taken, the vaccine strategy was the cheapest and the most effective intervention, dominating LLINs strategy[85]. Thus, in areas in which coverage of these interventions is not yet universal, it is important to understand the relative cost-effectiveness of the full suite of interventions and where the RTS,S malaria vaccine could contribute. Importantly, this needs to take into account the diminishing marginal returns associated with the scale-up of interventions that may lead to a higher unit cost at high levels of coverage [86].

d. Health Policy and programmatic issues

i. Interaction with other existing interventions& control strategies

According to the National New Vaccine Deployment plan developed by IVD (2021), the introduction of new vaccine needs sector wide approach interrelation and collaboration. These sector involvements consider the areas of planning and coordination, service delivery, demand delivery, demanddelivery, demand and evaluation, and surveillances. This goes beyond ministry of health and its sectors/departments through involving the policymakers, religious leaders, private and public health facilities, different immunisation partners (WHO, UNICEF, CDC, USAID) and other community influential people [87].The feasibility of policy framework for introduction of RTS, S/A01 in terms of sector collaboration was found to be very useful framework.

- **Disruption of others interventions**

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[82] Penny M, et al. 2016. Public health impact and cost-eff ectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. http://dx.doi.org/10.1016/ S0140-6736(15)00725-4

83 Galactionova K et al.2016. Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa., http://dx.doi.org/10.1016/j.vaccine.2016.11.042

84 Ndeketa L et al. 2020, Cost-effectiveness and public health impact of RTS,S/AS01E malaria vaccine in Malawi, using a Markov static model. [version 2; peer review: 2 approved. https://doi.org/10.12688/wellcomeopenres.16224.2)

85 Seo et al.2014. Cost-effectiveness analysis of vaccinating children in Malawi with RTS,S vaccines in comparison with long-lasting insecticide-treated nets. malariajournal.biomedcentral.com/track/pdf/10.1186/1475-2875-13-66.pdf

86 Winskill P, et al.2017. Modelling the cost effectiveness of introducing the RTS,S malaria vaccine relative to scaling up other malaria interventions in sub Saharan Africa. BMJ Global Health. doi:10.1136/bmjgh-2016

87Tanzania National COVID 19 vaccine Deployment Plan,2021

In all three countries where pilot was done Malaria vaccine introduction did not have an impact on the uptake of routine vaccinations, nordidit have an impact on health care seekingbehaviours for febrileillness, use of insecticide-treated nets (ITNs), or other child health activities such as deworming. In the midline household surveys, malaria vaccine uptake was 69-75% among children who had not used an ITN in the previous night, indicating the vaccine reaches children who may have lower access to, and lower use of, other malaria prevention measures. The other study conducted in Rwanda, found that Malaria vaccine had the different requirement of having 4-dose schedules for administration but the vaccine products differ in other aspects.

ii. Feasibility

- **The trends in routine EPI vaccine coverage in the country**

Tanzania Immunisation Program was established in the 1970s. It started with three vaccines which targeted three diseases namely Smallpox, Tuberculosis and Pertussis. It continues to expand its services by adding more vaccine as per resources availability and scientific evidences. Currently the program is having a total of routine nine vaccines types which prevents thirteen diseases. However, from the year 2021, the program started implementing COVID 19 vaccination campaign program. These vaccines are available and being delivered by all health facilities registered by the program, whichis 6784 both public and private facilities. Tanzania immunization services aimed to achieve and sustain the vaccination coverage of >90% nationally and >80% at every district in line with Global Vaccine 4 Action Plan (GVAP 2010 - 2020). Despite several challenges, the IVD program has achieved and sustained the coverage of DTP3, OPV3, PCV3, Rota2, and MCV1 above 90% at the national level for a period of 2016 to 2020, with exception of OPV3 in 2020 which dropped to 74%(Table 9).

The primary decisions regarding a broader recommendation for RTS, S/AS01 are to be based primarily on safety and impact considerations, however, the available feasibility data are encouraging. Despite RTS, S/AS01 being a new vaccine delivered through EPI and requiring an expanded schedule, reasonably high coverage of the first three doses (>74%) was achieved in all three pilot countries (Ghana, Kenya and Malawi). While its too early to assess fourth dose coverage, preliminary information suggests drop-out rates between dose 3 and dose 4 have been around 19-30% in Malawi and Ghana (after 9-10 months of implementation). Insufficient time has passedsince 4th dose introduction to assess drop-out rates in Kenya.

Despite high acceptance of RTS,S A01 in the pilot countries the IVD in collaboration with NMCP needs to plan well to tackle programmatic challenges such as: i) number of additional workloads, especially documentation, ii) limited training and supportive supervision, iii) confusion over eligibility and the schedule and how to handle missed doses, iv) lack of resources for community outreach, v)challenges with infrastructure and logistics, vi) the type, level and duration of protection, vii) vaccination timing, number of doses, and eligibility age, viii) adverse events and safety and ix) other issues, e.g. access and sub-national introduction

Table 9 : Performance indicators

Measure	Suggestedindicators	2016	2017	2018	2019	2020
Immunizationcoverage	Official coverageestimates % DTP3	98%	97%	97%	98%	98%
	Official coverageestimates % MCV1	99%	90%	99%	99%	99%
	Other official coverageestimates as per immunizationschedule% OPV 3	96%	93%	96%	91%	98%
	Most recentsurveycoverage % DTP3	97%[88]	89%[89]	No data	No data	89.1% [90]
	% Of fullyimmunizedchild (MR2)	57%	71%	79%	84%	88%
	% Of Councilsimplementing RED/REC strategy	No data	No data	52.4%	33.5%	8%
Access to immunization service	DTP1 coverage	99%	99%	99%	99%	99%
	MCV1 to MCV2 dropout	45%	26.1%	22%	20.2%	15.4%
	Proportion of MCV2 givenbeyond 2nd year of life		No data	No data	No data	No data
Immunizationdemand	% Drop-out DTP1-DTP3	7%	5.5%	7.2%	5.8%	3.5%
	% Drop-out DTP1-MCV1	2%	12.1%	5.5%	4.1%	6.1%
Immunizationequity	% Gap in DTP3 betweenhighest and lowestsocio-economic quintiles	18%[2]	No data	No data	No data	No data
	Number/percentage of districts with DTP3 coverage> 80%	148 (91%)	157 (93%)	166 (90%)	167 (91%)	178 (97%)
	Number of high-riskcommunitiesidentified for accelerated RI programming		3[91]	No data	No data	No data
	% Availability of RI services betweenurban-rural facilities	82% vs 73%[1]		87% vs 78%[92]		
	% Of districts with more than 1000 un/undervaccinatedchildrenidentified for accelerated RI programming	30%	25.4%	17%	28%	16.3%
	% Plannedoutreachvisitsconducted	52%	No data	No data	No data	No data
New vaccine's introduction	Number of new vaccines introducedinto the RI during the last plan period	1 (MR)	None	None	2 (IPV& HPV)	None
	PCV13-3rd dose coverage	95%	96%	97%	98%	97%
	Rotaviruscoverage	98%	96%	97%	98%	98%
Integration	Immunization services integratedwithNutritionalandother RCH services	Yes	Yes	Yes	Yes	Yes

- **What are the consequences of malaria vaccine on routine immunization services and primary health care in the country**

88 MR Campaign converge Survey 2014

89 TDHS 2015/2016

90 MR Campaign Survey 2019

91 UNICEF Enquit Assissent Report 2016

92 Service Assissent and Radines Assissent

As we mentioned above the routine immunization(RI) schedule involves the nine types of vaccines with maximum of three dose schedule provide at one month intervale.g., polio and pentavalent vaccines. The observed challenges are the dropout rate of the vaccines with two dose schedules where the second dose is more than a month, example HPV which needs six months and MR which needs nine months. With this program experiences before and during the introduction of RTS, S/AS01 malaria vaccine, the program needs to assess the programmatic feasibility of delivering a four-dose schedule, including new immunization contacts, in the context of routine health service delivery.

The operational feasibility of providing RTS, S/AS01 at the recommended 4-dose schedule will be evaluated in the context of routine health service delivery. The primary objective of the feasibility evaluation is to estimate the coverage of RTS, S/AS01 in the implementation areas. The vaccination schedule is the important factor in immunisation program as it is associated with dropout rate. The RTS,S/AS01 schedule is that,children receives 4 doses of RTS,S/AS01 vaccine at months 0, 1, 2 and 24 starting from 5th month of age. The coverage of the vaccine will in most cases be affected by the lost to follow up of the fourth dose which is being given 24th from the 3rd dose.The secondary feasibility objectives measure, in implementation and comparison areas, the coverage of recommended EPI vaccines; the coverage and utilization of ITN/LLIN and IRS; changes in malaria diagnosis and treatment practices; and the patterns of health-seekingbehaviour for febrilechildren [93,94].

According to GAVI, the dropout rate for RTS, S/AS01 malaria vaccine depends on the RI coverage and vaccine uptake rate for the specific countries. There are three scenarios for estimating the expected dropout rate which includes (i) Higher scenario assumes higher pace of adoption, higher number of surviving infants, higher coverage, then 15% 4th dose RTS,S/AS01 dropout (ii) Medium scenario assumes medium pace of adoption, medium estimate of surviving infants, lower coverage compared to the higher scenario, then 20% 4th dose RTS,S/AS01 dropout, and (iii) Lower scenario assumes lower pace of adoption, lower number of surviving infants, lowe rcoverage compared to the medium scenario, 25% 4th dose dropout.

The programme needs to consider number of activities as detailed in table 10 to ensure sccuesful impelementation of RTS, S/AS01 malaria vaccine.

93Proposed framework for policydecision on RTS,S/AS01 Malaria vaccine, version 13 2019-

94Pascale Vandoolaeghe &Lode Schuerman.The RTS,S/AS01 malaria vaccine in children 5 to 17 months of age at first vaccination,Nov 2016

Table 10 : Activities to be conducted to ensure successful implementation of RTS, S/AS01

SN	ACTIVITY	DESCRIPTION
1	Micro-planning	Meetings at national and district level for planning vaccine introduction activities
2	Training	Development of training curricula and materials, Training of trainers, training of supervisors, training of vaccinatorsat district/provincial level, training of monitors
3	Social Mobilization and Information, Education, and Communication (IEC)	• Meetings with Community leaders, IEC materials development, production of leaflets, posters, TV spots, and radio, media/journalist workshop • Launching
4	Vaccine/injection supply procurement	Personnel time spent on vaccination and traveling, per diem and transport costs associated with healthworker vaccination of infants and children
5	Service delivery	Personnel time spent on vaccination and traveling, per diem and transport costs associated withheal thworker vaccination of infants and children
6	Supervision, monitoring &evaluation	Supervisory trips by National and district-level program managers, production of registers and tallysheets, disease surveillance, and post-introduction evaluation
7	Waste management	Incineration and burial of syringes, safety boxes and vaccine containers
8	Cold chain	Purchase of additional cold chain equipment to store and transport vaccines

iii. Vaccine registration

- **National regulatory authority's requirements for licensing the vaccine for its intended use or a different use**

In order for a new vaccines to be allowed in Tanzanian Market, it has to be assessed and complied on quality, efficacy and safety information.Tanzania Medicines and Medical Devices Authority (TMDA)Act. Cap 219 [95]section 51 mandates TMDA to approval registration of Medicinal Products including vaccines if it is safe, efficacious and of acceptable quality. In addition the premises and manufacturing operation should complies with the current Good Manufacturing Practices requirements as provided in the TMDA regulations. TMDA has guidlines in place on documentation and requirements for submitting applications for marketing authorization of human vaccines reffered as "Guidelines on Submission of Documentation for Market Authorization of Human Vaccines, First Revision, March, 2020" which requires all requirements to be complied during product dossier submission.

Regarding the malaria vaccine RTS,S/AS01, the European Medicines Agency (EMA) issued a positive scientific opinion on this vaccine under Article 58 in July 2015, based on the results from the Phase 3 trial,

[95] *The TanzaniaMedicines and MedicalDevicesact , Cap 219 of 219*

concluding that the vaccine had an acceptable safety profile and that the benefits of the vaccine outweighed the risks [96] [97].

The dossier of Malaria vaccine RTS,S/AS01 from GSK is experted to be reviewed by WHO in the last quarter of 2021 to inform a potential recommendation for broader use of the vaccine in children in sub-Saharan Africa. In view of this, the first vaccine couldbe WHO pre-qualified in the first half of 2022 [98]. The malaria vaccines RTS,S/AS01 has been reccommded to be used in children below 5 years on area of moderate to high transimision areas. However before starting using this vaccines in our country, the RTS. S/AS01 has be approved by TMDA. GSK therefore will be required to submit dossier of RTS,S/AS01malaria vaccine to TMDA for approval of its registration. It is advised that, in order to streamline the approval process of the new vaccine, the GSK should agreed on the modality of review on which the dossier is going to be reviewed under the African Vaccine Regulatory Forum (AVAREF) joint review by experts from the member states. In case the queries are issued to the applicant and a joint review meeting will be called where the applicant will respond to the issues raised. Recommendations to the use of this vaccines will then be presented to the Heads of National Medicines RegulatoryAuthorities (NMRAs) for the final decision on authorization for use in the country.

iv. Impact on resources

- **Availability of human, technical & financial resources for distribution (including cold chain sustainability); consider additional training needs of health workers**

In all three countries where pilot was done, malaria vaccine introduction did not have an impact on the uptake of routine vaccinations, nor did it have an impact on health care seeking behaviours for febrile illness, use of insecticide-treated nets (ITNs), or other child health activities such as deworming. In the midline house hold surveys, malaria vaccine uptake was 69-75% among children wh ohad not used an ITN in the previous night, indicating the vaccine reaches children who may have lower access to, and lower use of, other malaria prevention measures [99]. Besides not causing any disruption in routine vaccination services, there was also high acceptance of RTS, S/AS01 in the pilot countries.

Further, implementation of new malaria vaccine (RTS, S/AS01) will require costs related to:

(i)Development of a training plan and training of health care staff across all health facilities on protocols to implement the vaccination programme, (ii) Strengthening of the national logistics and standard operating procedures to coordinate deployment of the vaccine, (iii) strengthening of distribution strategies in relation to existing cold chain capacity and transportation (iv) developing and distributing appropriate standard operating procedures (SOPs), protocols, or guidelines and (v) sensitization of all stakeholders at national,

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96 Malaria vaccine: WHO position paper-January 2016. Releveepidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weeklyepidemiological record / Health Section of the Secretariat of the League of Nations 2016; 91:33-51.

97World HealthOrganization (WHO) - StrategicAdvisory Group of Experts (SAGE) meeting October 2021.

98 WHO, World malaria report 2020.

99WHO: Full Evidence Report on the RTS,S/AS01 Malaria Vaccine, September 2021

sub-national and communitylevels [100]. The implementation of malaria vaccine (RTS, S/AS01) vaccine will require the IVD programme to consider all of the issues above for a smoother implementation. The programme can map out what has been achieved in previous new vaccine(s) introduction such as HPV, IPV, PCV etc including leveraging of financial and infractural resources for routine vaccine delivery.

v. Ability to evaluate

- **Availability of information systems to manage the vaccine supplychain&measurerelated performance metrics i.e. coverage& vaccine utilization**

For the successful introduction and implementation of RTS, S/AS01 vaccine, the IVD programme should ensure the availability of Standard operating procedures (SOPs), protocols, or guidelines covering roles of National logistics working group, clear roles and responsibility of key stakeholders, distribution strategies, stock management systems and general Infection Prevention Control (IPC) issues 101. The Tanzania IVD program uses both manual and an electronic vaccine information management system (VIMS) which has generally been performing quite well. The VIMS system collects a vast majority of routine and other information that collectively provide vaccine coverage and use in the country. The VIMS system should be reviewed to ensure it is in line with the developed guidelines and protocols to cover RTS, S of /AS01. The IVD and NMCP need to plan a New Vaccine Post-Introduction Evaluation (PIE) to be conducted approximately 6 to 12 months after introduction of RTS, S/AS01 to evaluate programmatic performance 102 that include: Vaccine utilization, Stock Management, Vaccine distribution, Vaccine managementPractices, Documentation and Pharmacovigilance.

- **Existence &reliability of surveillance system**

The IVD programme needs to adapt the existing surveillance and monitoring framework with a set recommended indicators (coverage, acceptability, disease surveillance etc.) of RTS, S/AS01 malaria vaccine. The system should consider collecting information from sites and stakeholders participating in vaccine delivery. In collaboration with the National Malaria Control Program (NMCP) there is a need to ensure available guidelines and protocols [103] are reviewed for the quality implementation of Malaria surveillance and response. The existing Malaria surveillance handbook [104] should clearly define the registration and reporting, whether individual or aggregate, and to what extent existing tools and systems can be re-used. The National Malaria Control Program (NMCP) in collaboration with stakeholders is implementing National Malaria Strategic Plan 2021-2025 [105]. The 2021-2025, strategic plan core strategic objectives include: *Integrated Malaria Vector Control (IMVC)*, *Malaria diagnosis*, *treatment & preventive therapies* and *Surveillance, Monitoring and Evaluation (SME)*. The District health information system-2(DHIS2) software that is used by the MOHCDGE is flexible software for collection, validation, reporting, analysis, and presentation of aggregated (statistical and anonymous) data to support health managers at

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100The World Bank. Assessing Country Readiness for COVID-19 Vaccines First Insights from the AssessmentRollout. March 2021

101MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY AND CHILDRENGUIDELINES FOR COVID-19 VACCINATION. July 2021

102Gurnani V, Singh P, Haldar P, Aggarwal MK, Agrahari K, Kashyap S, et al. (2020) Programmaticassessment of electronic Vaccine Intelligence Network (eVIN). PLoS ONE 15(11): e0241369. https://doi.org/10.1371/journal.pone.0241369

103 Protocol for Malaria Surveillance and Data QualityImprovement (MSDQI) Rollout and Malaria Surveillance and Response (MSR) RegionalReview

104 Malaria Surveillance and Response A Handbook for Regional, District, and HealthFacilityHealth Teams, 2017

105National Malaria Strategic Plan 2021-2025

any level. The National Malaria Control Program (NMCP) dashboard in the DHIS2 is used to collect 5 groups of indicators according to the HMIS tools and service delivery section/department namely: a) Uncomplicated Malaria Diagnosis (OPD); b) Malaria Test (Lab); c) Malaria Commodities (Pharm); d) Severe Malaria Morbidity and Mortality (IPD); and e) Preventive services (RCH). These data will ultimately provide information on malaria (clinical malaria, severe, and cerebral, a subset of severe); malaria associated anaemia (any, severe), hospital admissions (all cause, malaria related, non-malaria related); deaths (all cause, all cause excluding injuries, malaria associated in hospital), reduction in blood transfusions, and febrile convulsions. These data are critical in assessing the impact of RTS, SA01 malaria vaccine. There is a need of strengthening the system to collect data on the acceptability, coverage and hesitancy of RTS, S/AS01 malaria vaccine, and the capacity to monitor Adverse Effects Following Immunization (AEFI) includingcleardefinition for meningitis (probable, and confirmed), cerebral malaria, and an excess in femalemortalitycomparedwith male mortality, all thesewereobserved in Phase 3 clinical trials [106].

Safety surveillance is very important in the introduction of RTS, S/AS01 malaria vaccine. The IVD programme and NMCP need clear guidelines/SOPs that will cover: (i) procedures and tools for conducting vaccine pharmacovigilance activities (ii) availability of well-trained human resources to conduct surveillance of AEFI, (iii) availability and defined TORs of AEFI committee to review RTS, S/AS01, (iv) involvement of manufacturers to collect and report RTS, S/AS01 safety data to the national regulatory authority, v) a plan of active surveillance for RTS, S/AS01 adverse events, vi) defined roles and responsibilities and establish a coordination mechanism between relevant stakeholders, vii) data sharing mechanisms to share RTS, S/AS01 safety data and findings with relevant regional and international partners and viii) any compensation schemes if applicable.The IVD and NMCP systems should also be strengthened to capture any spontaneously reported vaccine-related adverse events, including febrile convulsions and rare and unexpected AEFI.

The country through TMDA and IVD program have an existing system for AEFIs monitoring [107]. AEFIs are reported immediately following immunization or later; however, minor AEFIs are reported in an aggregate manner. Serious AEFI cases follow a clear process of evaluation by a team of experts and documented accordingly. TMDA with the new molecule is mandated to conduct active surveillance with a target of reaching 30% of the vaccinated. Real time reporting on AEFIs is necessary not only for enhancing awareness of AEFIs on these new vaccines and thus increasing confidence of vaccination within the Tanzanian community, but also for making informed decision/s on vaccine use by the authorities.

vi. Acceptability

- **Perception of the public & medical community about the disease & the vaccine**

A study that was done in 2015, showed that 94.3 % of all respondents from Tanzania mainland were willing to vaccinate their children against malaria. The importance of vaccinating children below five years of age

106WHO: Full Evidence Report on the RTS,S/AS01 Malaria Vaccine, September 2021

107 en1554376427-TANZANIA AEFI GUIDELINES .pdf

was generally high (>88%)[108]. Regarding, mode of administrations and number of doses, the majority accepted. Another study in 2016, 84.2% of the mothers had perfect acceptance of malaria vaccine with 92% percent reported that they will accept the malaria vaccine despite the need to continue using insecticide-treated nets (ITNs) [109]. A study in Ghana, also observed that community members are likely to accept and prefer malaria vaccine to malaria drugs as a malaria control tool if the vaccine are as effective as other EPI vaccines [110].

Generally, these studies revealed that, the majority of respondents (>70%) had good knowledge of malaria prevention, mainly ITN ownership and it was more among respondents whose children received EPI vaccines.

vii. Social considerations

- **Non-health-related effects of vaccination, ethical considerations, legal implications, etc**

The community played an integral role in the uptake, acceptability and integration of the programme into the local setting. Caregiver decision making is tied to their relationship with others in their local community. The successful of the programme largely depends on the availability of the information regarding the benefit of the programme. Placing an emphasis on the need for the high standard of health care to be extended towards other members in the community. The local political leader has a significant influence on the successful of the programme. When the local leader is trusted by the community members and this individual approves of the programme, then the community will be much more comfortable.The community relations and local engagement has the potential to bring autonomy, transparency and respect to the work. From a utilitarian perspective, it can strengthen the RTS, S/AS01 malaria vaccine programme in the selected sites. The RTS, S/AS01 phase III studies had Community Advisory Boards (CABS)[111] which consisted of influential community members who supported the communication between communities and implementers. These have been effective and therefore need to be further strengthened to involve additional stakeholders with interests.

A challenge encompassing the voluntary nature of consent in RTS,S/AS01malaria vaccine is the vulnerable paediatric population it targets. Minors are unable to provide legal consent and parents are called upon to provide it on their behalf, many of whom may have a limited understanding of the terms informed consent and confidentiality [112]. Legal consent is not of useful to the nature of the vaccine, it probably be compulsory application. So more the society will receive the vaccine in appropriate manner according to the targeted groups of the society in Tanzania mainland.

viii. Equity

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108 Romore, I., Ali, A.M., Semali, I. et al. Assessment of parental perception of malaria vaccine in Tanzania. Malar J 14, 355 (2015). https://doi.org/10.1186/s12936-015-0889-7

109 Mtenga S, Kimweri A, Romore I, Ali A, Exavery A, Sicuri E, Tanner M, Abdulla S, Lusingu J, Kafuruki S. Stakeholders' opinions and questions regarding the anticipated malaria vaccine in Tanzania. Malar J. 2016 Apr 5;15:189. doi: 10.1186/s12936-016-1209-6. PMID: 27048260; PMCID: PMC4822277.

110 Febir, L.G., Asante, K.P., Dzorgbo, DB.S. et al. Community perceptions of a malaria vaccine in the Kintampo districts of Ghana. Malar J 12, 156 (2013). https://doi.org/10.1186/1475-2875-12-156

111 Shubis K, Juma O, Sharifu R, Burgess B, Abdulla S. Challenges of establishing a CommunityAdvisoryBoard (CAB) in a low-income, low-resource setting: experiencesfromBagamoyo, Tanzania. HealthRes Policy Syst. 2009 Jun 17;7:16. doi: 10.1186/1478-4505-7-16. PMID: 19534798; PMCID: PMC2702270.

112 Kulkarni PS. Currenttopics in researchethics in vaccine studies. Perspect Clin Res [serial online] 2013 [cited 2021 Dec 3];4:80-3. Availablefrom: https://www.picronline.org/text.asp?2013/4/1/80/106398

- **Universality, accessibility & gratuity of services for all the inhabitants in the country including vulnerable, hard to reach & immigrant populations**

The introduction of RTS,S/AS01 malaria vaccine, needs to ensure that objectives and target population are well defined and agreed to by key stakeholders at all levels, including representatives of target populations, community leaders, religious leaders, etc., and reflect the epidemiological situation. This is important to ensure protection of vulnerable populations, continuity of essential services, equity. Thoroughly needs assessment survey should be conducted to understand the needs, distribution of the target population and the actual requirement before distribution of vaccines.

IV. Discussion

RTS,S/AS01 is a pre-erythrocytic stage malaria vaccine based on the CSP combined with hepatitis B surface antigen adjuvanted with AS01 for prevention of hepatocyte infection of sporozoites. RTS,S/AS01 is intended to limit the ability of *P. falciparum* to infect, mature and multiply in the liver by eliciting humoral and cellular immunity to the PfCSP, which is abundantly present at the surface of the sporozoite.

In a phase 3 clinical trial, RTS,S/AS01 was found to have an efficacy of 18-26% in 6 to 12 weeks, and 28-36% in 5 to 17 months age groups against episodes of clinical malaria when given in four complete doses. Notably, the vaccine efficacy afer completion of four doses against severe malaria were (17-21%) and hospitalization caused by malaria (25-27%) in 6-12 weeks age group while the vaccine efficacy against severe malaria (28-32%) and hospitalization caused by malaria (37-40%) in the 5-17 months age group. Furthermore, during pilot implementation in the 5-17months age group, it was observed that the vaccine reduces: clinical malaria(39%), severe malaria (29%), malaria hospitalization (37%), severe malaria anemia (62%), and need for blood transfusion (29%) on top of other integrated malaria control interventions.

During clinical trials, three serious adverse events namely meningitis, cerebral malaria and mortality were more pronounced among participants in both younger and older age categories who received the candidate vaccine. However, these safety concerns were not found to be significant during the pilot implementation study which involved a larger sample size. Other non serious adverse events were tolerable and resolved spontaneously.Therefore, the evidence generated by the RTS,S Clinical Trials Pertnership demonstrates a low efficacy and favourable safety profile.

The storage, reconstitution and administration requirements of the RTS,S/AS01 malaria vaccine are feasible with the current IVD program. The vaccine can be concomitantly administered with most of the vaccines currently administered to 6-12 weeks agae group, although there is an increase in fever incidences following co-administration. In the 5-17 months age group, it can be challenging because most of the vaccines in routine vaccination are administered before 5 months of age. Considering that there are 17 regions with moderate to high malaria transmission, introduction of the RTS,S/AS01 vaccine is an add on to the existing integrated malaria control interventions.

Given the fact that the malaria vaccine intervention showed the efficacy of more than 36% on reduction of clinical malaria cases, anyone would recommend the intervention to compliment the existing malaria control measures. However the analysis of cost-effectiveness indicates that, the vaccine might be more expensive than current malaria control measures. In addition the vaccine availability and production capacity of manufacture seems to be lower only 15 million doses capacity per year, compared the overall current estimated demand of 100 Million doses.

The intervention of RTS,S Malaria vaccine is aimed to reduce the number of deaths in the population with high Malaria prevalence. It is therefore recommended that, at higher transmission intensities of Malaria prevalence, RTS,S Malaria vaccine remains highly cost-effective even under the vaccine properties and production capacity in order to reduce deaths to the target population. It should be noted that, the introduction of RTS,S Malaria vaccine will require additional significant resources allocation apart from the current Malaria Programme budget for its implementation.

The childhood vaccines knowledge of existing routine immunization schedules and benefits increased the level of willingness to use a malaria vaccine. The structure of the IVD programme in Tanzania is widely spread and accessible to the majority of Tanzanian caregivers and has the ability to monitor and evaluate the trend of vaccination. As the malaria vaccine is expected to be delivered through the available system of IVD programme, caregivers would expect the vaccine's benefits to be in line with those of other routine vaccinations. Therefore, informing caregivers about the benefits of vaccinating children under-five is likely to increase 'awerness to Caregivers in the upcoming malaria vaccines and their willingness to use for their children.

It should ne noted that, vaccination by injection method becomes a challenge when there is increasing frequency and high numbers of vaccines doses of which might be obstacle for caregivers to take their children for vaccination. In addition, it is anticipated that, as the routine vaccines to children end at the age of less than two years, parents might not take their children for the fourth dose of Malaria vaccine of which is proposed to be carried out 18 months after a third dose. These anticipated challenges require sustained social mobilization to ensure high acceptability of RTS, S/AS01 malaria vaccine.

Immunization clinics at health facilities and outreach clinics can be good avenues for informing caregivers about the malaria vaccine and importance of complying with scheduling required to attain full immune response. Furthermore, the real time reporting on AEFIs by TMDA to the public is necessary not only for enhancing awareness of AEFIs on these new vaccines but also increasing confidence of vaccination within the Tanzanian community and also helping in making informed decision/s on vaccine use by the Authorities.

V. Proposed recommendation (s) /options

- The introduction of RTS, S/AS01 Malaria vaccine to children aged 5-17months in areas of medium to high transmission of malaria was recommended pending;

i. Review of real data, other groups work and other countries that has piloted RTS, S/AS01 to inform on duration and effectiveness of vaccine and timing of vaccination to ensure protection below five years of age.
ii. The availability of data on the gaps in waning of immunity before a child reach five years
iii. Intensive social mobilization and acceptability studies regarding RTS. S/AS01

- The Government should facilitate registration and sustainable availability of RTS, S/AS01 malaria vaccines due low production capacity of vaccine by manufacturer
- The government to ensure sustainable funding to sustain existing malaria interventions as outlined in National Malaria Strategic Plan 2020–2025 that have significantly contributed to reduction of Malaria in the country
- Community and other stakeholders should be mobilized to understand the benefits of RTS, S/AS01 vaccine and other Malaria interventions.

VI. ANNEXES

- **Appendix I: Policy research question**
- **Appendix II: Evidence search and evaluation: process and results**
- **Appendix III: Recommendation framework and specific queries**

VII. Appendix I: Policy question

Policy question:	Should Malaria vaccines be introduced for use among children in Tanzania populace?
Population	Children (6-12 weeks and 5-17months)
Intervention	RTS, S/AS01 malaria vaccine
Comparison	No Malaria vaccine
Outcomes	Clinical Malaria Severe Malaria Severe Anemia secondary to Malaria Hospitalization due to Malaria Blood transfusion

VIII. Appendix II: Summary of Safety Studies on RTS,S/AS01 Vaccine

Study	Scope	Adverse Events	Reference	Comments (limitation)	Quality of evidence
each et al., Design of a phase III multicenter trial to evaluate the efficacy of the RTS,S/AS01 malaria vaccine in children across diverse transmission settings in Africa.Malar J. 2011 Aug 4;10:224. doi: 10.1186/1475-2875-10-224. Malar J. 2011. PMID: 21816029 Free PMC article. Clinical Trial.	This was a phase III, randomized, controlled, multicentre, participant- and observer-blind study. Enrolment occurred between May 2009 and February 2011. At the time of publication, follow up was on-going at 11 centres covering a wide range of transmission settings in seven countries in sub-Saharan Africa, including Tanzania. The paper details the design of the phase III multicentre efficacy trial of the RTS,S/AS01 malaria vaccine candidate. A minimum of 6,000 children in each of two age categories (6-12 weeks, 5-17 months) were enrolled. Children were randomized 1:1:1 to one of three study groups: (1) primary vaccination (comprises three doses at monthly intervals) with RTS,S/AS01 and booster dose of RTS,S/AS01 at 18 month post-primary course; (2) primary vaccination with RTS,S/AS01 and a control vaccine at time of booster; (3) primary vaccination with control vaccine and a control vaccine at time of booster. Subjects were to be followed to study month 32. The co-primary objectives are the evaluation of efficacy over one year post-dose 3 against clinical malaria when primary immunization is delivered at: (1) 6-12 weeks of age, with co-administration of DTPwHepB/Hib antigens and OPV; (2) 5-17 months of age. Secondary objectives include evaluation of vaccine efficacy against severe malaria, anaemia, malaria hospitalization, fatal malaria, all-cause mortality and other serious illnesses including sepsis and pneumonia. Efficacy of the vaccine against clinical malaria under different transmission	This study aimed at characterizing the potential indirect benefits of malaria control through vaccination using the complete morbidity data set collected. No adverse events were reported in the paper, as the study was ongoing.	Leach et al., 2011	Study was ongoing at the time of publication	

	settings, the evolution of efficacy over time and the potential benefit of a booster will be evaluated. In addition, the effect of RTS,S/AS01 vaccination on growth, and the safety and immunogenicity in HIV-infected and malnourished children will be assessed. Safety of the primary course of immunization and the booster dose will be documented in both age categories. There is no routine testing for HIV infection in this study, HIV tests are performed only if clinically indicated. Trial registration: Clinicaltrials.gov NCT00866619				
RTS,S Clinical Trials Partnership, et al., First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med. 2011 Nov 17;365(20):1863-75. doi: 10.1056/NEJMoa1102287.	This was an ongoing phase 3 study of the efficacy, safety, and immunogenicity of candidate malaria vaccine RTS,S/AS01 is being conducted in seven African countries, including Tanzania. From March 2009 through January 2011, we enrolled 15,460 children in two age categories — 6 to 12 weeks of age and 5 to 17 months of age — for vaccination with either RTS,S/AS01 or a non-malaria comparator vaccine. 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, we evaluated vaccine efficacy against severe malaria in both age categories. In the 14 months after the first dose of	In the older age category, serious adverse events were reported in 1048 of 5949 children (17.6%; 95% CI, 16.7 to 18.6) in the RTS,S/AS01 group and in 642 of 2974 children (21.6%; 95% CI, 20.1 to 23.1) in the control group. In the younger age category, the corresponding rates were 569 of 4358 children (13.1%; 95% CI, 12.1 to 14.1) in the RTS,S/AS01 group and in 293 of 2179 children (13.4%; 95% CI, 12.0 to 15.0) in the control group. Similar proportions of children died in each study group. In the older age category, 56 of 5949 children (0.9%; 95% CI, 0.7 to 1.2) died in the RTS,S/AS01 group and 28 of 2974 children (0.9%; 95% CI, 0.6 to 1.4) in the control group; in the younger age category, 49 of 4358 children (1.1%; 95% CI, 0.8 to 1.5) died in the RTS,S/AS01 group and 18 of 2179 children (0.8%; 95% CI, 0.5 to 1.3) in the	RTS,S Clinical Trials Partnership, et al.,2011	Study was ongoing at the time of publication	Strong reference. Vaccine-related Serious Adverse Events were reported, at least 10x more in the vaccinated group than the control group.

	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/AS01 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. ClinicalTrials.gov number NCT00866619	control group. Of the 151 children who died, 78 (52%) died in the hospital after a thorough medical assessment was made; 9% of deaths occurred at a health facility before completion of a full medical assessment, and 39% occurred in the community. Causes of death were similar in the two groups (Table 11 in the Supplementary Appendix). Ten children died with a diagnosis of malaria, which was confirmed on blood smear in 7 children. At least one serious adverse event that was considered to be related to a study vaccine occurred in 11 children in the older age category: 10 of 5949 children in the RTS,S/AS01 group reported 12 events (7 seizures, 3 episodes of pyrexia, 1 episode of myositis, and 1 injection-site reaction) and 1 of 2974 children in the control group reported 1 event (seizure). In the younger age category, serious adverse events that were considered to be related to a study vaccine occurred in 6 children: 3 of 4358 children in the RTS,S/AS01 group reported 3 events (1 injection-site reaction, 1 episode of pyrexia, and 1 episode of febrile convulsion), and 3 of 2179 children in the control group reported 3 events (2 episodes of pyrexia and 1 episode of anaphylaxis). All children who had seizures that were deemed to be related to a study vaccine recovered from the acute event; epilepsy subsequently developed in 1 child. Meningitis was reported more frequently in the RTS,S/AS01 group than in the control group, with 11 of 5949 children versus 1 of 2974 children in the older age category and 8 of 4358 children versus 1 of 2179 children in the younger age category, for a relative risk of 5.5 (95% CI, 0.7 to 42.6) in the older age category			

		and 4.0 (95% CI, 0.5, 32.0) in the younger age category. In the older age category, the incidence of generalized convulsive seizure within 7 days after vaccination (according to the Brighton Collaboration diagnostic certainty level of 1 to 3) was 1.04 per 1000 doses in the RTS,S/AS01 group (95% CI, 0.62 to 1.64) and 0.57 per 1000 doses in the control group receiving rabies vaccine (95% CI, 0.19 to 1.34), for a risk ratio of 1.8 (95% CI, 0.6 to 4.9). All seizures occurred in children with a history of fever; 23 occurred within 7 days after vaccination, and of those, 12 of 18 seizures occurred within 3 days after vaccination in the RTS,S/AS01 group and 2 of 5 seizures in the control group. In the younger age category, the incidence of generalized convulsive seizures within 7 days after vaccination was 0.16 per 1000 doses in the RTS,S/AS01 group (95% CI, 0.02 to 0.57) and 0.47 per 1000 doses in the control group receiving meningococcal vaccine (95% CI, 0.10 to 1.37), for a risk ratio of 0.3 (95% CI, 0.1 to 2.0).			
Witte et al., Safety and Immunogenicity of Seven Dosing Regimens of the Candidate RTS,S/AS01E Malaria Vaccine Integrated	This was a phase II open label in infants 1-7 days of age. Subjects were equally randomized across7 groups to receive 3 doses of RTS,S/AS01E at time points that included ≤7 days, 6, 10, 14 and 26 weeks, and 9 months with other EPI vaccines or without RTS,S/AS01E vaccine.	Unsolicited AE were reported in 0-5% in subject in any RTS,S/AS01 group. Local AE (pain, redness and swelling) were similar across all groups at around 5%,7% and 4% of the participants respectively. General AE (drowsness, irritability and loss of appetite were also similar in RTS, S/AS01 and the control group. Fever was more reported in RTS,S/AS01 (15%) compared to the control group. Generally, RTS,S/AS01 had a favourable safety profile, with no SAE attributed to it. Most	Witte D et al., 2018		Moderate (open label, no blinding

Within an Expanded Program on Immunizatio n Regimen: A Phase II, Single-Center, Open, Controlled Trial in Infants in Malawi. Pediatr Infect Dis J. 2018 May;37(5):4 83-491. doi: 10.1097/INF. 0000000000 001937. PMID: 29432383.		AEs were non serious and resolved spontaneously.			
Safety and immunogeni city of RTS,S/AS01 malaria vaccine in infants and children with WHO stage 1 or 2 HIV disease: a randomised, double-blind, controlled trial (October	HIV-infected children should be considered for RTS,S/AS01 vaccination, aiming to assess the safety of RTS,S/AS01 in HIV-infected children at two sites in western Kenya. Study design: randomised, double-blind, controlled trial at the clinical trial sites of the Kenya Medical Research Institute (KEMRI)-Walter Reed Army Institute of research in Kisumu and the KEMRI/US Centers for Disease Control and Prevention in Siaya. Study population: infants and children aged from 6 weeks to 17 months with WHO stage 1 or 2 HIV disease (documented positive by	The primary outcome was the occurrence of serious adverse events until 14 months after dose 1 of the vaccine, assessed in the intention-to-treat population Serious adverse events were noted in 41 (41·4%, 95% CI 31·6-51·8) of 99 RTS,S/AS01 recipients and 37 (36·6%, 27·3-46·8) of 101 rabies-vaccine recipients (relative risk 1·1, 95% CI 0·8-1·6). 20 (20·2%, 95% CI 12·8-29·5) of 99 RTS,S/AS01 recipients and 12 (11·9%, 6·3-19·8) of 101 rabies-vaccine recipients had at least one serious adverse event within 30 days after vaccination, mainly pneumonia, febrile	Lucas Otieno et al,2016		

2016	DNA PCR), Participants were randomly assigned (1:1) to receive three doses of either RTS,S/AS01 or rabies vaccine (both 0·5 mL per dose by intramuscular injection), given once per month at 0, 1, and 2 months. Data were obtained in an observer-blind manner, and the vaccine recipient, their parent or carer, the funder, and investigators responsible for the assessment of endpoints were all masked to treatment allocation (only staff responsible for the preparation and administration of the vaccines were aware of the assignment and these individuals played no other role in the study). ARTs were provided, even if the participants were not receiving ART before the study, and daily co-trimoxazole for prevention of opportunistic infections. Sample size: 200 children were enrolled to the study and randomly assigned 99 to receive RTS,S/AS01 and 101 to receive rabies vaccine. 177 (89%) of the 200 children enrolled completed 14 months of follow-up	convulsions, and salmonella sepsis. Five (5·1%, 95% CI 1·7-11·4) of 99 RTS,S/AS01 recipients and four (4·0%, 1·1-9·8) of 101 rabies-vaccine recipients died, but no deaths were deemed related to vaccination. Mortality was associated with five cases of pneumonia (1% RTS,S/AS01 recipients vs 3% rabies-vaccine recipients), five cases of gastroenteritis (3% RTS,S/AS01 recipients vs 2% rabies-vaccine recipients), five cases of malnutrition (2% RTS,S/AS01 recipients vs 3% rabies-vaccine recipients), one case of sepsis (1% rabies-vaccine recipients), one case of Haemophilus influenza meningitis (1% rabies-vaccine recipients), and one case of tuberculosis (1% RTS,S/AS01 recipients). RTS, S/AS01 was well tolerated when given to children with WHO clinical stage 1 or 2 HIV disease along with high antiretroviral and co-trimoxazole use. Children with HIV disease could be included in future RTS,S/AS01 vaccination programmes.			
Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary	Data from 8922 African children aged 5-17 months and 6537 African infants aged 6-12 weeks at first vaccination, we analysed the determinants of immunogenicity after RTS,S/AS01 vaccination with or without a booster dose. We assessed the association between the incidence of clinical malaria and anti-circumsporozoite antibody titres using a model of anti-circumsporozoite antibody dynamics and the natural acquisition of				

analysis of data from a phase 3 randomised controlled trial Lancet Infect Dis. 2015 Dec;15(12):1450-8. doi: 10.1016/S1473-3099(15)00239-X. Epub 2015 Sep 2	protective immunity over time.				
RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015 Jul 4;386(9988): 31-45. doi:	From March 27, 2009, until Jan 31, 2011, children (age 5-17 months) and young infants (age 6-12 weeks) were enrolled at 11 centres in seven countries in sub-Saharan Africa. Participants were randomly assigned (1:1:1) at first vaccination by block randomisation with minimisation by centre to receive three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20 (R3R group); three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group); or a comparator vaccine at months 0, 1, 2, and 20 (C3C [control group]	The frequency of SAEs overall was balanced between groups. However, meningitis was reported as a SAE in 22 children: 11 in the R3R group, ten in the R3C group, and one in the C3C group. The incidence of generalised convulsive seizures within 7 days of RTS,S/AS01 booster was 2·2 per 1000 doses in young infants and 2·5 per 1000 doses in children.	RTS,S Clinical Trials Partnership., 2015	NIL	

10.1016/S0140-6736(15)60721-8.					
Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa	Safety study in which. 8922 children (enrolled at 5–17 months) and 6537 infants (enrolled at 6–12 weeks) were 1:1:1-randomized to receive 4 doses of RTS,S/AS01 (R3R) or non-malaria control vaccine (C3C), or 3 RTS,S/AS01 doses plus control (R3C). Aggregate safety data were reviewed by a multi-functional team. Children were followed up for a median of 48 months (interquartile range 39–50 months) and infants for 38 months (34–41 months) after the first vaccine dose. Baseline characteristics were similar in the 3 study groups	The serious adverse event (SAE) incidences over the entire study period in the R3R (4malaria vaccine doses), R3C (3 Malaria vaccine doses) , and C3C(no malaria vaccine) groups were 24.2%, 25.3%, and 28.4%, respectively, in children and 26.6%, 27.6%, and 28.4% in infants . Across all groups and in children and infants, respectively, the most frequently reported SAEs were malaria (9.9%–14.2%; 8.3%–10.7%), pneumonia (6.8%–7.5%; 9.3%–10.0%), febrile convulsions (5.3%–6.2%; 4.1%–4.6%), gastroenteritis (5.0%–6.0%; 7.4%–7.9%), and anemia (4.2%–6.6%; 4.1%–5.3%). A total of 326 fatal SAEs were reported for children (R3R: 127 in 61 children; R3C: 94 in 51 children; C3C: 105 in 46 children) and 269 for infants (R3R: 85 in 51 infants; R3C: 104 in 55 infants; C3C: 80 in 42 infants). No fatality was considered by the investigators as related to vaccination. The most frequently reported fatal SAEs over the entire study period were malaria (0.3%–0.4%), pneumonia (0.2%–0.5%), gastroenteritis (0.2%–0.5%), anemia (0.2%–0.4%), and convulsions (0.3%) in the 5–17 months age group, and pneumonia (0.4%–0.7%), gastroenteritis (0.5%–0.6%), anemia (0.1%–0.6%), malaria (0.2%– 0.4%), and sepsis (0.2%–0.3%) in the 6–12 weeks age group. The incidence of febrile convulsions in children was higher during the first 2–3 days post-vaccination with RTS,S/AS01 than with control vaccine, consistent with the time window of post-vaccination febrile reactions in this study	Guerra Mendoza Y, et al., Hum Vaccin Immunother. 2019;15(10): 2386-2398. doi: 10.1080/21645515.2019.1586040. Epub 2019 Apr 23. PMID: 31012786; PMCID: PMC6816384.	Causality assessment does not show any association of the malaria vaccine with that SAE nor FAEs. However, the mentioned events are all associate with severe malaria. It is doubtful if the these are the only Events observed by the team	Weak

		(mostly the day after vaccination). A statistically significant numerical imbalance was observed for meningitis cases in children (R3R: 11, R3C: 10, C3C: 1) but not in infants. CM cases were more frequent in RTS,S/AS01-vaccinated children (R3R: 19, R3C: 24, C3C: 10) but not in infants. All-cause mortality was higher in RTS,S/AS01-vaccinated versus control girls (2.4% vs 1.3%, all ages) in our setting with low overall mortality. The observed meningitis and CM signals are considered likely chance findings, that – given their severity – warrant further evaluation in phase IV studies and WHO-led pilot implementation programs to establish the RTS,S/AS01			

Efficacy of RTS,S/AS01E malaria vaccine and exploratory analysis on anti-circumsporozoite antibody titres and protection in children aged 5–17 months in Kenya and Tanzania: a randomised controlled trial	Healthy children aged 5–17 months were enrolled in Kilifi, Kenya, and Korogwe, Tanzania. Computer-generated block randomisation was used to randomly assign participants (1:1) to receive three doses (at month 0, 1, and 2) of either RTS,S/AS01E or human diploid-cell rabies vaccine. The primary endpoint was time to first clinical malaria episode, defined as the presence of fever (temperature ≥37·5°C) and a Plasmodium falciparum density of 2500/μL or more. Follow-up was 12 months for children from Korogwe and 15 months for children from Kilifi. Primary analysis was per protocol. In a post-hoc modelling analysis we characterised the associations between anti-circumsporozoite antibodies and protection against clinical malaria episodes	82 of 415 children in the RTS,S/AS01E group and 125 of 420 in the rabies vaccine group had first or only clinical malaria episode by 12 months, vaccine efficacy 39·2% (95% CI 19·5–54·1, p=0·0005). At 15 months follow-up, 58 of 209 children in the RTS,S/AS01E group and 85 of 206 in the rabies vaccine group had first or only clinical malaria episode, vaccine efficacy 45·8% (24·1–61·3, p=0·0004). At 12 months after the third dose, anti-circumsporozoite antibody titre data were available for 390 children in the RTS,S/AS01E group and 391 in the rabies group. A mean of 15 months (range 12–18 months) data were available for 172 children in the RTS,S/AS01E group and 155 in the rabies group. These titres at 1 month after the third dose were not associated with protection, but titres at 6·5 months were. The level of protection increased abruptly over a narrow range of antibody concentrations. The most common adverse events were pneumonia, febrile convulsion, gastroenteritis, and P falciparum malaria	Ally Olotu,[a,*] John Lusingu, et al	Same Authors as the above paper	Same observation
Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group (PAG). Full Evidence Report on the RTS,S/AS01 Malaria Vaccine.	This is a background paper by PAG to review with the aim of characterizing the safety profile, efficacy and programmatic feasibility of RTS,S/AS01 vaccine. Sorce of data was the pilot implementation study involving 625,673 children in Ghana, Malawi and Kenya.	Three safety signals were identified in phase III clinical trial whereby there were higher cases of miningitis, cerebral malaria and increased all causes mortality among girls (rate ratio 10.5:1 ; 2.15:1 and 2.0 respectively). However, during sentinel hospital survaillance during piloting phase, The incidence rate ratio comparing rates of admission with meningitis in implementation and comparison areas, among vaccine-eligible children, was 0.81 (95%CI 0.43, 1.55). Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received RTS,S/AS01 vaccine, compared to 53% (2491/4672) of all other hospital			

September 2021		admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 0.73 (95%CI 0.31,1.71) There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis, and there were sufficient cases, and high coverage of the vaccine, to detect an excess of the magnitude observed in the Phase 3 trial. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.77 (95% 0.44, 1.35). The incidence rate ratio for admission with other forms of severe malaria (excluding cerebral malaria) was 0.70 (0.54, 0.89), but there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (0.57, 1.56), and test of interaction (p-value 0.808). The incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the broader case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.96 (95%CI 0.61, 1.52). Therefore, there was no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria, and there were sufficient cases to detect an excess of the magnitude observed in the Phase 3 trial, if it was present. The mortality ratio in the vaccine-eligible age group between implementing and comparison regions, was 0.93 (95%CI 0.84,1.03), a 7% reduction (95%CI -3%,16%). There was no			

		evidence that the mortality ratio differed between girls and boys (p 0.343). The mortality ratio in girls was 0.98 and in boys 0.90, yielding a relative mortality ratio (girls:boys) of 1.08 (95%CI 0.92,1.28). In this review, no SAE or AESI were identified as causally related to RTS,S/AS01			

IX. Appendix III: Recommendation framework

Criteria	Work Group Judgements	Evidence	Additional information
Problem			
Is the problem of public health importance?	**YES**	Malaria is the leading cause of illness and death in the United Republic of Tanzania. Overall, malaria contributes to (17%), 14%, and 8.3% of admissions, outpatient cases and mortality respectively[113]. Ninety-three percent (93%) of malaria burden in Tanzania is contributed by regions with moderate to high malaria transmission risk. Overall, children under-five account for two third of the total deaths. Among the 17 regions with moderate to high malaria transmission risk, under-fives are mostly affected contributing to 46%, of malaria cases, while malaria admissions and deaths among under-fives contribute 42% and 51% respectively.	Most of the data on the burden of malaria and current control measures are available, and routinely monitored by National Malaria Control Program.
Benefits and Harms			
How substantial are the desirable anticipated effects?	**Low**	This is demonstrated by low efficacy in protection against severe malaria (17-32%) and hospital admission (25-40%) as well as quick waning of immunity during clinical trials[114,115] . Similar findings	Most of the studies that evaluated safety and efficacy of the candidate vaccine were done by the same group

[113] *District Health Information System 2, 2020.*

[114] RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015 Jul 4;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8.

Criteria	Work Group Judgements	Evidence	Additional information
		were also identified during pilot implementation whereby in the 5-17months age group, it was observed that the vaccine reduces clinical malaria (39%), severe malaria (29%), malaria hospitalization (37%), severe malaria anemia (62%), and need for blood transfusion (29%)[116]. These beneficial effects were in combination with integrated strategies for malaria prevention and treatment interventions. Furthermore, there was no evidence of protection against malaria infection.	(Clinical Trial Partnership). More real life data on safety and efficacy of the candidate vaccine done by other different groups will be needed for consistency.
How substantial are the undesirable anticipated effects?	**Minimal**	Most of the adverse events were non- serious and transient. Most of reported fatal cases were not related to the candidate vaccine. Most reported serious adverse events during clinical trials were found not to be related to vaccination with RTS,S/AS01. The safety profile of the candidate vaccine was reported by the same group (Clinical Trial Partnership).	Real life data from post licensure stage will be needed for critical evaluation of safety and efficacy of the candidate vaccine.
Do the desirable effects outweigh the undesirable effects?	**Favour intervention**	RTS, S/AS01 has been found to have a low efficacy and favourable safety profiles. During pilot implementation in the 5-17months age group, it was observed that the vaccine reduces: clinical malaria (39%), severe malaria (29%), malaria	In recent years, there is changing in age burden of falciparum malaria in Sub-Sahara Africa with more burdens shifting to school age

[115] RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. PLoS Med. 2014 Jul 29;11(7):e1001685. doi: 10.1371/journal.pmed.1001685.

[116] Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group (PAG). Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. September 2021

Criteria	Work Group Judgements	Evidence	Additional information
		hospitalization (37%), severe malaria anemia (62%), and need for blood transfusion (29%) on top of other integrated malaria control interventions[3]	children (5-9 years) compared to underfives[117] . With time, this may impact the effectiveness of malaria vaccine on morbidity and mortality in the population. Therefore, real life data is needed for critical assessment of risk/benefit balance.
What is the overall certainty of this evidence for the critical outcomes? ***Effectiveness of the intervention*** ***Safety of the intervention***	**High** **High**	The clinical trials for safety and efficacy of the candidate vaccines were of high quality. They were RCT, double blinded, with appropriate statistical approach, and were closely monitored by the Data Safety Management Boards (DSMB) and European Medical Agency (EMA). However, most of the trials were conducted by the same group (RTS, S/AS01 Clinical Trials Partnership)	Availability of real life data on safety and effectiveness of the candidate vaccine conducted by different groups is needed for further characterization of safety and efficacy of the candidate vaccine.
Values			
Does the target population feel that the desirable effects are large relative to undesirable effects?	**UNCERTAIN**	The available data is mainly from one source	Additional data are needed
Is there important uncertainty about or variability in how much people value the main outcome?	**YES**	The duration of protection and determinants of immunogenicity after vaccination are unclear because of the lack of long-term follow-up in the phase 2 trials.	In-depth analyses of the duration of protection is important for both the application of RTS,S/AS01 in

[117] Griffin JT, Ferguson NM, Ghani AC. Estimates of the changing age-burden of Plasmodium falciparum malaria disease in sub-Saharan Africa. Nature communications. 2014 Feb 11;5(1):1-0.

Criteria	Work Group Judgements	Evidence	Additional information
		The available data has limited certainty as the observed serious adverse events are concluded to have no causal relationship to the vaccine by the Clinical Trials Partnership group. However, looking at the data presented between the vaccine and the control arms there is convincing consistent tendency for the vaccine to cause the meningitis, cerebral malaria and fatality.	Africa and for efforts to develop the next-generation of malaria vaccines based on circumsporozoite protein.
Acceptability			
Is the intervention acceptable to key stakeholders?	**YES**	With accordance to a study that was done in 2015, showed that 94.3 % of all respondents from Tanzania mainland were willing to vaccinate their children against malaria. The caregivers had high perception (>88%)[118] on the importance of vaccinating children below five years of age. Regarding, mode of administrations and number of doses, the majority accepted the vaccination Schedule. Another study in 2016, 84.2% of the mothers had perfect acceptance of malaria vaccine with 92% percent reported that they will accept the malaria vaccine despite the need to continue using insecticide-treated nets (ITNs)[119]. A study in Ghana, also observed that community members are likely to accept and prefer malaria vaccine to malaria drugs as a malaria control	These studies were done before the COVID-19 pandemic, therefore data on acceptability might have been affected by COVID 19 pandemics. This is due to the unpublished data showing that there is hesitancy observed for ongoing vaccination on COVID19 that might affect the acceptance of Malaria vaccines in current situations. Also, as most studies on acceptance of Malaria vaccines were carried out in 6 years ago, they might not represent the current situation. Furthermore, the

[118] *Romore, I., Ali, A.M., Semali, I. et al. Assessment of parental perception of malaria vaccine in Tanzania. Malar J 14, 355 (2015). https://doi.org/10.1186/s12936-015-0889-7*

[119] *Mtenga S, Kimweri A, Romore I, Ali A, Exavery A, Sicuri E, Tanner M, Abdulla S, Lusingu J, Kafuruki S. Stakeholders' opinions and questions regarding the anticipated malaria vaccine in Tanzania. Malar J. 2016 Apr 5;15:189. doi: 10.1186/s12936-016-1209-6. PMID: 27048260; PMCID: PMC4822277.*

Criteria	Work Group Judgements	Evidence	Additional information
		tool if the vaccine are as effective as other EPI vaccines[120].	study on acceptability to be conducted should take into the consideration the culture in different area on who has the final decision of the child to vaccinate between the parents (Mother or Father). In view of this, more information on acceptability are needed on this topic from moderate to high malaria transmission areas.
Resource Use			
Is the intervention a reasonable and efficient allocation of resources?	**Probably YES**	The addition of a malaria vaccine will complement to the existing malaria interventions, there by offering the potential for further reductions in malaria burden and death to the target population. The RTS,S vaccine candidate has shown modest efficacy in a Phase III trial conducted in several countries in SubSaharan Africa in a context of high coverage of insecticide-treated nets and optimal access to ACT. Addition of four doses of vaccine to these existing malaria interventions resulted in a 36.3% reduction in clinical malaria cases over 48 months of follow-up on average in children who received the first dose at age 5 to 17 months and 25.9% reduction over 38 months of follow-up on	Based on these various studies conducted on Costs Estimates for Introduction RTS,S Malaria Vaccine, there are a few noteworthy key differences in assumptions and cost calculations approach across these studies that attribute to the differences in cost estimates. Galactionova and colleagues[123] (2019) used a generic set of activities, assumptions and inputs to

[120]*Febir, L.G., Asante, K.P., Dzorgbo, DB.S. et al. Community perceptions of a malaria vaccine in the Kintampo districts of Ghana. Malar J 12, 156 (2013). https://doi.org/10.1186/1475-2875-12-156*

Criteria	Work Group Judgements	Evidence	Additional information
		averagein infants who received the first dose at age 6 to 12 weeks[121]. The ranges of cost-effectiveness from the literature suggest that, the vaccine might be more expensive than current means of malaria control[122]. While the details of the program are best tested in a trial setting, our analysis provides further support to the recommendation's focus on ''how best to" introduce the vaccine. It is further recommened that, deployment modalities shouldbe prioritized and include delivery of the vaccine along other health services and seekbroader synergies within the National Immunization Program. The data from the Ministry of Health, Community Development, Gender, Elderly & Children Supplementary Malaria Midterm Strategic Plan (2018 – 2020) shows that, there is a reduction of Malaria prevalence from 18.1% in 2008 to 7.3% in	estimate the costs, whereasBaral R. and colleagues (2021)[124,]study projected the activitiesadapted from the country-specific malaria vaccine plans for the pilot and are country specific. Thestudy by Baral R. and colleagues (2021)[1] identifiedsparecapacity for vaccine storage in two of the three countries and thereforedid not includeanyfixedcostsassociated with strengthening the cold chain in those settings reflecting the actual needs in country. This is contrast to the

[123] *Galactionova K, Bertram M, Lauer J, Tediosi F. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data.* Vaccine. 2015; 33:6710–6718. https://doi.org/10.1016/j.vaccine.2015.10.079 PMID: 26518406

[121] *RTS, S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015;386(9988):31–45.*

[122] *Bar-Zeev N, Tate JE, Pecenka C, Chikafa J, Mvula H, Wachepa R, et al. Costeffectiveness of monovalent rotavirus vaccination of infants in Malawi: a postintroduction analysis using individual patient-level costing data. Clin Infect Dis 2016;62(Suppl 2):S220–8.*

[124] *Baral R, Levin A, Odero C, Pecenka C, Tabu C, Mwendo E, et al. (2021). Costs of continuing RTS,S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries.* PLoS ONE 16(1): e0244995. https://doi. org/10.1371/journal.pone.0244995.

Criteria	Work Group Judgements	Evidence	Additional information
		2017 with target polution of moderate to high prevalence. These reduction is based on introduction and implementation of various Malaria internvetions. The intervention of RTS,S Malaria vaccine is aimed not to reduce transmission of Malaria, but rather to reduce the number of deaths in the population with high Malaria prevalence. It is therefore recommended that, at higher transmission intensities of Malaria prevalence, RTS,S Malaria vaccine remains highly cost-effective even under most conservative assumptions on vaccine properties, coverage, means of introduction and price in order to reduce deaths to the target population. It should be noted that, the introduction of RTS,S Malaria vaccine will require additional significant resources allocation apart from the current Malaria Programme budget for its implementation. In the view of that fact, the costs aspects should be well considered towards introduction and implementation of RTS,S Malaria Vaccine giving priorities to regions and population at high risk of Malaria prevalence. Under this scenario, the cost estimate is **USD21,817,619** per FVC with **533,993**	Sicuri et al.[10] which identify, and value incremental resource needs related to introduction of vaccine. Although all studies used a base vaccine price of $5 per dose, the study by Sicuri et al[125]. assumed the base price to include vaccine wastage as well as the procurementadd-oncosts, while the study by Baral R. and colleagues (2021)[1] assumed both wastage and procurement add-on as an addition to the baseline vaccine price. Further, Sicuri et al.[10] assumed full coverage of all children, while study Baral R. and colleagues (2021)[1] assumed a different vaccine coverage rate based on the

+ [125] Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The costs of implementing vaccination with the RTS,S malaria vaccine in five Sub-Saharan African countries. *Medical Decision Making Policy & Practice. 2019; 4:1–14. https://doi.org/10.1177/2381468319896280 PMID: 31903424*

Criteria	Work Group Judgements	Evidence	Additional information
		target population**,** if the vaccine purchase depends on 100% Government Fund. Alternatively, if the RTS,S Malaria Vaccine is acquired through donor funding, the RTS,S Malaria Vaccine should be provided toregions and population of bothhigh and moderate risk of Malaria prevalence at the estimated cost of **USD36,811,722** per FVC covering **2,842,604** target population. It is further recommended that, affordability of this new intervention, has to be well assessed against program financing and budgets for other vaccines as well as broader resources for health.	expectation from the EPI. Also, the vaccine drop-out rates substantially contribute to the cost per FVC. Although the actual coverage and wastage are not yetknown in the context of a 4-dose malaria vaccine, the study by Baral R. and colleagues (2021)[1] Estimate utilize anticipated coverage that varies by sub-regions/districts as estimated by the EPI representatives in respective countries.
Equity			
What would be the impact of the intervention on health equity?	**Probably reduced**	Based WHO recommendations RTS, S/AS01 malaria vaccine should be given to children under 5 years living in moderate and high transmission areas. This ensures appropriate use of resources, focusing on the affected group as per Country epidemiology of malaria. The malaria National Control Programme (NMCP) has data on the epidemiology of malaria in the Country, hence the target population for RTS, S/AS01 malaria vaccine will be clearly defined. In addition, the introduction of RTS, S/AS01 malaria vaccine will not replace other malaria interventions.	On regular basis, the NMCP needs to review *data on the epidemiology of malaria to continue guiding the target population requiring RTS, S/AS01*. Also, the program should consider the other special vulnerable groups and areas which has not been covered by the program like children with Sickle cell and villages or wards with very high transmission of malaria in very low transmission

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			Regions during the implementation of Malaria vaccination.
Feasibility			
Is the intervention feasible to implement?	**Probably YES**	The malaria vaccines RTS, S/AS01 is a new vaccine and has not been registered by Medicines and Medical Devices Authority of Tanzania (TMDA). In order for this vaccine to be registered for use in Tanzania and streamline the registration procedure of malaria vaccines RTS, S/AS01, will require the applicant to submit the application and agree to AVAREF joint review by experts from the member states. Therefore, malaria vaccines RTS, S/AS01 should be registered first before considering its introduction in the Country. **Regarding ability to evaluate**: The Tanzania IVD program uses both manual and an electronic vaccine information management system (VIMS) which has generally been performing quite well. The VIMS system collects a vast majority of routine and other information that collectively provide vaccine coverage and use in the country. The National Malaria Control Program (NMCP) dashboard in the DHIS2 is used to collect [5] groups of indicators according to the HMIS tools and service delivery section/department namely: a) Uncomplicated Malaria Diagnosis (OPD); b) Malaria Test (Lab); c) Malaria Commodities (Pharm); d) Severe Malaria Morbidity and	Additional information on registration from TMDA is needed before introduction of RTS, S/AS01 malaria vaccine in Tanzania. Also, the Government should ensure sustainable availability of the vaccines considering the production capacity of the manufacturing facility annually which is not more than 15,000 doses. NMCP& IVD need to updates regarding system upgrading or modification to capture the information on malaria vaccine data. The systems should be reviewed to ensure they are in line with the developed guidelines and protocols to cover RTS, S/AS01. The IVD Program and NMCP

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		Mortality (IPD); and e) Preventive services (RCH). These data will ultimately provide information on malaria (clinical malaria, severe, and cerebral, a subset of severe); malaria associated anaemia (any, severe), hospital admissions (all cause, malaria related, non-malaria related); deaths (all cause, all cause excluding injuries, malaria associated in hospital), reduction in blood transfusions, and febrile convulsions. These data are critical in assessing the impact of RTS, SA01 malaria vaccine.	need to plan a New Vaccine Post-Introduction Evaluation (PIE) to be conducted approximately 6 to 12 months after introduction of RTS, S/AS01 to evaluate programmatic performance[126] that include: Vaccine utilization, Stock Management, Vaccine distribution, Vaccine management Practices, Documentation and Pharmacovigilance.

[126] *Gurnani V, Singh P, Haldar P, Aggarwal MK, Agrahari K, Kashyap S, et al. (2020) Programmaticassessment of electronic Vaccine Intelligence Network (eVIN). PLoS ONE 15(11): e0241369. https://doi.org/10.1371/journal.pone.0241369*