

Use of RTS Vaccine as Prevention Malaria in Children

Wulan Rahmadhani^{1*}, Sarwono², Nuning Juni Setia Ningsih³, Susi Hendriyati⁴

^{1,2,3,4}Faculty of Health, University of Muhammadiyah Gombong

*Corresponding author ; wulan02@gmail.com

ARTICLE INFO

Received 06/04/2022
Revised 10/01/2023
Accepted 31/01/2023

Keywords

Malaria
Children
Vaccine
RTS

ABSTRACT

Background:

Malaria cases are found almost all over the world, especially countries with tropical and subtropical climates, therefore, the population at risk for malaria is estimated at 2.3 billion or 41% of the world's population. As many as 35% of the world's population live in areas that are at risk of transmission of *Plasmodium falciparum*, and about 1 billion people live in areas that are at low risk and there is still transmission of Malaria. The purpose of this literature review is to analyze the results of a previous study on the use of the RTS vaccine for malaria prevention in children.

Method: The method used is a literature review. In the first stage, it starts by straightening the article using *search engine* Pubmed and Google scholar. The keywords used in the article search are "malaria, children, vaccines, RTS". **Results:** From the article, it was found that the use of RTS vaccine to prevent the incidence of malaria is a promising approach considering the increasing number of drug resistance. This vaccine has an efficacy of 80% for the prevention of parasite invasion in the preerythrocytic stage.

Conclusion: The use of RTS vaccine is effective for malaria prevention efforts.

This is an open access article under the [CC-BY-SA](#) license.



1. Introduction (**Heading 1**) (bold, 11pt)

Malaria is a disease that provides high morbidity and mortality in the world [1]. This disease has been known for a long time but is still a major public health problem in several tropical countries, namely in most of Africa, Latin America, Southeast Asia (Thailand and Indonesia) [2]. Based on data from the World Malaria Report, World Health Organization (WHO), there were 219 million cases of malaria that occurred in the world in 2019 [3]. This figure shows an increase compared to malaria cases in 2016, which was 217 million cases [4]. Malaria cases that are not handled properly and correctly can lead to death. The malaria death rate in 2017 reached 435,000 cases [3]. Malaria is still commonly found in Indonesia, especially in the eastern region. *Annual Parasite Incidence* (FIRE). The API value is derived from the number of positive cases of malaria per 1,000 population in one year. Indonesia's API number in 2016 was 0.77 [5]. This shows that Indonesia is a country with a high endemicity of malaria [6]. The cause of malaria infection is *Plasmodium sp.* There are five types *plasmodium* that can infect humans, namely *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium knowlesi*. The parasite that causes malaria is carried by the mosquito vector *Anopheles sp* [7].

Malaria is an infectious disease caused by parasites of the genus *Plasmodium* which are transmitted through mosquito bites *Anopheles* female [8]. Malaria transmission can also occur from sick people to healthy people through mosquito bites [8]. The seeds of this malaria disease which are contained in the blood of sick people are sucked in by mosquitoes and then breed in the mosquito's body, then the mosquito bites a healthy person again and suffers from malaria [9].

Malaria cases are found almost all over the world, especially countries with tropical and subtropical climates, therefore, the population at risk for malaria is estimated at 2.3 billion or 41% of the world's population [4]. As many as 35% of the world's population live in areas at risk of transmission of *Plasmodium falciparum*, and about 1 billion people live in areas with low risk and transmission of Malaria [10]. The incidence of malaria in Indonesia is estimated at 4, 9 million of the 262 million population. Malaria cases in 2017 recorded 261,617 cases which have resulted in the death of at least 100 people. As many as half of the total 514 districts/cities in Indonesia have reached the malaria-free category. That is, there are 72 percent of the population in Indonesia living in malaria-free areas [5].

Efforts to reduce malaria morbidity and mortality are carried out through malaria eradication programs that include early diagnosis, prompt and appropriate treatment, and vector surveillance and control in terms of public education about environmental health [11]. These three things are intended to break the chain of malaria transmission. The treatment given is a radical malaria treatment which can kill all stages of the parasite in the human body [12]. Anti-malarial treatment currently used in the national program is Artemisinin-based Combination Therapy (ACT) with artemisinin derivatives and aminoquinolone groups [13]. Malaria can be prevented by using anti-malarial drugs as chemoprophylaxis that inhibits the development of the liver stage (pre-erythrocytic) or that kills the parasite at the asexual stage in the blood. Prophylaxis is used when visiting endemic areas and continues to be taken after leaving the area for four weeks [14]. However, the use of chemoprophylaxis and treatment using antimalarial drugs is becoming increasingly complex due to the increasing incidence of resistance. Therefore, it is necessary to develop better prevention methods using vaccines [3].

Vaccines are very useful in reducing malaria morbidity and mortality. A major obstacle in vaccine development is the ability of parasites to change their antigens. An effective malaria vaccine must be targeted, namely being able to overcome the parasite at various stages of development, generate humoral and cellular immune responses, and activate memory cells [15]. Thus this vaccine should be able to lead to exo-erythrocytic (liver stage) and erythrocytic (blood stage) parasitic forms, and be able to trigger humoral and cellular immune responses, overcome genetic restrictions and stimulate memory cells [6].

For the successful development of a multi-valent malaria vaccine, it is necessary to identify the antigen potential [11]. Today many studies that lead to the development of a malaria vaccine see the urgency of the deadly disease of malaria. The Malaria Vaccine Initiative (MVI) has launched the first generation malaria vaccine named RTS, S/AS01 in 2015. WHO together with the Ministries of Health of Ghana, Kenya and Malawi started implementing the vaccine in 2018 [12]

The development of a malaria vaccine is currently aimed at two broad groups. The first is for populations in malaria endemic areas, and the second is for travelers from non-endemic countries visiting endemic countries [6]. The principle of vaccination is to make a person who has never been exposed to *Plasmodium* immune by exposing it to weakened *Plasmodium*. In this case, the sporozoite is the most important form because it corresponds to the *Plasmodium* form that mosquitoes enter into the human body [17]. This concept was tried in the 1970s by weakening sporozoites through radiation, but the wide variety of *Plasmodium* species prevented this concept from being developed at that time [19]. Nowadays, the main problem is parasite resistance which develops rapidly [14] Apart from the sporozoite phase, it is possible that the vaccine concept works at other stages in the *Plasmodium* life cycle [20]. Theoretically every stage of *Plasmodium* development in the human body can be made a vaccine [6]. Preerythrocytic (hepatic) vaccine is based on the concept of inhibiting trophozoite release from liver schizonts, namely by inducing cytotoxic T lymphocytes to destroy infected liver cells [18]. Erythrocyte vaccine is expected to inhibit the multiplication of trophozoites released by liver schizonts or prevent trophozoite invasion into erythrocytes [15]. There is also the concept of making a vaccine that is able to prevent the attachment of erythrocytes to the walls of blood vessels. The sexual phase can also be used as the basis for vaccine development [17]. in preventing further transmission through mosquitoes [6]. An effective malaria vaccine must be right on target that is capable of overcoming the parasite [1]. Based on the above background, the authors are interested in analyzing the results of previous studies on the use of the RTS Vaccine as a prevention of Malaria in children.

2. Materials and Method

The method used is *literature review*. In the first stage, it starts by straightening the article using *search engine* Pubmed and Google scholar. The keywords used in the article search were Children, Malaria, RTS Vaccine. The articles obtained will be reviewed to obtain articles that meet the predetermined criteria. The journals that have been found are then determined according to the inclusion criteria and exclusion criteria, namely IC1: journals published by Google Scholar and Pubmed obtained as many as 51 articles, IC2: journals published in 2014-2021, IC3: qualitative and quantitative research types, IC4: journals non-duplicate published on Google scholar and Pubmed. After conforming to IC1-IC4, only 17 articles remained. Then IC5 was selected based on the compatibility of article titles and abstracts with the purpose of this literature review, which has main content analyzing RTS Vaccine as prevention of malaria in children and only 8 journals were selected for analysis. Strategies in searching for literature can be seen in the following figure:

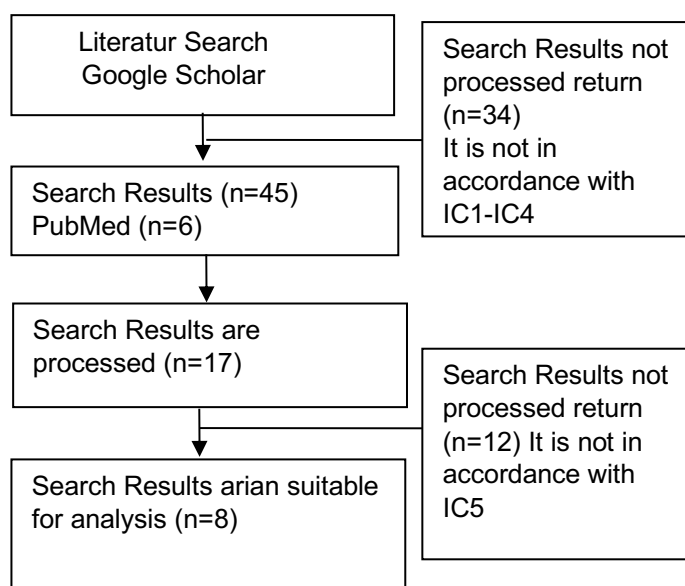


Figure 1. Flow of literature review

3. Results and Discussion

3.1. Results

The author explores journals through journal databases based on the suitability of predetermined criteria and predetermined keywords, namely malaria, children, vaccines, RTS.

Table 1. Literature review results

Author's name	Heading	Method	Sampling techniques	Research results
Carlota Dobaño et al (2019)	RTS,S/AS01E immunization increases antibody responses to vaccine-unrelated Plasmodium falciparum antigens associated with protection against clinical malaria in African children: a case-control study	Case study	purposive sampling	RTS,S/AS01E immunization decreased antibody responses to parasite antigens considered as markers of exposure (MSP142, AMA1) and levels correlated with risk of clinical malaria over 1-year follow-up. In addition, we show for the first time that RTS,S vaccination increased IgG levels to a specific group of pre-erythrocytic and blood-stage antigens (MSP5, MSP1 block 2, RH4.2, EBA140, and SSP2/TRAP) which levels correlated with protection against clinical malaria (odds

				<p>ratio [95% confidence interval] 0.53 [0.3–0.93], $p=0.03$, for MSP1; 0.52 [0.26–0.98], $p=0.05$, for SSP2) in multivariable logistic regression analyses.</p>
<p>Daniel Chandramohan et al (2019)</p>	<p>Seasonal malaria vaccination: protocol of a phase 3 trial of seasonal vaccination with the RTS,S/AS01E vaccine, seasonal malaria chemoprevention and the combination of vaccination and chemoprevention</p>	<p>randomised, controlled trial</p>	<p>purposive sampling</p>	<p>Results from the trial will be discussed with the study communities at the end of the study, presented at national and international conferences and in peer-reviewed, open access journals. Trial results will be shared with the WHO's technical expert groups and Malaria Policy Advisory Group. Strong links have been established already with the MoHs, NMCPs and EPI programmes in Burkina Faso and Mali. The trial team has also established good links with many other organisations involved in the delivery of SMC trials, including the SMC ACCESS programme and with the WHO staff responsible for conducting the RTS,S/AS01E implementation studies. Thus, if it is found that RTS,S/AS01E vaccine is a useful replacement or an addition to SMC regimens, routes have already been established through which this knowledge could be disseminated rapidly.</p>
<p>Liriye Kurtovic (2019)</p>	<p>Induction and decay of functional complement-fixing antibodies by the RTS,S malaria vaccine in children, and a negative impact of malaria exposure</p>	<p>Case study</p>	<p>purposive sampling</p>	<p>RTS,S vaccination induced anti-CSP antibodies that were mostly IgG1, with some IgG3, IgG2, and IgM. Complement-fixing antibodies were effectively induced by vaccination, and targeted the central repeat and C-terminal regions of CSP. Higher levels of complement-fixing antibodies were associated with IgG that equally recognized both the central repeat and C-terminal regions of CSP. Older age and higher malaria exposure were significantly associated with a poorer induction of functional antibodies. There was a marked decay in functional complement-fixing antibodies within months after vaccination, as well as decays in IgG subclasses and IgM. Statistical modeling suggested the decay in complement-fixing antibodies was mostly attributed to the waning of anti-CSP IgG1, and to a lesser extent IgG3</p>

Navneet Arora (2021)	Towards Eradication of Malaria: Is the WHO's RTS,S/AS01 Vaccination Effective Enough?	Case study	purposive sampling	The RTS,S/AS01 vaccine prevents malaria; however, it should be considered another addition to the malaria-control program and not as an eradication tool because of its relatively low to modest efficacy.
Parera, M., dan Tiala, M.E (2015)	Potency Vaccine Plasmodium falciparum Phase Pre-Erythrocytic Rts,S As Immunoprophylaxis	Case study	Total sampling	Efficacy vaccine RTS,S/AS01 against severe malaria in the group age combined this is 34.8%. Efficacy of RTS,S/AS01 promising and developed for the future as immunoprophylaxis.
Mukh Syaifudin (2014)	The Role of Immune Factors and Protein Profile in Research and Development Vaccine Malaria Irradiation	Case study		This test can be carried out by several methods, including sample electrophoresis on polyacrylamide through gel process SDS-PAGE followed by coloring gel with Commasie-Blue or other dyes, ELISA, flow cytometry, and proteomics. This test is carried out on samples of vaccine material after irradiation either for detection of pure antigen or antigen-antibody complexes formed after vaccine administration. The protein profile or expression can be either the parasite itself or the result of recombination or cloning in a bacterial cell such as Escherichia coli. Further tests, for example, are western blot analysis after the SDS-PAGE process for characterization or isolation of antibodies by transferring them to nitrocellulose membranes. The protein itself can be homologous or heterologous
Komang Dendi Juliawan (2019)	RTS, S/AS01 First Generation Malaria Vaccine	Case study	Purposive sampling	The use of RTS vaccine to prevent the incidence of malaria is a promising approach given the increasing number of drug resistance. This vaccine has an efficacy of 80%.
RolyGosling ,Lorenzvon Seidlein	The Future of the RTS,S/AS01 Malaria Vaccine:An Alternative Development Plan	Case study	Purposive sampling	rts vaccine, S/AS01-immunity trigger give protection the same one against parasites with circumsporozoite protein potentially different shape than vaccines other wich circulating in sub-saharan Africa.

3.2. Discussion

Based on the results of previous studies, it is shown that RTS is designed to trigger the human immune system to fight the parasite that causes malaria, namely *Plasmodium falciparum*, which enters the host's bloodstream through mosquito bites and infects liver cells. This vaccine is designed to prevent the parasite from infecting the liver, where it can mature, multiply, reenter the bloodstream, and infect red blood cells, which can cause a wide range of clinical symptoms [15]. RTS is the first malaria vaccine to be in phase III clinical trials. In these trials it was shown that RTS provided protection against malaria in children [15]. Phase I and II clinical trials assessed the safety and efficacy of the vaccine in adult volunteers in the United States and Belgium [1]. Then followed by adults, adolescents, children and infants in malaria endemic areas in Africa. Phase I clinical trial results show that the RTS,S vaccine is able to provide partial protection for children and infants in Africa [2]. Phase III clinical trials were conducted in Africa in May 2009 and concluded in early 2014. The trial involved 15,459 infants and children in 11 cities in 7 African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania). [13]. This clinical trial is the largest malaria vaccine trial ever conducted in Africa [13]. Clinical results in a phase III trial showed a reduction in malaria morbidity in 50% of samples of infants and toddlers aged 5-17 months at the first vaccination [11]. Further analysis was carried out by re-vaccinating RTS after 18 months and it was found that infants and toddlers experiencing clinical malaria cases were reduced by 46% [11]. These results were achieved by the presence of malaria interventions such as the use of bed nets with insecticides used by 80% of trial participants [15]. In the primary series of third dose vaccination, malaria cases were reduced by 26%. The fourth dose of RTS,S was administered after 8 months from the primary dose and cases of malaria were reduced by 39%. Administration of a fourth dose provides long-term protection against clinical malaria [13].

Based on the results of these clinical trials, the RTS,S vaccine is safe and shows acceptable tolerability in experimental people [12]. Common side effects after vaccination are local reactions such as pain and swelling [14]. Some children may develop a febrile reaction accompanied by generalized seizures but recover completely within seven days. Very severe adverse events in the trial (requiring hospitalization) were never reported [17]. This will be followed during phase IV clinical trials especially for the incidence of meningitis and increased risk factors for severe malaria because some cases can occur years after vaccination without a clear association with vaccination [11]. In January 2016 the WHO Strategic Advisory Group of Experts (SAGE) and the Malaria Policy Advisory Committee (MPAC) will test this vaccine using a pilot implementation program. On 24 April 2017, the WHO regional officer (WHO/AFRO) announced that the ministries of health of Ghana, Kenya and Malawi would collaborate on the Malaria Vaccine Implementation Program (MVIP) by administering four doses of RTS,S/AS01 to 750,000 children in Ghana, Kenya and Malawi. . Three doses are given to children aged 5-9 months followed by a fourth dose 15-18 months later [13]. Therefore, in 2017 the status of the RTS,S/AS01 vaccine entered phase four, namely the phase to see the effectiveness and side effects of the vaccine if used for a long period of time. This MVIP started in early 2018 [9]. Circumsporozoite protein is one of the Sporozoite Surface Proteins (CSP) which plays a role in the process of parasitic invasion in the erythrocytic phase [11]. When *Anopheles* sp. The infected release sporozoites into the skin of mammals when they bite to find food, the sporozoites will move actively towards the dermis and penetrate the blood vessels [17]. Sporozoites circulating in the blood vessels will then enter the liver cells by crossing the sinusoid barrier. Circumsporozoite proteins form a dense layer on the protein surface that attacks hepatocytes as initial interactions. The C terminal of the CSP can specifically bind to hepatocytes [12]. Sporozoites will move actively towards the dermis and penetrate blood vessels [17]. Sporozoites circulating in the blood vessels will then enter the liver cells by crossing the sinusoid barrier. Circumsporozoite proteins form a dense layer on the surface of proteins that attack hepatocytes as initial interactions. The C terminal of the CSP can specifically bind to hepatocytes [12]. Sporozoites will move actively towards the dermis and penetrate blood vessels [17]. Sporozoites circulating in the blood vessels will then enter the liver cells by crossing the sinusoid barrier. Circumsporozoite proteins form a dense layer on the surface of proteins that attack hepatocytes as initial interactions. The C terminal of the CSP can specifically bind to hepatocytes [12].

The development of the RTS vaccine has focused on the central amino acid repeat region containing the immunodominant B cell epitope. However, vaccine construction has progressed rapidly to combine the amino acid repeat region with the C terminal containing TSR, B cell epitope and T cell epitope [13]. These epitopes are not only immunogenic, but can form antibodies that inhibit sporozoi invasion [10]. People who are immunized using the RTS vaccine will form antibodies that focus on the repeat region to form an immunodominant region of protein [14]. However, adults who live in endemic areas and are naturally bitten by infected vectors can be immune from malaria because they already have high levels of antibodies against terminal C and other non-recurrent regions. Individuals who are not immunized with RTS vaccine receive CD4+ and CD8+ cell-dependent protection against C-terminal Plasmodium falciparum [14]. Overall, the protective efficacy of the RTS vaccine may provide partial protection in humans is 30-50%, so there is clearly room for improvement in the RTS vaccine [17]

4. Conclusion

After years of research and clinical trials, the first-generation malaria vaccine was officially implemented in early 2018 in several malaria-endemic areas in Africa. The vaccine is named RTS. The use of RTS vaccine to prevent the incidence of malaria is a promising approach given the increasing number of drug resistance. This vaccine has an efficacy of 80% for the prevention of parasite invasion in the pre-erythrocytic stage.

Declaration

Acknowledgments: The author would express gratitude to who help and participation in this research. Conflicts of Interest: The authors declared that there is no conflicts of interest in this research.

References

- [1] Guinovart, "Insights into long-lasting protection induced by RTS,S/AS02A malaria vaccine: further results from a phase IIb trial in Mozambican children," *PLoS One*, vol. 4, 2019.
- [2] Ubillos, "Development of a highthroughput flexible quantitative suspension array assay for IgG against multiple Plasmodium falciparum antigens," *J. Malar.*, vol. 17, 2018.
- [3] WHO, "Monitoring Health for the SDGs, Sustainable Development Goals. Geneva: World Health Organization; 2019.,", 2019.
- [4] World Health Organization, "Monitoring Health for The SDGs," 2017.
- [5] Kemenkes RI, "Riset Kesehatan Dasar," 2018.
- [6] Chandramohan, "Effect of adding azithromycin to seasonal malaria chemoprevention," *New Engl. J.*, vol. 112, 2019.
- [7] DEPKES RI, "Klasifikasi umur menurut kategori," 2019. .
- [8] Cairns, "Analysis of preventive interventions for malaria: exploring partial and complete protection and total and primary intervention effects," *Am J Epidemiol*, vol. 151, 2015.
- [9] Jeitao, "Revising the who verbal autopsy instrument to facilitate routine cause- of- death monitoring," *Glob Heal. Action*, 2013.
- [10] Neafsey, "Genetic diversity and protective efficacy of the RTS,S/AS01 malaria vaccine.,", *New Engl. J.*, vol. 373, 2015.
- [11] Campo, "vaccination is associated with serologic evidence of decreased exposure to Plasmodium falciparum liver- and blood-stage parasites," *Mol Cell Proteomics*, vol. 14, 2015.
- [12] Swysen, "Development of standardized laboratory methods and quality processes for a phase III study of the RTS, S/AS01 candidate malaria vaccine," *J. Malar.*, 2015.
- [13] Moncunill, "Distinct helper T cell type 1 and 2 responses associated with malaria protection and risk in RTS,S/AS01E vaccinees," *Clin Infect Dis*, vol. 65, 2017.
- [14] Piaggio, "Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement," *JAMA*, vol. 295, 2016.
- [15] Vidal, "Development of quantitative suspension array assays for six immunoglobulin isotypes and subclasses to multiple Plasmodium falciparum antigens," *J Immunol Methods*, vol. 455, 2018.
- [16] R. F. Aniroh, U., & Fatimah, "Tingkat Kecemasan Ibu Primigravida dalam Menghadapi Persalinan Ditinjau dari Usia Ibu dan Sosial Ekonomi," *J. Ilmu Keperawatan Matern.*, vol. 2, no. 2, 2019.
- [17] Olotu, "Individual-participant pooled analysis of phase 2 data," *Lancet Infect Dis*, vol. 3, no. 4, 2013.

- [18] Reiter K, Shimp LR, Kotova S, Smith PD, Hurt DE, et al. 2009. Structure of the Plasmodium falciparum circumsporozoite protein, a leading malaria vaccine candidate. JBC Papers in Press. 284(39):26951–26963.