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POTENCIAL OF ACTION

OF THE LATEST VACCINES DEVELOPMENT AGAINST HUMAN MALARIA

POTENCIAL DE ACCIÓN DE LAS ÚLTIMAS VACUNAS DESARROLLADAS CONTRA LA MALARIA HUMANA

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ABSTRACT

Malaria is the most danger disease caused by Plasmodium parasite which is presented in different endemic and non-endemic areas around the world, where it can cause different clinical complications that could end in death. Due to the amount of people affected by malaria in different counties, vaccination is considered the unique form to prevent infection reducing the number of people dying and eliminating malaria from different zones despite the development of resistance against antiparasitic drug treatments that have been used to control the disease. In fact, several vaccines have been developing during the last years but many of them have achieved successful results over than others and some of them have being discontinued in investigation because of its low results and possible side effects. This article describes the potential action of the latest vaccines development during the recent years and which of them represent more clinical importance for public health use.

Keywords: Malaria, plasmodium, plasmodium falciparum, plasmodium vivax, vaccines.

RESUMEN

La malaria es la enfermedad más peligrosa provocada por el parásito Plasmodium, la cual está presente en diferentes áreas en endémicas y no endémicas alrededor del mundo, en donde esta puede causar diferentes complicaciones clínicas que pueden terminar en la muerte. Debido a la cantidad de personas afectadas por la malaria en diferentes países, la vacunación es considerada como la forma única de prevenir la infección reduciendo el número de personas muertas y eliminando la malaria de diferentes zonas a pesar de la resistencia que ha desarrollado contra los tratamientos con medicamentos antiparasitarios para controlar la enfermedad. De hecho, varias vacunad se han venido desarrollando en los últimos años, en donde algunas han logrado resultados favorables y otras han dejado de ser investigadas por sus bajos resultados o posibles efectos secundarios. Este artículo describe la acción potencial de las ultimas vacunas desarrolladas las cuales representen una importancia clínica en la salud pública.

Palabras clave: Malaria, plasmodium, plasmodium falciparum, plasmodium vivax, vacunas.

INTRODUCTION

Malaria is an infectious disease caused by several species of apicomplexan parasites within the genus ***Plasmodium***. In humans, there are six ***Plasmodium*** species responsible for causing malaria: ***P. falciparum, P. knowlesi, P. malaria, P. ovale curtisi, P. ovale wallikeri and P. vivax***. Together, they cause approximately half million deaths per year. Among all the species, ***P. falciparum*** and ***P. vivax*** are the most studied parasites due to their high frequency of infection and clinical complications caused in thepatients (Epstein et al. 2017).

The life cycle of ***Plasmodium*** species is complex since the parasites transit among sexual and asexual stages and evolved to survive in different cell environments. This begins when an ***Anopheles*** female' mosquito, carrying the parasite sporozoites (Spz) in its salivary glands, takes a blood meal resulting in injecting Spz into the bloodstream of a human host (Mancipe et al. 2019). The Spz first infect liver cells, where they multiply asexually over the following 7–10 days, period in which the patient is asymptomatic. Different from other species, ***P. vivax*** and ***P. ovale*** pass through a dormant stage called hypnozoites which can hold the progression of the infection for weeks or even years after transmission took place. Now in the form of merozoites (Mrz), the parasites are released from the liver cells in vesicles and travel to the capillaries (Rénia & Goh, 2016). The vesicles eventually burst, discharging the Mrz to enter the bloodstream where they disperse and enter erythrocytes. Inside here, the parasites undergo asexual reproduction generating trophozoites which mature to schizonts. The schizonts burst generating merozoites which egress the cell and invade more erythrocytes, repeating the cycle of growth, replication, egress, and invasion. The realize of Mrz into the bloodstream and rupture of injected erythrocytes trigger clinical symptoms which develop in malaria disease.

P. falciparum and ***P. vivax*** incubation time are 12-18 and 9-14 days, respectively. The pathology includes signs like intermittent fever, headache, vomit, chills, abdominal pain, and sweating symptoms which can potentially develop in chronic and fatal hemolysis. Finally, a small number of parasites in asexual stages commit to sexual cycle, forming microgametocytes (male) and macrogametocytes (female). Once mature, the gametocytes in the blood stream can be taken up by female mosquitoes, continuing the transmission of the parasites (Mawson, 2013).

The distribution of malaria cases is reported around the world specially in countries with tropical and subtropical areas, environments in which mosquitoes are distributed. In South America, ***P. vivax*** is the most common species, affecting specially rain forest and coastal regions during dry season (Morales, Quinatoa, & Cagua, 2021). The presence of ***P. falciparum*** in this region is confirmed. However, a study published in 2019 suggests a decrease in the population of this species in Brazil and Argentina, countries where most of the malaria cases are asymptomatic.

In 2015, the World Health Organization (WHO) reported that the 83% of malaria cases inthis region correspond to: Venezuela (30%), Brazil (24%), Peru (19%), and Colombia (10%). Additionally, a study carried out in 2018 showed an association between human migration and an increase of malaria cases (96%) in the border between Ecuador and Peru (Recht et al. 2017).

To fight against malaria, the most used methods remain to be vector control and drug therapies. However, ***P. falciparum*** developed resistance to monotherapies and sesquiterpenes like artemisinin-based combination therapies (ACTs), even in alternated strategies, becoming a problem to eliminate the disease. The main cause of the resistanceis the irresponsible use of antimalarial drugs like chloroquine, lumefantrine, amodiaquine, sulphadoxine-phyrimethamine, quinine, piperaquine and mefloquine, and a lack of healthcontrol even in countries with quality drug components and strong healthcare systems.Due to the development of antiparasitic drug resistance, it is important to improve malaria control beyond administration and prescription or elimination program to deal with emerging resistance, inadequate new antimalarial treatment, or poor compliance ineffected countries. Although the parasites might be sensible to drugs at the beginning of the application, longer and higher doses of the drugs, may develop parasite resistance, meaning the failure of the treatment (Mancipe et al. 2019).

In fact, elimination of the disease requires a better solution to replace failing drugs therapies, specially to treat undetected cases. Thus, the development of a vaccine represents a significant and crucial step of a prophylactic mechanism of protection againstmalaria, inhibiting the gametocytes developing from the parasites and the onset of hard symptoms (Mancipe et al. 2019). This review aims to describe the latest vaccines against malaria, their mechanism of action, and the phase of the study that has reached until these days.

METHODS

PubMed, Scielo, Google Scholar, PMC, Springer, EMBASE and Science Direct were used to search academic content. The inquiry parameters were any published work among 1987 and 2021 in either Spanish or English language. The Key words used were "malaria", "***Plasmodium***",

"*Plasmodium falciparum*", *"Plasmodium vivax*" and "vaccines". A total of 80 published articles were retrieved, 30 of which were considered relevant to this review for they explain vaccine's projects and studies against *Plasmodium* species. The selectedarticles were carefully analyzed according to their main theme, including vaccine elaboration, clinical research, clinical phases of the studies, and reported secondary effects.

RESULTS

Life cycle of *Plasmodium*

P. Falciparum and *P. vivax* pass through two cycles that undergoes their development inside two hosts. Into the vector occurs the sexual cycle and, in the human, the asexual one (Figure 1).

Sexual cycle of Plasmodium

The sexual life cycle of *Plasmodium* begins when a female *Anopheles* mosquito takes a blood meal containing gametocytes from the bloodstream of an infected human host. Male and Female gametocytes taken reach the mosquito's midgut and undergo fertilization and maturation, forming ookinete. Ookinetes migrate to the hemocoel to form oocysts. Once mature the oocysts burst releasing sporozoites, which migrate to the mosquito's salivary glands where they are ready for transmission (Prudêncio et al, 2006).

Asexual cycle of Plasmodium

The infection from malaria begins when the female *Anopheles* mosquito carrying Spz are deposited under human skin. This cycle is divided in two processes that happen inside the liver (pre-erythrocytic stages) and into the bloodstream (erythrocytic stages). After invasion, the pre-erythrocytic phase begin by Spz migration to the liver to infect hepatic cells which undergoes the development of merozoites (Mrz). P. falciparum Mrz are released to the bloodstream to enter into the erythrocytic stages, while P. vivax Mrz have the ability to remain as hypnozoites (Hpz) into the hepatic tissue waiting for reactivation which refers asymptomatic cases (Prudêncio et al, 2006). Consequently, the erythrocytic phase is placed by Mrz invasion that entry into erythrocytes by receptor–ligand low-affinity interaction inducing membrane deformation with (EBA-175, EBA-140 and EBA-181) antigens and reticulocyte binding homolog (Rh1, Rh2a/Rh2b and Rh4) families. The consequent invasion undergoes the sequential formation of ring, trophozoites, and schizonts (Scz) stages. Mature infected Scz go to infect more erythrocytes (Prudêncio et al, 2006).

Gametocyte's stage develops during 10 days inside erythrocytes and their maturation take place into V phases. These correspond to the infectious stage that can be transmitted from human's bloodstream to female Anopheles mosquito. However, the immaturegametocyte-infected erythrocytes (GIE) from I to IV phases are hidden in deep tissues toavoid clearance by the spleen (Kepple et al. 2021). An ***in vitro*** study suggests that in order to develop into phase ***V, Plasmodium*** parasites interfere with erythropoiesis by infecting primary erythroblasts, completing their maturation within them and reaching blood circulation. While circulating in the bloodstream, they can be transmitted to a female ***Anopheles*** mosquito (Neveu & Lavazec, 2021)). Importantly,the proteins expressed in GIE onto their surface act as antigens for transmission-blockingvaccines that prevent transmission and decrease anemia in malaria patients.

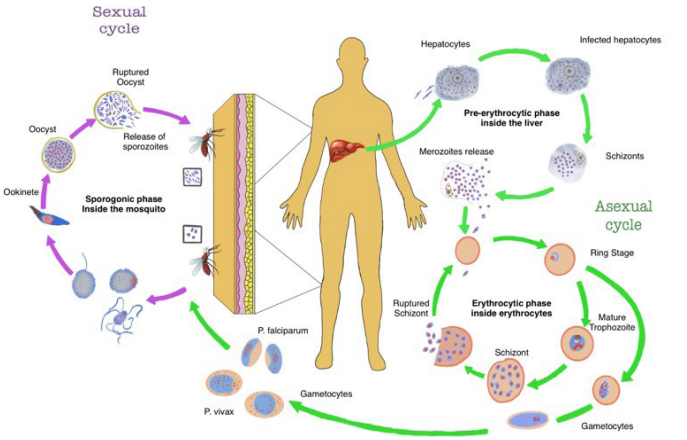

Figure 1. ***Plasmodium*** life cycle into two host (vector – female ***Anopheles*** mosquito and human). Sexual cycle develops inside mosquito once it takes gametocytes from human via blood meal. Asexual cycle occurs when the vector delivers into human bloodstream, these parasites migrate to the liver pre-erythrocytic phase and then pass to erythrocytic phase for gametocytes development inside RBC.

Source: Scheme modified from CDC U.S. Department of Health & Human Services.

Clinical infection of Plasmodium falciparum and Plasmodium vivax

Development of ***Plasmodium*** during RBC invasion and maturation generates clinicalsymptoms (Table 1).

Table 1: Clinical features presented in malaria infection caused by *Plasmodiumfalciparum* and *Plasmodium vivax* strains (Dayanand et al. 2018)

	P. falciparum	P. vivax
Children and adults	Fever, headache, nausea, vomiting, general malaise, anemia, hemolysis, hemagglutination, renal and cerebral damage, vasculitis. Abnormal level of consciousness, multisystem failure and dead. Acute respiratory distress syndrome (ARDS). Complications: Cerebral malaria	Periodic fever (occurs 48 hours), chills, sweats, shivering, headache, myalgias, arthralgias, weakness, nausea, vomiting. Acute respiratory distress syndrome (ARDS). Severe anemia Complications: Splenomegaly (sometimes splenic rupture)
During pregnancy	Hyper parasitemia, hypoglycemia and pulmonary edema.	Low birth weights, abortion, premature delivery, maternal anemia.

Vaccines against Plasmodium

Malaria is a widespread life-threatening infection that affects great number of countries intropical and subtropical regions. Thus, the development of vaccines against parasites is crucial for the control of this major health problem. The efficiency and efficacy of the vaccines depends on a series of studies such the molecular and cellular mechanisms of invasion that the parasites use to enter the host cells, analysis of the components of the vaccine, dosage and way of administration and patients' immune response. Some of the main strategies used for the generation of such vaccines are:proteins against-pre-erythrocytic phase, attenuated parasites and viral vectors vaccines

Pre-erythrocytic vaccines

Pre-erythrocytic vaccines aim to obstruct sporozoites swiftly and competently, just after the inoculation into the dermis before the transit from venous capillary beds to the liver. How hepatocyte invasion is prevented is a matter to be elucidated but is most likely achieved via antibodies that opsonize sporozoites. The main target of the vaccine is the circumsporozoite protein (CSP) (Laurens, 2018).

RTS, S vaccine

RTS, S /AS01 is the most studied, publicized and leading anti-malarial vaccine. It was created in 1987 and was developed against ***P. falciparum*** malaria. Early studies in this vaccine showed that radiation-attenuated sporozoites demonstrated protection against malaria. Later, The CSP antigen was identified as a target of immune response for this reason this protein was sequenced, cloned, and analyzed in deeper detail. Following, thehepatitis B surface antigen, was used as a carrier matrix for the CSP central repeat regionand the C-terminal region, containing T and B cell epitopes and an immunogenic adjuvantAS01 (Laurens, 2020). The efficacy of this vaccine is limited by the polymorphism in T cell epitopes and their T cell responses.

The RTS, S/AS01 vaccine is currently in pilot implementation (phase 4) in Ghana, Kenyaand Malawi to address the safety in public health. After the efficacy showedin Phase 3 testing on African countries. The study registered 15.459 participants, counting8922 children 5-17 month of age and 6.537 infants 6-12 weeks of age. Results of phase 3 display efficacy over 36% among children between 5-17 months of age after 4 doses delivered as a lyophilized injection administrated intramuscularly. About vaccine safety, this vaccine carries an increase of febrile seizures within 7 days after vaccination, after 7days all subjects recovered and didn't show any second effect (Rts, 2015)

Table 2: Potential malaria vaccine against *P. falciparum* and *P. vivax* targeting pre- erythrocytes stage during asexual cycle. Information adapted from WHO. 2021. Malaria Vaccine Rainbow Tables. 15 April 2021.

Vaccine	Antigen	Adjuvant	Mechanism of action	Status
P. Falciparum				
RTS, S	Pf CSP (207-395) & HepB-sAg	AS01E	Inhibits sporozoite motility, prevents hepatocyte invasion	Pilot implementatio n, phase 4 pharmacovigil ance baseline
RTS, S Fractional dose regimes	Pf CSP (207-395) & HepBsAg	AS01B / AS01E	Inhibits sporozoite motility, prevents hepatocyte invasion	Phase 2b clinical testing in endemic areas
ChAd63	TRAP + ME epitopes (CS,	MVA	Inhibits sporozoite	Phase 2b clinical testing
	LSA1, LSA3, STARP, EXP1, pb9)	ME- TRAP	motility, prevents hepatocyte invasion	In endemic areas
PfSPZ Vaccine	PfSPZ (radiation- attenuated whole- organism sporozoites)	AS01B	Inhibits sporozoite motility, prevents hepatocyte invasion	Phase 2b clinical testing in endemic areas
PfCelTOS FMP012	CelTOS (cell- traversal protein for ookinetes and sporozoites)	GLA-SE	Inhibits sporozoite motility, prevents hepatocyte invasion	Phase 1a clinical testing
CSVAC	CS		Inhibits sporozoite motility, prevents hepatocyte invasion	Phase 1a clinical testing
R21	R21 (CSP-HBsAg fusion protein)	AS01B	Inhibits sporozoite motility, prevents hepatocyte invasion	Phase 1a clinical testing
R21	R21(CSP-HepBsAg fusión protein)	Matrix- M1	Inhibits sporozoite motility, prevents hepatocyte invasion	Phase Ib Randomised, controlled, single-blind study.
Adjuv R21 (RTS, S-biosimilar) with ME- TRAP combined	CSP less- HepBsA + Me-TRAPg	Matrix- M1		Phase I/IIa clinical testing
P. vivax				
VMP001	Plasmodium vivax CSP	AS01B	Inhibits sporozoite motility, prevents hepatocyte invasion	Phase 1/2a Clinical testing
VMP002 second generation E. coli expressed P. vivax CSP- based vaccine	P. vivax Circumsporoz oite protein (modified version of VMP001)			Preclinical testing

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

Erythrocytic vaccines

The development of symptoms and clinical complications of the disease appears during parasite blood-stage infection. For that reason, it is important to get vaccines that could prevent complications like death. The erythrocytic vaccines act over merozoites surface proteins, which attack red blood cells, generating mimic and acquiring acquired immunityby neutralizing antibodies that block invasion and limiting parasite replication after leavingthe liver controlling parasitemia (Ouattara & Laurens, 2015)

MSP1, MSP2, MSP3 and GLURP vaccines

These types of vaccines include antigens as merozoite surface protein 1, 2, and 3 (MSP1,MSP2 and MSP3); and glutamate-rich protein (GLURP), the major B-cell epitope found during blood stage parasite, the propose of them is control parasite multiplication cooperating with FcyII receptors in the generation of IgG antibodies that recognize RBC epitopes. There is important evidence about antibody responses against MSP3 and GLURP in southest Asia with over 50% of results, MSP1 shows high results in Gambia, Sierra Leone and Ghana with low parasitemia and malaria attacks (Soe et al. 2004). However, the MSP3 and is the only one that remains in phase II evaluation.

GMZ2 vaccine

This vaccine corresponds to a hybrid combination between N-terminal region of GLURP and C-terminal region of MSP-3, applied 3 times with 1 month a part, it works by producinghigh amounts of cytophilic antibodies (IgG) against GLURP and MSP-3 antigens protecting from clinical features present during the disease by the antibody-dependent cellular inhibition (ADCI) process (Dayanand et al, 2018). It has shown good tolerability, safety and immunity in Germany and Africa tests, but its efficacy is still low to be used as a secure malaria vaccine approved by public health, it is necessary to improve formulation or chance for apotent adjuvant because it does not complete an increased protection with naturally acquired immunity.

AMA1 vaccine

It is created by the apical membrane antigen 1 (AMA1) merozoites surface protein foundin the neck of the rhoptries during the last four hours of ***Plasmodium*** erythrocytic cycle development, which is considered as an main target due to capacity to activate humoral and stronger cellular response producing parasite grown-inhibitory antibodies that neutralize AMA1 preventing merozoites to invade RBC (Mueller et al. 2003). It includes three doses applied by intramuscular injection for two months. Moreover, this vaccine shows T-cell proliferation and humoral and cell immune response. However, the sides effects presentsare erythema and swelling corresponding to hypersensibility. For that reason, it isnecessary to develop more studies about the number of doses that are going to be appliedand the time between them.

SPf66 vaccine

SPf66 vaccine was first published in 1987 by the Colombian scientist Manuel Elkin Patarroyo of the ***Instituto National de Inmunología*** in Bogotá. It is a synthesized chemical vaccine created to reduce the number of parasites present in blood, leading natural immunity development for ***Plasmodium falciparum***. (Patarroyo, et al., 1987) This vaccine was tested during the 90's proving its safety, immunogenetically and protective achievements, where three dose of the vaccine where good tolerated in Thailand and Colombia for ***Plasmodium falciparum*** with 38-60% of efficacy. However, new studies did not shown evidence of major protection against***Plasmodium falciparum*** in Africa, where new episodes of malaria appears, it has shown alow efficacy of 28% and do not give any protections in endemic areas. On the other hand, there is suggestions about the use of a new adjuvant QS-21 instead of the aluminum hydroxide (alum) or Freud's adjuvant that could improve its functionality and specificity, But, the US manufactured product tested for SPf66 was not identical to the Colombian one, suggesting the implementation of adequate standardizing procedures to get correct comparation between results (Lengwiler, Penn, & Harries, 2018)

PvDBP vaccine

It is the only one project development against ***Plasmodium vivax,*** its mechanisms correspond to production of antibodies that block interaction with DARC erythrocyte ligand. But it remains in the phase 1 human clinical trial despite it is the most promising candidate. (Rawlinson et al. 2019)

Table 2: Potential malaria vaccine against *Plasmodium falciparum* and *Plasmodium vivax*targeting blood stages during asexual cycle. Information adapted from WHO. 2021. Malaria Vaccin Rainbow Tables. 15 April 2021.

Vaccine	Antigen	Adjuvants	Mechanismof action	Status
P. Falciparum				
MSP3	Merozoiteprotein Surface 3 (MSP3)	Aluminum hydroxide (Al (OH)3)	Inhibits erythrocyteinvasion	Phase 2 clinicaltesting
MSP2	Merozoite protein surface 2	Aluminum hydroxide (Al (OH)3)	Inhibits erythrocyteinvasion	Phase 1 clinicaltesting
GLURP	Glutamate- rich protein (GLURP)	Aluminum hydroxide (Al (OH)3)	Inhibits erythrocyteinvasion	Phase 1 clinicaltesting
GMZ-2	Glutamate- rich protein (GLURP) and MSP3	Aluminum hydroxide (Al (OH)3)	Inhibit erythrocyte invasion	Phase 2 clinicaltesting
pfAMA1-DiCo	Apical membrane antigen 1 (AMA1)	AS01BAS01A Aluminum hydroxide (Al (OH)3)GLA-SE	Inhibit erythrocyte invasion	Phase 2b clinical testing
P27A	Malaria protein PFF0165c(P27A)	Aluminum hydroxide (Al (OH)3)GLA-SE	Inhibit erythrocyte invasion	Phase 1a/1b clinical testing
SE36	N-terminal domain of serine repeat antigen (SERAS)	Aluminum hydroxide (Al (OH)3) gel	Inhibit erythrocyte invasion	Phase 1b clinical testing
Chad63 Rh5 +/- MVA RH5	Reticulocyt e-binding protein homolog 25 (RH5)	--	Inhibit erythrocyte invasion	Phase 1a clinical testing
Pfs25	Surface protein 25	--	Inhibit ookinete developmentin mosquito midgut	Phase 1 clinicaltesting
PRIMVAC	VAR2CSA fragment	Alhydrogeland GLA- SE	Inhibit erythrocyte invasion	Phase 1a/1b clinical testing
PAMVAC	VARCSA fragment	AlhydrogelGLA-SE GLA-LSQ	Inhibit erythrocyte invasion	Phase 1a/1b clinical testing
SPf66	Merozoiteantigens	Aluminum hydroxide (Al (OH)3) QS-21	Reduce the amount of parasite inblood	Inactive clinical
P. Vivax				
PvDBP	Receptor-binding domain of P. vivax Duffy binding protein	Glucopyra nosyl lipidadjuvant-stable emulsion (GLA-SE)	Inhibits parasite	Phase 1 clinicaltesting

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

Gametocytes Vaccines

Table 3: Potential malaria vaccine against ***P. falciparum*** and ***P. vivax*** targeting sexual stages during asexual cycle. Information adapted from WHO. 2021. Malaria Vaccine Rainbow Tables. 15 April 2021.

Project vaccine	Antigen	Adjuvants	Mechanismof action	Currentstatus
P. Falciparum				
Pfa24 VLP	Pfs25	Alhydrogel		Phase 1 clinical Phase 2a clinical
Pfs25-EPA/Alhydrogel	Pfs25			Phase 1b Clinical
Pfs230D1M-EPA/Alhydrogel and/or Pfs25/EPA/Alhydrogel	Pfs25M Pfs230D1M			Phase 1 Clinical
Pfs230D1K-EPA/Alhydrogel and Pfs25-EPA/AS-1	Pfs25M Pfs 230D1M			Phase 1 Clinical
ChAd63 Pfs25=IMX313/MVAPfs25-IMX313	Pfs25			Phase 1a Clinical
Pfs25	Pfs25	Montanide ISA-51		Phase I1Inactive- Clinical

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

DISCUSSION

This article revisited the life cycle and potential vaccines against ***P. vivax*** and ***Pfalciparum***. In medical terms, during erythrocytic stages, the clinical features represent private and public health interest because of the high prevalence of cases during decades.For that reason, it is necessary to eradicate the affection by vaccination. However, it is remarkable to establish priorities for the vaccines already completed and accepted for used in each of the stages for plasmodium development during transmission. RST, S is apre-erythrocytic vaccine that prevents hepatocyte invasion corresponding to the most studied and tested vaccine (phase 4) in Ghana, Kenya, and Malawi getting high efficacy with 4 intramuscular doses with low side effects, except for meningitis. It is important to highlight that this vaccine do not work against severe malaria. The estimated price for each dose is $5, making it expensive for programs to buy it and administer it through thelow-income countries, considering the logistics that involve applying four doses in minors (Gulland, 2015). In recent events, Bharat Biotech has taken over the production of RTS, S/AS01 malaria vaccine and giving a donation of 10 million doses for the Malaria Vaccine Implementation Programme (MVIP).

On the other hand, erythrocytic vaccines against red blood cell invasion represent a solution for the progress of symptoms and clinical complications. There are several amounts of vaccine being evaluated. But most of them remain un pr-clinical stages that no guarantee its efficacy. SPf66 was the first vaccine against malaria generated for erythrocyte stage which began with effective results, but it is no longer evaluated or investigated because of its low efficacy in US trials where even its formulation was incorrect making different opinions about its use (Valero et al. 1993). Vaccines created based on MSP1, MSP2, MSP3 and GLURP remain in evaluation because of their specificity to theparasite but it is necessary to improve investigation given that only MSP3 is in a high levelof clinical trial (Sirima et al 2011). AMA-1 represent a developed vaccine with good results in different counties, but it is necessary to continue proving its efficacy due to side effects that coulddelay successfully. Moreover, there is only one type of vaccine developed for ***Plasmodium vivax*** PVDBP, that has shown good results, but it remains in a low phase ofevaluation (Gupta et al. 2011). And the most developed vaccine in this stage corresponds to the GMZ2vaccine which works based in a combination between MSP3 and GLURP due to the evidence shows during each evaluation, where its interaction presents an important levelof response against the development of the disease by blocking erythrocyte invasion (Jepsen et al. 2013).

CONCLUSION

In conclusion, the development of vaccines against malaria is going forward but it is necessary to improve investigation and invest in resources for that, due to the importanceof getting a fully approved vaccine that can trigger the population decreasing the numberof patients being infected for ***plasmodium*** and affected by clinical complications due to each strain. Each person is vulnerable for being infected by any of the stains of the parasites where ***P. falciparum*** and ***P. vivax*** becomes the most dangerous parasite that develops into a human by a vector carrier that affects erythrocytes resulting in potential diseases that also affect during pregnancy. However, it is necessary to select the vaccinethat have better action and results like RST, S during pre-erythrocytic stage which is the most advance vaccine created, proved, and accepted by the WHO to be applied in different countries.

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