Plasmodium vivax Vaccine Candidates: Molecular Targets and Challenges in Vaccine Development

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ABSTRACT

Plasmodium vivax is a major source of malaria morbidity outside of Africa, posing unique problems for vaccine development due to its complex biology, which includes latent liver-stage hypnozoites that promote recurrent infections. P. vivax, on the other hand, has many distinct antigens, spreads fast, and cannot be grown in vitro, making vaccine development problematic. This analysis provides a comprehensive overview of the top P. vivax vaccine candidates at all phases, including pre-erythrocytic, erythrocytic, and transmission-blocking. It includes important antigens like circumsporozoite protein (CSP), thrombospondin-related adhesive protein (TRAP), Duffy binding protein (DBP), merozoite surface protein-1 (MSP-1), and transmission-blocking targets like Pvs25, Pvs28, Pvs230, and Pvs47. We discuss important issues such as antigenic polymorphism, the lack of correlates of protection, and the difficulty of targeting hypnozoites. Recent advances in vaccination stages, such as mRNA-based technologies, viral vectors, and multi-stage immunization techniques, hold promise for overcoming these challenges. To generate an effective P. vivax vaccine, we must understand more about parasites, develop innovative vaccine designs, and collaborate on a global scale.

Keywords – P. vivax, malaria vaccine, transmission-blocking vaccine, Duffy binding protein, antigenic diversity, hypnozoite etc.

INTRODUCTION

Malaria is one of the world's most widespread vector-borne diseases and remains a major threat in tropical and subtropical regions. In 2024, the World Health Organization (WHO) estimated approximately 282 million malaria cases and more than 600,000 deaths worldwide, highlighting the continued burden of the disease despite extensive control efforts (World Health Organization [WHO], 2024). Repeated infections are common in endemic regions because naturally acquired immunity is incomplete and develops slowly over time (Cowman et al., 2016). Among the human malaria parasites, P. falciparum and P. vivax account for the majority of infections. While P. falciparum has historically been linked with severe and fatal malaria, P. vivax was long considered relatively benign. However, recent evidence shows that P. vivax can also cause severe anemia, respiratory distress, and other serious complications, making it an increasingly important public health concern (Baird, 2013; Rahimi et al., 2014). Although P. falciparum and P. vivax share several biological and genetic features, important differences exist. P. vivax preferentially invades reticulocytes (young red blood cells) and forms dormant liver stages known as hypnozoites, which can remain latent for weeks, months, or even years before causing relapse (Mueller et al., 2009). In addition, P. vivax develops transmissible gametocytes early during infection, enabling transmission before symptoms become evident (Price et al., 2007). Vaccine development against P. vivax remains challenging. Unlike P. falciparum, for which the RTS,S vaccine has shown moderate success, no licensed vaccine is currently available for P. vivax (Draper et al., 2018). Major barriers include antigenic polymorphism, relapse caused by hypnozoites, and the inability to maintain continuous in vitro culture systems for the parasite (Roobsoong et al., 2023). Nevertheless, several promising vaccine targets have been identified,

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including circumsporozoite protein (CSP), merozoite surface protein-1 (MSP-1), Duffy binding protein (DBP), and transmission-blocking antigens such as Pvs25 (Bergmann-Leitner et al., 2010; Arevalo-Herrera et al., 2011). Vaccine strategies commonly target the pre-erythrocytic, blood, and transmission stages of the parasite life cycle. A deeper understanding of these stages and associated antigens is essential for developing an effective P. vivax vaccine.

Table 1. This table is showing the comparison between P. falciparum and P. vivax

Feature	**P. falciparum**	**P. vivax**
Hypnozoite stage	Absent	Present
Relapse	No	Yes
In vitro culture	Continuous	Limited
Vaccine progress	RTS, S approved	No licensed vaccine
Host cell preference	All RBCs	Reticulocytes
Antigenic diversity	High	Very high

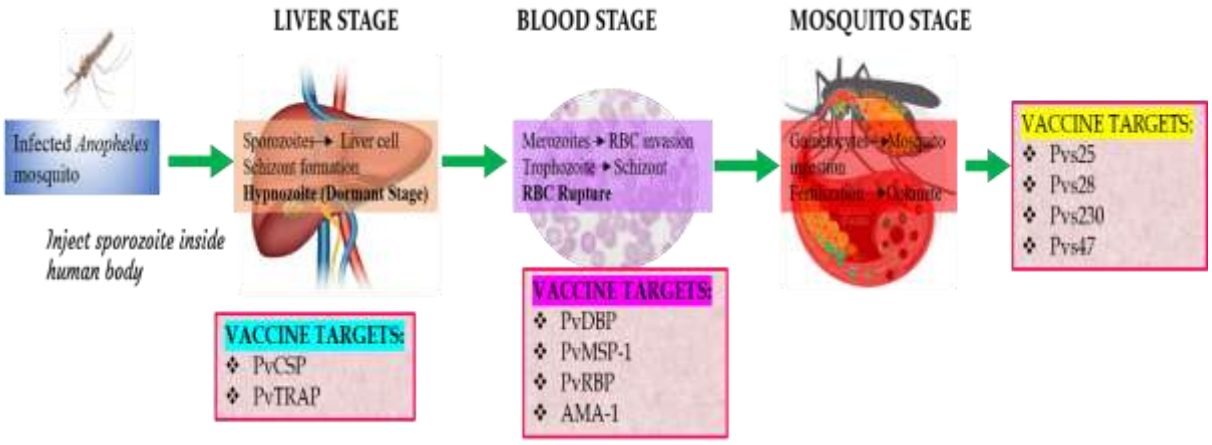

Figure 1. In this figure the P. vivax life cycle is highlighting major vaccine targets across different stages

Pre-Erythrocytic Vaccine (Liver Stage)

Pre-erythrocytic vaccinations attack the malaria parasite before it can enter the liver. Their primary purpose is to either prevent sporozoites from penetrating hepatocytes or to remove infected liver cells before the parasites reach the blood stage (Hoffman et al., 2015; Longley et al., 2022). This method is especially critical for P. vivax malaria because the parasite may produce hypnozoites, which are latent liver-stage forms that can remain hidden for weeks, months, or even years before reactivating to induce relapses (Payne et al., 2017; Longley et al., 2022). Preventing initial liver infection may thereby diminish both primary illness episodes and subsequent relapses. So yet, only a few vaccine ideas have gained widespread attention. The best recognized is circumsporozoite protein, or PvCSP, which is highly produced on the surface of sporozoites and aids the parasite's invasion of liver cells (Hoffman et al., 2015). Another promising option is PvTRAP, a protein involved in parasite movement and host-cell invasion that has been shown to induce robust cellular immune responses (Moreno-Pérez et al., 2017). More recently, researchers have looked into combining CSP and TRAP in multivalent vaccine formulations to boost both antibody and T-cell protection. Longley et al. (2022) are also looking at new delivery technologies such viral vectors, DNA vaccines, recombinant proteins, and mRNA platforms to increase vaccine effectiveness and durability. However, significant obstacles persist. It is still challenging to define the specific immune responses necessary for long-term protection, particularly against latent hypnozoites. Furthermore,

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advancing potential vaccine candidates from controlled laboratory investigations to large-scale field trials necessitates significant financing, infrastructure, and meticulous long-term planning. Despite advances, significant scientific and logistical challenges need to be addressed.

P. vivax Circumsporozoite Protein (PvCSP): PvCSP is the primary surface protein identified on P. vivax sporozoites, and it is required for parasite attachment and infection of liver cells. Its structure consists of a highly variable core repeat region with more conserved N- and C-terminal domains that aid in host-cell recognition and binding. Because PvCSP is exposed on the sporozoite surface, it has become a key target for vaccinations designed to prevent infection before parasites enter the bloodstream. However, the core repeat area is extremely polymorphic, thus vaccinations based on one version may not be effective against others. This genetic variety makes developing a widely protective vaccination challenging (Hoffman et al., 2015; Payne et al., 2017).

P. vivax Thrombospondin-related adhesive protein (PvTRAP): PvTRAP is a micronemal protein that facilitates sporozoite gliding motility and entrance into host cells. It has sticky areas, such as an A-domain and a TSR (thrombospondin type I repeat), which allow the parasite to engage with host receptors. PvTRAP is thought to be a good vaccination target since it plays important roles during early infection and can produce significant cellular immune responses. Immune responses to PvTRAP, however, can differ between individuals, and the level of protection conferred may not necessarily extend across genetically diverse parasite strains. These issues continue to hinder vaccine development (Moreno-Pérez et al., 2017; Longley et al., 2022).

Erythrocytic Stage Vaccine (Blood Stage)

Blood-stage vaccines target the asexual erythrocytic phase of P. vivax. This is when the parasite proliferates inside Red Blood Cells (RBCs), causing malaria clinical symptoms. As a result, it's an obvious target for vaccine research. Researchers studied many antigens that aid the parasite's invasion of RBCs, including Duffy binding protein (DBP), merozoite surface protein-1 (PvMSP-1), reticulocyte-binding proteins (PvRBPs), and apical membrane antigen-1 (AMA-1). Among these, DBP stands out. It is the primary protein that the parasite employs to attach to the Duffy antigen receptor for chemokines (DARC) on reticulocytes (Perera et al., 1998). But here's the catch: DBP's receptor-binding portion, known as DBP-II, varies greatly according on the strain. As a result, the immune response frequently fails to cover all of the distinct parasite kinds, and the vaccination does not always operate as intended. Some members of the PvRBP family, such as PvRBP2b, include more conserved areas. Scientists are investigating them as potential vaccine targets in the hopes of providing wide-ranging protection. PvMSP-1 and AMA-1 also play important roles in cell invasion, however they have a high degree of genetic diversity. That makes it hard for the immune system to keep up if the vaccine only relies on those targets. So, the present technique is rather practical: combine numerous conserved antigens in a single vaccination, focusing on areas that is conserved and do not change significantly. This might assist reduce strain-specific immunity problems. Overall, blood-stage vaccinations show great potential for lowering malaria incidence, but the barrier is massive. Antigen variety and complex invasion processes make it difficult to develop a vaccine that provides widespread, long-term protection. Duffy Binding Protein (DBP) warrants special recognition. It plays an important role in getting the parasite into reticulocytes via binding to DARC. The majority of vaccination attempts are concentrated on the DBP-II area, which is critical for invasion. What's the problem? DBP's binding domain is very varied, resulting in immunological responses that frequently only act against specific strains (Perera et al., 1998; Payne et al., 2017). That's one of the most significant challenges for a DBP-based vaccination.

Duffy Binding Protein (DBP) - DBP is a major ligand of P. vivax merozoites that binds to the reticulocytes' Duffy antigen receptor for chemokines (DARC), allowing RBCs to invade. Because this interaction is required for blood-stage infection, DBP is a primary vaccination target. Antibodies to DBP can hinder receptor binding and prevent parasite invasion. However, extensive genetic polymorphism, strain-specific immune responses, and evidence of Duffy-independent invasion complicate vaccine development and may reduce broad protective efficacy (King et al., 2008; Gunalan et al., 2016).

Merozoite Surface Protein-1 (PvMSP1) - PvMSP-1 is found on the parasite's surface and aids in its ability to attach onto and infiltrate RBCs. The protein is cut into several fragments, but the C-terminal area remains rather consistent—this section is particularly crucial for communicating with the host cell. Even while PvMSP-1

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stimulates an immune response, the sections of the protein that vary greatly between parasite strains make it difficult to employ as a single vaccine target (Putaporntip et al., 2002; Liang et al., 2020).

Reticulocyte-Binding Proteins (PvRBPs) - PvRBPs aid the parasite in targeting and infiltrating reticulocytes. One member, PvRBP2b, stands out because it interacts to the host cell's transferrin receptor 1 (TfR1). When comparing PvRBPs to other invasion proteins, you can find that some areas are rather conserved. That's excellent news for researchers wanting to use them as vaccine targets. However, the family is not simple—there is a lot of genetic variation and backup among these proteins, which makes creating an effective vaccination difficult (Gruszczyk et al., 2018; Ntumngia et al., 2018).

Apical Membrane Antigen-1 (AMA-1) - When the parasite invades RBCs, AMA-1 is essential for the formation of the moving junctions. It works with rhoptry neck proteins to assist the parasite enter the host cell. While AMA-1's function remains consistent, its most recognizable locations vary greatly, particularly where our immune system prefers to focus. This makes it difficult to develop vaccinations that provide long-term protection (Arnott et al., 2013; Cole et al., 2022).

Vir (Virulence) genes - The vir gene family produces proteins that appear on the parasite's surface, allowing it to avoid the immune system and remain alive. These genes are mainly found around the ends of chromosomes, where they like to shake things up—there's a lot of variety even amongst parasite clones. They're obviously vital for creating sickness and evading immune defenses. However, these genes vary greatly from parasite to parasite, and researchers are still unsure how they all function. This makes them difficult targets for vaccine development (Gupta et al., 2014; Bernabeu et al., 2022).

Transmission-Blocking Vaccines (Sexual Stage)

Transmission-blocking vaccinations, or TBVs, function differently than regular malaria immunizations. Rather of immediately protecting the person receiving the injection, these vaccines try to disrupt the malaria cycle within the insect. That is, they assist safeguard entire populations by interrupting transmission at the source. Researchers have focused on many interesting P. vivax targets, including Pvs25, Pvs28, Pvs230, and Pvs47. These proteins appear throughout the parasite's sexual and mosquito phases. Pvs25 and Pvs28 are particularly notable among them. They are both located on the surface of the ookinete, which is the stage that invades the mosquito's stomach. When a person's immune system produces antibodies against these surface proteins, they can prevent the parasite from developing within the mosquito (Tsuboi et al., 1998). Interestingly, combining Pvs25 and Pvs28 appears to perform even better, creating a greater blocking effect, suggesting that a multi-antigen strategy has significant promise. It's not just about those two, however. Pvs230 promotes fertilization, whilst Pvs47 allows the parasite to bypass the mosquito's immunological defenses. Both seem like excellent prospects for future TBVs. While TBVs have performed well in preclinical trials, there are still significant challenges. Maintaining high antibody levels over time is difficult, and widespread distribution of these vaccinations remains a significant problem.

P. vivax Sporozoite Surface Protein 25 (Pvs25): Pvs25 is found on the surface of ookinetes in the mosquito midgut and plays an important role in parasite growth and transmission. Researchers discovered that it is largely conserved around the world and elicits potent transmission-blocking antibodies. Is there a catch? Antibody levels usually diminish after a while. Scientists are striving for improved formulations to ensure long-term protection (Tsuboi et al., 1998; Wu et al., 2008).

P. vivax Sporozoite Surface Protein 28 (Pvs28): Pvs28 is an ookinete surface protein that allows the parasite to live and thrive within the mosquito. It is structurally similar to Pvs25, and when used together, they perform better in blocking transmission. Despite considerable fluctuation, Pvs28's core functional components remain consistent, making it a promising candidate for a transmission-blocking vaccine (Hisaeda et al., 2000; Malkin et al., 2005).

P. vivax Sporozoite Surface Protein 230 (Pvs230): Pvs230 is found on the surface of gametocytes and contributes to both fertilization and parasite growth within the mosquito. The protein has several cysteine-rich domains that allow it to interact with other proteins. When antibodies target Pvs230, they can prevent the parasite

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from spreading. However, the protein's large size and complex structure make developing a vaccine difficult (Chen et al., 2020).

P. vivax Sporozoite Surface Protein 47 (Pvs47): Pvs47 is a protein that helps malaria parasites avoid mosquito immune defenses, allowing the parasite to be spread. It exhibits a substantial level of genetic variety, which varies according to the mosquito species. If we target Pvs47, we can disrupt the parasite's capacity to live within mosquitos. However, because its genetic composition varies by location, any vaccination must account for these regional variations (Molina-Cruz et al., 2015; Canepa et al., 2018).

Table 2 summarizes the primary P. vivax vaccine candidate antigens, including their target life-cycle phases, biological functions, and important development hurdles. These antigens are pre-erythrocytic, blood-stage, and transmission-blocking techniques intended to reduce infection, illness severity, and parasite transmission.

Table 2: Key Vaccine Candidates and Challenges

Antigen	Stage	Function	Major Challenge
PvCSP	Liver	Sporozoite invasion	High polymorphism
PvTRAP	Liver	Motility & invasion	Variable immunity
DBP	Blood	RBC invasion	Strain-specific response
PvMSP1	Blood	RBC attachment	Genetic diversity
Pvs25	Mosquito	Ookinete survival	Short antibody duration

Gaps in Current Research

Despite substantial progress in discovering vaccine candidates, many main complications continue to delay the development of an effective vaccine against P. vivax malaria. One of the most important drawbacks is the lack of a stable continuous in vitro culture method for P. vivax. Unlike P. falciparum, P. vivax preferentially infects young reticulocytes, making long-term laboratory maintenance challenging. This limits thorough functional research, antigen screening, and preclinical vaccine evaluations (Bermúdez et al., 2018; Roobsoong et al., 2023). Another significant barrier is the presence of hypnozoites, which are latent liver-stage forms unusual to P. vivax. These latent parasites can reawaken weeks or months after the initial infection, resulting in recurring relapses. Because the biology of hypnozoites remains poorly known, creating vaccinations that prevent relapse or remove latent infections is very problematic (Reyes-Sandoval et al., 2021). Genetic diversity among parasite populations hinders vaccine development. Important antigens such as circumsporozoite protein (CSP), Duffy binding protein (DBP), and merozoite surface proteins (MSPs) exhibit significant variation among endemic locations. This variety may impair the efficacy of vaccines created for a small number of strains (Veiga et al., 2023). The issue is especially important in nations like India, where region-specific variations might differ significantly from globally researched isolates. Furthermore, there is no clear correlation of protection for P. vivax immunity. Researchers have yet to identify reliable immunological markers that indicate whether a vaccinated individual is protected, making vaccination studies difficult to understand and compare. Overcoming these biological, technological, and epidemiological challenges is critical for creating widely protective vaccines and moving global malaria eradication forward.

Challenges in P. vivax Vaccine Development

It is difficult to develop a vaccination against P. vivax. The parasite's life cycle presents several obstacles due to its complex nature. The latent liver stage, or hypnozoites, is one major issue. These can lurk in the liver for a very long time before reappearing to produce relapses, frequently long after a person appears to have healed. It is difficult to ensure long-lasting protection since scientists still don't completely understand hypnozoites and none of the current vaccination techniques effectively target them (Wells et al., 2010). The degree to which the

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parasite's proteins can alter is another problem. Many of the proteins that scientists want to include in vaccines vary from strain to strain. Therefore, a vaccination that effectively combats one type of parasite may have little effect on another, particularly in different regions of the world (Chenet et al., 2012; Payne et al., 2017). Moreover, P. vivax has an advantage since it may spread through mosquitoes before any symptoms appear. This implies that the immune system has less time to react to whatever you teach it through a vaccine (Arévalo-Herrera et al., 2010). Additionally, there is yet no efficient technique for P. vivax long-term laboratory cultivation. This makes it more challenging to carry out research and quickly assess new vaccine ideas (Popovici & Ménard, 2015). To be honest, the type of immune response required for protection is still up for debate among experts, which makes determining if a new vaccination is effective much more difficult. You have much more ambiguity when you consider the genetic variations across parasite populations worldwide. According to Howes et al. (2015), a vaccination that performs well in one area may not work well in another. When you combine all of this, it becomes clear why creating a successful P. vivax vaccine is still so \difficult.

Future Perspectives and Emerging Strategies

Despite all the obstacles, vaccine development continues to advance, and there is genuine optimism for the future. For instance, scientists may readily test novel designs with mRNA vaccines, which thus far elicit robust immune responses. They are also adaptable, allowing you to quickly adjust them and target many parasite components simultaneously (Maruggi et al., 2023). Additionally, scientists are focusing on the portions of parasite proteins that remain mostly unchanged among strains. They are placing bets on the things that are consistent rather than pursuing locations that are always changing. This technique may result in vaccinations that offer protection against a greater variety of illnesses. New computational tools and breakthroughs in protein design make finding these stable targets much quicker these days (King et al., 2018). Multi-stage vaccinations are an additional intriguing strategy. Instead of targeting a single stage of the parasite's life cycle, these vaccines attempt to prevent infection, alleviate illness symptoms, and stop transmission all at once (Herrera et al., 2020). As experimental models improve and more real-world data becomes available, advancement in this field is accelerating. Understanding how human immune systems respond to P. vivax remains a significant component of the puzzle (Stanisic et al., 2018). As scientists combine modern technology with greater biological knowledge, they are coming closer to developing a vaccine that works in the real world.

CONCLUSION

Developing a vaccine for P. vivax has been difficult, owing to the parasite's unique characteristics. Unlike P. falciparum, P. vivax can remain latent in the liver as hypnozoites. These concealed forms do not just disappear; they might reawaken weeks or years later, producing relapses and allowing the parasite to propagate (Wells et al., 2010). Current vaccinations do not effectively address these latent phases; therefore, this is a significant challenge. There is more. The primary vaccine targets for P. vivax, such as CSP and the Duffy binding protein, exhibit a high level of genetic variability (Chenet et al., 2012; Payne et al., 2017). Because of this variability, it is difficult to develop a single vaccination that protects everyone, everywhere. Furthermore, the parasite understands how to evade the immune system. It modifies its surface proteins and occasionally conceals, making vaccine design even more difficult (Molina-Cruz et al., 2015). Researchers still have challenges in the lab, since they are still unable to maintain P. vivax growing in culture indefinitely, making it difficult to test novel vaccine concepts. However, there aren't only barriers. Newer vaccination platforms, such as mRNA and viral vectors, provide the sector with new alternatives (Maruggi et al., 2023).A Teams are looking on multi-stage vaccines that target the parasite at several stages of its life cycle, including before it enters RBCs, while it is in the blood, and even when it is in the mosquito. Transmission-blocking vaccines—such as Pvs25, Pvs230, and Pvs47—stand out here. These have showed promise in preventing the parasite from spreading between individuals by limiting its duration within the mosquito (Scaria et al., 2022). To develop a viable P. vivax vaccine, researchers must address the issue of liver-stage hypnozoites, find strategies to cope with the parasite's variety and evasive maneuvers, and devise new techniques to study it. Maintaining momentum in research, developing lab models, and collaborating worldwide will be critical to ultimately releasing an effective, widely accessible vaccine into the public.

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