Review Paper:

Revolutionizing Malaria Diagnosis: A computer aided approach for the Detection of *Plasmodium vivax* using Machine and Deep Learning techniques

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Abstract

Machine learning (ML) and Deep learning (DL) methods are widely applied in the medical field because of their high diagnostic accuracy. Malaria is one such illness that is brought on by Plasmodium vivax (P. vivax) and spread by the female Anopheles mosquito. P. vivax has a substantial negative impact on health around the globe. Although research has been done on diagnosis and detection through various techniques, there are still multiple gaps in P. vivax diagnosis. This review focuses on the number of deaths caused by the P. vivax species worldwide, as well as the most recent developments in ML and DL approaches for diagnosing malaria. In order to successfully diagnose malaria, an ML approach must overcome a number of obstacles.

Currently, a number of studies are being conducted to examine the interpretability of models using ML and DL techniques for P. vivax identification. It also examines the potential for P. vivax detection in the future. Through the use of modern, widely-used methodologies like ML and DL, this study will contribute to our knowledge of the P. vivax malaria situation as on today and will help us to uncover its background including its biology, global endemicity, methods of diagnosis through ML and DL techniques and the challenges involved.

Keywords: *Plasmodium vivax*, machine le215arning, deep learning, biology, drug resistance.

Introduction

Data digitization in the pharmaceutical sector has increased significantly in recent years. However, the challenges of learning, analysing and applying such data to complex clinical situations come along with digitization[21]. In the majority of the tropical world, malaria remains a severe problem, accounting for hundreds of millions of illnesses and hundreds of thousands of fatalities annually, despite significant progress in some areas[10]. Malaria, which is caused by Plasmodium parasites and results in over 200 million clinical cases and 600,000 child deaths yearly, is one of the worst diseases that people are aware of. Outside of Africa, *Plasmodium vivax (P. vivax)* is the most prevalent parasite among the five varieties of Plasmodium that infect people. Only temporary and poor immune protection are provided by the periodicity of *P. vivax* transmission and recurrent liver stages obstruct control and eradication tactics[22].

In malaria research, machine learning (ML) has proven to be an efficient tool for addressing a range of issues, such as identifying medication resistance-related evolutionary selection, classifying and identifying parasites in red blood cells (RBCs) and finding new antimalarial drugs. Algorithms used in deep learning (DL), a subset of ML, frequently make use of vast amounts of data in their quest to extract and learn a hierarchy of representations. DL and particularly neural networks, have been investigated for use in population genetics including other diseases[11]. Malaria diagnosis and monitoring remain persistently difficult, especially in low-resource environments where there are often few specialists to analyse the microscopy images and insufficient computing power to perform automated analysis.

To guarantee prompt and precise diagnosis and treatment, healthcare providers must have access to lightweight automated technologies that can assist with malaria monitoring and diagnosis. Recently, automated malaria detection using thin blood smear microscopy images has been made possible by the application of supervised ML techniques, enabled by the availability of vast volumes of annotated data and the advancement of computational resources[25,29].

Recent developments in the use of several DL algorithms for the detection of malarial parasites have shown encouraging results which served as the impetus for the study. One type of lightweight deep convolutional neural network (CNN) is called MobileNet which performs faster and is smaller than previous models due to its depth wise separable convolution basis. This framework yields quite good classification accuracy for photos with a uniform backdrop size, organization and reduced noise.

This study accumulated all the data from the reputable databases such as ScienceDirect, PubMed and Scientific Reports. The inclusion criteria for this study were articles selected between the years 2010 to 2024, original articles and review articles, articles in English language and articles related to ML and DL techniques regarding malaria. The

exclusion criteria were articles in non-English languages, articles published before year 2010, irrelevant articles, thesis, conference papers. Articles with inadequate data and those not related to ML and DL approaches for malaria were also excluded. The mosquito transmission cycle (i.e. Figure 1) was created using Bio Render software and clinical trial data was accumulated from the *clinicaltrials.gov* website. The clinical trials selection process for *P. vivax* (Figure 2) was designed following PRISMA guidelines.

Biology of *P. Vivax*

P. vivax resistance to methods for controlling and eradicating malaria is mostly explained by its biology. First, laboratory diagnosis is particularly challenging for low-density blood-stage infections of *P. vivax*, which are common, particularly in regions that are almost completely eradicated. Secondly, as hypnozoites-dormant liver stages that could subsequently trigger relapses and parasites may remain in human hosts for a few months. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common inborn enzyme defect, may also experience significant haemolysis when using primaquine, the only licensed antimalarial with hypnozoitocidal action. This means that the only effective treatment for vivax malaria is to use medications that target both the liver and blood stages.

The early development of mature gametocytes aids in the transmission of *P. vivax*, in contrast to *Plasmodium falciparum* (*P. falciparum*)[12]. A Giemsa-stained blood smear can be used to easily identify significant biological differences between *P. falciparum* and *P. vivax*. Because only reticulocytes are often infected in vivax malaria, the typical parasitaemia is rather low, which frequently necessitates the use of thick smears to concentrate blood for precise diagnosis. Non-expert microscopists may find it difficult to identify parasites since maintaining good morphology is sacrificed in favour of a large improvement in sensitivity when the blood is not fixed. The observation of distinctive morphological characteristics is crucial for differentiating between different *Plasmodium* species.

Schüffner's dots which are tiny dark granules in the reticulocyte cytoplasm, are actually caveola-vesicle complexes of parasite origin that are exported into the reticulocyte's cytoplasm and proliferate as *P. vivax* grows. Another morphological feature that distinguishes *P. vivax* is its spherical shape, which is similar to that of the asexual stages. Lastly, peripheral blood contains all *P. vivax* blood-stage development phases[2].

The female Anopheles mosquito's proboscis introduces sporozoites into the epidermal dermis of humans where they are housed in the salivary glands of the infected person. A portion of the inoculum reaches the bloodstream and invades the liver's hepatocytes in a matter of minutes. Depending on the species of *Plasmodium*, the parasite transforms into a large exoerythrocytic form over the course of the next five to eight days. Thousands of merozoites are crammed into a parasite's parasitophorous vacuolar membrane (PVM). The membrane separates into tiny vesicle packets containing merozoites as the parasite ages. Erythrocytic invasion is the result of them being discharged into the bloodstream.

Depending on the species, the parasite divides mitotically and grows cytoplasmically inside the erythrocyte during the course of the next 48 hours. They could mature directly into a gametocyte (sexual) or schizont (asexual). The fully transmissible stage V gametocyte is produced by gametogenesis, which requires bone marrow sequestration and takes 10 to 12 days. As a result, *P. falciparum* sexual stages are not seen in the peripheral blood. On the other hand, it is thought that *P. vivax* sexual phases appear much earlier. However, it remains unclear whether *P. vivax* sexual commitment occurs at a young age[3]. Malaria is typically instigated by single-celled microorganisms of the *Plasmodium* group.

Studies reveal that malaria is most frequently spread by an infected female *Anopheles* mosquito and these mosquito bites transmit the parasites from the saliva of the mosquito into the person's blood. The parasites then transport to the liver where they develop and replicate. Figure 1 shows the mosquito transmission cycle.

Current Standard Treatment Regimen for *P. Vivax*: Clinical suspicion, a trustworthy blood diagnostic and access to potent medication regimens for hypnozoiticidal (radical cure) and schizonticidal (blood stage) treatments are necessary for the clinical management of *P. vivax* malaria. Currently, artemisinin combination therapy (ACT) or chloroquine is used to treat *P. vivax* malaria while the infection is in the blood stage. Although chloroquine has been the go-to medication for treating vivax malaria for about 70 years, *P. falciparum* has developed and spread worldwide resistance to chloroquine, making alternative therapies necessary for *P. falciparum* and other human malarias.

The use of ACTs, with the exception of artesunate-sulphadoxine-pyrimethamine, enables uniform treatment for all cases of malaria and acts as a safety precaution in the event of a misdiagnosis or an undetected mixed *P. falciparum* infection. In most parts of the world, chloroquine is still effective against *P. vivax* infections despite decreasing susceptibility, with the exception of Indonesia, Sabah and Oceania, where resistance is of high grade. While ACTs are significantly more expensive than chloroquine, a combined treatment significantly reduces operating costs[8].

Primaquine is the sole commercially available hypnozoitocidal drug, although its usage is restricted due to the risk of haemolysis in people with G6PD deficiency and the potential for reduced adherence to the currently recommended 14-day treatment schedule. Relapses from the latent hypnozoite phases of the parasites are thought to be the primary cause of most *P. vivax* recurrences.

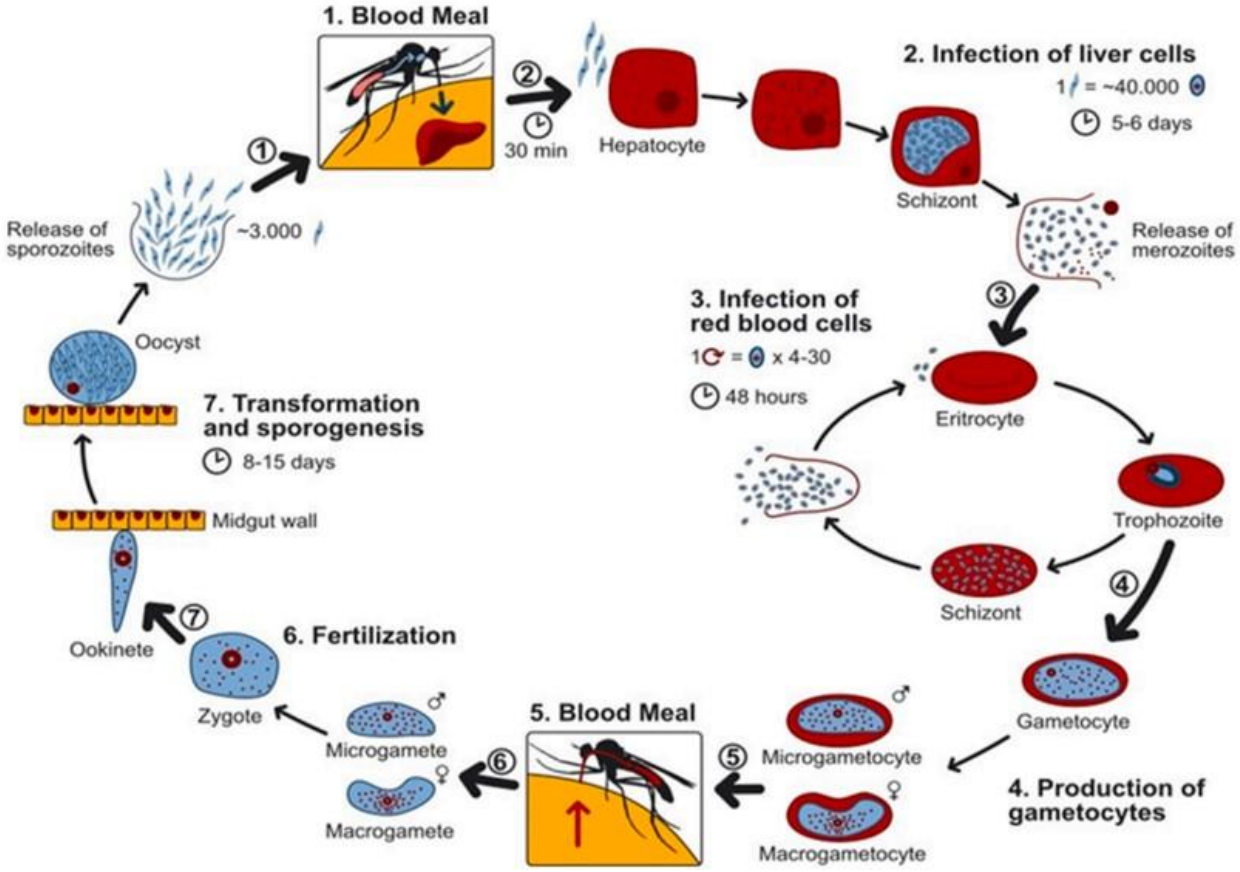

Figure 1: Mosquito transmission cycle

Therefore, as Nations work to eradicate all malarial species, it is becoming increasingly important to develop a safe and efficient radical therapy to address the parasite's blood and liver stages[9].

Current Scenario of *P. Vivax* Cases in India: Of all the countries, India is expected to have the highest *P. vivax* load. Of the 2.14 million cases of *P. vivax* that were confirmed worldwide in 2014, 18% occurred in India. *P. vivax* is the cause of all malaria cases in India approximately three-quarters; in 2014, 380,000 cases were confirmed in the public sector. Nearly half of all malaria cases in the recent past were caused by *P. vivax*. *P. vivax* is a notable and important pathogen in children. Even though they make up only 12% of the population overall, children in India account for almost 30% of all *P. vivax* cases[5].

India, which has the largest national malaria control program in the world, sees *P. vivax* patients making up 47% of all malaria cases annually and they are the subject of more than 40% of *P. vivax* publications. Research from Gujarat State in Western India has demonstrated the presence of *P. vivax* malaria with a long incubation period. Research conducted in Delhi (north/central India) between 1988 and 1993 demonstrated the presence of regional vivax malaria strains with a protracted incubation period. The findings of research done in Aligarh supported the presence of *P. vivax* in Central India, which has a protracted incubation period. The genotyping results of *P. vivax* conducted in Kolkata, in the eastern portion of the country, showed that the infection was predominantly locally transmitted 81% of the time with long incubation and 19% of the time with short incubation.

A few other symptoms including jaundice, haemoglobinuria, convulsions and pulmonary oedema, were found in occasionally reported instances of complicated vivax malaria from Brazil and India. Patients in India died from a variety of symptoms including cerebral malaria, anaemia, thrombocytopenia, jaundice, renal failure and respiratory distress. For instance, observations at one Indian hospital showed that 15% of the patients with vivax malaria had documented occurrences of severe illness[15]. A thorough understanding of the current incidence and prevalence of the disease is necessary for India to eradicate malaria. India is responsible for 70% of malaria cases and 69% of malaria-related deaths in Southeast Asia. However, data indicates that over the last ten years, reported cases and deaths from malaria have consistently decreased.

In order to eradicate malaria in India, a thorough understanding of the disease's incidence and prevalence must be obtained. In Southeast Asia, India is responsible for 69% of malaria deaths and 70% of malaria cases.

Nonetheless, over the previous ten years, data show that the number of recorded malaria cases and deaths has been consistently declining. To combat malaria, Indian States have been categorized according to their annual parasite

incidence (API): low, moderate and high. More significantly, district-level classification is maintained within each state.

In fact, the district is designated as the planning and execution unit for the malaria elimination program in the National Framework for Malaria Elimination in India. The Nation's ability to significantly scale up current illness control and public health precautions will be essential to its success and diagnosing malaria cases will be a crucial component of these efforts[20]. In India, severe cases of vivax malaria have also been documented, accounting for approximately half of all occurrences of vivax malaria in South East Asia in 2018[14].

Global Endemicity due to Infection of *P. Vivax*: One of the main causes of morbidity in malaria-endemic regions of Asia, Oceania, Central America, South America and the Horn of Africa is *P. vivax*. It plays a significant role in low birth weight and early pregnancy loss, which raise infant mortality rates[30]. With an estimated 14 million infections globally in 2017, the majority of *P. vivax* malaria cases are concentrated in six countries: Ethiopia, India, Pakistan, Afghanistan, Indonesia and Papua New Guinea (PNG). The greatest problem is found in isolated rural areas with frequently inadequate or underfunded health system infrastructure. In children, the prevalence peaks between the ages of two and six. Recent research showed that in Sub-Saharan Africa, *P. vivax* infections were reported in both Duffy-positive and Duffy-negative hosts[4]. Approximately 97% of all malaria occurrences occur in States in India that are highly endemic for the disease including Andhra Pradesh, Madhya Pradesh, Bihar, Maharashtra, Odisha, West Bengal and the North East regions[16].

The Role of ML and DL Methods in *P. Vivax* Detection: This primary goal of this study was to investigate studies on computer-aided, automated and systematic diagnostic approaches for malarial disease caused by *P. Vivax*. This has been more challenging in the existing system due to the observance of low parasitaemia levels in malarial infections when compared to the *P. falciparum*. Conventional image processing methods were employed in previous studies for segmenting *P. vivax* which provided manually cropped infected image regions.

Thus, various quantitative experimental tests were conducted for the classification stage. Additionally, these tests were based on the cell level. However, the main objective in diagnosis a malaria patient is detecting and classifying every cell including false-positive cells as well as parasites. Furthermore, good cell-level classification does not necessarily ensure better performance at the patient level. Numerous studies have been conducted on the diagnosis of *P. vivax*. Among them, Umer et al[28] proposed a novel Stacked CNN framework that improved malaria diagnosis through an automated method, without considering hand-built aspects. Additionally, the fivefold cross-validation process led to increased accuracy in parasite detection. These findings showed that by altering the depth and filter sizes, the convolutional layers could extract various types of information for the classification process. Bi et al[7] suggested a high-precision, cost-effective and stable method for identifying apple leaf disease by implementing MobileNet model.

Further, this study compared the precision and efficacy of the suggested method with well-known CNN models such as Inception V3 and ResNet 152. Deelder et al[11] introduced a robust and rapid detection system for the automatic diagnosis of *P. vivax* parasites by utilizing a cascaded You Only Look Once (YOLO) system. This model consisted of the YOLO V2 model and the outcomes form this system were compared to traditional V2 models. From these comparisons, the suggested method improvised the precision of mean average compared to other traditional models. Nevertheless, there were some computational complexities in this model, which impacted the accuracy.

Abraham[1] introduced an intelligent framework based on a simple CNN for the diagnosis of malaria parasites via images of thin blood smears. From the experimental analysis, the outcomes of the suggested model achieved significantly higher sensitivity (97%). Additionally, this study proposed a false-positive reduction technique using grey-level co-occurrence matrix (GLCM) features. This technique effectively reduced false positives. Mukherjee et al[18] depicted a method for automated malaria parasite identification using thin blood smear images.

Further, this study carried out texture and intensity-based analysis for diagnosing blood cell particles in pre-processed images. These extracted blood particles were sent to the CNN. This CNN model was trained with dataset, which was publicly available followed by images of Giemsa-stained blood smears. From this analysis, this method achieved a good dice score (0.95). Sharma et al[23] provided an in-depth analysis of deep learning and transfer learning, such as MobileNet V2, in the detection of malarial diseases. This study developed a MobileNet V2 model that incorporated bottleneck identities to diagnose *P. Vivax*.

Challenges

Innovative strategies specifically designed to address the parasite's distinct biology and epidemiology will be needed to tackle the challenges of *P. vivax*. Early diagnosis and treatment of the condition could help to solve this major issue. Although it requires more time and experience, the gold standard for diagnosing malaria involves examining peripheral blood smears under a microscope[8,13]**.** To develop a ML model that can efficiently count and sort the RBCs in a thin blood smear microscopy image in order to diagnose malaria, several issues still need to be resolved. One of these issues is the significant differences in the appearance between the blood smear photographs. The hue, contrast and consistency of smear images vary because of different methods used for smear preparation and staining.

When applied to blood smears prepared at various sites, this variability presents generalization issues that make it more difficult to apply learned ML models. A large number of cells that overlap or contact one another, cause detection and segmentation issues in thin blood smear images, which presents another hurdle. This is a significant problem for the diagnosis and surveillance of malaria, as it necessitates precise cell counting to compute parasitaemia, or the parasite burden[27].

The distinct features of the *P. vivax* parasite, which set it apart from other *Plasmodium* species, include its high potential for transmission resulting from early and continuous gametocyte production. Its propensity to relapse and form long-lasting, dormant liver stages, its high infectivity to mosquitoes and its shortened vector development cycle, are largely responsible for the difficulties in controlling and eliminating vivax malaria[1].

The following features of *P. vivax* biology are likely to contribute to the difficulties in managing and eradicating vivax malaria. Two factors contribute to its high potential for transmission: (1) its ability to relapse from long-term, dormant liver stages (the hypnozoites); and (2) its early and continuous gametocyte production, high infectivity to mosquitoes and shorter development cycle in the vector host compared to other *Plasmodium* species. Due to these traits, *P. vivax* can spread more widely throughout the world into temperate regions and can be transmitted by migratory mosquito vectors during cooler weather.

Long believed to be a benign, self-limiting infection, *P. vivax* is becoming more and more evidence that this is not the case and that the disease's total burden, economic impact and severity have all been underestimated. People of all ages have been known to become incapacitated by vivax malaria, which can cause severe anaemia, respiratory distress, recurrent fever episodes, and, in certain cases, unfavourable pregnancy outcomes.

Thus, the idea that vivax malaria is innocuous is called into question by a growing number of clinically severe reports of complicated and deadly situations. An extra difficulty for the prevention and control of vivax malaria programs currently in place is the growing resistance to chloroquine, the main frontline treatment for the disease. This emphasizes how urgently more work must be done to develop new tools that are especially directed against *P. vivax*[2].

Antimalarial Drug Resistance

P. vivax has more gradually displayed indications of resistance to chloroquine than *P. falciparum*. The molecular basis and mechanism of this resistance have proven to be elusive. More than 30 years ago, a traveller returning from PNG showed signs of chloroquine resistance.

Since then, Indonesia and Oceania have experienced high levels of chloroquine resistance; as a result, Artemisinin Combination Therapy (ACT) is being employed in these regions in place of chloroquine. Treatments for vivax malaria that are highly effective include artesunate-mefloquine, artesunate-pyronaridine, dihydroartemisinin-piperaquine and artemether-lumefantrine. Amodiaquine is not as well tolerated as dihydroartemisinin-piperaquine, despite being more effective than chloroquine against resistant *P. vivax*. Additionally, resistance in *P. falciparum* is common in *P. vivax*-endemic areas.

Therefore, amodiaquine-containing regimens are not advised for *P. vivax* infections that are resistant to chloroquine. Although *P. vivax* is showing signs of gradually developing resistance to chloroquine, chloroquine is still effective in the majority of malaria-endemic locations. Low-level resistance to chloroquine may go undetected because the concurrent administration of primaquine (for radical cure) causes significant independent asexual stage activity.

Since there is no molecular marker of resistance and few *in vitro* tests are available for vivax malaria, the epidemiology of chloroquine resistance is poorly characterized. *P. vivax* exhibits antifolate resistance easily due to easily recognized mutations in Pvdhfr. Geographically, antifolate resistance is prevalent. Additionally, *P. vivax* has natural resistance to sulphonamides. For this reason, treating *P. vivax* with the artesunate-sulphadoxine-pyrimethamine ACT is not recommended[8].

Clinical Trials Status on *P. Vivax*

The largest clinical trial database currently accessible is ClinicalTrials.gov[26]. To identify and characterize clinical trials for *P. vivax*, we concentrated on the active trials registered on ClinicalTrials.gov for this evaluation. Figure 2 illustrates the clinical trials selection process for *P. vivax* following PRISMA guidelines and table 1 depicts the current ongoing clinical trials on the *P. vivax.*

Recent advancements have shown that AI can discover drugs and can conduct virtual clinical trials more effectively, which lower the risk of regulatory compliance problems. Even certain industries, like Protai and Netabolics, are prospering in their efforts to create AI-driven drug discovery platforms and to forecast novel medications through the digitization of human cells[4].

Discussion

An international group of committed scientists has persevered despite decades of neglect, constructing research tools and models for *P. vivax* research to uncover new aspects of this parasite's distinct biology and, eventually, develop treatments tailored to *P. vivax*. There are many new opportunities. The use of animal and human models for the entire life cycle, the characterisation of reticulocyte invasion, recent advancements in stem cell research and the study of hepatocyte biology have made it evident which areas should be prioritized in order to build on current resources and to optimize our potential.

Table 1
Current ongoing clinical trials on the *P. vivax*

S.N.	Clinical Trials.gov ID	Title of the study	Intervention/ Treatment	Phase	Age	Enrollment	Type of study	Study Design	Start Date	Completion Date (Estimated)
1.	NCT05788094	ACT vs CQ with Tafenoquine for *P. Vivax* Mono-infection	➢ Drug: Dihydroartemisinin-piperaquine plus tafenoquine (450 mg adult dose) ➢ Drug: Chloroquine plus Tafenoquine (450 mg adult dose) ➢ Drug: Artemether-Lumefantrine plus Tafenoquine (450 mg adult dose)	Phase 4	18 Years and older (Adult, Older Adult)	606	Interventional	Primary Purpose: Treatment; Randomized; Interventional Model: Parallel Assignment	2023-06-26	2025-08-31
2.	NCT04704999	Southeast Asia Dose Optimization of Tafenoquine	➢ Drug: Tafenoquine ➢ Drug: Chloroquine ➢ Drug: Artemether 20mg-Lumefantrine 120 mg	Phase 4	2 Years and older (Child, Adult, Older Adult)	700	Interventional	Primary Purpose: Treatment; Randomized; Interventional Model: Parallel Assignment	2024-07-22	2028-02-07
3.	NCT05044637	Study to Evaluate Primaquine for Radical Cure of Uncomplicated *P. Vivax* Malaria in Children	➢ Drug: Primaquine	Phase 2	6 Months to 14 Years (Child)	150	Interventional	Primary Purpose: Treatment; Randomized; Interventional Model: Parallel Assignment	2021-08-26	2023-12-01
4.	NCT05071079	A Controlled Human Vivax Malaria Infection Study Through Inoculation of Infected Erythrocytes	➢ Biological: An inoculum of malaria parasitised red blood cells with whole dose blood-stage inoculum ➢ Biological: An inoculum of malaria parasitised red blood cells with 1:5 dilution blood-stage inoculum ➢ Biological: An inoculum of malaria parasitised red blood cells with 1:10 dilution blood-stage inoculum ➢ Biological: An inoculum of malaria parasitised red blood cells with 1:20 dilution blood-stage inoculum	Not Applicable	20 Years to 55 Years (Adult)	48	Interventional	Primary Purpose: Other; Randomized; Interventional Model: Parallel Assignment	2022-05-23	2025-11

5.	NCT04083508	Vivax Malaria Human Infection Studies in Thailand	Other: Mosquito bites	Not Applicable	20 Years to 55 Years (Adult)	6	Interventional	Primary Purpose: Other; Interventional Model: Single Group Assignment	2020-10-05	2025-09-30
6.	NCT04411836	Effectiveness of Novel Approaches to Radical Cure with Tafenoquine and Primaquine	➢ Drug: Tafenoquine ➢ Drug: Primaquine	Phase 3	18 Years to 100 Years (Adult, Older Adult)	960	Interventional	Primary Purpose: Treatment; Randomized; Interventional Model: Parallel Assignment	2021-04-25	2024-09-30
7.	NCT05361486	Radical Cure (RC) With Tafenoquine or Primaquine After Semi-quantitative G6PD Testing: A Feasibility Study in Peru	➢ Other: Training on revised algorithm ➢ Other: Enhancing Pharmacovigilance ➢ Other: Supervision of malaria services in selected facilities. ➢ Diagnostic Test: G6PD testing ➢ Drug: Tafenoquine ➢ Drug: Primaquine ➢ Other: Follow Up Visit at Day 3 [+2 days] after treatment start	_	6 Months and older (Child, Adult, Older Adult)	40	Observational	Observational Model: Ecologic or Community; Time Perspective: Prospective	2023-08-28	2024-10-31
8.	NCT05540470	Radical CURE for Malaria Among Highly Mobile and Hard-to-reach Populations in the Guyanese Shield	➢ Drug: PART ➢ Drug: Malakit ➢ Other: Cross-sectional pre- and post-Intervention surveys ➢ Other: Qualitative Study	Not Applicable	18 Years and older (Adult, Older Adult)	5000	Interventional	Primary Purpose: Treatment; Non-Randomized; Interventional Model: Parallel Assignment	2022-09-12	2025-12-12
9.	NCT04706130	Rigorous Assessment of *P. Vivax* Relapses and Primaquine Efficacy for Radical Cure	➢Drug: Primaquine ➢Drug: Artesunate	Phase 4	15 Years and older (Child, Adult, Older Adult)	200	Interventional	Primary Purpose: Treatment; Randomized; Interventional Model: Parallel Assignment	2021-04-15	2024-12-31
10.	NCT05058885	*P. Vivax* Among Duffy Negative Population in Cameroon	_	_	1 Year and older (Child, Adult, Older Adult)	900	Observational	Observational Model: Other; Time Perspective: Cross-Sectional	2022-05-02	2024-06-30

11.	NCT0587 9224	Short Course Primaquine for the Radical Cure of *P. Vivax* Malaria - Indonesia	➢ Combination Product: Revised case management package	Not Applicable	6 Months and older (Child, Adult, Older Adult)	11250	Interventional	Primary Purpose: Other; Interventional Model: Single Group Assignment	2023-08-07	2025-07-31
12.	NCT0587 4271	Short Course Primaquine for the Radical Cure of *P. Vivax* - Papua New Guinea	➢ Combination Product: Revised case management package	Not Applicable	12 Months and older (Child, Adult, Older Adult)	5850	Interventional	Primary Purpose: Other; Interventional Model: Single Group Assignment	2023-07-10	2025-07-31
13.	NCT0422 8315	Biomarkers of *P. Vivax* Relapse	➢ Drug: Primaquine	Not Applicable	18 Years and older (Adult, Older Adult)	100	Interventional	Primary Purpose: Treatment; Randomized; Interventional Model: Parallel Assignment	2019-11-19	2024-12-31
14.	NCT0591 3973	Study of the *P. Vivax* Transmission-blocking Vaccine Pvs230D1-EPA/Matrix-M to Assess Safety, Immunogenicity and Transmission-blocking Activity in Healthy Malaria-naive Adults	➢ Drug: Pvs230D1-EPA/Matrix-M	Phase 1	18 Years to 50 Years (Adult)	200	Interventional	Primary Purpose: Prevention; Non-Randomized; Interventional Model: Sequential Assignment	2023-08-04	2025-05-15
15.	NCT0337 5983	*Plasmodium* Immunotherapy for Advanced Cancers	➢ Biological: Blood-stage infection of *P.vivax*	Phase 1, Phase 2	18 Years to 70 Years (Adult, Older Adult)	20	Interventional	Primary Purpose: Treatment; Interventional Model: Single Group Assignment	2017-11-23	2026-07-31
16.	NCT0278 6589	*Plasmodium* Immunotherapy for Lung Cancer	➢ Biological: Blood-stage infection of *P. vivax*	Phase 1, Phase 2	18 Years to 70 Years (Adult, Older Adult)	30	Interventional	Primary Purpose: Treatment; Interventional Model: Single Group Assignment	2016-06-27	2023-12-30
17.	NCT0416 5590	*Plasmodium* Immunotherapy for Advanced Malignant Solid Tumors	➢ Other: Plasmodiumimmunotherapy	Phase 1, Phase 2	18 Years to 70 Years (Adult, Older Adult)	60	Interventional	Primary Purpose: Treatment; Interventional Model: Single Group Assignment	2019-10-24	2026-10-31
18.	NCT0347 4822	*Plasmodium* Immunotherapy for Breast and Liver Cancers	➢ Biological: Blood-stage infection of *P.vivax*	Phase 1, Phase 2	18 Years to 70 Years (Adult, Older Adult)	60	Interventional	Primary Purpose: Treatment; Interventional Model: Single Group Assignment	2018-08-10	2026-06-30

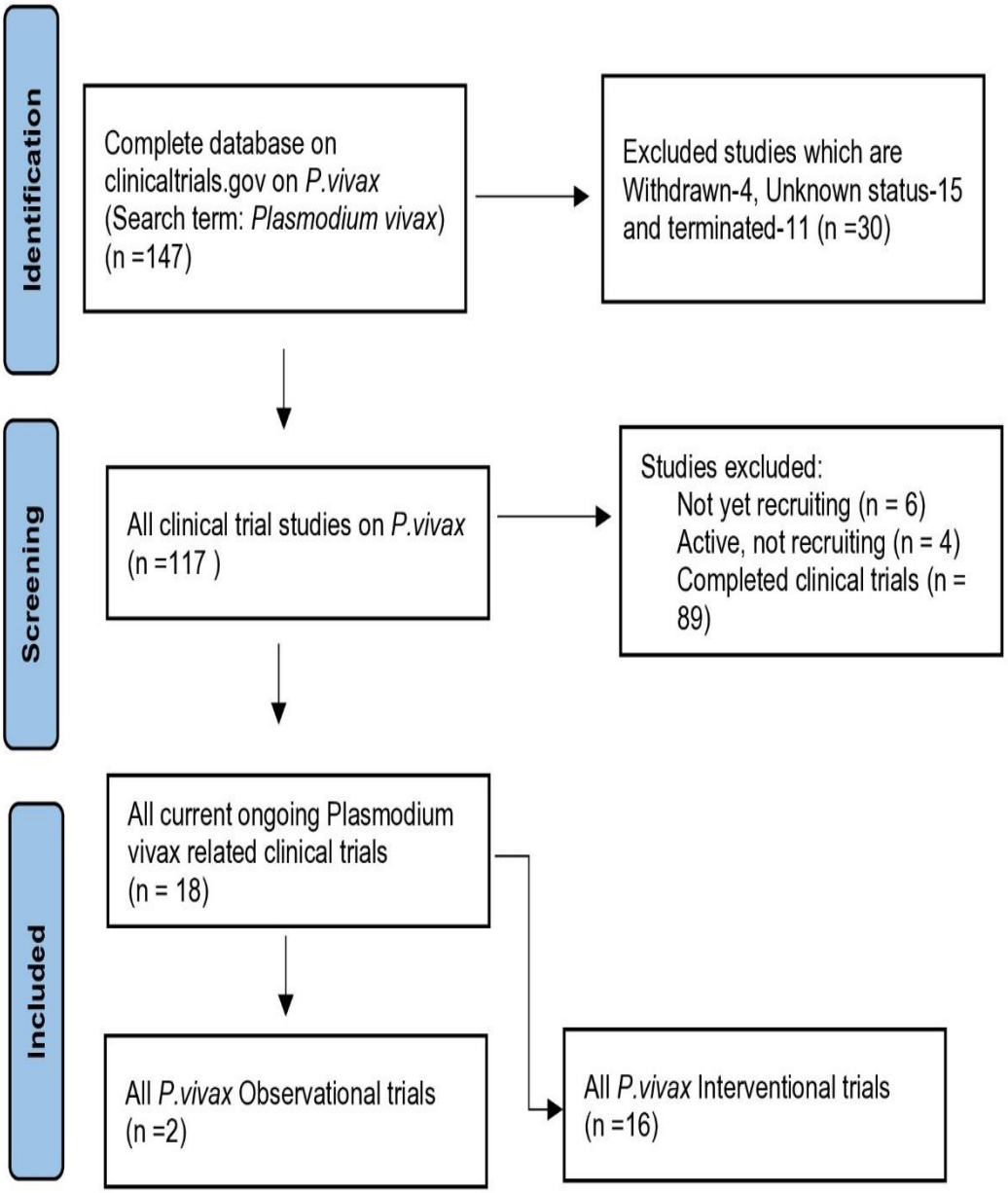

Figure 2: PRISMA guidelines for Clinical trials selection process on *P. vivax*

To be more precise, we must: 1) determine which host cell will facilitate invasion and blood-stage development, 2) synthesize the hepatocyte characteristics necessary for pre-erythrocytic development and the formation of hypnozoites *in vitro*, 3) make it easier to obtain *P. vivax* single-clonal populations derived from sustainable sources and 4) develop techniques for stable parasite transfection through genetic modification. In the event that *P. vivax* is not available, the closely related *Plasmodium cynomolgi* (*P. cynomolgi*) and *Plasmodium knowlesi* (*P. knowlesi*) offer appropriate models for reticulocyte invasion, hypnozoite production and reactivation.

The aforementioned activities aim to enhance current resources and provide crucial novel tools to propel *P. vivax* research and development efforts, thus expediting the trajectory towards the complete eradication and abolition of this parasite[6].

The Indian Government has published a roadmap to eradicate malaria by 2030 as part of its support for this project. It is widely acknowledged that eradicating malaria from a Nation will improve health, quality of life and will reduce poverty[17]. The goal of WHO Global Technical Strategy (GTS) for malaria is to eradicate the disease worldwide by 2030. India and other Asia-Pacific Nations have committed to eradicate malaria by 2030 and a 50% reduction in the disease's death rate is a requirement for the entire world. Together with partners and key stakeholders, the aim of the WHO GTS, the National Framework for Malaria Elimination (NFME) 2016–2030, the Malaria Elimination Roadmap and the Asia Pacific Leaders Malaria Alliance (APLMA) is to eradicate malaria nationally by 2030. A further goal is to lower the API to less than 1 in order to enhance living standards, to promote health and to reduce poverty[2].

Conclusion

Malaria continues to be a serious hazard to global health, with high death rates. Malaria diagnosis and monitoring remain persistently difficult, especially in low-resource environments where there are often few specialists to analyse the microscopy images and insufficient computing power to perform automated analysis. To guarantee prompt and precise diagnosis and treatment, healthcare providers must have access to lightweight automated technologies that can assist with malaria monitoring and diagnosis. Recently, automated malaria detection has begun to incorporate supervised ML techniques due to the availability of enormous volumes of annotated data and increases in processing power. We may infer from the performance metrics evaluation that *Plasmodium* can be reliably detected in thin blood smear samples using a basic CNN trained with a supplemented small training set.

ML technologies are promising for a number of *P. vivax* diagnosis applications. This approach of discovery aligns nicely with worldwide efforts to eradicate malaria because there are multiple gaps in *P. vivax* diagnosis. It is critical to diagnose malaria accurately before starting treatment in order to lower fatality rates, to avoid antimalarial drug resistance and to minimize unnecessary side effects from incorrectly prescribed medication.

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