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Worldwide Epidemiology of Plasmodium Vivax Malaria and its Clinical Management

Abstract Plasmodium vivax malaria is one of the most common vector-borne parasitic infections worldwide. P. vivax clinical manifestations include lung injury, renal dysfunction, hepatic dysfunction and extreme thrombocytopenia etc. P. vivax contributes around 70% of malaria cases in Pakistan with variable severity, but 47% of total severe vivax malaria cases have been reported in India. Elimination of P. vivax is very difficult because of its ability to form dormant stages of the liver. Insecticide-treated nets and insecticides are used to control malaria in malaria-endemic regions. Chloroquine is used as the first line of the agent in P. vivax malaria treatment. ACTs are also very effective because of their fast medical and parasitological response than that of chloroquine. Due to increasing drug resistance among P. vivax, scientists have tested with mass drug administration to eradicate malaria. In spite of all this, the P. vivax vaccine would be the last resort in the eradication of P. vivax malaria.

Key Words: Plasmodium Vivax, Malaria, Epidemiology, Long Incubation, P. Vivax Prevention, P. Vivax Treatment

Introduction

Globally, major causes of mortality and morbidity are vector-borne parasitic infectious diseases. In the recent era, malaria is a vector-borne parasitic infection, one of the most common, which can be caused by one of the five Plasmodium species, i.e., *P. vivax, P. falciparum, P. malariae, P. knowlesi and P. ovale* [Al-Awadhi et al., 2021]. Plasmodium vivax presents a significant challenge to accomplishing the worldwide exertion to eradicate malaria by 2030. Plasmodium vivax has been more geologically scattered than that of *P. falciparum*, and its transmission happening over a more extensive temperature range than that of *P. falciparum*. The worldwide distribution and factors that are related to *P. vivax* occurrence in more extensive geographic regions in tropical, subtropical and mild zones have extensively been audited recently.

Major characteristics of P. vivax jumbling its elimination and control contain the ability of parasite of forming dormant liver stages (hypnozoites), which can result in deterioration weeks up to months after an underlying infection while remaining contagious to the mosquito vector, they have the ability to keep circulating at low peripheral parasite densities, and the premature production of (gametocytes), i.e. sexual stages that permit the transmission by parasite before gametocytocidal treatment and clinical presentation. P. vivax malaria has also undergone evolution itself so that it can live in a greater diversity of vectors of Anopheles. Hence accumulatively, these characteristics sustain transmission and survival of parasites in areas with extreme climates and give out greater pliability than that of P. falciparum against vector control activities and conventional parasites (Figure.1)

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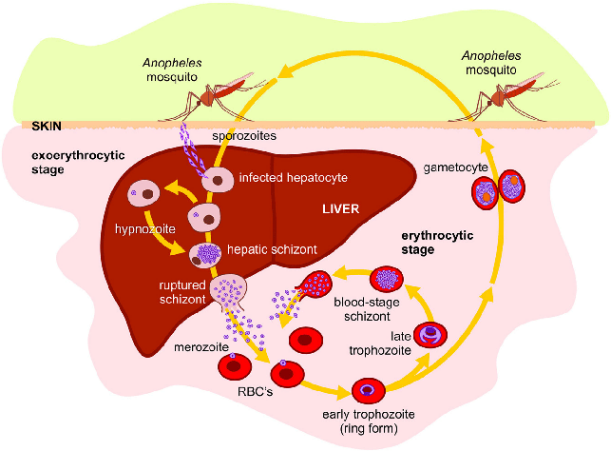

Figure 1: Life cycle of *P. vivax* (Lima-Junior and Pratt-Riccio, 2016)

P. vivax is still significant health trouble for the public, influencing the poorest and vulnerable commodities of greater than 49 endemic nations [Kondrashin et al., 2018]. In the course of the last two decades, the expenditure in managing malaria and eradication programs have assisted considerably reduce the worldwide malaria fever map. However, in regions where Plasmodium falciparum and *P. vivax* are co-endemic, Plasmodium vivax has been turning into the prevalent cause of malarial fever in various regions. The increasing extent of *P. vivax* features the more prominent capability of transmission of this species which is owing to various biological features that vary notably from *P. falciparum*. (Table .1)

Table 1. *P. Vivax* Biological Features that Increase the Capacity for Spread and Transmission (Auburn et al., 2021)

Biological Properly	Challenge	Potential Solutions
Low-density infections	Clinical illness and transmission occur at low-level parasitaemia, which is hard to diagnose	High-sensitivity molecular diagnostics such as PCR and large volume uPCR
Liver-stage reservoir	Hepatic reservoir is difficult to diagnose and results in recurrent infections that sustain ongoing transmission and confound the assessment of TES	Serological markets to identify individuals with recent exposure and high risk of relapse who can be offered radical cure. Genotyping of infections initially and at the time of recurrence to refine classifications (recrudescence, reinfection, or relapse) in clinical and epidemiological studies
Early gametocytaemia prior to clinical presentation	Enhances transmission prior to antimalarial treatment	Early diagnosis and treatment of clinical illness, prevention of relapses, and transmission interventions such as indoor residual spraying with insecticides and LLINs
Capacity to develop in mosquitoes at low ambient temperatures	Wide range of ecological receptivity, enhancing transmission	Transmission interventions such as indoor residual spraying with insecticides and LLINs

LUN, long-lasting insecticide treated net; TES, therapeutic ellicacy studies; uPCR, ultrasensitive PCR,

Short Term to Long Term Incubation Ration in *P. vivax* Malaria

Plasmodium vivax populaces having prolonged incubation period were initially limited in regions where the climate is temperate like eastern, focal Europe, and northern areas of America and Asia, while *P. vivax* having short term incubation has been largely dispensed in regions that have warm and sub-tropical climate. Nonetheless, in the south, a well-organized proliferation trend of *P. vivax* having long

term incubation has been occurring during the last few decades. For example, *P. vivax,* with a prolonged incubation period, comprised around 70–80% of the all-malaria fever cases before the dispatch of malaria control activities on a large scale in the European region. Main clinical indications usually took place during the span of 8-to 14-months, following declination of disease. However, in the southern European areas, the extent of vivax malaria having long incubation represented about 10% of all malaria fever cases, while the leftover cases were of vivax malaria fever that had short incubation [Joshi et al., 2008]. (Figure.2)

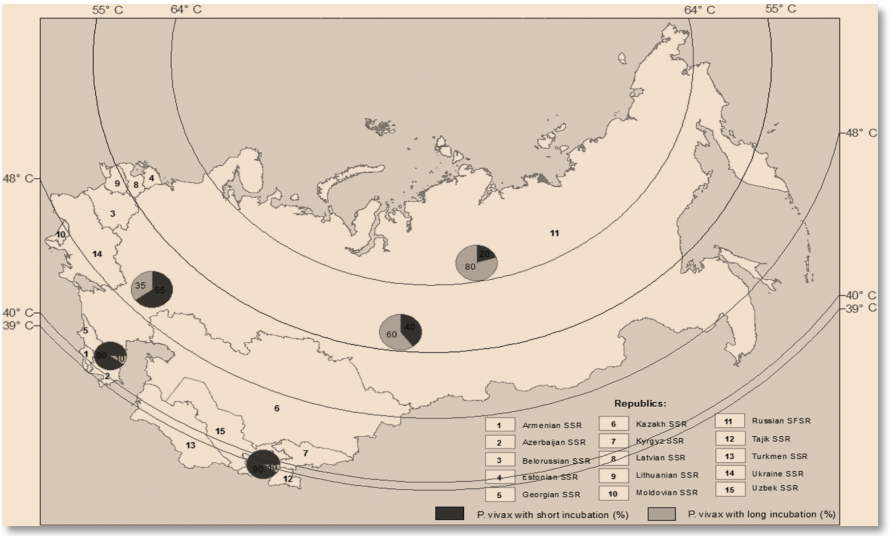

Figure 2: *P. Vivax* Ratio of Short Incubation to long Incubation (Kondrashin et. al., 2018)

Worldwide Increase in Severe *P. Vivax* Malaria

Currently, *P. vivax* is present in 51 nations across the Horn of Africa, Central and South America, the Pacific and Asia islands. Malaria's dominating causing agent in Asia and other Asia-Pacific areas are *P. vivax*. It is furthermore prevalent in the horn of Madagascar, Africa, and other central and South America's parts; so far, it has been removed from Russia, North America and Europe. As could be anticipated, around 40% of total publications on *P. vivax* come from India that has the largest national malaria control program in the world. The yearly count of *P. vivax* cases in India comprises 47% of all malaria cases [Baird, 2015]. Severe sequential cases of *P. vivax* have been found in the USA, Pakistan and Indonesia. Sporadic cases have also occurred in Bangladesh, Cambodia, China, Laos, Thailand, the Middle East, Afghanistan, Korea, African Horn's countries, Madagascar, Brazil and Papua New Guinea [Douglas et al., 2014]. Generally speaking, serious sickness having an acute infection that includes injury of lungs having respiratory trouble, injury of the kidney due to kidney dysfunction, jaundice and dysfunction of hepatic system, seizures/delirium/comma or extreme thrombocytopenia etc.

The syndromes severity varied largely in the various regions of the world, having serious anemia being most noticeable in spaces of large transmission, incessant setbacks and chloroquine's resistance [Rahimi et al., 2014]. Anemia related to Plasmodium vivax is a great risk for kids. Consequently, in Indonesia's pandemic domains of malaria, almost 25% of all the inpatients are children having apparent anemia [Poespoprodjo et al., 2009]. Severe P. vivax-related anemia was the major reason for death at the degree of about 10.3 per thousand cases in hospitalized children in Papua (Indonesia) [Douglas et al., 2014]. P. vivax-related anemia's details in pregnant ladies were set in Russia. Frequently present difficulties were premature delivery, extended course of the ailments, early abortions, and most importantly, enhanced relapsing frequency at the end of pregnancy and instantly post-delivery.

Preventive Measures

Insecticide-Treated Nets

Insecticide-treated nets are playing a major role to combat malaria fever in most of the malaria-endemic region. Almost 25,000,000 insecticides treated nets from 2017 to 2019 were disseminated yearly in the

malaria-endemic areas. The efficiency of ITNs relies upon different elements, which includes adherence, distribution, coverage, maintenance, levels of insecticide resistance and vector gnawing patterns [Ngufor et al., 2017]. A large portion of the essential vectors in Southeast Asia shows crepuscular gnawing patterns that are exophilic in nature, so they can decline the insecticide-treated nets efficacy in hindering malaria fever.

Insecticide-treated nets have no immediate antagonistic effect towards relapse, which is frequently the primary driver of *P. vivax* malaria (if proportions of relapse surpass the 50%, then relapses appear to be the fundamental driver of infections caused by Plasmodium vivax). Regardless of all the mentioned limits, insecticide-treated nets can give a halfway advantage and are the adjunct strategy to hinder the infections mainly caused by *P. vivax* and meddle with the transmission [Protopopoff et al., 2018]. Long-lasting nets, in which the insect's poison lasts for the natural existence of the net, are an essential advancement.

Insecticide use

Insecticide's usage to combat the malaria mainly focuses on Indoor Residual Spraying and Long-Lasting Nets, despite the fact that there is an assortment of different methodologies. Organophosphates, pyrethroids, organochlorides are approved by WHO for Indoor Residual Spraying. Between 2000 and 2009, more than 3,200 metric tons of insecticides were utilized to combat the malaria fever vectors in *P. vivax* endemic areas. Worldwide insecticides utilization for forming treatments and high-level malarial fever managing programs make it very difficult for the vector population to produce insecticide resistance [Mouchet, 1988].

Treatment of *Plasmodium Vivax* Malaria

Chloroquine has been utilized as a drug of choice for P. vivax infections since 1947. The usual treatment routine is that 25 mg /kg of the drug is given for three days and can also be given as 10 mg/kg at first followed by 10 mg/kg at 24 hrs and 5 mg/kg at 48 hrs [World Health Organization, 2015]. Chloroquine absorption through the mouth in a solid-state is reliable in any case, even when patients are prostrate [Chu & White, 2021], and parenteral treatment is required in very rare cases. Intravenous or intramuscular artesunate is given to all those victims, who firstly needed the parenteral medications for serious vivax malaria until they can take oral drug accurately. ACT's treatment is also very effective and has quick clinical as well parasitological feedback than chloroquine.

The post-treatment suppression of initial relapses depends upon the elimination pharmacokinetics of ATC coadjutant drug—mefloquine, amodiaquine, pyronaridine and piperaquine. ACTs offer the same duration of suppression as provided by chloroquine, though artemether-lumefantrine offers a very short period of suppression [Smithuis et al., 2010]. ACTs and chloroquine both are effective and well-tolerated antimalarial drugs. Pediatric preparations are available for piperaquine, and pyronaridine-artesunate, artesunate-amodiaquine, dihydroartemisinin, artemether-lumefantrine and the dosage regimens are related to those drugs used for falciparum malaria. Tafenoquine and Primaquine also have effective clinical activities; however, their therapeutic response is very slow as compared to that of ACTs and Chloroquine, so they must not be utilized as monotherapies to treat blood-stage infections of Plasmodium vivax [Pukrittayakamee et al., 1994]. Paracetamol standard treatment doses can be used to cure high fevers, and vomiting can be prevented with antiemetics. In case patients give indications of serious Plasmodium vivax malaria fever, then the treatment is the same as that is prescribed for the falciparum malaria fever.

Alternative Ways to Deal with P. Vivax Elimination

Vaccines and Mass Drug Administration

Recent evidence found out that increases in PvCRT copy number associated with the Plasmodium vivax resistance to chloroquine. The molecular basis for artemisinin resistance in the malarial parasite has also been described recently. Molecular analysis of P. vivax isolates from the GMS region revealed a high diversity, and ex vivo analysis show less sensitivity to pyronaridine, quinine, chloroquine, mefloquine, dihydroartemisinin, piperaquine and artesunate. Vaccine's production to provide defence against the P. vivax malaria is lagging far behind. P. vivax attaches to the Duffy antigen receptor of chemokines through a Duffy binding protein that is the target for two blood-stage vaccines, and both vaccines are in the initial stage of production. There is propitious research for Plasmodium vivax vaccine targets and vaccination procedures; still, it is improbable to be available in the upcoming future [Payne et al., 2017].

Due to the absence of a long-lasting defensive vaccine against Plasmodium vivax malaria, scientists

have tested with mass drug administration of antimalarial medications to eradicate malaria. To have an enduring effect, MDAs are being used for eliminating malaria due to Plasmodium vivax, which need to include 8-aminoquinolines [Kondrashin et al., 2014]. Utilization of TQ in modified drug administration could be effective as a single dosage regimen and most probably can achieve higher scope in the market than that of multiple-dose regimens. Two recent ongoing improvements give hope that radical therapy and hypnozoites clearance will become available extensively. A long-acting 8-aminoquinoline TQ and PQ shorter courses are supposed to enhance the efficiency and could offer alternatives to the current treatment choices [Lorenz von Seidlein, 2021]. Ivermectin is a new addition to the antimalarial drug regimens used in modified drug administration. Field studies have revealed an executing effect of Mass Ivermectin Administrations to combat malaria vectors as well as enduring impact against all malarial ailments.

Conclusion

Plasmodium vivax presents a significant challenge to accomplishing the worldwide exertion to eradicate malaria by 2030. Almost 40% of all the literature publications on Plasmodium vivax are coming from India, where the yearly count of severe Plasmodium vivax malaria cases comprises 47% of all the malarial cases. Plasmodium vivax presents a significant challenge to accomplishing the world efforts to eradicate malaria by 2030. Among the main features of Plasmodium, vivax epidemiology is the changes in the ratio of the short-incubation Plasmodium vivax to long-incubation Plasmodium vivax. Proper diagnosis and management of Plasmodium vivax malaria, use of preventive measures like ITNs and antimalarial drugs like chloroquine and ACTs are enhancing the treatment strategies against Plasmodium vivax malaria. But the challenge is to make all these managements very effective as the resistance against antimalarial drugs has been produced in Plasmodium vivax. Due to the absence of a long-lasting defensive vaccine against Plasmodium vivax malaria, scientists have tested with mass drug administration of antimalarial medications to eradicate malaria. Due to the rapid spread of drug-resistant parasitic variants and hypnozoites development, the last resort to eradicate P. vivax malaria is the Plasmodium vivax vaccine development.

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