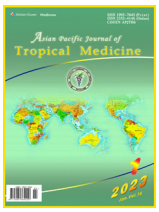

Perspective

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Time to stimulate *Plasmodium vivax* research in India: A way forward

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India bears the largest *Plasmodium (P.) vivax (Pv)* malaria burden and contributes 48% of *Pv* cases globally[1]. The efforts of government and private bodies to control malaria have successfully reduced the number of *Plasmodium falciparum* (*Pf*) malaria cases in several countries, including India. However, there has been a consistent increase in *Pv* cases, particularly in regions where both parasites coexist. Consequently, *Pv* presents an obstacle to elimination and is more challenging to eradicate than *Pf* for several reasons: 1) *Pv* has a wider geographic range since it can thrive in colder climes; 2) vector control methods are less effective because *Pv* parasite-carrying mosquitoes bite early, rest outdoors, and consume blood outdoors; 3) current diagnostic tools cannot detect low-density *Pv* infections and dormant hypnozoites; 4) hypnozoites can trigger multiple malaria episodes, and *Pv* gametocytes are produced earlier, enabling transmission even before clinical symptoms; and 5) 14-day primaquine is the only effective drug against hypnozoites; however, it can cause life-threatening haemolytic anaemia in individuals with glucose 6-phosphate dehydrogenase (G6PD) deficiency, which makes primaquine treatment difficult[2].

Pv has an evolutionary path distinct from *Pf* (which causes a lethal form of malaria), being closely associated with *P. cynomolgi* which is responsible for infection in Asian macaque monkeys[3]. Due to this evolutionary path, *Pv* shows unique biological features such as 1) preference to invade reticulocytes; 2) earlier production of gametocytes; 3) formation of dormant hypnozoites[4]. *Pv* also has unique morphological features, including 1) the small dark granules in the reticulocyte cytoplasm, known as Schüffner's dots; 2) the sexual stage of *Pv* parasites has a round shape similar to the asexual stages[4]. The biological basis for the development of *falciparum* severe malaria *via* sequestration of *P. falciparum*-infected erythrocytes in the host vital organs, and involvement of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) in promoting the cytoadherence of infected erythrocytes in severe malaria are well described. In the case of *Pv* infections, a group of variable proteins expressed on the reticulocyte surface are suggested to have a role in mediating the cytoadherence of infected erythrocytes to endothelial cells and the placenta[4]. Another key feature of *Pv* biology is the hypnozoites which are metabolically active and remain dormant for weeks to months before reactivating. Furthermore, it is evident that relapses in *Pv* infections are due to hypnozoites[4].

Pv infection has been perceived as benign until recently, despite life-threatening complications reported[4]. Patients with *Pv* infection were found positive for both asexual and sexual parasites in the peripheral circulation, enhancing community transmission. Besides, *Pv* sporozoites develop faster in the mosquito midgut compared to those with *falciparum*. *Pv* malaria in pregnancy is also associated with maternal anaemia and low birthweight neonates[5]. In developing countries where co-infections are frequent, *Pv* hypnozoites can be activated by systemic bacterial and parasitic infections, which is the most common cause of relapse in *Pv* patients. However, *Pf* continues to be the main area of interest for most malaria researchers. We conducted a 20-year PubMed search on January 08, 2023, using the terms "India" and either "*Plasmodium falciparum*" or "*Plasmodium vivax*" to determine the extent of *Pv* research in India (2002-2022). This search turned up 3 515 and 1 231 articles on *Pf* and *Pv* in India, respectively, which emphasises the need for researchers, funding agencies, and malaria elimination programmes to invest in *Pv* research to develop 1) tools that can detect hypnozoites and 2) a short and effective treatment against hypnozoites.

Pv only infects reticulocytes that account for 1%-2% of red blood cells in adult peripheral blood[6]. These cells are fragile, have rapid maturation, and complicated techniques are needed to get enriched samples. Therefore, it is challenging to maintain a reliable long-term *Pv* culture to facilitate needed research. Hence, the *P. knowlesi* culture as a *vivax* model has been used to understand the unique biology of *Pv*. Moreover, to detect and treat *Pv* hypnozoites, microRNAs (miRNAs) can be an excellent approach. Studies have shown the association of miR-3158-3p with severe *Pf* malaria in Indian adults and Mozambican children, highlighting a

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promising biomarker candidate for diagnosis across age groups and geographical regions[7]. Similarly, let-7b-5p, miR-16, 24, 28-3p, 144, 150, 191, 194-5p, 221/222, 378-5p, 451, 520f-3p, 3667-5p, and 7977 miRNAs were found associated with *Pv* infection[7]. However, they require further validation in large sample sizes before developing multiplex miRNA-based assays to detect low-density peripheral *Pv* infections and hypnozoites. In addition, miRNA mimics and inhibitors (antimiRs) are two categories of miRNA-based therapeutics[7]. The miR-34 mimic, MRX34, has reached Phase Ⅰ clinical trials for treating cancer. Similarly, an antimiR against miR-122 has reached Phase Ⅱ trials for treating patients with the hepatitis C virus. Based on these promising results, *Pv*-associated miRNAs (mentioned above) can also be investigated for their potential to treat hypnozoites.

Lessons from countries such as Iran and Sri Lanka as well as China's successful malaria elimination programs can be adapted to overcome *Pv* cases in India[8]. Chinese malaria elimination programs mainly targeted three components: the source of infection, individuals susceptible to infection, and the mosquito vectors[9]. Mass drug administration with different antimalarials was used during and between malaria seasons to clear the hypnozoite reservoir and protect susceptible individuals. This led to a reduction from 13 million malaria cases to only 1 million. Elimination was achieved in regions where *Pv* was transmitted by *Anopheles (An.) sinensis*. For vector control, indoor residual spraying was of limited effectiveness. However, a field trial with insecticide-treated nets demonstrated a significant decrease in the indoor vector density of *An. sinensis* and *An. lesteri*. Furthermore, the use of new irrigation schemes to improve agriculture productivity in China led to a substantial reduction in malaria morbidity[10]. Similarly, Sri Lanka's national strategy for malaria elimination was based, broadly, on the World Health Organization guidelines for elimination, which included targeted vector control, intensified case surveillance and radical treatment, and case investigation and response[11].

This article provides a basis for further *Pv* research to eliminate malaria in India. Development of new tools for early *Pv* diagnosis and case management as per the local needs should be a prerequisite along with robust healthcare systems. The elimination of malaria will be facilitated by improved public-private partnerships, greater clarity in research, and strong political commitment. The Global Malaria Eradication Programme of the 1960s was extremely successful in eradicating malaria from several parts of the world, but it failed to accomplish its goal in India due to technical, financial, and operational negligence. Reinforcing the goal of eliminating malaria from India offers a chance to take lessons from the past and make malaria-free India.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

HG and SN did the literature search; HG and SN drafted the manuscript; PKB gave intellectual comments and reviewed the final version.

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