Editorial

Plasmodium vivax Vaccine Research: Insights from Colombian Studies

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In recent years, heightened awareness of the heavy public health, economic, and social burdens attributable to malaria, has led to increased interest and support by both public and private sectors for malaria-related research and control. This interest, accompanied by some remarkable successes in achieving control in selected areas, has led to a renewed optimism about the long-term feasibility of achieving elimination and, ultimately, eradication of malaria throughout the world, if new tools can be developed to enable eradication efforts. Most of this renewed interest has focused on *Plasmodium falciparum* infections, which cause the greatest morbidity and mortality, most of it in sub-Saharan Africa. Approximately 40% of the world's population, however, lives at risk of malaria caused by *Plasmodium vivax*, which is responsible for significant morbidity, particularly in South and Central America, Asia, and the eastern Mediterranean.¹ To successfully expand malaria elimination efforts and ultimately to achieve eradication, it is crucial to concurrently develop strategies that target other major species infecting humans, particularly *P. vivax*, which has a widespread distribution and a demonstrable public health and socioeconomic impact on a range of populations throughout the world.^{1,2}

The majority of malaria vaccine development efforts today are concentrated on *P. falciparum*, with a goal of having a highly efficacious vaccine by 2025.³ Although there has been good progress on *P. falciparum*-focused vaccines, a single species approach to malaria vaccine development is unlikely to achieve malaria elimination and eradication. Currently, more than 70 *P. falciparum* vaccine research projects have been initiated, over 30 have been tested in humans, and one (RTS,S) is currently in Phase 3 trials. In contrast, only two *P. vivax* vaccine candidates have undergone clinical testing.⁴ Because of the co-endemicity of *P. vivax* and *P. falciparum* in many regions, the eventual development of a multi-species vaccine regimen that can be used in a variety of high-risk populations would be most appropriate. However, because *P. vivax* vaccine development lags behind that of *P. falciparum*, increased efforts are required to identify and test potential *P. vivax* vaccine candidates. In addition, it will be critical to expand our understanding of the biology and epidemiology of *P. vivax* to effectively design appropriate vaccines and evaluate them in clinical and field settings.

A few research groups have focused on *P. vivax*. One such group—the Malaria Vaccine and Drug Development Center (MVDC) in Cali, Colombia—has developed a multi-disciplinary, cross-functional research program on *P. vivax*. Results of their *P. vivax*-related investigations, presented in this supplement, provide important insights into key aspects of *P. vivax* biology, immunology, and transmission dynamics that will be

informative for those interested in development of vaccines against vivax malaria as well as for those with an interest in malaria elimination and eradication.

Although the disease burden of *P. vivax* varies regionally, its widespread distribution in many tropical, sub-tropical, and temperate regions places an estimated 2.6 billion people at risk of *P. vivax* malaria each year, greater than that of *P. falciparum*.^{2,5} In addition, many regions, such as Korea, the Amazon region, and Afghanistan have witnessed a re-emergence of malaria, predominantly caused by *P. vivax*, over the past several decades.^{6–8} Outside of Africa, *P. vivax* accounts for more than 50% of all malaria cases.¹ In Colombia, *P. vivax* causes 65% of reported clinical malaria cases.⁹ In Africa *P. vivax* malaria accounts for between 5% and 20% of all malaria in eastern and southern Africa, and Madagascar, making up 6–15 million cases of malaria in Africa alone.¹ Taken together, these data indicate that *P. vivax* malaria has a significant presence both outside and within Africa.

With an estimated 70–391 million cases annually, it is not surprising that *P. vivax* imposes a significant disease burden across the world.^{2,5} Although not associated with high mortality rates as is *P. falciparum*, *P. vivax* infection unleashes its own distinctive pathobiology in the human host that can result in severe disease. Acute *P. vivax* infection, consisting of repeated episodes of fever, malaise, chills, and pronounced paroxysms, causes serious and incapacitating illness, that can often be more agonizing than uncomplicated *P. falciparum* infection.¹⁰ High fever and rigors are more common in *P. vivax* compared with *P. falciparum*, possibly because of the greater synchronicity of schizont rupture in *P. vivax* infections or its ability to elicit a strong host inflammatory response, including TNF- α , at a lower parasitemia level.^{2,11} Unlike *P. falciparum* malaria, this pathobiology affects individuals of all ages because most areas affected with *P. vivax* tend to have low transmission and thus a flat age-incidence curve.¹ Moreover, the ability of *P. vivax* hypnozoites to remain dormant in the liver and relapse at varying intervals can lead to repeated debilitating malaria episodes. This also makes *P. vivax* more difficult to eliminate from an afflicted individual and from a population.

Though commonly believed to be a “benign” malaria, several studies and case reports have shown that *P. vivax* infections do cause severe malaria, similar to *P. falciparum* malaria. In fact, since 1920 there have been at least 45 reports of cerebral malaria caused by *P. vivax* infection.¹² Recent studies conducted in India, Indonesia, and Papua New Guinea have shown that *P. vivax* does cause severe malaria—albeit at lower rates than *P. falciparum* malaria. A report from Rajasthan, India reviewed 11 cases of severe malaria caused by *P. vivax* infection in 2003 including cerebral malaria, coma, acute respiratory distress syndrome, severe anemia, jaundice, circulatory collapse, and renal failure.¹³ In one recently

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published prospective study conducted in Indonesian Papua, it was reported that those admitted to the hospital with *P. vivax* infection (mostly children) experienced an increased risk for severe malaria compared with those admitted with *P. falciparum* infections; severe anemia (Hb < 5g/dL), respiratory distress, coma, and death comprised the severe complications seen in *P. vivax*-infected patients.¹⁴ Similarly, a study conducted in Papua New Guinea reported that *P. vivax* caused 21% of all severe malaria cases (mostly children < 5 years of age), and of these, 26% presented with neurological complications.¹⁵ Respiratory distress was more commonly present in *P. vivax* associated severe malaria, especially in children < 5 years of age, supporting previous evidence that *P. vivax* may sequester within the pulmonary microvasculature.¹⁵ *Plasmodium vivax* infection during pregnancy is also associated with an increased risk of anemia in the mother and a reduction in mean birth weight.¹⁶

Because the pathogenic mechanisms are not clearly understood, it is apparent that *P. vivax* causes severe malaria with a wide range of clinical manifestations, and is a significant global public health problem. Although currently available tools for control have shown some significant efficacy against *P. falciparum*, it is likely that they will not have the same impact on *P. vivax* because of the distinct biology and survival mechanisms of this parasite species. Interrupting transmission of *P. vivax* is challenging, in part because gametocytes usually appear in the circulation at about the same time as the asexual blood-stage parasites and before onset of clinical symptoms or disease. Transmission of *P. vivax* thus can occur before drug treatment is clinically indicated and initiated. Additionally, the ability of the dormant phase to relapse months to years after the initial infection enhances the parasite's long-term survivability and transmission capabilities. Day-biting mosquitoes that transmit *P. vivax* render bednets less effective for *P. vivax* control than for control of *P. falciparum*. Therefore, it is likely that the proportion of disease related to *P. vivax* will increase in many co-endemic areas as *P. falciparum* control measures take effect. Previous evidence from the island of Vanuatu has shown that *P. vivax* is more difficult to eliminate from a population than *P. falciparum* using currently available control methods. In the 1990s a combination of malaria control methods, including mass drug administration, insecticide-treated bed nets, and larvae eating fish was implemented in Vanuatu, an island with a greater prevalence of *P. falciparum* infections than *P. vivax*.¹ Within one year of initiating these control methods, *P. falciparum* was eliminated; however, it took five years to eliminate *P. vivax*.¹ The Vanuatu experience thus illustrates that *P. vivax* is less susceptible to current control methods, and argues for the need to develop more targeted approaches—notably the development of a highly efficacious vaccine against *P. vivax*—to reduce the burden of *vivax* malaria globally.

As described in this supplement, investigators at the MVDC in Cali have developed a translational research program focused on addressing the multiple aspects of *P. vivax* vaccine development. The Center has effectively used the resources of its regions, including the availability of *Aotus* monkeys, accessibility to endemic regions with varying transmission levels, and populations of both malaria-naïve and malaria-exposed individuals. These capabilities have allowed the center to conduct pre-clinical and clinical testing of potential vaccine antigens,^{17,18} maintain an insectary of

Anopheles albimanus mosquitoes that can be infected with naturally occurring *P. vivax* parasites, and develop the *P. vivax* sporozoite challenge model for humans. In addition, scientists at the MVDC have the ability to regularly assess *P. vivax* epidemiology and examine the transmission dynamics in areas of co-endemicity of *P. vivax* and *P. falciparum*, which will be useful for determining the future impact of a potential vaccine in this type of endemic region. Understanding these various aspects of *P. vivax*, and conducting these types of cross-functional studies allow for a stepwise approach in moving *P. vivax* vaccine development forward. Results from these investigations are presented in this supplement, and provide critical data that can be used in designing the next steps for vaccine development.

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