

The Potential Role of Vaccines in the Elimination of *Falciparum* Malaria and the Eventual Eradication of Malaria

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(See the perspectives by Hall and Fauci, on pages 1639–43, and Miller and Pierce, on pages 1644–5.)

There has been a recent call for global malaria eradication. The prospects of achieving this ambitious goal are diminished by the limited tool set now available—namely, the lack of a licensed malaria vaccine. This is in large part because the multistage *Plasmodium* parasites that cause malaria have a much more complex life cycle and larger genomes than do the viruses that cause smallpox and polio, the only infectious agents that have been completely or nearly eradicated from the world by vaccines. We think that (1) vaccines could play as important a role in the elimination of *Plasmodium falciparum* as they have played in the global eradication of smallpox and the elimination of polio from the Western Hemisphere, and (2) they ultimately could be an important component of the armamentarium used to eliminate

the 3 other species of *Plasmodium* parasites that infect only humans: *P. vivax*, *P. malariae*, and *P. ovale*. In this Perspective article, we argue that the linchpin of such an effort must be a highly effective pre-erythrocytic-stage vaccine, and we describe how elimination could be accomplished based on the epidemiology of malaria in different transmission settings. We also discuss how a highly effective sexual- and mosquito-stage vaccine could complement the effectiveness of such a pre-erythrocytic-stage vaccine in geographically focused programs to eliminate *P. falciparum*.

THE CALL FOR MALARIA ERADICATION

In October 2007, at a meeting convened by the Bill and Melinda Gates Foundation in Seattle, Washington, the conveners issued a call for malaria eradication [1]. That halcyon call has transformed the way that malariologists in the 21st century think about the disease and the approaches and tools that should be used to reduce its burden. Of the 5 species of *Plasmodium* that cause human malaria, 4 (*P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*) are transmitted only between humans and mosquitoes. The fifth species, *P. knowlesi*, is a zoonosis that pri-

marily infects nonhuman primates. Eradication will require the interruption of malaria transmission globally (ideally, transmission of all 5 *Plasmodium* species), and this task will be extremely difficult to accomplish.

The vast majority of cases of severe malaria, as well as >95% of deaths attributed to malaria, are the result of infection with *P. falciparum*, and this parasite has developed the most resistance to treatment with antimalarial drugs. For these reasons, reduction in disease and death due to *P. falciparum* has been the primary objective of most malaria research and control efforts to date. In this article, we focus on the potential use of vaccines for elimination and eradication of *P. falciparum*, and we identify challenges in developing and deploying vaccines for the 4 other *Plasmodium* species that cause human disease.

During the past 60 years, *P. falciparum* has been eliminated from the United States, Canada, Europe, and parts of Asia and the Middle East, mostly as a result of environmental and mosquito control measures but also as a result of surveillance for and treatment of cases of both clinical malaria disease and asymptomatic malaria infection. Continued expansion of these efforts will undoubtedly lead to elimination of *P. falciparum* from

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other geographic areas in the next 10–20 years. However, in the parts of the world where *P. falciparum* transmission is most intense and where the disease causes the most morbidity and mortality, we believe that new tools will be needed to eliminate malaria caused by *P. falciparum*. An international initiative, the Malaria Eradication Research Agenda (MalERA), has begun working under the auspices of the Roll Back Malaria partnership to identify the key knowledge gaps and the research needed to develop the type of tools required if malaria is to be eradicated. It is our view that, when used together with other measures, a highly effective *P. falciparum* vaccine that prevents infection of humans and transmission of *P. falciparum* to mosquitoes could be a critical tool for achieving complete elimination of *P. falciparum* from these areas in the world.

Smallpox is the only infectious disease that has been eradicated. Polio was eliminated from the Western Hemisphere, but it still persists in some regions of Africa and Asia and is intermittently reintroduced to the Western Hemisphere. The eradication of smallpox and the regional elimination of polio were accomplished with vaccines. Developing a vaccine for *P. falciparum* has proved more difficult than developing vaccines for smallpox and polio. Even if a highly effective vaccine for *P. falciparum* is developed, successful use of that vaccine to eliminate *P. falciparum* will require overcoming challenges not faced by vaccines for the elimination of smallpox and polio.

Smallpox and polio viruses are transmitted directly from human to human. *P. falciparum* has an intervening host, the mosquito, which can amplify transmission by producing thousands of infectious sporozoites that can be introduced into multiple individuals when the infected mosquito feeds. More importantly, a single infection with smallpox virus or a polio virus strain renders an individual immune to further infection with that virus or strain and, therefore, incapable of trans-

mitting the pathogen if subsequently exposed. Individuals who have had repeated exposure to *P. falciparum* acquire immunity that reduces malaria disease, but they can still become infected with parasites, which can in turn be transmitted to mosquitoes. Thus, a vaccine will have to do better than natural infection. Furthermore, as the transmission intensity of *P. falciparum* decreases, it is likely that immunity in the population will decrease, and the susceptibility of the population to *P. falciparum* will increase.

The basic reproduction number describes the transmission intensity of malaria parasites. In the absence of immunity or control measures, this number is referred to as R_0 , and in the presence of immunity and control, it is referred to as R_c . The basic reproduction number describes the number of new cases of *P. falciparum* that will arise from a single case. R_0 cannot be directly measured, but it is a useful heuristic for thinking about malaria elimination.

If R_0 or R_c is <1 in a given human population, *P. falciparum* will be eliminated from that population. In various settings in sub-Saharan Africa, R_0 has been estimated to be <10 and >3000 [2]. If the R_0 or R_c for *P. falciparum* in an area is <10 , a vaccine that prevents transmission by $>90\%$ of exposed individuals will lead to elimination of *P. falciparum*. If the R_0 or R_c in an area is <5 , a vaccine that prevents transmission by $>80\%$ of infected individuals will lead to elimination of *P. falciparum*. For a vaccine that prevents transmission by 50% of infected individuals to be able to eliminate malaria, R_0 or R_c would have to be driven down to <2 by nonvaccine interventions. These calculations are based on protection of an entire population in an area of contiguous malaria risk. It is unlikely that any immunization campaign will cover 100% of exposed individuals in a given population, and the lower the transmission intensity, the greater the chance that every individual will be capable of efficiently transmitting *P. falciparum*. Thus, for a vaccine to

be effective in eliminating *P. falciparum*, it will have to be highly effective at preventing transmission and will have to be administered to a high proportion of the entire population of an area of contiguous risk.

Where the malaria risk is limited to discrete populations, R_0 or R_c must be maintained at <1 to eliminate malaria in that population. When the number of new cases of local transmission is very low, any imported new cases can quickly drive R_0 or R_c back up, and an outbreak or even an epidemic can result in that population. This is why many malaria elimination campaigns have historically been tried first on island populations, where rates of imported malaria are relatively low, and subject to monitoring and control. Circumscribed “islands” of malaria risk also permit interventions to be applied to an entire population at risk. Where populations have contiguous risk of malaria across large geographic areas (such as much of sub-Saharan Africa) and/or where the mobility of infected humans between “islands” of risk is high (eg, across malaria-free Thailand between the malarious Thai-Burmese and Thai-Cambodian borders), applying interventions to the entire population simultaneously will be very challenging. This has implications for vaccine delivery strategies and for the duration of protection that will be needed for vaccines to succeed in elimination schemes.

P. falciparum sporozoites are transmitted to humans when a female *Anopheles* species mosquito feeds. The sporozoites rapidly invade hepatocytes, where it takes a minimum of 5.5 days for single sporozoites to develop to mature liver-stage schizonts, each of which contains tens of thousands of parasite forms called merozoites. These merozoites rupture from the hepatocytes, and each can invade an erythrocyte. Over 48 h, each merozoite can develop to a mature erythrocytic-stage schizont that contains 10–20 merozoites. These merozoites rupture from the erythrocytes and initiate the 48-h cycle of rupture, in-

vasion, development, and rupture, which causes the disease known as malaria. Alternatively, some merozoites can develop into sexual-stage parasites called gametocytes. Mosquitoes ingest these gametocytes when they feed, and the gametocytes develop in the mosquito, becoming sporozoites in ~14 days.

APPROACH TO VACCINES FOR ELIMINATION

There are 2 approaches to developing a vaccine that would prevent transmission of *P. falciparum*. The first approach is to prevent the development of gametocytes in humans. The only human data demonstrating that this can be done come from studies of vaccines that prevent the development of erythrocytic-stage infection by inducing immune responses against sporozoites and/or infected hepatocytes, thus preventing full development of schizonts in the liver. This is called a preerythrocytic-stage vaccine. Such a vaccine would be ideal, because it would prevent disease as well as transmission, providing direct benefit to the vaccinated individual. The second approach is to block transmission of parasites to mosquitoes by inducing immune responses against the sexual stages of the parasites (ie, gametocytes and gametes) and/or the mosquito stages of the parasites (ie, zygotes and ookinetes). This is called a sexual- or mosquito-stage vaccine. Although it could be an effective elimination/eradication tool, this type of vaccine, by itself, would not prevent disease in the infected individual. However, the combination of both preerythrocytic- and sexual-stage activity in a multicomponent transmission-blocking vaccine would be additive and, perhaps, synergistic in reducing transmission. In other words, if used together, a preerythrocytic-stage vaccine that is 90% effective and a sexual- and mosquito-stage vaccine that is 90% effective could reduce and eventually interrupt *P. falciparum* transmission by $\geq 99\%$, and if 100% population coverage were achieved, it could

be expected to eliminate *P. falciparum* from an area with an R_0 or R_c of <100 .

It has been demonstrated that immunization of humans by bites from mosquitoes carrying radiation-attenuated *P. falciparum* sporozoites can protect $>90\%$ of recipients against experimental challenge with *P. falciparum* sporozoites and that this protection lasts for ≥ 10 months [3]. A preerythrocytic-stage vaccine based on radiation-attenuated *P. falciparum* sporozoites is under clinical development and has entered a phase 1 clinical trial with experimental challenge initiated in 2009 [4, 5]. There has also been considerable interest in developing a sexual- and mosquito-stage vaccine, and one such vaccine targeting the surface proteins of both *P. falciparum* and *P. vivax* mosquito stages has also entered clinical trials [6]. However, it has yet to be demonstrated that such a vaccine can reduce transmission of *P. falciparum* to humans.

Our premise is not that malaria *can* be eradicated with vaccines. Rather, our view is that *if* malaria is going to be eliminated and, eventually, eradicated from the areas in which the malaria burden is greatest, it will require effective vaccines that block transmission, and we believe that this can best be achieved with preerythrocytic-stage vaccines that completely block infection.

With the use of existing tools, malaria has been, and can again be, eliminated from islands of risk, either actual sea islands like Sardinia, or “islands” of circumscribed risk, like the United Arab Emirates, which was recently certified malaria free by the World Health Organization [7]. However, where the risk of malaria is high and contiguous over large areas and where poor health systems and civil strife preclude continuous application of antivector tools and drug treatment and prevention, elimination and ultimate eradication will be extremely difficult, if not impossible, without the availability of radically different and better tools. Clearly, great reductions in malaria incidence can be achieved

with the use of existing tools, not only on islands but also in some settings in sub-Saharan Africa [8]. When control measures are applied to areas surrounded by the risk of contiguous malaria, these gains are hard fought and short-lived because, as was well-documented in a famous study conducted in Garki, Nigeria [9], parasites reinvade from the periphery through human migration, and they reemerge after the breakdown of control if transmission is below detectable limits. Thus, for sustained elimination, effective transmission-blocking measures must be successfully applied more or less simultaneously over large areas. This is very challenging, as is illustrated by the transient success of an attempt in Nicaragua to eliminate malaria by treating the entire country with antimalarial drugs simultaneously [10].

The longest-acting antimalarial drugs last only a few months, residual indoor insecticide spraying can last up to a year, and insecticide-impregnated bed nets can last up to 3 years. However, the antimalarial effects of each of these interventions depend on the compliance of the populations using them, and none has transmission-blocking efficacy that approaches the efficacy possible with a highly effective vaccine. Moreover, many vaccines provide protection that lasts for years. Of the tools that are available or envisioned, only a highly efficacious, long-lasting vaccine would provide the degree and duration of transmission-blocking needed to achieve the simultaneous protection applied across a whole population at contiguous risk that is required to reduce and maintain $R_0 < 1$ for that entire area. Vaccines are also generally safer than drugs and therefore are, for prophylactic reasons, more acceptable for administration to people who are not sick and, in later stages of elimination, to people who are at very low personal risk for the disease. All of the available tools will need to be used in a coordinated fashion with vaccines that prevent infection and transmission, if progress is to be made toward

regional elimination and global eradication of *P. falciparum* malaria.

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