A Malaria Vaccine for Control: More Progress

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(See the article by Sacarlal et al, on pages 329–36, and the article by Kester et al, on pages 337–46.)

Malaria remains the world’s major parasitic infection, causing hundreds of millions of febrile episodes and 1–2 million deaths annually—that is, 150–300 deaths occurring hourly day after day [1, 2]. It is well known that the greatest burden of falciparum malaria is borne by children and pregnant women in tropical Africa. Yet, people living on the Indian subcontinent and in other parts of Asia, Latin America, and the Western Pacific also are substantially affected by malaria disease and malaria-associated death, including disease and death caused by Plasmodium vivax, the toll of which is underappreciated (table 1) [2–4]. Malaria is also an important threat to nonimmune travelers to the tropics, causing thousands of cases of illness and occasional deaths.

Global interest in controlling malaria disease and interrupting malaria transmission has increased greatly over the past decade. In 1997, the Multilateral Initiative on Malaria was developed with the goal of improving the capacity of Africa to perform malaria research [5]. Since then, the Roll Back Malaria Partnership and Global Malaria Programme at the World Health Organization (WHO); the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria; the United States President’s Malaria Initiative; the World Bank Malaria Booster Program; the United Nations Children’s Fund; and other programs/organizations have focused on increasing funding for and delivery of existing antimalarial interventions. For now, these tools consist chiefly of artemisinin-based combination treatments and other drugs, use of long-lasting insecticide-treated bed nets, and, in some situations, spraying of insecticide within houses. With this set of tools targeting control (defined by the WHO as reducing disease rates to “acceptable” levels), dramatic reductions in malaria recently have been achieved in many countries, including some in Africa [6]. Malaria has even been completely eliminated from areas of endemicity with low levels of transmission and relatively good health infrastructure [7]. These success stories have generated such optimism that Bill and Melinda Gates, other donors, and, following their lead, malariologists, are talking again about eradication [8]. This renewed esprit de corps is occurring 54 years after the first global campaign for malaria eradication began in a similar fashion of optimism based on the availability of chloroquine for treatment and dichlorodiphenyltrichloroethane (DDT) for house spraying and almost 40 years after the program ended in a pall of discouragement, in part because of the development of resistance to these tools by parasites and mosquitoes.

Where do vaccines fit into the plan for malaria control and eradication? One element of the current optimistic thinking is that, after decades of promising advancements in the laboratory, followed by failure of vaccine candidates to provide adequate protection in the field, there finally is a malaria vaccine that prevents malaria. Developed by GlaxoSmithKline Biologicals and the Walter Reed Army Institute of Research, RTS,S (adjuvanted with AS02A or AS01B) targets the circumsporozoite protein (CSP) of Plasmodium falciparum; the vaccine is a viruslike particle expressed in Saccharomyces cerevisiae that comprises recombinant hepatitis B surface (S) antigen and a fusion protein containing the repeat (R) and C-terminal (T) regions of the CSP fused to the recombinant S antigen (hence, the name “RTS,S”) [9, 10]. A series of phase 1/2 trials of this vaccine in children and infants in malarious areas has demonstrated 30%–56% efficacy against clinical disease and up to 66% efficacy against infection, as well as a good record of safety and tolerability [11–14].

In this issue of the Journal, Sacarlal et al [15], report a 45-month follow-up study of 1465 Mozambican children aged 1–4 years who received the RTS,S/AS02A vaccine or control vaccine in the first of these pediatric efficacy trials. Their report of ef-
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As part of an effort to improve on these efficacious rates of 26% against all malaria episodes over nearly 4 years, 32% against a first or only episode of clinical malaria, and 38% for the prevention of severe clinical episodes is noteworthy [15]. After 45 months, the prevalence of parasitemia was significantly lower among vaccine recipients than in the control group (12% vs. 19%). The magnitude of the protective effect at the end of follow-up is modest, but the more important observation is that there is no evidence of a postimmunization “rebound” effect whereby the vaccine interferes with the natural acquisition of immunity to malaria by children living in areas where malaria is endemic.

As part of an effort to improve on these efficacious levels, the vaccine developers have assessed a new adjuvant system, AS01B, which differs from AS02A mainly in that it is liposomal based rather than contains an oil-in-water emulsion; both systems have the immunostimulants monophosphoryl lipid A and QS21 (a triterpene glycoside purified from the bark of *Quillaja saponaria*). On the basis of the promising observations of improved immunogenicity in mice and monkeys as a result of administration of RTS,S/AS01B vaccine [16], Kester et al [17] studied the RTS,S/AS01B and RTS,S/AS02A vaccines in non-immune adult volunteers and compared their findings with those for a group of nonvaccinated individuals in a randomized trial; malaria challenge was performed after completion of the initial vaccine series, and protected vaccine recipients were again challenged 5 months later. In this issue of the Journal, Kester et al reported that both vaccine formulations were safe and well tolerated by the 102 vaccine recipients [17]. The AS01B formulation may have better efficacy: 50% of such subjects became infected with malaria parasites at challenge, compared with 68% of subjects who received the AS02A formulation, although this difference was not statistically significant. This efficacy level is very similar to that seen in a recent field efficacy trial of RTS,S with the AS01E adjuvant in Kenyan and Tanzanian children (adjusted efficacy, 53%) [14]. With RTS,S/AS01B, there was a prolongation of time until detection of parasitemia after the initial challenge; 4 of 9 initially protected volunteers in both the RTS,S/AS01B and the RTS,S/AS02A groups did not develop parasitemia after their second challenge, compared with nonvaccinated subjects, all of whom became infected. Anti-CSP antibody titers were somewhat better with the AS01B adjuvant system; these titers, as well as CSP-specific CD4+ T cells, correlated with protection, providing a better understanding of the mechanism of protection and surrogate markers for efficacy.

It is very good news that RTS,S in the formulation with the less immunostimulatory adjuvant system showed measurable efficacy and no evidence of rebound almost 4 years after immunization, even in the face of a decreasing annual rate of incidence of clinical malaria at the Mozambique study site, from 0.70 to 0.15 episodes/person-years at risk throughout the observation period. These results suggest that this vaccine could be a valuable addition to the toolbox for malaria control, with a substantial influence on the disease burden in children. What remains to be learned is whether the vaccine will contribute to interrupting malaria transmission.

RTS,S targets the preerythrocytic stage of the *P. falciparum* life cycle (figure 1), and it was conceived as an infection-blocking vaccine. However, it does not completely prevent infection, and none of the published clinical trials has reported postimmunization rates of gametocytes, the sexual stage of the parasite that is transmitted to mosquitoes. Careful review of blood smear specimens for gametocytes from these published studies could provide clues as to whether the vaccine has any effect on malaria transmission—either transmission blocking or transmission enhancing. Gametocyte carriage increases when malaria parasites are stressed, e.g., by drugs or immunity [18], and it is possible that a vaccine that protects the individual recipient against disease could have an unintended paradoxical effect of increasing the risk of transmission of the infection to others.

### Table 1. Malaria Cases in the World Caused by *Plasmodium falciparum* and *Plasmodium vivax*, 2004–2005

<table>
<thead>
<tr>
<th>Region</th>
<th><em>P. falciparum in 2005</em></th>
<th><em>P. vivax in 2004</em></th>
<th><em>P. falciparum</em> plus <em>P. vivax</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population at riska, no. (range); %</td>
<td>Cases, b</td>
<td>Population at riska, no. (range); %</td>
</tr>
<tr>
<td>Africa</td>
<td>521</td>
<td>365 (215–374); 57</td>
<td>50</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1314</td>
<td>119 (66–224); 34</td>
<td>1347</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>142</td>
<td>15 (9–26); 4</td>
<td>890</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>176</td>
<td>12 (5–25); 4</td>
<td>211</td>
</tr>
<tr>
<td>Americas</td>
<td>55</td>
<td>4 (2–8); 1</td>
<td>78</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>1 (0–1); &lt;1</td>
<td>20</td>
</tr>
<tr>
<td>All</td>
<td>2212</td>
<td>516 (297–658); 100</td>
<td>2596</td>
</tr>
</tbody>
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a Expressed as millions of individuals.
b Expressed as millions of cases.

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Kester et al noted that studies are currently evaluating vaccines on the basis of the presence of blood-stage antigens merozoite surface protein–1 (MSP-1) and apical membrane antigen–1 (AMA-1), with use of the same adjuvant systems as RTS,S, with the goal of developing a more highly efficacious second-generation vaccine. Strong consideration should be given to including a transmission-blocking component in a multistage, multiantigen RTS,S-based vaccine. Of course, the greatest boon to eradication will be a vaccine that blocks transmission by preventing development of gametocytes in humans or maturation to sporozoites in mosquitoes. Several research groups are working on such transmission-blocking vaccines, both for *P. falciparum* (Pfs25) and for *P. vivax* (Pvs25) [9, 19, 20]. We hope that the malaria vaccine community will work together to match the best antigens with the best adjuvant systems, to build the best possible vaccine for malaria elimination and eradication.

Constructing the ideal malaria vaccine piece by piece might work, but it will not
be easy. In addition to combining antigens targeting multiple stages of the parasite life cycle, multiple alleles of some antigens may be needed. Although RTS,S has not yet shown evidence of selecting "vaccine-resistant" strains [21], blood-stage antigens like MSP-1 and AMA-1 are highly polymorphic, and it is likely that \( \geq 2 \) variants will be needed to protect against naturally diverse variants. By the time the individual components of a multicomponent vaccine are designed, manufactured, and subjected to preclinical and clinical testing both alone and in combination, it could turn out to be just as quick to take on a different thorny challenge—manufacturing a live attenuated whole-organism parasite vaccine in mosquitoes [22]. Multistage, multiantigen vaccines, attenuated sporozoite vaccines, and other transmission-blocking vaccines are far upstream of RTS,S in the development pipeline. However, it is clear that radically better and new tools will be needed for the sustained interruption of transmission that will be required for permanent elimination of malaria in areas where transmission is currently high.

Even if RTS,S/AS01B and the next generations of malaria vaccines prove to be better at preventing disease in individuals than at blocking infection and transmission, they can still play an important role in reducing malaria disease and associated deaths. At the same time, we need intensified research and development not only of vaccines that block transmission but, also, of better antivector methods and effective transmission-blocking drugs. These new interventions will accelerate elimination of malaria from countries and contribute to achieving global eradication.

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**References**


