A Malaria Vaccine for Control: More Progress

Joel G. Breman, Christopher V. Plowe

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 endemcity 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, malarialogists, 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 [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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EDITORIAL COMMENTARY

P. vivax and P. falciparum

• coside purified from the bark of Quillaja saponaria

an oil-in-water emulsion; both systems
are liposomal-based rather than contains
which differs from AS02A mainly in that

assessed a new adjuvant system, AS01B,
efficacy, the vaccinated subjects have
did not develop parasitemia 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>Population at risk a</th>
<th>Cases, b no. (range); %</th>
<th>Population at risk a</th>
<th>Cases, b range (%)</th>
<th>Cases, b range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>521</td>
<td>365 (215–374); 57</td>
<td>50</td>
<td>&lt;1</td>
<td>215–374</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1314</td>
<td>119 (66–224); 34</td>
<td>1347</td>
<td>90–248 (63)</td>
<td>156–472</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>142</td>
<td>15 (9–26); 4</td>
<td>890</td>
<td>20–77 (20)</td>
<td>29–103</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>176</td>
<td>12 (5–25); 4</td>
<td>211</td>
<td>11–34 (9)</td>
<td>16–59</td>
</tr>
<tr>
<td>Americas</td>
<td>55</td>
<td>4 (2–8); 1</td>
<td>78</td>
<td>10–28 (7)</td>
<td>12–36</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>1 (0–1); &lt;1</td>
<td>20</td>
<td>1–4 (1)</td>
<td>1–5</td>
</tr>
<tr>
<td>All</td>
<td>2212</td>
<td>516 (297–658); 100</td>
<td>2596</td>
<td>132–391 (100)</td>
<td>429–1049</td>
</tr>
</tbody>
</table>

a Expressed as millions of individuals.
b Expressed as millions of cases.
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 ≳ 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-organisms 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