EDITORIALS

A Hopeful Beginning for Malaria Vaccines

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An effective human malaria vaccine has been sought for over 70 years, with little success.[1] A successful malaria vaccine used in conjunction with other control interventions would help reduce and eventually eliminate the considerable global disease burden caused by malaria. Many different antigens have been identified as potential targets for malaria-vaccine development. One of these, the repetitive sequence of four amino acids in the circumsporozoite antigen on the surface of the sporozoite of *Plasmodium falciparum*, arguably the most important of the human malarias, is the basis for the RTS,S vaccine.[2] This vaccine was subjected to extensive studies involving human volunteers, the results of which indicated a potential protective efficacy of about 40% when the vaccine was used in combination with an effective adjuvant therapy.[3,4] Subsequently, a number of field studies have indicated that in endemic areas, this vaccine could have a rate of efficacy of about 30% against clinical disease and about 40% against new cases of infection.[5,6] This is the first candidate malaria vaccine to show significant protection in laboratory- and field-based clinical studies.

The evaluation of the safety and efficacy of malaria vaccines in infants and children is of utmost importance because most deaths and illness from malaria occur in these age groups, in areas of moderate-to-high transmission. In this issue of the *Journal*, Abdulla et al.[7] describe their safety and immunogenicity trial in which the RTS,S vaccine was used in combination with the AS02D adjuvant (ClinicalTrials.gov number, NCT00289185). The RTS,S/AS02D vaccine had a reasonable safety profile as compared with the control hepatitis B vaccine, and anticircumsporozoite-antibody titers were detectable in more than 98% of the infants receiving the RTS,S/AS02D vaccine. In this trial, RTS,S was given along with other vaccines for children (a vaccine containing diphtheria and tetanus toxoids, whole-cell pertussis vaccine, and conjugated *Haemophilus influenzae* type b vaccine), according to the Expanded Program on Immunization (EPI) schedule. There was no interference with immune responses to the EPI vaccines. This result suggests that it will be feasible to provide RTS,S together with other routine children's vaccines, making its delivery in endemic areas much easier and less costly. During the 6-month period after immunization, the incidences of malarial infection and clinical disease in the RTS,S group were reduced by 65% and 59%, respectively. There was a correlation between a reduced risk of infection and increased circumsporozoite antibody titers. There was no association, however, between a reduction in the incidence of clinically active malaria and an increased circumsporozoite-antibody titer.

Also in this issue, Bejon et al.[8] report on a phase 2b safety and efficacy trial of the RTS,S vaccine combined with the AS01E adjuvant, in children 5 to 17 months of age (NCT00380393). The RTS,S/AS01E vaccine was associated with fewer severe adverse events than the control rabies vaccine. Overall, there was an unadjusted rate of efficacy of 60% against all episodes of *P. falciparum* clinical malaria, with anticircumsporozoite-antibody titers detectable in more than 99% of the recipients of the RTS,S/AS01E vaccine. However, as in the trial by Abdulla et al., there was no evidence that protection against clinical disease was correlated with anticircumsporozoite titers in children vaccinated with RTS,S/AS01E. The AS01E adjuvant used by Bejon et al. was developed to enhance the immune response to the circumsporozoite target antigen and, it was hoped, provide greater efficacy than the AS02D adjuvant used

by Abdulla et al. and in earlier clinical studies of RTS,S.

A comparison of the two articles reveals that the mean circumsporozoite antibody titers among the children receiving the RTS,S/AS01E vaccine were approximately 10 times that among those receiving the RTS,S/AS02D vaccine. However, although the overall mean antibody titers were lower with the AS02D adjuvant, both in the trial by Abdulla et al. and in a previous trial involving infants in Mozambique,[9] the protection against infection and clinical disease was similar to that in the trial of AS01E by Bejon et al. In the studies by Abdulla and Bejon and their colleagues, the efficacy against clinical disease did not differ whether AS01E or AS02D was used as an adjuvant, but the efficacy with either is greater than the 30% rate reported in a previous trial.[6] Whether the higher antibody titers associated with the use of AS01E might translate into a longer duration of protective efficacy for the RTS,S vaccine remains to be demonstrated.

The correlation of reduced incidence of infection with higher antibody levels is encouraging and intuitive, given the biologic basis of infection. Correlations between antibody levels and protection against disease are more difficult to reconcile in the context of the biologic features of malaria and the target of this vaccine. In humans, there are two main developmental stages of the malaria life cycle: the exoerythrocytic stage in the liver, involving the sporozoite and hypnozoite, and the erythrocytic stage in the blood, involving the merozoite. Immunity acquired against one form of the malaria parasite does not operate against other forms. Sporozoites — the target of RTS,S — are injected into humans through mosquito bites, infect hepatocytes, and initiate the development of other liver-stage parasites. One sporozoite produces thousands of merozoites that parasitize erythrocytes to initiate the blood stage of infection, which in turn produces the clinical disease of malaria. Thus, if immune responses generated by "leaky" pre-erythrocytic vaccines such as RTS,S fail to block just a single sporozoite from invading or developing in the hepatocyte, then a blood-stage infection will follow, and typical paroxysmal fevers and, perhaps, severe malarial disease will manifest.

Although the results of Abdulla et al. and Bejon et al. are promising, the baseline incidence of malaria was low in each study area. Evaluations of vaccine-efficacy studies can be complicated by the introduction of insecticide-treated bed nets and artemisinin-based combination drug treatments through ongoing control programs across sub-Saharan Africa.[10] Recent reports indicate that, in some areas in which malaria is endemic, such as in the Gambia in West Africa and Kenya and Tanzania in East Africa, there have been dramatic reductions in the malarial disease burden.[11,12]

However, as the RTS,S vaccine heads into phase 3 trials in 2009, large areas across Africa still have moderate-to-intense malaria transmission. Malaria transmission of yet higher intensity, with greater and more continuous assault by mosquito-injected sporozoites, could affect the efficacy of this vaccine.[6] This is the first malaria vaccine to reach this stage of development, and it will be essential to learn how it performs in areas of more intense transmission. Only then will we have a clear idea of what effect it will have on the well-being of children in Africa and elsewhere and its role in malaria control. It is, indeed, a hopeful beginning.

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Real-World Therapies and the Problem of Vivax Malaria

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Wellems and Miller[1] wrote of two worlds of malaria: one, of the residents of rural tropical areas in which the disease is endemic, and the other, of travelers to those areas, who typically have greater resources. The distinction is sharp, valid, and important in considering the development of tools to combat the global burden of malaria. Drugs considered safe and effective in one world may not be so in the other.[2] The majority of the hundreds of millions of people in whom malaria will develop over the next year will obtain and consume antimalarial medication without medical supervision. Although the licensing of complex or poorly tolerated therapeutic regimens requiring clinical screening for contraindications may be perfectly suitable for populations with access to close clinical supervision, distributing the same regimen in the rural tropics is reckless.

Two other worlds of malaria are those with and without endemic *Plasmodium vivax*. Vivax malaria was known as "benign tertian malaria" for more than a century and is still viewed as rarely dangerous; evidence suggests a historical underestimation of both the burden of disease and the potential for death with *P. vivax* infection.[3-7] Endemic vivax malaria occurs throughout the tropics, except where there is a natural absence of anopheline mosquitoes (east of Vanuatu in the South Pacific) or among populations lacking the Duffy receptor on red cells (in much of Africa). Vivax malaria stands alone among the plasmodia infecting humans in its capacity to reach well into the temperate latitudes, as it does today — up to the Korean peninsula and across the southern temperate latitudes of Asia to the Mediterranean Sea. Approximately 2.6 billion people are at risk, and estimates of annual infections range from 70 to 390 million,[3,4] with about 80% occurring in South and Southeast Asia. Vivax malaria accounts for at least 70% of the malaria burden in the Americas.

Objective examination of the clinical evidence underpinning available therapies for *P. vivax* infection reveals a conspicuous neglect of this parasite.[5] More importantly, the analytical tools for critically assessing experimental or standard therapies may be considered insufficient, at best, for the task of identifying the treatments that are safe and effective and capable of reducing the disease burden of vivax malaria.

The distinction between the worlds of malaria with and without *P. vivax* finds expression in the study by Karunajeewa et al.[8] (Australian New Zealand Clinical Trials Registry number, ACTRN12605000550606) reported in this issue of the *Journal*. This state-of-the-art clinical trial evaluates the safety, tolerability, and efficacy of therapeutic options among young children exposed to endemic falciparum and vivax malaria in Papua New Guinea. By virtue of the analytical tools applied, the findings with regard to *P. falciparum* provide useful insights. The estimated 88% efficacy of dihydroartemisinin–piperaquine falls well below other estimates of efficacy for this combination against this parasite. The authors point to both suboptimal absorption of piperaquine and to cross-resistance between chloroquine and piperaquine by local parasites in vitro as a possible basis for the relatively poor performance of the drug combination. Their carefully assembled evidence makes a compelling case for the selection of artemether–lumefantrine for treatment of uncomplicated falciparum malaria in northwestern Papua New Guinea.

The authors have much less analytical leverage with regard to the data on *P. vivax*, however. The liver stage of *P. vivax* responsible for relapse (the hypnozoite) casts a nearly opaque shadow of ambiguity across the data. The curve showing occurrences of recrudescent infection provides almost no useful information for discerning the advantage of one therapeutic option over another: