Safety and Immunogenicity of a Recombinant Nonglycosylated Erythrocyte Binding Antigen 175 Region II Malaria Vaccine in Healthy Adults Living in an Area Where Malaria Is Not Endemic

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The morbidity and mortality associated with malaria continue to exact a heavy price on many developing nations. The World Health Organization (WHO) estimates that 3.3 billion individuals live in areas where malaria is endemic, with 247 million cases and a million deaths reported for the year 2006 (41). In 1998, the Roll Back Malaria Partnership was launched to coordinate international malaria containment efforts and included the wide dissemination of long-lasting insecticidal nets, artemisinin-based combination therapy, indoor residual spraying of insecticide, and intermittent preventive treatment in pregnancy. In 2006, the success of implementing these interventions was variable, with some countries reporting a 50% decrease in the number of malaria cases and other countries reporting stable levels of transmission (5, 8, 13, 41).

Some pieces missing from the available armamentarium to fight malaria are safe and effective vaccines. Plasmodium falciparum is the species associated with the greatest morbidity and mortality. The approach to the development of a P. falciparum vaccine has paralleled the multistage nature of P. falciparum infections: preerythrocytic vaccines target the sporozoite or its antigens to achieve protection from infection; erythrocytic vaccines target the merozoite antigens to achieve protection from severe disease; and transmission-blocking vaccines utilize the gametocyte, zygote, or oocyte antigens to prevent sporogonic development in the vector (4, 11, 15, 16, 34, 35, 40). A multicomponent or multistage vaccine has also been proposed as a solution to the heterogeneity of the host’s immune response and the parasite antigens.

One antigen of interest in the development of P. falciparum erythrocytic vaccines is the erythrocyte binding antigen 175 (EBA-175). EBA-175 was the first P. falciparum ligand identified to have a role in high-affinity binding of the merozoite to the host’s red blood cells (RBCs) (1, 7). EBA-175 binds to the RBC glycophorin A sialic acid residues, and the interaction constitutes a major invasion pathway. The cysteine-rich second region of EBA-175 (EBA-175-RII) is the erythrocyte binding domain of the protein and is highly conserved among laboratory and clinical P. falciparum strains (19, 37). Antibodies against EBA-175-RII have been detected among individuals living in areas where malaria is endemic, with an increasing prevalence with age and a trend of disease attenuation at high antibody levels (27, 28). Antibodies directed against EBA-175-RII are capable of blocking the merozoite invasion of RBCs (39). Interestingly, anti-EBA-175-RII antibodies not only were capable of blocking the sialic acid-dependent invasion pathways but also inhibited alternative, sialic acid-independent pathways (24, 30).

Taken together, the aforementioned data suggest that EBA-175-RII is a plausible vaccine candidate, especially when incorporated into a multicomponent vaccine to overcome allelic heterogeneity and/or the use of sialic acid-independent pathways by the parasite (2, 3, 27, 29). Sim and colleagues evaluated the immunogenicity of a DNA vaccine that expressed EBA-175-RII in mice, rabbits, and monkeys and found the vaccine to be safe and immunogenic (38). The antibodies produced were shown to inhibit the merozoite invasion of RBCs,
and one of three vaccinated *Aotus* monkeys was protected from fulminant disease upon challenge (38). Jones and colleagues evaluated the immunogenicity and efficacy of 4 doses of a DNA vaccine expressing EBA-175-RII, a recombinant EBA-175-RII vaccine with adjuvant, or a combination of DNA and EBA-175-RII protein vaccines (17). Vaccinated monkeys had lower levels of parasitemia on challenge with parasitized RBCs than did control monkeys, and 3 of 4 monkeys receiving the DNA-protein combination had mild symptoms that did not require treatment (17). The promising preclinical data have prompted the development of a recombinant vaccine for use in human clinical trials.

The expression of nonglycosylated EBA-175-RII (EBA-175-RII NG; referred to as EBA-175 in the rest of the text) was initially performed in a baculovirus expression system (when expressed by *P. falciparum*, the protein is nonglycosylated); however, the system’s productivity was low. Expression of codon-optimized EBA-175 in the yeast *Pichia pastoris* resulted in high-yield production of properly folded protein (42). Preclinical studies of the recombinant vaccine in mice have shown the vaccine to have an acceptable safety profile and an immunogenicity that is enhanced by the use of adjuvants. The expectation that the vaccine may be stored at a wide range of temperatures in developing countries necessitated a choice of vaccine excipient and adjuvant that allow maximum antigen stability. A study performed by Peek and colleagues demonstrated improved antigen stability for an aluminum phosphate adjuvant (Adju-Phos) and sucrose coformulation (31).

We performed a phase I clinical trial to evaluate the safety and immunogenicity of escalating doses of recombinant EBA-175 with Adju-Phos in healthy young adults residing in a region where malaria is not endemic.

(MATERIALS AND METHODS

**Subjects.** Study subjects were adults between the ages of 18 and 40 years with no known acute or chronic medical conditions. We excluded subjects who lived previously in regions where malaria is endemic, were diagnosed with malaria in the past, had received a malaria vaccine, or were expected to travel to a region of malaria endemicity during the study period. We also excluded subjects who had immunosuppression due to medications or underlying conditions.

**Vaccine.** The study product was manufactured by Cambrex Biosciences, Inc., and Hollister STER Laboratories, LLC. The vaccine was manufactured according to good manufacturing practices. The purity of the antigen used in the clinical trial was >97%. The vaccine was released in August 2005 and maintained all stability parameters, including a specification of >90% antigen binding to aluminum, throughout its clinical use. The vaccine was supplied in single-dose vials. Each 2-ml vial contained EBA-175 at the desired concentration, 5% sucrose, 0.5 mg Adju-Phos, and sodium phosphate buffer. The adjuvant dose was constant, at 0.5 mg, for all tested vaccine dosages. The placebo used was normal saline.

**Study design.** The study was a phase I, double-blinded, placebo-controlled dose escalation study to assess the safety and immunogenicity of EBA-175 with alum adjuvant given intramuscularly at 0, 1, and 6 months. The EBA-175 doses used were 5 µg, 20 µg, 80 µg, and 160 µg. Each study group consisted of 20 subjects: 18 subjects received the study article, and 2 subjects received placebo. The study groups were enrolled sequentially, and dose escalation proceeded subjects: 18 subjects received the study article, and 2 subjects received placebo.

**Study procedures.** After signing an informed consent document, the subjects were screened for eligibility by review of the inclusion-exclusion criteria and medical history, a targeted physical examination, blood tests, urinalysis, and pregnancy testing (for females). Subjects were randomized to receive placebo or vaccine by use of the R program (R Foundation for Statistical Computing, Vienna, Austria). An unblinded nurse who was not subsequently involved in the assessment of vaccine reactogenicity administered vaccine or placebo intramus-
decided to discontinue contraception. 2 subjects completed all in-clinic visits but not the final phone interview to collect SAE data. 1 subject had an acute illness at the time of the third dose, and 1 subject was diagnosed with hypogonadism, with symptoms predating his enrollment that were not disclosed. The demographics of study subjects are presented in Table 1. There were no significant differences in the distributions of the baseline characteristics among the different study groups.

**Vaccine reactogenicity.** Headache was the most common solicited systemic AE experienced by subjects across treatment groups, followed by malaise and fatigue. Most of the solicited AEs were mild to moderate in severity (Table 2). Three subjects experienced severe solicited systemic AEs: 1 subject in the group receiving 20 μg EBA-175 experienced severe headaches 6 days after the 1st injection but no severe headaches after the 2nd or 3rd injection; 1 subject in this group reported severe feverishness, chills, and headaches associated with abdominal cramps 6 days after the 1st injection but no severe symptoms after the 2nd or 3rd injection; and 1 subject in the group receiving 160 μg EBA-175 reported severe arthralgias, myalgias, and malaise associated with an episode of gastroenteritis 3 days after the 1st injection but no severe symptoms after the 2nd or 3rd injection. The percentages of subjects who experienced any solicited systemic AE were not significantly different between study groups (Fig. 1).

There were 36 unsolicited AEs that were considered to be associated with the study products; all were mild to moderate in intensity. There were no SAEs reported during the study. The percentage of subjects in each group who experienced any unsolicited AE is shown in Fig. 1. The frequencies of subjects experiencing unsolicited AEs in the placebo, 5-μg, 20-μg, 80-μg, and 160-μg groups were 9.4% (95% confidence interval [CI], 8.5 to 10.3%), 16.7% (95% CI, 8.2 to 27.3%), 66.7% (95% CI, 59.0 to 75.5%), 33.3% (95% CI, 13.3 to 59.0%), and 5.6% (95% CI, 0.1 to 27.3%), respectively. Subjects in the group receiving 20 μg EBA-175 at 5-μg (95% CI, 0.1 to 27.3%) had a significantly higher frequency of unsolicited AEs than did those in the other groups (P < 0.05): the risk ratios for experiencing an unsolicited AE for the 20-μg versus 5-μg, 80-μg, and 160-μg groups were 2.30 (95% CI, 0.72 to 3.88), 1.39 (95% CI, 0.00 to 2.77), and 3.53 (95% CI, 1.28 to 5.77), respectively.

Most of the injection site AEs were mild to moderate in intensity, with pain being the most common complaint. Only 2 adverse events were graded as severe: 1 subject in the group receiving 80 μg EBA-175 and 1 subject in the group receiving 160 μg EBA-175 experienced grade 3 erythema and induration following the 3rd injection. The percentage of subjects in each group who experienced any injection site AE is shown in Fig. 1. All 4 vaccine groups had significantly higher frequencies of injection site AEs than the placebo group (P < 0.05).

**Serologic response.** We performed ELISAs to measure the anti-EBA-175 antibody levels before and 14 days after each vaccine dose. No appreciable antibody levels were observed at baseline or 14 days following the first vaccine for all study groups. Fourteen days after the 2nd dose, subjects who received EBA-175 at any of the tested doses had antibody geometric mean titers (GMTs) that were significantly higher than that of the placebo group (P < 0.05) (Fig. 2). Specifically, there were 18.24-fold (95% CI, 7.87- to 42.26-fold), 91.29-fold (95% CI, 44.77- to 186.14-fold), 96.72-fold (95% CI, 48.04- to 194.70-fold), and 68.91-fold (95% CI, 31.77- to 149.48-fold) rises in GMT compared to that of the placebo group for the 5-μg, 20-μg, 80-μg, and 160-μg groups, respectively. The statistically significant rise in GMT was maintained 14 days after the 3rd dose, when we found 297.67-fold (95% CI, 145.45- to 609.21-fold), 458.68-fold (95% CI, 299.79- to 701.78-fold), and 537.53-fold (95% CI, 204.59- to 1,412.32-fold) rises in GMT compared to that of the placebo group for the 5-μg, 20-μg, 80-μg, and 160-μg groups, respectively. The statistically significant rise in GMT was maintained 14 days after the 3rd dose, when we found 297.67-fold (95% CI, 145.45- to 609.21-fold), 458.68-fold (95% CI, 299.79- to 701.78-fold), and 537.53-fold (95% CI, 204.59- to 1,412.32-fold) rises in GMT compared to that of the placebo group for the 5-μg, 20-μg, 80-μg, and 160-μg groups, respectively. The statistically significant rise in GMT was maintained 14 days after the 3rd dose, when we found 297.67-fold (95% CI, 145.45- to 609.21-fold), 458.68-fold (95% CI, 299.79- to 701.78-fold), and 537.53-fold (95% CI, 204.59- to 1,412.32-fold) rises in GMT compared to that of the placebo group for the 5-μg, 20-μg, 80-μg, and 160-μg groups, respectively. After the 2nd dose, subjects who received EBA-175 at the 5-μg dose had significantly lower antibody levels than those who received EBA-175 at doses of 20, 80, and 160 μg (P < 0.05). However, 14 days after the 3rd dose, only subjects who received 80 μg of EBA-175 had antibody levels that were significantly higher than those of subjects who received 5 μg of EBA-175 (Fig. 2).

**Growth inhibition assay.** We tested the ability of the anti-EBA-175 antibodies to inhibit the growth of *P. falciparum*
parasites before vaccination (day 0) and 14 days after the 3rd dose (day 194). At baseline, all study groups had a negligible ability to inhibit the growth of *P. falciparum*. On day 194, vaccine recipients of any EBA-175 dose had a significantly higher mean percent *P. falciparum* growth inhibition than placebo recipients. Receiving EBA-175 at a dose of 80 \(\mu g\) or 160 \(\mu g\) resulted in a significantly higher mean percent *P. falciparum* growth inhibition than receiving an EBA-175 dose of 5 \(\mu g\) (Fig. 3). On day 0, we found no correlation between the anti-EBA-175 levels measured by ELISA and the percent growth inhibition for any dose level, using the Spearman correlation coefficient test. However, on day 194, there was a significant correlation between anti-EBA-175 levels and percent growth inhibition for all tested doses (\(P < 0.001\) for the 5-, 20-, and 160-\(\mu g\) groups and \(P = 0.003\) for the 80-\(\mu g\) group) and for all groups combined (\(P < 0.001\)).

**Red blood cell binding assay.** Two subjects who received EBA-175 at the 160-\(\mu g\) dose had insufficient serum volumes to perform the study, and 2 other subjects did not receive all vaccine doses. The RBC binding assay was performed on sam-

| Table 2. Solicited adverse events by treatment group |
|-----------------------------------------------|
| **Adverse event** | **EBA-175 at 5 \(\mu g\)** | **EBA-175 at 20 \(\mu g\)** | **EBA-175 at 80 \(\mu g\)** | **EBA-175 at 160 \(\mu g\)** | **Placebo** |
| | \((n = 18)\) | \((n = 18)\) | \((n = 18)\) | \((n = 18)\) | \((n = 8)\) |
| **Systemic AEs** |  |
| Fever |  |
| Any | 0 (0) | 1 (5.6) | 1 (5.6) | 1 (5.6) | 0 (0) |
| Grade of \(\geq 2\) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Feverishness |  |
| Any | 2 (11.1) | 5 (27.8) | 4 (22.2) | 2 (11.1) | 0 (0) |
| Grade of \(\geq 2\) | 1 (5.6) | 1 (5.6) | 2 (11.1) | 1 (5.6) | 0 (0) |
| Myalgia |  |
| Any | 4 (22.2) | 6 (33.3) | 5 (27.8) | 2 (11.1) | 1 (12.5) |
| Grade of \(\geq 2\) | 1 (5.6) | 2 (11.1) | 3 (16.7) | 1 (5.6) | 1 (12.5) |
| Chills |  |
| Any | 1 (5.6) | 2 (11.1) | 4 (22.2) | 4 (22.2) | 0 (0) |
| Grade of \(\geq 2\) | 1 (5.6) | 1 (5.6) | 2 (11.1) | 1 (5.6) | 0 (0) |
| Headaches |  |
| Any | 13 (72.2) | 12 (66.7) | 10 (55.6) | 9 (50.0) | 5 (62.5) |
| Grade of \(\geq 2\) | 3 (16.7) | 7 (38.9) | 6 (33.3) | 3 (16.7) | 2 (25.0) |
| Nausea |  |
| Any | 1 (5.6) | 4 (22.2) | 7 (38.9) | 2 (11.1) | 0 (0) |
| Grade of \(\geq 2\) | 1 (5.6) | 1 (5.6) | 2 (11.1) | 1 (5.6) | 0 (0) |
| Malaise |  |
| Any | 0 (0) | 4 (22.2) | 6 (33.3) | 3 (16.7) | 0 (0) |
| Grade of \(\geq 2\) | 0 (0) | 2 (11.1) | 0 (0) | 2 (11.1) | 0 (0) |
| Fatigue |  |
| Any | 5 (27.8) | 6 (33.3) | 8 (44.4) | 5 (27.8) | 2 (25.0) |
| Grade of \(\geq 2\) | 1 (5.6) | 1 (5.6) | 3 (16.7) | 2 (11.1) | 1 (12.5) |
| Arthralgia |  |
| Any | 3 (16.7) | 1 (5.6) | 3 (16.7) | 2 (11.1) | 1 (12.5) |
| Grade of \(\geq 2\) | 1 (5.6) | 0 (0) | 2 (11.1) | 1 (5.6) | 1 (12.5) |
| Generalized itching |  |
| Any | 1 (5.6) | 2 (11.1) | 1 (5.6) | 1 (5.6) | 0 (0) |
| Grade of \(\geq 2\) | 0 (0) | 0 (0) | 1 (5.6) | 0 (0) | 0 (0) |
| **Injection site reactions** |  |
| Pain |  |
| Any | 14 (77.8) | 16 (88.9) | 17 (94.4) | 17 (94.4) | 1 (0) |
| Grade of \(\geq 2\) | 1 (5.6) | 3 (16.7) | 4 (22.2) | 1 (5.6) | 0 (0) |
| Itching |  |
| Any | 2 (11.1) | 2 (11.1) | 2 (11.1) | 2 (11.1) | 0 (0) |
| Grade of \(\geq 2\) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Erythema |  |
| Any | 7 (38.9) | 8 (44.4) | 9 (50.0) | 8 (44.4) | 2 (25.0) |
| Grade of \(\geq 2\) | 0 (0) | 0 (0) | 1 (5.6) | 2 (11.1) | 0 (0) |
| Induration |  |
| Any | 2 (11.1) | 8 (44.4) | 9 (50.0) | 7 (38.9) | 2 (0) |
| Grade of \(\geq 2\) | 0 (0) | 0 (0) | 2 (11.1) | 2 (11.1) | 0 (0) |
| Edema |  |
| Any | 0 (0) | 1 (5.6) | 1 (5.6) | 0 (0) | 0 (0) |
| Grade of \(\geq 2\) | 0 (0) | 0 (0) | 1 (5.6) | 0 (0) | 0 (0) |

*a* EBA-175 denotes EBA-175-RII NG plus Adju-Phos.  
*b* For erythema and induration, we used the maximum reported diameter on the diary card or during the in-clinic examination.
samples from the remaining 14 subjects who received the vaccine. Day 194 sera from all tested subjects qualitatively inhibited the binding of recombinant EBA-175 to RBCs. The baseline day 0 sera from all subjects did not inhibit the binding of recombinant EBA-175 to RBCs.

DISCUSSION

We present safety and immunogenicity data from the first trial evaluating the use of recombinant EBA-175 with adjuvant in humans. Overall, the vaccine was safe and well tolerated at the tested doses. Grade 3 injection site AEs occurred in 2 subjects, were mostly related to the size of the lesions, and were not associated with functional limitations. Solicited and unsolicited systemic AEs were mostly mild to moderate in intensity and were self-limited, occurring at comparable frequencies in placebo and vaccine recipients. Severe systemic reactions occurred in 3 subjects following their first dose, with no recurrence following subsequent doses, making a relationship to the vaccine less likely. No SAEs were noted in the study. In particular, we documented no instance of anaphylaxis or immediate-type hypersensitivity reactions, a type of reaction noted in some clinical trials evaluating other malaria vaccine constructs (18, 23). Although the sample size is small enough to make the likelihood of missing such an event a possibility, our findings provide reassurance to advance the development

FIG. 1. Percentages of subjects who experienced solicited systemic, unsolicited systemic, and solicited local adverse events. **, $P < 0.05$ for comparisons of the frequencies of unsolicited adverse events between the 20-μg group and the 5-μg, 80-μg, and 160-μg EBA-175 groups; *, $P < 0.05$ for comparisons of the frequencies of local adverse events between the placebo group and the 20-μg, 80-μg, and 160-μg EBA-175 groups.

FIG. 2. Antibody geometric mean titers (log scale) for the 5 study groups prevaccine (day 0), 14 days after the 1st dose (day 14), 14 days after the 2nd dose (day 42), and 14 days after the 3rd dose (day 194). *, $P < 0.05$ for comparisons of the placebo antibody levels to the levels in the 5-μg, 20-μg, 80-μg, and 160-μg EBA-175 groups on days 42 and 194; §, $P < 0.001$ for comparisons of the antibody levels in the 5-μg group to the levels in the 20-μg, 80-μg, and 160-μg groups on day 42; ¶, $P < 0.05$ for comparison of the antibody levels in the 5-μg group to the levels in the 80-μg group on day 194.
of the vaccine. There may be a difference in the injection site and systemic reactogenicities of the vaccine between malaria-naive and semi-immune subjects living in areas of endemicity, with the latter group being the more important target of vaccine development efforts. Clinical trials in areas of endemicity will help to resolve this issue.

The vaccine was immunogenic at the tested dosages. To produce appreciable levels of anti-EBA-175, at least two doses of vaccines were required. A partial dose-response effect was observed: the higher vaccine doses (20, 80, and 160 μg) resulted in significantly higher anti-EBA-175 levels than the lower vaccine dose (5 μg) following the 2nd dose, but after the 3rd dose only the 80-μg dose resulted in antibody levels that were significantly higher than those elicited in the 5-μg group. Increasing the vaccine dose from 80 μg to 160 μg did not result in improved antibody levels. A threshold anti-EBA-175 level at which one expects a disease-modifying effect is currently not known. However, current evidence suggests that anti-EBA-175 increases in prevalence with age in areas where malaria is endemic, and higher levels may be associated with clinical protection (27, 28).

There is no single in vitro immune correlate of protection against malaria. As a result, an evaluation of the functional properties of the antibodies becomes important. We have demonstrated that the antibodies elicited by the study vaccine have functional activity and that higher antibody levels correlate with improved activity. All tested sera from subjects who received the highest dose were able to inhibit the binding of recombinant EBA-175 to RBCs (a surrogate for erythrocyte invasion). Although sera from subjects who received lower doses were not tested, the antibody levels produced in response to vaccination with 160 μg EBA-175 were not significantly different from those elicited by lower doses, suggesting that a similar result would be obtained. All tested doses of the vaccine elicited antibodies capable of inhibiting parasite growth in vitro, with the highest two doses resulting in the highest percentages of growth inhibition. Although it is important to demonstrate functional properties of the antibodies, the relationship to protection from disease is unclear. In at least one instance, researchers found that a higher percentage of P. falciparum growth inhibition did not significantly correlate with protection from clinical disease in residents of an area where malaria is mesoendemic (32). However, Crompton et al. reported recently that in children living in Mali, the higher the level of P. falciparum growth inhibition, the lower was the risk of malaria, and they showed that the odds ratio of experiencing a malaria episode for children with a GIA level of <40% was 10.4 compared to children with a GIA level of 40% or more (9). The P. falciparum growth inhibition associated with a certain vaccine depends on the antigen, adjuvant, and species in which the vaccine is tested. For example, adding the cpg adjuvant to a PIMSP142–C1–Alhydrogel vaccine in humans increases the GIA value from 3% to 14% (12). Using an adenovirus vector to deliver apical membrane antigen 1 (AMA-1) or MSP1α2, Bruder et al. demonstrated 99% and 60% inhibition of P. falciparum growth, respectively (6). Moreover, good functional properties of antibodies produced in response to a malaria vaccine candidate in naïve subjects may not translate to similar findings in semi-immune subjects. For example, Malian subjects who received a vaccine based on AMA-1 had good antibody responses, but the biologic activity of the total IgG did not change from that prevaccination, despite findings of high P. falciparum growth inhibition and antibody levels when the vaccine was tested in naïve subjects (10, 20). Subsequent analysis suggested that this difference was due to the fact that other antimalarial antibodies in the Malian volunteers reduced the GIA effect of anti-AMA-1 antibodies (22). Taken together, the data show that the EBA-175 vaccine elicits a relatively low P. falciparum growth inhibition activity. The biologic significance of this finding is unclear, especially since the most important target populations for the vaccine are individuals living in areas where malaria is endemic and because EBA-175 will

FIG. 3. Mean percent growth inhibition of Plasmodium falciparum by sera from subjects in all study groups at baseline (day 0) and 14 days after the third dose (day 194). *P < 0.05 for comparison of the growth inhibition of sera from placebo recipients to that for all other study groups; §P < 0.05 for comparisons of the P. falciparum growth inhibition by sera from recipients of 5 μg EBA-175 to that by sera from recipients of 80 μg and 160 μg EBA-175.
likely be one antigen in a multicomponent vaccine; these conditions were not tested in this trial.

EBA-175 is a blood-stage antigen, and vaccination with this recombinant antigen is thus hypothesized to exert a disease-attenuating effect via antibodies, antibody-mediated cellular inhibition, and cell-mediated immunity (26, 36). It is unlikely that immunity against a single blood-stage antigen will be sufficient to provide meaningful protection against malaria disease severity, given the genotypic and phenotypic diversity of the organism and the variability of the host’s immune response. The evaluation of various candidate antigens is under way by various groups, thus facilitating the potential for a multiantigen vaccine.

This study has its limitations, including the small sample size, short duration of follow-up, and use of a subject population that does not represent the individuals for whom the vaccine will be most critical. However, the facts that the vaccine was well tolerated and elicited antibody levels with anti-P. falciparum functional activity in vitro provide reassuring preliminary findings for development of the product. The next logical step is an evaluation of the vaccine’s safety and immunogenicity in individuals living in areas where malaria is endemic.

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