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REVIEW

The malaria vaccine — Status quo 2013

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Summary It has been 40 years since David Clyde's landmark induction of sterile immunity against deadly falciparum malaria through immunization by exposure to 1000 irradiated mosquitoes, and the first recombinant *Plasmodium falciparum* vaccine, RTS,S/AS01, is now in Phase III testing. Interim reports from this largest ever Phase III pediatric trial in Africa show the malaria vaccine decreased clinical and severe disease by 56% and 47% respectively in 5–17 month olds, and by 31% and 26% respectively in infants participating in the Expanded Programme on Immunization. Final data in 2014 will more fully describe the efficacy of RTS,S/AS01 over time against all falciparum malaria cases under a variety of transmission conditions, results essential for decisions on licensure and deployment. Meanwhile, candidate components of a second-generation malaria vaccine are emerging. A field trial of the polymorphic blood stage vaccine AMA-1/AS02 demonstrated no overall efficacy (ve = 17%, $P = 0.18$), yet a sieve analysis revealed allele-specific efficacy (ve = 64%, $P = 0.03$) against the vaccine strain, suggesting AMA-1 antigens could be part of a multicomponent vaccine. Initial trials of new antigens include the highly conserved pre-erythrocytic candidate PfCelTOS, a synthetic *Plasmodium vivax* circumsporozoite antigen VMP-001, and sexual stage vaccines containing antigens from both *P. falciparum* (Pfs25) and *P. vivax* (Pvs25) intended to interrupt transmission. Targets for a vaccine to protect against placental malaria, the leading remediable cause of low birth weight infants in Africa, have been identified. Lastly, renewed efforts are underway to develop a practical attenuated-sporozoite vaccine to recapture the promise of David Clyde's experiment.

A fronte praecipitium, a tergo lupi[a]

Malaria, a preventable and curable infectious protozoal disease caused by any of five plasmodial species, is endemic in 99 countries.[1–6] The global burden of malaria is unknown due to significant lack of specific diagnosis and widespread under-reporting of cases. The WHO estimates there were 215 million cases and 655,000 deaths attributable to malaria in 2010. However a detailed model of global deaths attributable to malaria in 2010 from the Seattle Institute for Health

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[a] *"A precipice in front, wolves behind." Anon.*

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Metrics estimates there 1,238,000 deaths (95% CI: 929,000–1,685,000), almost double the WHO's estimates underscoring the challenges in assessing and combatting this disease. Young children, women in first pregnancy[7] and travelers from non-endemic lands are most severely affected. Dire public health consequences of malaria, especially long term impairment of cognition after cerebral malaria,[8] increased morbidity and transmission of both HIV and malaria in the setting of dual infection,[9] and staggering estimates of malaria's burden of disability, have prompted renewed calls for eradication. Resurgent global malaria elimination campaigns, focused principally against *Plasmodium falciparum* in Africa, are predicated upon greater use of insecticide-treated nets (ITNs), indoor-residual spraying of insecticides (IRS), rapid diagnostic tests (RDTs) and of the last remaining effective treatment for multiple drug-resistant malaria, the artemisinin-based combination therapies (ACTs). Yet poverty, politics, population movements, poor supply chains and the proliferation of counterfeit antimalarial drugs hinder elimination and foreseeably preclude eradication of malaria, especially in Africa. Safe, effective malaria vaccines could be cost effective for elimination and eradication under a variety of circumstances.

The WHO's comprehensive Rainbow Table of malaria vaccine projects has been recently reviewed,[10,11] which runs the gamut from preclinical antigens to the Phase 3 RTS,S/AS01 trials underway in Africa. Further, a research agenda has carefully outlined development goals required to ensure that malaria vaccines play not only a role in protecting individuals against malaria, but in preventing transmission of the disease.[12] This report briefly highlights the several recent programmatic advances that suggest one or more malaria vaccine efforts could eventually play a substantive role in the elimination and subsequent eradication of malaria.

Pre-erythrocytic vaccines

A vaccine eliciting sterile immunity would effectively target sporozoite and/or hepatic stage parasites to prevent asexual and sexual blood stage infection, and thus prevent both symptomatic infection due to asexual parasitemia (i.e. clinical malaria) and gametocytemia and thereby stop block infection of the anopheline intermediate host and block transmission of malaria to others. Although sterile immunity is not demonstrated to occur in nature, Clyde demonstrated the proof of concept in human volunteers immunized with irradiated sporozoites delivered by exposure to 1000 mosquitoes. These volunteers were shown to be protected against subsequent challenge with mosquito-borne malaria.[13] This impractical method, since confirmed by others,[14] has led to efforts to replicate sterile immunity, chiefly through the development of subunit vaccines representing pre-erythrocytic antigens,[15] and a commercial program to develop an attenuated parasite vaccine for children and travelers.[16,17]

Malaria challenge model

The establishment and standardization of the malaria challenge model involving exposure of healthy volunteers to 5 mosquitoes infected with *P. falciparum* has been adopted globally as a safe, cost-effective means of establishing the initial efficacy of malaria vaccines and drugs. This challenge model has been most useful in predicting the efficacy in the field of pre-erythrocytic vaccines, in particular RTS,S/AS02 and RTS,S/AS01.[18,19] Recent use of intradermal injection of cryopreserved *P. falciparum* sporozoites to achieve controlled human infection may closely approximate the natural route of infection and allow wider use of the malaria challenge model, but must first reach a consistent infection rate of 100% in control volunteers to yield statistically meaningful results in comparative Phase 2 studies.[20]

RTS,S as a traveler's vaccine

Working together since 1987, the Walter Reed Army Institute of Research and GlaxoSmithKline Biologicals (GSK) developed a particulate hybrid recombinant protein antigen representing a portion of the circumsporozoite protein (PfCSP) containing known B-cell epitopes of the tetrapeptide repeat region ("R") and C-terminal T-cell epitopes ("T") and the hepatitis B surface antigen ("S") co-purified with additional "S" particles known as "RTS,S." After the failure of weakly-adjuvanted formulations of RTS,S, this team developed RTS,S formulated with the AS02 adjuvant system now referred to as "RTS,S/AS02",[21] the first prototype to confer significant, but short lived protection, against homologous malaria challenge in malaria-naïve adults[22,23] and in adult Gambian males against diverse strains.[24,25] This was soon followed by the co-development of RTS,S/AS01, an even more potent formulation which conferred ~50% protection in malaria-naïve adults against malaria challenge, short of the development threshold of 80% for a traveler's vaccine,[26] but offering great promise as a pediatric vaccine for use in malaria endemic lands.

RTS,S as a public health vaccine

Encouraged by these results, a coalition led by GSK and the Malaria Vaccine Initiative at PATH with funding from the Bill and Melinda Gates Foundation embarked on an ambitious plan to develop adjuvanted RTS,S as a pediatric vaccine in Africa. Alonso and colleagues working at meticulously well prepared sites in Mozambique conducted the first pediatric randomized, placebo-controlled efficacy studies with a 6 month efficacy period and reported 29% (95% CI 11.0–44.8%, $P = 0.004$%) efficacy for time to first clinical episode and an efficacy of 57.7% (95% CI 16.2–80.6; $P = 0.019$) for severe disease.[27] A follow-up report found protection continued for 18 months after immunization.[28] Next, Aponte and colleagues conducted the first efficacy trial of RTS,S/AS02 in infants and using an intention to treat analysis reported an adjusted vaccine efficacy of 65.9% (95% CI 42.6–79.8%, $P < 0.0001$).[29] These trials led to follow on Phase 1 and 2 age de-escalation, dose ranging, and EPI-vaccine interaction studies of RTS,S/AS02 and RTS,S/AS01 in young children and in infants at site throughout Africa which confirmed earlier promising safety, immunogenicity, and efficacy data. Carefully designed Phase III trials of RTS,S/AS01 were undertaken in 15,000 children in two age categories, 6–12 weeks of age and 5–17 months of age, at