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MILESTONE 16

The quest for a vaccine against malaria

Malaria is mainly caused by *Plasmodium falciparum*, a eukaryotic parasite that is transmitted to humans through mosquito bites. A single parasite is able to initiate an infection. Worldwide, there are more than 200 million cases of malaria each year, with approximately 500,000 deaths. More than 80% of cases are in children under 5 years old and 90% of deaths occur in sub-Saharan Africa.

The high burden of malaria in Africa has persisted, despite continued preventive measures, owing to drug resistance in *P. falciparum* and the emergence of insecticide-resistant mosquitoes. A preventive vaccine has been a long-sought goal. The scientific proof of principle that malaria infection can be prevented following vaccination began with immunization studies of mice with attenuated (irradiated) sporozoites in the 1960s. In the 1980s, the identification of the circumsporozoite protein (CSP), the major protein expressed on the surface of the infecting sporozoite, which is essential for mediating liver infection, opened the door for development of a recombinant vaccine. CSP consists of an amino terminus, a central repeat region containing 39 NANP repeats and a carboxyl terminus that contains the T cell epitopes.

In 1987, scientists from GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR) used a truncated form of CSP linked to hepatitis B surface antigen (HBsAg) to produce RTS. RTS was then co-expressed in yeast cells with another free HBsAg to produce RTS,S. In 1997, an open-label trial showed that six out of seven healthy volunteers who received an RTS,S vaccine were protected against malaria. The study also reported that an adjuvant system, containing an oil-in-water emulsion with the immunostimulants monophosphoryl lipid A (MPL) and *Quillaja saponaria* fraction 21 (QS21), improved vaccine efficacy to 86% compared with 29% for adjuvant-free RTS,S. In 2001, a randomized trial in 306 adult men in The Gambia, Africa, showed 34% efficacy of RTS,S.

As children are particularly susceptible to malaria, in 2004, GSK and the Programme for Appropriate Technology in Health (PATH)-Malaria Vaccine Initiative conducted a double-blind, phase IIb, randomized controlled trial to examine the efficacy of RTS,S/AS02A (oil-in-water based adjuvant system containing MPL and QS21) in children 1–4 years of age in Mozambique, Africa. The vaccine efficacy was 29.9% for the first clinical episode and 57.7% for severe malaria. A similar randomized trial of 214 infants 10–18 weeks of age was carried out in Mozambique in 2007 for 6 months with a 3-month follow-up. It was shown that RTS,S/AS02D had a vaccine efficacy of 65.9%. These results indicated that development of an effective vaccine against malaria was feasible.

In 2011, a phase III randomized, controlled, double-blind trial of this vaccine with more than 15,000 children recruited from seven African countries showed that RTS,S/AS01 provided protection (~50% vaccine efficacy) against malaria in African children 5–17 months of age for up to 1 year. Of note, immune responses and protective efficacy were more limited in young infants 6–12 weeks of age. Extended follow-up revealed an efficacy of 28% against all malaria episodes over a median of 4 years, and 36% for those who had received a booster dose. These data show that while RTS,S/AS01 was relatively protective during the first months after administration, a gradual decline in efficacy was observed during extended follow-up. Further evidence for reduced protection over time came from a study from 2016 that investigated RTS,S/AS01 efficacy over a 7-year period, as part of a double-blind, randomized, controlled, phase II trial in 447 African children who were 5–17 months of age. The data showed that in the 5th year after vaccination, those vaccinated were less protected than those who had received a placebo.

A large-scale malaria vaccine implementation programme coordinated by the World Health Organization to investigate RTS,S/AS01 efficacy is now ongoing in Malawi, Ghana and Kenya. The programme aims to vaccinate about 360,000 children per year from 2019 to 2023, and will examine safety, compliance with the booster dose and reduction in mortality.

A key aspect in the development of the RTS,S vaccine was the recognition that adjuvants are important for enhancing protection. Furthermore, giving a delayed, fractionated dose of RTS,S/AS01 increased protection, and recent findings indicate that this involves improved T follicular helper cell and B cell responses. Durability of very high antibody titres remains a major obstacle for malaria vaccine efficacy, and future studies will need to assess how to keep antibody levels high through other adjuvants, vaccine delivery systems or vaccine regimens, or by including other epitopes to make additional neutralizing antibodies.

Recent potential alternatives to a vaccine include monoclonal antibodies, which could be used for inducing high-level, short-term protection that may apply to seasonal control or elimination campaigns. Nevertheless, the development of the RTS,S vaccine has substantially improved our chances of reaching the long-held goal of an efficient and safe vaccine against malaria.

Francois Mayer,
Nature Microbiology

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