

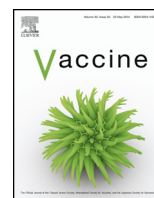
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## Editorial

## Malaria vaccines getting close to clinical reality



An important enabling concept for malaria vaccine development has been the knowledge that clinical and parasitological immunity develops after a number of naturally acquired malaria infections [1]. Almost half a century ago it was shown that naturally acquired antibodies were able to control parasitemia in humans [2]. Seminal attenuated sporozoite studies in animal and human models strengthened the belief that a highly protective vaccine was achievable [3]. Expectations were further boosted with the advent of recombinant protein technology in the mid-1980s. Effective vaccines were expected just around the corner, with new candidates announced at regular intervals. As the years went by, however, success did not readily materialize, feeding skepticism as to whether a malaria vaccine was a realistic goal. As an example, at least 6 sequential formulations of the immunodominant circumsporozoite protein were tested against controlled human malaria infection and were rejected due to poor efficacy [4] before the first encouraging protection signal was reported [5].

However, recent years have seen landmark achievements. In 2015, for the first time, a meeting of experts, commissioned by the European Medicine Agency (EMA), concluded with a positive recommendation for the use of the malaria vaccine RTS,S (Mosquirix) in very young children, after a period of more 30 years of clinical development [6]. Although modest in protective efficacy and with options for improvement lined up for testing, RTS,S in its current configuration may nevertheless become a welcome addition to the toolbox of malaria control measures. Importantly, it will serve as a benchmark for next generation malaria vaccines, helping to identify those with sufficiently improved efficacy to merit further testing and development. Assuming that RTS,S proceeds to licensure for use in endemic areas, post-licensure follow-up and pharmacovigilance studies as well as precise and transparent communication to the community about benefits and limitations should be prioritized. Additional good news is that at least seven other recombinant protein vaccine candidates, based on either traditional or novel antigens, or on antigen combinations, are undergoing clinical testing [7]. Finally, major progress is being made by whole parasite vaccine approaches including manufacturing techniques, regimens and routes of administration [8–10].

Looking back over the past three decades, overly optimistic viewpoints found their origin in the gross underestimation of the complexity of parasite biology and protective immunity as well as the technological and clinical challenges involved. In hindsight, we note the absence of vaccines against any human parasitic infection to emulate, and the many adaptive mechanisms allowing the malaria parasite to evade the human immune response. Addressing these pressing issues for effective vaccine development requires substantial and appropriate financial investments. There

is no simple or cheap solution to such complex scientific and technical challenges.

Accordingly, approaches to vaccine development have evolved over the decades. Originally, the main efforts were targeted at *Plasmodium falciparum* life-cycle stage-specific proteins with emphasis on blood stages, in order to mimic naturally acquired immunity and reduce clinical disease. However, effective blood stage vaccines did not emerge, and leading candidates achieved strain-specific protection at best [11]. The more recent focus on malaria eradication and transmission reduction has shifted the emphasis to pre-erythrocytic- and sexual stage-protein vaccines [7,12].

The evolution in vaccine development has gradually clarified impediments to success and has led to significant progress:

- (1) *Poor immunogenicity of individual vaccine candidate antigens.* The introduction of virally vectored platforms and prime boost strategies has substantially increased desired immune responses [13], while the options for particulate delivery of recombinant proteins have strengthened this critical vaccine platform [14]. An intriguing and innovative concept has been the targeted substitution of amino acids to improve MHC binding of conserved, biologically critical peptide epitopes [15].
- (2) *Genetic and/or antigenic diversity of the selected target proteins.* This has resulted in poor efficacy in field trials in particular for blood stage antigens that are under heavy and constant immune pressure. Multiple approaches are under investigation to cover genetic diversity of natural *P. falciparum* variants and have made progress in the induction of strain-transcending immune responses [16].
- (3) *Insufficient breadth and coverage of the induced immune response based on mostly single antigens.* One way forward is to mix and match individual antigens, particularly cross-stage antigens expressed in different parts of the life cycle. Alternatively, intact attenuated live parasite approaches may counter immune evasion through polymorphism by presenting the immune system with 100s of antigens [8].

With regard to subunit vaccines, major emphasis and effort are now focused on a subset of a dozen or so candidate proteins ([http://www.who.int/immunization/research/development/Rainbow\\_tables](http://www.who.int/immunization/research/development/Rainbow_tables)) that are critical for progression in the life cycle and therefore attractive as targets for immune effector functions. It is, however, well appreciated that these proteins have not been systematically selected. It is therefore of paramount importance to supply the pipeline with more and even better candidates, and to develop methods for prioritization. The recent development of systems biology and immunomics approaches has facilitated

a rational approach to antigen discovery and should accelerate progress [17].

Recent studies have confirmed the great potency of whole parasites attenuated in various ways to induce sterile protection in animals and in the controlled human malaria infection model [8–10]. Clinical development of a cryopreserved radiation-attenuated whole sporozoite vaccine has recently made a leap forward by showing high level efficacy after intravenous administration [24]. The manufacture, cryopreservation and administration of these vaccines require innovative approaches that are unconventional in traditional vaccinology.

Vaccine testing primarily focuses on young children in sub-Saharan Africa as the most susceptible risk group but there are other special groups, including malaria-naïve travelers and military personnel [18] as well women of child-bearing age, where the risk of severe diseases during pregnancy is great [19]. Specific approaches and/or vaccine candidates are under investigation.

While *P. falciparum* is primarily responsible for the malaria burden in sub-Saharan Africa, *Plasmodium vivax* is a major source of morbidity in Asia and South America, equal to or surpassing *P. falciparum* in some areas. *P. vivax* is increasingly recognized for its ability to induce severe disease, for the difficulty of reducing disease burden in the community, and for the extreme challenge of elimination. Although modest compared to *P. falciparum* in program activities, there is progress toward clinical development of *P. vivax* vaccines and this would benefit from further prioritization [20].

Mathematical modeling of vaccine implementation under a range of epidemiological scenarios provides support and guidance for control and elimination strategies using a variety of vaccine approaches and combinations [21]. The achievement of these diverse objectives will be facilitated if funders can optimally frame vaccine development policy and streamline the associated pipelines [22].

The incidence of malaria has dropped by 40% over the past 15 years with an encouraging fall in morbidity and mortality. The prevalence in children age 2-up-to-10 across endemic Africa has halved since the year 2000 due to better implementation of existing tools [23]. Notwithstanding this progress, the absolute figures are still unacceptably high, and in many areas progress is stalled. The inability to eliminate the parasite from its heartland using existing measures is abundantly clear. The availability of a strongly efficacious vaccine would enable further progress, and renew prospects for eradication. Given the current momentum, we are optimistic: the era of malaria vaccine deployment is now indeed realistically just around the corner!

### Conflict of interest statement

Robert W. Sauerwein declares no conflict of interest; Thomas L. Richie is a salaried, full time employee of Sanaria Inc., the developer and sponsor of Sanaria PfSPZ Vaccine, PfSPZ Challenge, and the PfSPZ-CVac vaccine approach.

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