Why haven't we made an efficacious vaccine for malaria?

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Malaria, caused by *Plasmodium* spp., is annually responsible for approximately 780,000 deaths and more than 225 million clinical infections worldwide. In the past ten years, over 40 malaria vaccines designed to generate immunity against subunit components of liver or blood-stage parasites, or whole sporozoites, have undergone clinical trials. Many show excellent protection in pre-clinical and initial phase I and phase IIa trials, but none have progressed to the stage of a vaccine that protects in the field. Even the leading malaria vaccine candidate RTS,S was found in phase IIIb trials to provide only modest protection against both clinical and severe malaria in young infants. Which leads to the question: why haven't we been able to make an efficacious malaria vaccine?

Plasmodium spp. are efficient at establishing repeated, new and chronic clinical and sub-clinical infections, despite the best control efforts. It could be argued that malaria vaccine development is hindered by the complexity of the life cycle of the parasite and the vast repertoire of polymorphic proteins. However, given that so many vaccines have shown great promise in pre-clinical studies and then failed to completely protect in the field, suggests that perhaps we also need to consider whether the parasite has mechanisms to evade immunity. If the parasite does evade immune responses, then no vaccine will ever provide adequate protection.

Two longitudinal studies, undertaken in malaria-endemic Mali, allude to immune evasion. First, intensive *P. falciparum* (*Pf*) biweekly testing of 251 children and adults for seven months, found no evidence of acquired sterile immunity to *Pf* infections, despite years of exposure to intense malaria transmission [1]. Furthermore, a study tracking *Pf*-specific memory B cells over a year found that their numbers increased after acute malaria and then, after six months of decreased *Pf* exposure, contracted to a point slightly higher than pre-infection levels [2]. The loss of these memory B-cell responses could explain why protection, which for most vaccines trialled was based on antibodies, was not robust or long-lived.

Perhaps more telling are studies of $MSP1_{19,}$ which was a leading malaria vaccine candidate. In clinical trials undertaken in Kenya, the vaccine generated high titres of antibodies but did not protect against infection [3]. An evaluation of this vaccine, in an experimental mouse model, also found that vaccination generated excellent titres of protective antibodies and vaccine-specific memory B cells [4]. However, these responses were short-lived in mice exposed to malaria [4]. Further investigation revealed that malaria caused changes to dendritic cells, which decreased their capacity to support memory B-cell survival [5]. These laboratory-based studies thus suggest a possible reason for why memory B cells generated by vaccines or following the wet season are unable to protect against infection. There is ample further evidence that *Plasmodium* spp. might compromise dendritic cell functions [6] required to generate long-lasting immunity.

If the parasite escapes immunity by modulating immune responses, could we put immunity back on track by blocking immune signals or by using recombinant proteins to mimic signals absent during malaria? One study to show that this might be possible found that simultaneous blockade of programmed cell death 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3) pathways reinstated immunity against malaria and accelerated clearance of the infection [7]. However, the cost and difficulty in administering such treatments are considered insurmountable. Whilst this is true for Africa, other parts of the world such as India and the armed forces of developed countries also face this disease, albeit on a smaller scale, and have economies better placed to adopt such treatments. If such a treatment were put in place for these countries or organizations, it could then move into Africa. Given that millions have died and that an exact figure cannot be placed on the financial cost of vaccine development or the cost to economies as a result of malaria, it is high time to think seriously of new treatments for this disease.

CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

REFERENCES

1. Tran TM *et al* (2013) *Clin Infect Dis* **57:** 40–47
2. Weiss GE *et al* (2010) *PLoS Pathog* **6:** e1000912
3. Ogutu BR *et al* (2009) *PLoS ONE* **4:** e4708
4. Wykes MN *et al* (2005) *J Immunol* **175:** 2510–2516
5. Liu XQ *et al* (2012) *Eur J Immunol* **42:** 3291–3301
6. Wykes MN, Good MF (2008) *Nat Rev Microbiol* **6:** 864–867
7. Butler NS *et al* (2011) *Nat Immunol* **13:** 188–195

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Endless paces of degeneration—applying comparative genomics to study evolution's moulding of longevity

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Why can mice not live more than five years and dogs not more than 30, yet bats can live over 40 years and humans over a century? Differences in longevity between closely related species are one of the greatest mysteries in biology, and identifying the processes responsible could ultimately presage the development of therapies against a multitude of age-related diseases. The variation in mammalian longevity must have a genomic basis, with recent