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Forum

# Obstacles to the development of a safe and effective attenuated pre-erythrocytic stage malaria vaccine☆

W. Ripley Ballou*

*Worldwide Clinical Development, GlaxoSmithKline Biologicals, Rue de l'Institut 89, 1330 Rixensart, Belgium*

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**Abstract**

Attenuated pre-erythrocytic stage malaria vaccines protect humans from sporozoite challenge. Current technology limits the feasibility of their commercial scale production and poses a significant risk of contamination with transmissible agents. Overcoming these barriers will be very challenging. In contrast, subunit vaccines appear quite feasible and show great promise as candidate malaria vaccines.


*Keywords:* Malaria; Sporozoite; Attenuated; Subunit; Vaccine

## 1. Introduction

The need for a safe and effective malaria vaccine is indisputable and serious work towards this goal has been underway for more than three decades. Many credible and scientifically sound strategies have emerged, and a number of these have progressed to the point where viable candidate vaccines have entered the rigorous process of clinical development [1]. The feasibility of developing an attenuated sporozoite vaccine has been for much of the past 40 years been considered impractical, but more recently, the subject has received increased scientific and commercial attention. Unfortunately, very few of the basic technical hurdles that make the development of an attenuated sporozoite vaccine so challenging have fundamentally changed. In contrast, recent progress with a number of highly feasible vaccine candidates has been very encouraging and it is now widely accepted that the development of a safe and effective subunit malaria vaccine is indeed possible.

Scientists who work on malaria vaccine development and the agencies that support this research have an obligation to critically review the strengths and weaknesses of different vaccine development strategies if for no other reason than to be certain that the limited available resources are directed appropriately. For more than 20 years I have been engaged in malaria vaccine development efforts and have personally been involved in the design and development of a number of malaria vaccine candidates. I have conducted many trials of candidate malaria vaccines, including clinical studies that used the irradiated sporozoite vaccine model. In this forum I will draw from this experience to review what I see as some of the most significant scientific and technical barriers to the development of a safe and effective attenuated malaria parasite vaccine.

## 2. Malaria vaccine strategies

There are three general classes of malaria vaccines: those that target the pre-erythrocytic stages, those that target the asexual blood stages, and those that target transmission by the mosquito. To date, only vaccines targeting the pre-erythrocytic stages, especially those based on or including key portions of the circumsporozoite (CS) protein of *Plasmodium falciparum*, have been shown to reproducibly confer protection of humans against infection and clinical disease [2].

Why has the pre-erythrocytic vaccine strategy been so successful? In the 1960s, Nussenzweig et al. [3] showed that malaria sporozoites, the form of the parasite that is infectious for

*Abbreviations:* CS, circumsporozoite.

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* Tel: +32 2 656 6659; fax: +32 2 656 8044.
*E-mail address:* ripley.ballou@gskbio.com

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the vertebrate host, could be attenuated by X-irradiation and used to vaccinate animals against an infectious sporozoite challenge. This intriguing result was confirmed in several different parasite–host pairs. Most importantly, it was shown that humans could be successfully immunized with attenuated *P. falciparum* sporozoites. Subsequently, they and others investigated the immunologic basis of this protection and revealed that a principal target of immune responses to immunization with irradiated sporozoites was the CS protein, a membrane-anchored molecule abundantly distributed on the surface of the sporozoite [4].

It is now recognized that the immunity induced by radiation-attenuated sporozoites is quite complex, involving both humoral and cellular immune responses directed against the CS protein and other liver stage antigens [5–7]. Moreover, an apparent requirement for successful immunization with attenuated sporozoites is that they actually invade liver cells and persist as at least partially developed exoerythrocytic schizonts. Over-attenuated or dead sporozoites are poorly protective and elimination of the aborted liver stages by drug treatment prevents the development of effective immunity [8]. Thus, antigens expressed by persistent liver stage parasites appear to be critical to the induction and maintenance of protective immunity, which inhibits further sporozoite invasion and/or kills liver cells subsequently infected with viable parasites. A major question posed by these data is whether vaccination with the entire parasite (an attenuated sporozoite vaccine) was required or whether vaccination with a well-characterized portion of the parasite, properly presented to the immune system (generically referred to here as subunit vaccines) would be sufficient.

It is not disputed that experimental radiation-attenuated sporozoite vaccines have conferred a high level of protection to a small number of adult human volunteers. Following a full course of immunization (cumulative exposure over several months to the bites of more than 1000 infected mosquitoes) efficacy has been shown to persist in most subjects for nearly a year [9]. Immunity, however, comes at a cost: in almost all experimental systems examined, relatively large numbers (tens of thousands) of parasites must be repeatedly injected to provide solid protection. This may be due to the fact that radiation attenuation is not precise and some proportion of the damaged parasites contributes little to effective immunity. In addition, inherently poor immunogenicity may be a characteristic of many malaria antigens and the presence of relatively large numbers of persistent immature liver stage parasites after vaccination may be required to adequately expand memory T cell effector populations in the liver [10].

Given the complexity of the malaria parasite, the many early disappointments with subunit vaccines, and the superior efficacy of attenuated sporozoite vaccines in experimental models, it should not be surprising that some have argued that the latter strategy is a logical way to proceed [11]. However, it appears that the technical challenges presented by the development of such a vaccine are generally not well understood, and it is alarming that discussions about this strategy have failed to acknowledge certain inherent safety risks associated with the manufacture and use of such vaccines [12].

## 3. Epidemiological considerations

An attenuated sporozoite vaccine has been proposed as a suitable strategy to prevent the severe malaria burden that now exists in infants and young children in SubSaharan Africa [11]. To accomplish this objective, the vaccine would most likely be administered to infants as part of the Program for Expanded Immunization. Because immunity to sporozoites might be boosted by repeated exposure to infected mosquitoes, some investigators have predicted that infants living in malaria-endemic regions will not require revaccination. Although this is possible, I am aware of no data that actually support this contention. Indeed, mechanisms by which the irradiated sporozoite vaccine is believed to protect argue that the relatively small number of infectious sporozoites a child would be exposed to each year likely would be cleared by vaccine-induced immunity before they reach the liver. Data from human and murine challenge models indicate that persistent exposure to attenuated liver stage parasites is necessary to sustain protection [8, 9, 13] and once these are gone, immunity against re-infection is lost rapidly. More importantly, there are sound epidemiological reasons why the induction of high level immunity to infection in the first years of life may not be a wise approach. In regions of holoendemic transmission, infants and young children certainly suffer disproportionately high rates of severe morbidity and death due to infection with *P. falciparum* [14]. However, in contrast to immunity against clinical episodes which takes years to develop, acquisition of immunity to severe malaria disease occurs rapidly in this setting, developing after the child has experienced only one or two clinical episodes [15]. There is a significant risk that a vaccine that completely prevents infection would simply shift the occurrence of severe disease to older age groups. That disease displacement should be expected is supported by epidemiological data from regions where malaria transmission is unstable: in populations with infrequent and limited exposure to the parasite, severe malaria occurs across a much larger age range [16].

Alternatively, it has been argued that a rational strategy for protecting children from severe malaria disease is to substantially reduce, but not completely eliminate exposure to infectious sporozoites. This appears to be a likely mechanism by which so called ‘leaky’ interventions including insecticide-impregnated bednets [17], intermittent chemoprophylaxis [18,19], and at least one subunit CS-based candidate vaccine [20] have been shown to limit the number of infections and reduce the overall risk of severe malaria. Moreover, because these interventions do not eliminate all exposure to asexual stage parasites, they still permit ‘natural’ immunity against disease to develop. If, in the future, a blood stage vaccine becomes available that is shown to limit parasite density it should also be able to prevent severe disease. Such a vaccine could either be used on its own or combined with another vaccine candidate, and immune responses to a blood stage vaccine are quite likely to be boosted by subsequent malaria infections.