The long road to vaccine development

After more than four decades of basic research and clinical trials, the World Health Organization (WHO) has recommended the malaria vaccine RTS,S for widespread use among children living in malaria endemic areas. Pioneering studies using rodent malaria models directed by Ruth S. Nussenweig at the New York University School of Medicine demonstrated in the late 1960s that immunization with attenuated sporozoites — the infective stage of Plasmodium — induces immune responses that protect against parasite infection (1). These studies also identified the circumsporozoite protein (CSP), the sporozoite-specific molecule recognized by the protective immune responses that is the antigen incorporated in the RTS,S vaccine (2). The CSP is expressed on the surface of sporozoites of different Plasmodium species and contains a central domain of tandem repeats that represent approximately 30% of the entire sequence. Extensive experimental evidence indicates that binding of antibodies to these repeats immobilizes the sporozoites, preventing infection of hepatocytes, an obligatory stage of this infection (Figure 1). The RTS,S vaccine is a hepatitis B virus–like particle that contains a genetically fused portion of the repeat domain and the C-terminal region of the P. falciparum CSP (3).

Clinical data for RTS,S

The first successful human trial demonstrating protection against infection by P. falciparum sporozoites was conducted in 1996 at the Walter Reed Army Institute of Research using RTS,S developed by Glaxo Smith Kline (4). Several phase II and III vaccine trials were conducted in endemic areas in the last 15 years, and the results consistently indicated that immunization of children 6 to 12 weeks and 5 to 7 months old induces a protective immunity that neutralizes sporozoite infection or attenuates the clinical severity of the infection. An extensive phase III trial that included different endemic areas of Africa indicated that the efficacy against clinical malaria, a few weeks after the last immunization, begins at 74% in children aged 5 to 17 and decreases to 28% and 9% after 1 and 5 years, respectively. In children aged 6 to 12 weeks, the efficacy was estimated to begin at 63% and waned to 11% and 3% after 1 and 5 years, respectively (5). The protective effect of this vaccine is short-lived, and it appears to depend on the intensity of transmission in different endemic areas. This decreased efficacy correlates with reduced levels of anti-CSP antibodies, indicating that protection depends on sustained high levels of circulating antibodies (6). There is only limited information on vaccination of adults. In The Gambia, RTS,S immunization of adults induced short-lived protection from infection on 34% of vaccinees (7), while no significant protection was observed in Kenya (8).

The implementation of RTS,S vaccine programs is a positive first step and according to the WHO it could reduce severe disease in 30% of vaccinated children (9). However, as this vaccine does not provide extensive sterile immunity, and RTS,S-induced immune responses do not interfere with the infectivity of gamocytes (the transmission stages of Plasmodium), most children and adults will carry parasites that will infect mosquitoes. Thus, transmission will remain unchanged, ensuring continuous endemicity.

Next-generation malaria vaccines on the horizon

There is a consensus that major improvements are necessary to develop a vaccine that is likely to have a greater epidemiological impact in endemic areas. Since the development of RTS,S in the late 1980s, continuing research has greatly increased our understanding of the protective immune mechanisms that neutralize parasite infectivity. This research has also yielded a better characterization of factors influencing vaccine-induced immune responses. In fact, new vaccine candidates have been developed that consist of antigenic domains similar to RTS,S expressed in different platforms such as nanoparticles, mRNA, and others. Recently, human trials using a nanoparticle, R21, were conducted with children in Burkina Faso and the initial results indicate that 1 year after 3 immunizations, this vaccine conferred a 77% protection from severe disease (10). New R21 trials in areas with different transmission intensities should provide comprehensive information on the efficacy of this vaccine compared to RTS,S. Another vaccine candidate, attenuated P. falciparum sporozoites, was also evaluated in adults living in Mali, and the estimated protective efficacy was 29% by proportional analysis (11). A recent trial of this attenuated sporozoite vaccine in Kenya failed to demonstrate significant efficacy in 5- to 12-month-old children (12).

Considerable advances have been achieved regarding the structure and fine specificity of anti-CSP protective antibodies. Recent biophysical studies have characterized the binding properties of protective antibodies, and crystallography studies have defined the precise conformation of the CSP epitopes recognized by these antibodies (13). Importantly, studies with protective human monoclonal antibodies obtained from individuals immunized with sporozoites have identified unique antigenic moieties within the repeat domain of the CSP, which are recognized by protective antibodies but are not included in the RTS,S vaccine (14-16). Thus, there are good reasons to expect that a new generation of structure-based vaccines containing additional antigenic moieties expressed in platforms with enhanced immunogenicity will improve the quality of the antibody
due to a decreased immune response against blood stages observed in these individuals (18). This strongly suggests that combining anti-sporozoite and anti-blood stage vac-
cines may not be just desirable but perhaps 
critically needed. Consequently, anti-sporo-
zoite vaccines like RTS,S are an important 
first step in the development of multi-stage 
vaccines that will one day become a power-
ful tool to help with malaria eradication.

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responses that are likely to occur during the 
infection. In contrast, the protective anti-
body responses against malaria sporozoites 
induced by RTS,S depend on the neutralizing 
effect of antibodies present at the moment 
of sporozoite infection. This neutralization 
needs to occur swiftly, as sporozoites may 
reach hepatocytes as soon as 10 to 15 min-
utes after injection (17). After hepatocyte 
invasion, antibodies are no longer effective, 
and eventually the CSP antigen will no lon-
ger be expressed. Thus, any recall response 
that may occur after the infection will have 
no effect on the ongoing infection.

Most malarialogists believe that a vac-
cine capable of inducing protective immuni-
ty against all the stages of parasite infection is most likely to have the highest impact on infection, morbidity, and transmission of malaria. In this regard, it is worth mention-
ing that studies in Africa indicate that 
children in areas of moderate transmission 
who were vaccinated and protected after 
immunization with RTS,S undergo a signifi-
cant increase in rebound episodes of clinical malaria 3 to 6 years later, and this is likely

Ongoing challenges
The protracted development and moderate 
efficacy of the RTS,S vaccine, in sharp con-
trast with the swift development of highly 
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Another aspect that has yet to be 
systematically explored is the development 
of vaccines designed to induce CD8⁺ T cell 
immunity in humans. While the protective 
effect of CD8⁺ T cells that recognize para-
site epitopes presented by infected hepatocytes is firmly established in animal models, 
translating this knowledge to develop new 
human vaccines is still a major challenge, due to severe methodological limitations.
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