Briefing Document: National decision-making framework for malaria vaccines

Status of malaria vaccines: development process and the product pipeline

This is one of seven briefing papers produced for a country consultation to develop a decision-making framework for the use of future malaria vaccines. It was developed under the guidance of the consultation steering committee: Alan Brooks, PATH Malaria Vaccine Initiative (MVI); Dr. Carter Diggs, US Agency for International Development; Sarah Ewart, MVI; Dr. Dorothée Kinde-Gazard, Minister of Health, Benin; Annique Lennon, MVI; Dr. Rose Macauley, World Health Organization (WHO) Regional Office for Africa (AFRO); Dr. John Marshall, Consultant to PATH; Dr. Zarifah Reed, WHO; Dr. Magda Robalo, WHO AFRO; and Dr. Rick Steketee, PATH Malaria Control and Evaluation Partnership in Africa.

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1. Malaria: an introduction to the disease

The complex life cycle of the malaria parasite *Plasmodium falciparum* can be broken down into four stages—pre-erythrocytic (divided into the sporozoite stage and liver stage), blood, and sexual (Figure 1). It is important to consider the parasite life cycle because vaccines are designed to affect one or more of the stages listed above. A vaccine's impact on malaria disease and transmission depends on what stage of the parasite life cycle the vaccine targets.

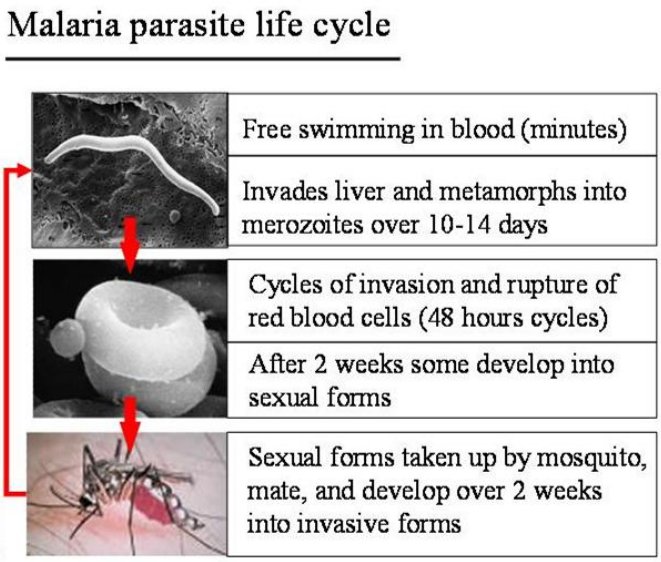

Figure 1. Life cycle of the malaria parasite

Infection occurs when sporozoites are introduced into a human by an infected female mosquito (sporozoite stage). Within minutes of entering the bloodstream, the sporozoites migrate into the liver, where they remain for one to two weeks and undergo a maturation process (liver stage). Once the parasites have developed, the infected liver cells rupture, releasing the parasites into the bloodstream. There, the parasites infect red blood cells (blood stage). It is during this stage that the symptoms of malaria develop.

After approximately ten days, some of the parasites develop into sexual forms (sexual stage), which can then be taken up by the female mosquito during her next blood meal. If the normal cycle continues, the parasites picked up from the infected person mature into sporozoites in the mosquito, and these sporozoites can be passed on to another individual, beginning the cycle again.

2. A malaria vaccine

Vaccines work by preparing the human immune system to identify and weaken or destroy pathogens (invading microbes capable of causing disease) when they enter the body. The body of someone who is immune recognizes antigens (specific parts of the pathogen), allowing the immune system to interfere with the normal functioning of the pathogen. At each stage of the malaria parasite life cycle, multiple antigens develop that interact with the human host's immune system, providing multiple potential targets for a malaria vaccine. Ideally, a vaccine would be effective against any stage of malaria. However, it is likely that the first generation vaccine would target one or two stages (e.g., pre-erythrocytic stage and/or the blood stage).

2.1. Duplicating natural immunity

Over time, steady natural exposure to the malaria parasite (by infection) results in short-term immunity against the disease. To maintain natural immunity, repeated infection is needed. [1] Adults in malaria-endemic areas experience fewer symptoms than do children. Children, especially those under two years of age, have had little to no previous exposure to malaria to prepare their immune systems, and therefore infection often leads to sickness and sometimes

[1] Moorthy VS, Good MF, Hill AV. Malaria Vaccine Developments. *The Lancet.* 2004; 363:150-155.

death. Some malaria vaccine candidates are designed to duplicate natural immunity, without exposing individuals to severe disease or death.

2.2. Protection by stages

Vaccine development targets one or more stages of the malaria parasite life cycle. A vaccine's target determines its effect on infection, disease, and transmission of malaria. For example, vaccines directed at the sporozoite or liver stages (before the parasite enters the red blood cells) are aimed at preventing infection and therefore disease.

Blood-stage vaccines are aimed at prevention of parasite growth and development once an individual is infected. Instead of preventing disease entirely, blood-stage vaccines might mimic naturally acquired immunity by allowing infection of the blood and possibly even mild, survivable disease, through which individuals would develop immunity. In this manner, the burden of severe disease and death could be minimized.

A third type of vaccine, transmission-blocking vaccines, ideally would prevent transmission of the parasite to other mosquitoes. A transmission-blocking vaccine would not prevent illness or infection in individuals who are vaccinated, but would be able to prevent the further spread of malaria by mosquitoes from people that are infected to others who are not.[2]

2.3. Multiple pathways to success

Combining vaccine approaches may offer the greatest chance of success. Recent laboratory studies have demonstrated that the combination of two malaria antigens may be possible.[3] A combination approach to a malaria vaccine would mean a vaccine that includes antigens from different stages of the parasite life cycle, potentially producing sporozoite stage, liver stage, blood stage, and transmission-blocking protection all at once. The complexity of the parasite life cycle and associated scientific hurdles are major reasons that no vaccine for malaria, or for any other parasitic disease, has ever been developed.

3. Vaccine development pathway

Moving a potential vaccine from research to testing as a promising vaccine candidate involves scientific uncertainty and considerable work. The development process, in which a vaccine candidate moves from early research through a series of clinical trials, involves unpredictability, substantial costs, and the constant possibility of failure. The purpose of clinical trials is to provide substantial evidence that a product is safe and effective when administered to humans.

Clinical trials are conducted in phases (generally Phase 1 through Phase 4), each of which provides information for future steps in testing and product development. The process of

[2] Dubovsky F, Rabinovich R. Malaria Vaccines. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia, PA: Saunders; 2003:1283-1287.

[3] Pan W, Huang D, Zhang Q, et al. Fusion of two malaria vaccine candidate antigens enhances product yield, immunogenicity, and antibody-mediated inhibition of parasite growth in vitro. *Journal of Immunology*. 2004; 172(10):6167-74.

producing a successful candidate can take more than ten years, may involve as many as 50,000 to 100,000 volunteers, and may cost upward of US$500 million.[4]

Phase 1 trials are conducted to assess safety of a product and identify common adverse events. These trials usually involve a small number of participants. Phase 1 malaria trials conducted in regions where malaria is not endemic are referred to as "Phase 1a" trials. Once safety and immunogenicity are demonstrated, clinical research moves into "Phase 1b," where the studies are repeated in a region where malaria is endemic. Similarly, Phase 2a and 2b trials provide preliminary information on the vaccine's efficacy in the target population in countries where malaria is nonendemic and endemic, respectively. Phase 2b trials include up to 2,000 participants.

A vaccine that performs well in Phase 2 trials is later assessed in Phase 3, in which 5,000 to 10,000 participants may be involved. If Phase 3 trials are also successful, the manufacturer applies for permission to license and sell the vaccine. Once the product is in use, regulatory agencies and companies continue to monitor side effects in Phase 4 trials.

Clinical trials may also provide information on the product profile and characteristics (described below) and how it may be implemented with or combined with existing health care delivery systems, such as national immunization programs and other malaria control interventions.

4. The impact of product profile

The characteristics of a vaccine will play a critical role in the public health impact. Cost, efficacy, duration of protection, schedule, and number of doses are among the critical characteristics that determine how a vaccine is used. Some of these characteristics can be considered and potentially altered early in vaccine development, such as by testing the vaccine in clinical trials on an Expanded Programme on Immunization (EPI) schedule. Other characteristics, such as efficacy, are difficult to influence. Currently, malaria vaccines are being targeted as a priority for infants on the EPI schedule, as well as for older children up to five years of age. Eventually, vaccines for adults and pregnant women may be feasible.

Vaccines have proven to be safe, provide high levels of protection, and be relatively inexpensive. An effective malaria vaccine ideally will have these same characteristics, although early vaccines may not match the levels of efficacy seen in vaccines against other disease. Production and technical challenges also mean that malaria vaccines are likely to cost dollars per dose, as opposed to the pennies paid for many traditional vaccines that have been available for decades. However, even partially effective vaccines will have a substantial impact on public health and be cost-effective.[5]

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[4] PATH Malaria Vaccine Initiative. *Clinical Trials: Crucial Steps on the Road to a Malaria Vaccine.* Bethesda: PATH; 2004. MVI Technical Series. Available at: http://www.malariavaccine.org/files/MVI_clinical_trials_paper.pdf

[5] Briefing Paper: Analysis of the demand for a malaria vaccine: outcome of a consultative study in eight countries.

The protection provided by a malaria vaccine can be expressed in a variety of ways—reduction in mortality rates, reduction in the incidence of severe malaria, and reduction in the incidence of symptomatic or clinical malaria. These are all valid endpoints (overall outcome that the protocol is designed to evaluate) that could be used to evaluate the efficacy of a malaria vaccine. Arguably, these three examples are in order of greatest importance; protection from death is much more important than protection from malaria that is simply symptomatic (i.e., a case that only produces mild disease). Furthermore, as indicated above, a vaccine that allows mild disease may be more likely to generate long-lasting protection by allowing individuals to survive and develop immunity.

5. Product pipeline

The precise timelines for the development of a successful vaccine are unknown, and any of the current candidates could lead to an effective vaccine. There are almost 90 different candidates at some stage of the research and development pipeline (Figure 2), although most of these are in very early stages of research and have not entered clinical trials.

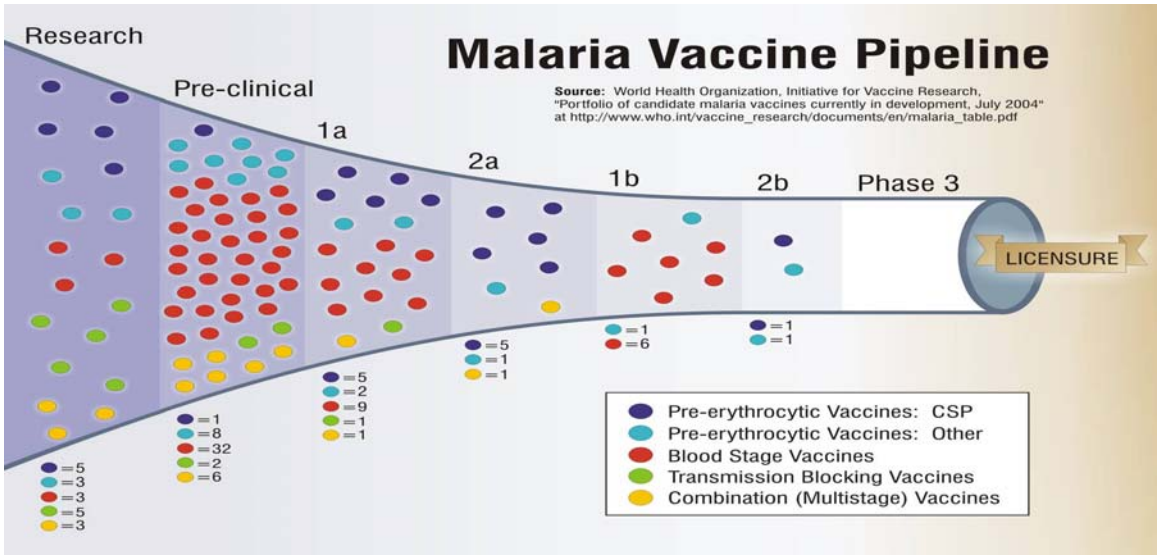

Figure 2. Malaria vaccine pipeline. (CSP:circumsporozoite protein).

The most advanced candidate, known as RTS,S,(a pre-erythrocytic vaccine) is being tested in Phase 2 trials and is expected to proceed to Phase 3 trials. Other vaccine candidates may be a number of years behind RTS,S although preliminary efficacy data on one or more blood-stage vaccines are expected during 2006. Those data will allow better predictions about the rate of future progress.

6. Implications for decision-making

- Research over the past decades has not yet produced a licensed malaria vaccine. Only one candidate (Spf66) has gone through Phase 3 trials, and that candidate failed.[6] However,

[6] Le Bras M, Malvy D. Antimalarial vaccination: advances and controversies. *La Revue du Praticien.* 1998; 48(3):291-5.

recent scientific advances, new commitments from governments and donors, new investments from the vaccine industry, and new collaborations through public-private partnerships are all reasons for hope.

- Vaccines may target different stages in the parasite life cycle, and therefore may have different impact on infection, disease, and transmission. Vaccines can target one or more stages in the life cycle. Most likely, a malaria vaccine will need to prevent disease while still allowing people to build up natural immunity to malaria.
- It usually takes at least ten years and more than $500 million to develop a vaccine from the production of the first clinical trial materials to licensure. The most advanced candidate, known as RTS,S, is being tested in Phase 2 trials and is expected to proceed to Phase 3 trials. Other vaccine candidates may be a number of years behind RTS,S although preliminary efficacy data on one or more blood-stage vaccines are expected during 2006.
- Malaria vaccines will play a critical role in impacting the disease and also serve as a complement to other strategies, such as bednets and drugs. A vaccine, particularly early vaccines, should not be assumed to replace other malaria prevention and treatment strategies. Careful consideration of the unique characteristics and profile of a vaccine relative to the strengths of other interventions is required.