

# Clinical Trials: Crucial Steps on the Road to a Malaria Vaccine

## Technical Series

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Malaria vaccine development has traveled a long, uneven road. The combination of extremely limited funding, extremely difficult science, and relative lack of interest in the industrialized world has made it difficult to progress as quickly as malaria's toll demands.

In recent years we have begun to understand the parasite well enough and had adequate technology to produce promising malaria vaccines. From initial proof of principle (observation that bites from irradiated mosquitoes produce immunity) to the most recent evidence of vaccine-induced protection (clinical trials in Papua New Guinea and The Gambia), we know that a malaria vaccine is feasible. Today the task is to get enough potential malaria vaccines to and through the series of clinical trials needed to bring the world a licensed product. This paper

provides an overview of the clinical trial process, specifically as it relates to malaria vaccines, and indicates possible outcomes at each phase.

## Vaccine Clinical Trials—An Overview

The past several decades have seen a significant change in the way that we manufacture and evaluate drugs and vaccines. Subjective, anecdotal experience has been replaced by scientific methods providing greater and greater objectivity, rigor, and efficiency in assessing the impact of a drug or vaccine and in comparing one against another. Clinical trials are a primary manifestation of scientific method in modern pharmacology.

Vaccine clinical trials are long-term studies aimed at assessing the safety, efficacy, and immunogenicity of a new vaccine product. Sometimes trials also assess how well the product meshes with existing healthcare delivery systems, such as national immunization programs.

Clinical trials are carried out in phases—each phase informing the developers about the next steps of testing and development. The full set of clinical trials for a successful candidate can take more than ten to twelve years, may involve as many as 50,000 to 100,000 volunteers, and may cost upwards of \$500 million.

Few vaccine candidates survive this rigorous process—one reason pharmaceutical research and development (R&D) is so expensive. Creation of a malaria vaccine for young children, one of the most important vaccine-development challenges in the world today, is no exception. Yet the goal will be achieved—

### Malaria—A Serial Killer

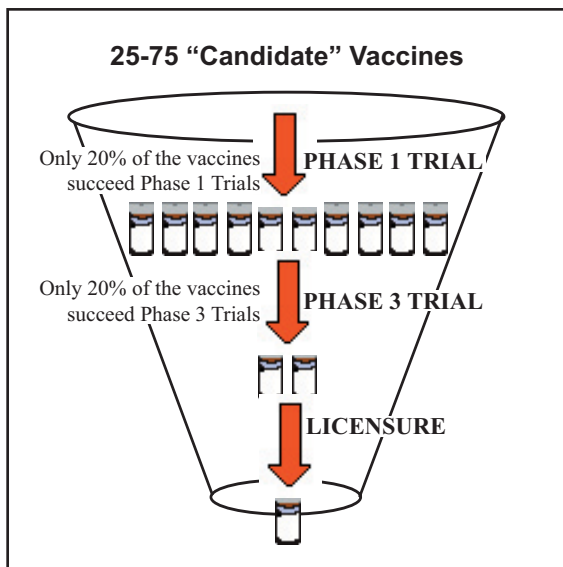
Malaria is a parasitic infection transmitted by mosquitoes. **Over one-third of humankind is at risk, and 500 million cases occur annually.** Malaria can damage the nervous system, kidneys, and liver. Severe cases can quickly lead to death.

**Estimates of malaria mortality range from one to three million deaths per year.** Most of these fatalities are African children under five years old. Even those who survive can suffer recurring bouts of malaria, resulting in chronic malnutrition, anemia, and increased risk of other diseases.

*“The malaria epidemic is like loading up seven Boeing 747 airliners with people every day, then deliberately crashing them into Mt. Kilimanjaro.”*

Dr. Wen Kilama  
African Malaria Network (AMANET)

we are already seeing modest, but promising, results. The clinical trials currently underway are providing an unprecedented depth of understanding of this killer disease, along with potential means of taming it.



### The Longer Term Goal vs. the Nearer Term Probability

An ideal malaria vaccine would:

- Be highly effective in infants, children, and adults;
- Be safe and have no serious side effects;
- Confer long-term immunity without multiple boosters;
- Be easy to administer within existing immunization programs and schedules;
- Not interfere with other childhood vaccines;
- Be easy and inexpensive to manufacture; and
- Be affordable in low-resource settings (similar to childhood vaccines already in national immunization programs).

From what we know today, the more likely first generation malaria vaccines will:

- Be moderately effective in preventing disease and designed for infant use;
- Be safe and have low incidence of serious side effects;
- Confer shorter term immunity than that of current childhood vaccines;
- Be possible to administer within existing immunization programs and schedules;
- Not interfere with other childhood vaccines;
- Be difficult and expensive to manufacture; and

- Be affordable and accessible in low-resource settings with the help of donor governments, foundations, and multilateral agencies.

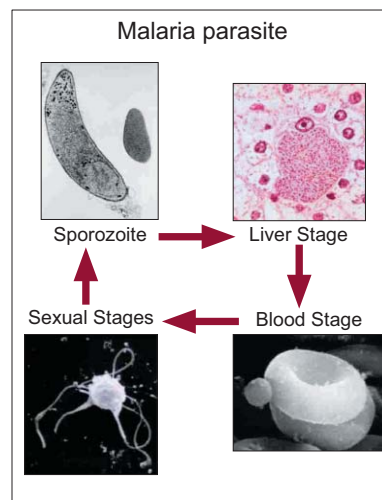
While a less-than-ideal vaccine is expected to have significant public health impact<sup>1</sup>, lack of some desired characteristics could affect how and where the vaccine is implemented. For example, if annual or biannual booster doses are necessary, there will be an increased burden on the health system. Or, if the best product limits severity of infection and reduces morbidity and mortality but does not prevent all disease, governments and individuals will have more to consider in deciding whether, when, and how to use the vaccine. This is why carefully designed and executed clinical trials are so important—they help us understand the strengths and weaknesses of each vaccine formulation, and guide the way to the best, if not the ideal, solution.

### Why is it so difficult to create a malaria vaccine?



- Ten antigenic targets
- Of which only two induce protective antibodies

Most vaccines in use today prevent bacterial and viral infections. But parasites are much more complex, with 10-100 times more genetic information than simpler organisms.



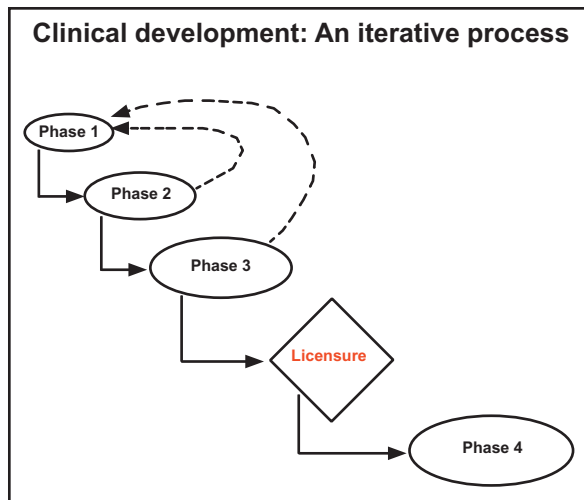
- 4 life stages
- Many potential targets at each stage
- Over 5000 potential antigenic targets in total
- Adapts to the immune system

## Malaria Vaccine Clinical Trials: Crucial Steps Forward

Bench research and animal modeling help identify vaccine candidates with strong potential, but only evaluating vaccines in people can provide the answers we need. Since a malaria vaccine will be of greatest value in malaria-endemic areas, candidates aimed at saving lives there must be assessed in the developing world. This reality introduces additional challenges. Depending on the site, trial infrastructures may have to be created though, when feasible, vaccine development programs build on existing research efforts.

### Four phases, except it's not that simple...

Clinical trials typically are designed in four phases, each focusing on some overlapping and some new research questions, and with increasing numbers of volunteers involved in each subsequent phase. However, most pharmaceutical research does not end up being a straightforward, linear process—rather it tends to be quite iterative. Knowledge gained through encouraging as well as “disappointing” trial results often informs further evolution of the product, which is again put through the same or an earlier trial phase until it is deemed ready to “graduate” to the next phase—or is rejected as a candidate altogether.



### Added benefits

Even failure of a vaccine candidate can contribute to the success of the overall effort. This is true when clinical trial data advance scientific inquiry, when the scientific community gains experience that will be useful in the future, or when a failed or marginal vaccine formulation can be dropped so resources can be refocused on still-promising candidates.

## Ending Deaths from Malaria

Combating malaria is a complex proposition. Underuse of bednets, drugs, and insecticides, perhaps combined with environmental and other factors, means **more people are dying from malaria today than 40 years ago.**

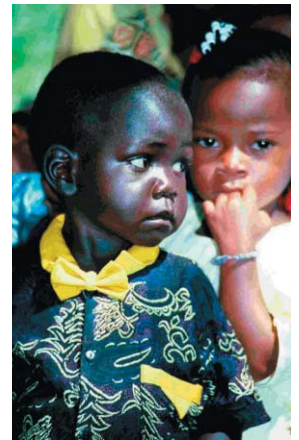


Photo: Richard Franco

Defeating malaria in the foreseeable future will require much better implementation of existing tools, development of new drugs and insecticides to combat resistance, and development of malaria vaccines.

Sometimes drug and vaccine developers get lucky when their clinical trials demonstrate unexpected benefits:

- Early on, researchers sought to develop a vaccine to prevent acute hepatitis B disease in adults. But clinical trials demonstrated an even more important effect: when given to infants, the vaccine prevented liver cancer associated with early infection. This makes hepatitis B the world's first anti-cancer vaccine.
- Ivermectin, originally developed as a de-worming drug for animals, later proved extremely effective for treating river blindness in humans.
- Prevnar®, a vaccine designed to prevent invasive pneumococcal disease (manifested as meningitis, ear infections, pneumonia, and other illnesses) in children under age two, seems also to have a herd immunity effect in adults. After its introduction in 2000, researchers noticed a drop in pneumococcal disease in non-immunized adults, probably due to a reduction in the number of bacteria in children who would normally spread the disease.<sup>2</sup>

That said, the malaria vaccine and public health communities cannot simply hope that some good will come from each malaria vaccine trial. Trials must be carefully designed to ensure that vital information will be gained even if a specific candidate does not perform well. Those data increase the chance that improved vaccine formulations will succeed in the next round of trials.

## Phases 1-4 of Malaria Vaccine Clinical Trials— Cautious Expansion Based on Facts, Not Faith

The road to vaccine licensure is long and often full of potholes and dead ends as well as successes. As noted, completing all the clinical trials needed for licensure may take ten to twelve years or longer.

### Vaccine development: A rigorous process

Typically, vaccine development begins with basic and applied research to identify potential candidates, modeling to predict how the candidate will interact with the immune system, product manufacture for clinical trials, and regulatory approval to use the vaccine in human clinical trials. Researchers create detailed trial protocols following strict scientific guidelines and with extensive attention to human subject protection. The protocol explains what the trial seeks to accomplish; how it will do so; how many volunteers are needed; who is eligible to participate; what products will be tested and at what dosage; what kinds of medical tests and care will be provided to volunteers; and what information will be gathered about participants. It also provides clear definitions of the study's measurable endpoints.

Clinical trial phases for malaria vaccines vary somewhat from that of other vaccines due to the force of infection seen in malaria, and the ability to safely assess preliminary efficacy in volunteers not normally exposed to the disease.

**Phase 1** trials are small, usually involving under 100 volunteers, and last up to a year from recruitment to initial data analysis. These early trials assess safety of the product in humans and identify common adverse events, if any. Phase 1 malaria vaccine trials also evaluate the vaccine's ability to produce an immune response and may be used to determine an appropriate dosage for further trials. For malaria, safety trials conducted in non-endemic countries (usually the country of vaccine origin) are commonly called Phase 1a trials. Once safety and immunogenicity have been demonstrated there, trials are conducted in endemic countries—Phase 1b. Phase 1b malaria vaccine trials are generally conducted in adults first, then in children if the vaccine appears safe in adults.

Should the product be deemed safe enough to proceed to **Phase 2** trials, several hundred to a few thousand volunteers can be recruited into a trial lasting up to two or more years. The current exception to this for malaria

is sporozoite challenge trials, designated as Phase 2a.<sup>3</sup> In Phase 2a trials, a small number of malaria-naïve volunteers in non-endemic countries are vaccinated and later exposed to malaria-carrying mosquitoes to see how long it takes for them to become infected. At the first sign of infection, volunteers are treated with a malaria drug that is highly effective against the strain of malaria to which they were exposed. Phase 2a trials give a preliminary indication of the vaccine's efficacy before the vaccine is taken to Phase 2b—endemic country—trials. Key research questions at Phase 2 can include:

- Confirmation of safety,
- Immunogenicity,
- Optimal vaccine composition, number of doses, and schedule,
- For malaria vaccines, preliminary efficacy if the trial is specifically designed to show it, and
- In young children, interference with other childhood vaccines.

### Steps in Malaria Vaccine Development

As critical as they are, clinical trials are but one part of the vaccine development process. Here's how they fit.

**Basic Research:** Potentially useful antigens identified

**Applied Research:** Vaccine concepts created

**Preclinical Development:** Evaluation in animals

**Process Development:** Create and validate manufacturing process for clinical trial product

**Phase 1a/b Clinical Trials:** Safety and immune response

**Phase 2a/b Clinical Trials:** Safety, immune response, preliminary efficacy

**Phase 3 Clinical Trials:** Safety and efficacy

**Licensure:** Regulatory approval for distribution

**Introduction:** Lives saved

**Phase 4 Clinical Trials:** Follow-up safety and effectiveness

Sometimes people become overly optimistic about successful Phase 2 results, hoping that the product can soon be brought to market. With malaria vaccines in particular, a series of Phase 2 trials will be needed. Briefly, these trials will assess the vaccine:

- In a stepwise fashion in age groups ranging from

adults to infants,

- In a variety of countries with different malaria transmission rates and seasonality, and
- In countries that might have different strains of malaria parasites, to assess its safety and efficacy across strains.

After any one of these Phase 2 trials, the vaccine might need to be reformulated and then reassessed in Phase 1 or 2 trials.

If the vaccine performs well in a series of Phase 2 trials, a pivotal **Phase 3** trial is conducted, assessing the safety and efficacy of the vaccine in tens of thousands of volunteers. Phase 3 trials must be large enough to allow governments to be absolutely sure the vaccine works

under varied conditions, including different malaria transmission patterns, before it is distributed to the population. Phase 3 malaria vaccine trials will last three to five years from trial enrollment through follow-up. As is true with vaccines against other diseases, a Phase 3 trial will not necessarily result in a licensable product.

If, however, Phase 3 results demonstrate safety and sufficient efficacy, the manufacturer applies for permission to license and market the product and submits a plan for **Phase 4**—long-term, post-licensure monitoring of safety. This is to ensure that any rare, serious adverse events, including possible delayed side effects, are detected early on—events that may not be evident until the vaccine is used by millions of people. Phase 4 studies also look at vaccine effectiveness—

**Table: Typical Clinical Trial Phases for Malaria Vaccines**

Phase 1	Phase 1a	Phase 1b	Phase 2a	Phase 2b	Phase 3	Phase 4
<b>Location</b>	Non-endemic country	Endemic country	Non-endemic country	Endemic country	Endemic country	Endemic country
<b>Average number of participants</b>	Fewer than 30 volunteers per study	Fewer than 100 volunteers per study	Fewer than 30 volunteers per study	Several hundred to a few thousand volunteers per study	Tens of thousands of volunteers in total	Hundreds of thousands to millions of product users in the marketplace (post-licensure study)
<b>Purpose</b>	To find a safe dosage  To observe how the product affects the human body  To measure immunogenicity	To find a safe dosage  To observe how the product affects the human body  To expand measures of immunogenicity in a malaria-exposed population	To continue to monitor safety and potential side effects  To measure immunogenicity  To measure preliminary efficacy against infection	To continue to monitor safety and potential side effects  To measure immunogenicity  To measure preliminary efficacy against infection and/or disease  Can help determine optimal dosage and schedule	To continue to monitor safety, potential side effects, and efficacy	To continue to monitor safety, side effects (looking for very rare events) and effectiveness in a large population of users.  To measure duration of protection over a longer term  To assess public acceptance of the vaccine
<b>Duration</b>	Up to 12 months	Up to 12 months	Up to 12 months	Up to 2+ years	3 to 5 years	4 to 6 years

especially in relation to secondary, positive effects (such as reducing anemia, in the case of a malaria vaccine) and durability of protection. Phase 4 trials can last as long as four to six years. Table 1 summarizes the phases of malaria vaccine clinical trials.

Again, most vaccine candidates do not proceed in a linear fashion through the four phases—negative results at any stage can require investigators to revise their product or protocol and retest until they get a “green light” to carry on at the next level or decide to drop the product altogether.

## Meeting the Challenge

The search for a safe and effective malaria vaccine has not been and will not be easy. Nor will it be straightforward or quick, because of the nature of the parasite and its interaction with its human host. But substantial progress has been made, with two candidates reaching Phase 2b trials in the past two years and several others reaching Phase 2a. The design and conduct of these trials is critical to continued—and accelerated—progress toward a life-saving malaria vaccine.

### Useful Resources

- The MVI website: [www.malariavaccine.org](http://www.malariavaccine.org)
- “Overview of Vaccine Safety” from the U.S. National Immunization Program website [www.cdc.gov/nip/vacsafe/](http://www.cdc.gov/nip/vacsafe/)
- “Glossary of Clinical Trials Terms” from another U.S. government website [www.clinicaltrials.gov/ct/info/glossary](http://www.clinicaltrials.gov/ct/info/glossary)
- “Guidelines for the Evaluation of *Plasmodium Falciparum* Vaccines in Populations Exposed to Natural Infection” from the World Health Organization website [www.who.int/tdr/publications/publications/malaria\\_vaccine.htm](http://www.who.int/tdr/publications/publications/malaria_vaccine.htm)
- Portfolio of Candidate Malaria Vaccines Currently in Development, July 2004 [http://www.who.int/vaccine\\_research/documents/en/malaria\\_table.pdf](http://www.who.int/vaccine_research/documents/en/malaria_table.pdf)
- Ethical considerations arising from vaccine trials [http://www.who.int/vaccine\\_research/documents/en/manu774\\_.pdf](http://www.who.int/vaccine_research/documents/en/manu774_.pdf)
- Sachs, J. and Malaney, P., *The Economic and Social Burden of Malaria*, Nature 415, 680 - 685 (2002) <http://www.nature.com/nature/insights/6872.html>
- Plotkin, Stanley A. and Orenstein, Walter A., *Vaccines*, W.B. Saunders Company, Philadelphia, P.A., 2003.
- Sherman, Irwin W. (ed.), *Malaria: Parasite Biology, Pathogenesis, and Protection*, American Society for Microbiology, Washington, D.C., 1998.

### Endnotes

<sup>1</sup> A modeling study is currently underway to help predict the public health impact of potential first-generation malaria vaccines.

<sup>2</sup> Per [http://www.stronghealth.com/news/article.cfm?art\\_ID=241](http://www.stronghealth.com/news/article.cfm?art_ID=241), study reported in May 1, 2003 issue of the *New England Journal of Medicine*, Vol. 328, No. 18

<sup>3</sup> Scientists are working to develop challenge models for vaccines against the blood stage of the parasite’s life cycle as well.