MALARIA VACCINE INITIATIVE

FACT SHEET

Clinical trials

Steps in malaria vaccine development

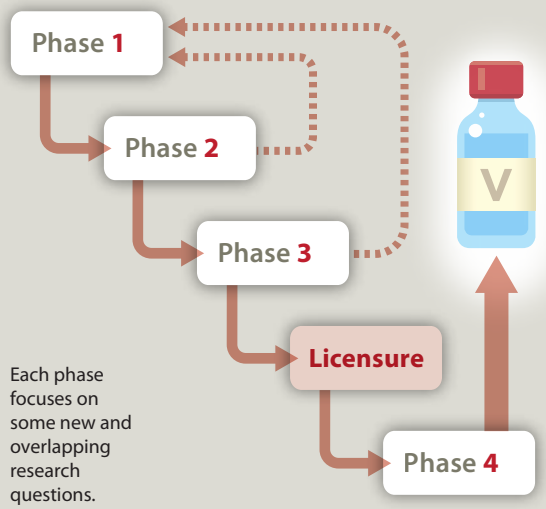
Rationale for clinical trials

Clinical trials are a critical source of data for decisions around vaccine development. While MVI does not perform individual clinical trials, we seek to ensure that all clinical trials adhere to the highest scientific and ethical standards and are designed and run in a way that provides "supportable" data on the candidate. We also try to ensure that the trial is of a quality that will be accepted by regulatory agencies. Vaccine clinical trials assess the safety and efficacy of a new vaccine product, as well as its ability to provoke an immune response. Trials may 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 focuses on some overlapping and some new research questions and informs developers about the next steps of testing and development. Pharmaceutical research tends to be an iterative rather than a linear process (see figure at right).

Knowledge gained through "disappointing" trial results often informs further research on the product, until it is deemed ready to move to the next phase or is rejected as a candidate. The following is a summary of the typical clinical trial phases for malaria vaccines.

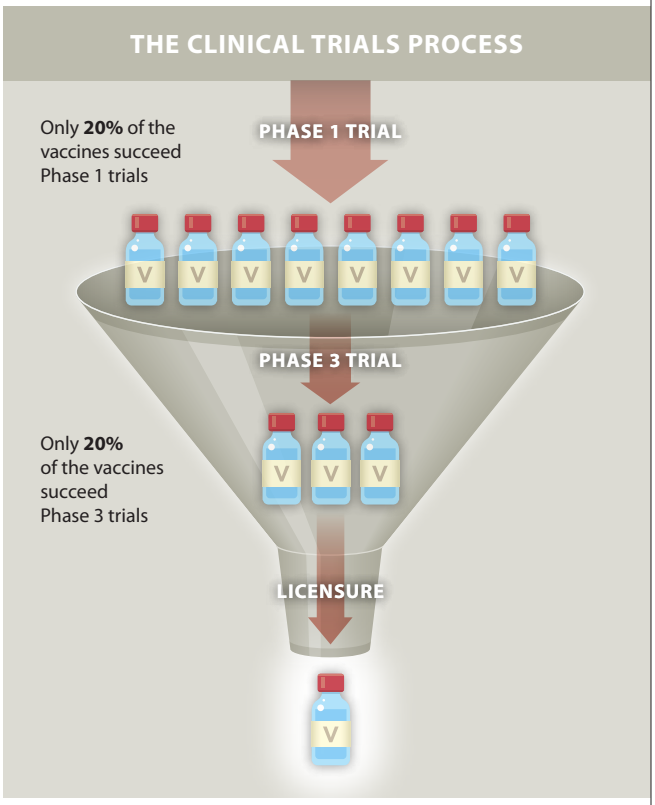
CLINICAL DEVELOPMENT: AN ITERATIVE PROCESS



Each phase focuses on some new and overlapping research questions.

Research and preclinical development	**Research and preclinical development** includes identifying relevant antigens, creating the vaccine concept, conducting preclinical evaluation, and developing the vaccine manufacturing process.
PHASE 1 clinical trials	**Phase 1 clinical trials** assess the safety of the product in humans and evaluate its ability to produce an immune response. These early trials usually involve fewer than 100 volunteers and last up to one year from recruitment to initial data analysis. For malaria, safety trials conducted in non-endemic countries are commonly Phase 1a trials. Once safety and immunogenicity have been demonstrated, trials are conducted among malaria-exposed populations in endemic countries and are classified as Phase 1b. If the product is found to be safe, it proceeds to Phase 2 trials.
PHASE 2 clinical trials	**Phase 2 clinical trials** monitor safety, potential side effects, immune response, preliminary efficacy against infection and clinical disease, and determine optimum dosage and schedule. Phase 2 trials could involve several hundred to a few thousand volunteers and last two or more years. In Phase 2a trials, malaria-naïve volunteers in non-endemic countries are vaccinated and later exposed to malariacarrying mosquitoes to see how long it takes them to become infected. At the first sign of infection, volunteers are treated with a malaria drug. Phase 2a trials give a preliminary indication of a vaccine's efficacy before the vaccine moves to Phase 2b endemic-country trials. If the vaccine performs well in a series of Phase 2 trials, it moves to a pivotal Phase 3 trial.
PHASE 3 clinical trials	**Phase 3 clinical trials** monitor safety and potential side effects and evaluate efficacy on a large scale. These trials must be large enough to ensure that the vaccine works under varied conditions, including different malaria-transmission patterns. Phase 3 malaria vaccine trials last three to five years from trial enrollment through follow-up. If Phase 3 results demonstrate safety and sufficient efficacy, the manufacturer applies for permission to license and market the product and submits a plan for long-term, post-licensure safety monitoring. **Submission** to regulatory authorities: The vaccine application is submitted to regulatory authorities for approval to market. **Introduction** involves making the vaccine available for use.
PHASE 4 clinical trials	**Phase 4 clinical trials** involve safety and effectiveness monitoring and measuring duration of protection. This additional monitoring ensures that any rare, serious adverse events, including possible delayed side-effects, are detected early, as such events may not become evident until the vaccine is used by millions of people. Phase 4 studies also look at durability of protection and at vaccine effectiveness, especially in relation to secondary, positive effects (such as reducing anemia, in the case of a malaria vaccine). These trials can last four to six years.

A full set of clinical trials for a successful candidate can take 10 to 12 years, involve 50,000 to 100,000 volunteers, and cost $500 million or more (see figure at right). Few vaccine candidates survive this rigorous process, which is one reason pharmaceutical research and development (R&D) is so expensive. Creating a malaria vaccine for young children and pregnant women—one of the most important vaccine-development challenges today—is no exception. Yet, malaria vaccine developers are confident the goal will be achieved and are already seeing promising results.



THE PATH MALARIA VACCINE INITIATIVE (MVI) is a global program established at PATH through an initial grant from the Bill & Melinda Gates Foundation. MVI's mission is to accelerate the development of malaria vaccines and ensure their availability and accessibility in the developing world. MVI's vision is a world free from malaria. For more information, please visit **www.malariavaccine.org**.

PATH is an international, nonprofit organization that creates sustainable, culturally relevant solutions that enable communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public —and private— sector partners, PATH helps provide appropriate health technologies and vital strategies that change the way people think and act. PATH's work improves global health and well-being. For more information, please visit **www.path.org**.