



Malaria Vaccine Technology Roadmap

August 2006



**MALARIA
VACCINE**
TECHNOLOGY
ROADMAP



Preface



Scientists have been working for decades to develop a preventive malaria vaccine. While they have successfully demonstrated that such a vaccine is possible, many challenges continue to impede progress on the road to an effective malaria vaccine. As a result, the Malaria Vaccine Advisory Committee to the World Health Organization (WHO), coordinated by the WHO Initiative for Vaccine Research (IVR), called for a collective effort to explore and address the challenges. This effort resulted in the Malaria Vaccine Technology Roadmap process.

The Malaria Vaccine Technology Roadmap process was jointly sponsored by the Bill & Melinda Gates Foundation, the PATH Malaria Vaccine Initiative (MVI), and the Wellcome Trust. A Roadmap Working Group, consisting of representatives of the sponsors and IVR, guided the process. Members of the malaria vaccine funders group¹ served as active participants and advisors. Energetics Incorporated assisted with the coordination of the process.

Over the course of a year and a half, the Roadmap process, described below, involved more than 230 experts representing 100 organizations from 35 countries (for a list of participants, see Appendix A). During the first two meetings, leading representatives from the malaria vaccine community² identified the challenges facing malaria vaccine development, established a vision and goal, and developed a shared plan to accelerate malaria vaccine development. In a series of subsequent Stakeholder Meetings and consultation through the internet, the process sought input from the wider malaria vaccine community.

- Participants at the Vision Meeting, held in October 2004, in Hinxton, UK, identified a vision and goals and defined the challenges which need to be addressed to accelerate progress in malaria vaccine development.

- The Roadmap Workshop, held in March 2005, in Provence, France, convened participants to address the challenges identified during the Vision Meeting—creating action plans and identifying the highest priority initiatives that could accelerate malaria vaccine development.
- Three Stakeholder Meetings, held in Bethesda, Maryland, USA; Durban, South Africa; and Oxford, UK during 2005, provided additional opportunities to share results and to seek feedback from the broader malaria vaccine community regarding their expectations and potential roles in implementing a holistic malaria vaccine development strategy.

These five meetings were then followed by a synthesis process. Key experts reviewed the results of the meetings, considering carefully the collective input of the malaria vaccine community. These experts then provided recommendations about which activities could serve as strategic areas of investment to accelerate significantly the development of a malaria vaccine. Based on further discussions with the malaria vaccine funders group, these recommendations were collated into the priority areas described in this document, the *Malaria Vaccine Technology Roadmap*.

Existing funders of malaria vaccine development have extended their support to the Roadmap process as a mechanism for better coordination and improved resourcing for malaria vaccine research and development. The malaria vaccine funders group calls upon new and existing partners to join them in supporting these priority areas by using the Roadmap as a path to continue to accelerate progress toward the goal of an effective malaria vaccine.

¹ The malaria vaccine funders group, an informal group of some of the key funders of malaria vaccine development, includes the Bill & Melinda Gates Foundation, the European & Developing Countries Clinical Trial Partnership, the European Malaria Vaccine Initiative, the European Union, the PATH Malaria Vaccine Initiative, the US Agency for International Development, the US National Institute of Allergy and Infectious Disease, the Wellcome Trust, and the World Health Organization Initiative for Vaccine Research.

² The phrase “malaria vaccine community” is used in this document to represent a diverse group including: scientists from the public and private sectors engaged in malaria vaccine research and development, funding organizations supporting these efforts, experts who develop policies related to malaria vaccines, and national and global decision-makers who will ultimately choose whether and how to introduce an effective malaria vaccine into public health systems. Participants in the Roadmap process from the malaria vaccine community can be found online at: <http://www.malariavaccineroadmap.net>.



Photo courtesy of Wendy Stone

1 Malaria Vaccines: An Urgent Need

Vision

The malaria vaccine community will develop an effective vaccine that prevents severe disease and death caused by *Plasmodium falciparum* malaria in children under five in sub-Saharan Africa and other highly endemic regions. Efficient global coordination and collaboration will stimulate the malaria vaccine pipeline and accelerate progress towards this achievement.

Strategic Goal

- By 2025, develop and license a malaria vaccine that has a protective efficacy of more than 80% against clinical disease³ and lasts longer than four years.

Landmark

- By 2015, develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year.

³ While the relationship between vaccine impact on clinical disease and death is complicated, many scientists believe that a vaccine that provides protection against clinical disease will provide an equivalent or higher protection against severe disease and death.

The world urgently needs a malaria vaccine to relieve the human suffering associated with the parasitic disease that kills more than one million people—most of them African children—every year. Hundreds of millions more people suffer from the effects of malaria. While drugs, insecticide-treated bednets, and other interventions are being used to reduce malaria's impact, the disease remains a tenacious adversary. A safe, effective, and affordable malaria vaccine would create a powerful public health benefit by closing the gap left by other interventions.

Recognizing this urgent need, researchers, funders, and others in the malaria vaccine community are committing to changing the way the community works. The ultimate driver of their individual efforts is not only to publish and to fund their own research but also to develop a viable product—a malaria vaccine—that can save millions of lives.

There are many positive developments in the community. Evidence exists that a malaria vaccine is possible and the global vaccine research and development process continues to benefit from scientific discoveries. The malaria vaccine funding landscape is improving with increased cooperation among funders and rising philanthropic and government commitments. Mechanisms exist to “push” funding for malaria research and development through product development partnerships such as the European Malaria Vaccine Initiative and MVI. The development of “pull mechanisms” such as advance market commitments (AMCs) and the International Finance Facility for Immunization suggest that donors are beginning to plan for the future purchase of new vaccines for neglected diseases. There are also signs of increasing interest in malaria vaccine development by industry.

However, the malaria vaccine community stands at a crossroads with some challenges unresolved. The hurdles to malaria vaccine development include scientific unknowns, inadequate funding, too little cooperation among scientists and among funding agencies, limited private-sector involvement, mixed levels of interest from developing countries, and as yet uncertain mechanisms for procuring and distributing a successful vaccine. While noteworthy developments such as those identified above have improved this picture, better resourcing, coordination, and collaboration are still needed.



To address these challenges, the global malaria vaccine community came together to establish a shared vision and goals and to identify the activities that could address some of the above-mentioned challenges. The resulting Malaria Vaccine Technology Roadmap outlines a plan for how the players can work differently to accelerate the development of an effective malaria vaccine, establishing a landmark of 2015 for a first-generation vaccine and 2025 for a second-generation vaccine. To create the Roadmap, more than 230 experts, representing 100 organizations from 35 countries, shared their collective knowledge and insights in a series of meetings held on three continents during a nine-month period between 2004 and 2005.

Priorities

To achieve the vision and goals, the malaria vaccine community has identified 11 priority areas that, if pursued, could accelerate the pace of progress. These priorities, composed of both new initiatives and ongoing efforts that require additional resources, represent the top priorities of the community. The priorities fall into four categories: research, vaccine development, key capacities, and policy and commercialization. They are described briefly below and in greater detail in the chapters that follow.

■ Research

1. Develop a standard set of immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines.
2. Standardize clinical trial design and assessment to allow comparison of data and to determine correlates of protection.
3. Use state-of-the-art approaches, including functional genomics, to characterize the biological functions of proteins at the interface of host-parasite interactions and to identify novel potential antigen candidates.
4. Develop web-based information-sharing tools to strengthen connections between the laboratory and the clinic.

■ Vaccine Development

5. Establish a systematic approach for prioritizing sub-unit vaccine candidates using accepted pre-clinical criteria.
6. Pursue multi-antigen, multi-stage, and attenuated whole-parasite vaccine approaches.

■ Key Capacities

7. Establish readily accessible formulation and scale-up process development capacity for malaria vaccines.
8. Build and broaden good clinical practice (GCP) clinical trial capacity in Africa and other malaria-endemic regions to accommodate the growing number of trials required for malaria vaccine development.

■ Policy and Commercialization

9. Establish and maintain country-level dialogues to facilitate decision-making on malaria vaccine policy.
10. Secure sustainable financing for future procurement of vaccines.
11. Develop novel regulatory strategies to expedite approval while ensuring safety.

These priorities originated from the 55 key activities that were drawn from more than 225 specific scientific and policy challenges identified through a series of five meetings held on three continents in 2004 and 2005. If appropriately resourced, implementing these priorities could considerably shorten the time required to develop a malaria vaccine.

Moving Forward

In order to achieve the vision outlined in the Roadmap, action will be required by both scientists and funders. Scientists and others in the community should commit to finding a balance between productive collaboration and healthy competition. By sharing information, scientists can increase learning across studies, accelerating progress toward an effective vaccine. Perhaps the strongest message from the 230 experts who participated in the process was that new resources will be needed to fund research of vaccine candidates and to advance promising candidates through clinical development. A 2005 report by the Malaria Research & Development Alliance suggests that only US\$79 million was invested in malaria vaccine development in 2004. More financial resources will be required annually to achieve the goals identified in this process. In particular, additional resources will be necessary to address the priorities identified through this process. Finally, increased collaboration is needed to enhance synergy and reduce redundancy across portfolios.



Photo courtesy of PATH

2 Research

Four activities represent the highest priorities needed to advance malaria vaccine research:

1. Develop a standard set of immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines.
2. Standardize clinical trial design and assessment to allow comparison of data and to determine correlates of protection.
3. Use state-of-the-art approaches, including functional genomics, to characterize the biological functions of proteins at the interface of host-parasite interactions and to identify novel potential antigen candidates.
4. Develop web-based information-sharing tools to strengthen connections between the laboratory and the clinic.

At least until a highly efficacious malaria vaccine is licensed, the malaria vaccine community should continue to pursue a robust pipeline of candidates supported by a strong research base. There are very few malaria vaccine candidates poised to meet the Roadmap's landmark of licensing a first-generation vaccine by 2015. Scientists believe that a rational, evidence-based approach is required in order to achieve the goal of licensing a highly efficacious second-generation vaccine by 2025. While evidence-based decision-making remains essential, critical gaps in knowledge still exist. These include the following:

- Incomplete understanding of mechanisms of infection and disease.
- Incomplete understanding of mechanisms of immunity.

Progress in understanding infection, disease, and protective immunity has been slowed by the inability to compare data generated by scientists in the laboratory and the clinic. The priorities described below are designed to increase knowledge and maximize learning in the community by improving the ability to make comparisons across data sets and by using new tools.

1. Develop a standard set of immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines.

The malaria vaccine community would like to be able to compare experimental results and evaluate vaccine-induced immune responses across studies of similar vaccines. This requires standardizing characterization procedures, such as immunological and functional assays and the reagents and protocols used at each stage of malaria vaccine product evaluation. Past standardization efforts have been slow to develop, particularly when they have required tailored approaches. For example, different assays may be needed to test different candidates, depending on the candidate's target antigen, protective immune mechanism, and stage of development. For

such assays, standardizing reagents and standard operating procedures can aid in generating results that are robust and reproducible and therefore allow comparison among vaccine candidates.

Agreeing on standard immunological assay methodologies is not trivial, but several efforts are underway to begin the process. These early-stage efforts should be communicated to and supported by the wider community in order to ensure that they result in standard assays that are amenable to high throughput and reflect current scientific understanding. Once established, methods to encourage adherence with these standards should be developed. For example, researchers could use an independent and readily accessible laboratory with built-in assay validation and quality-control standards to perform certain assays under blinded conditions.

Ultimately, a compendium of recommended assays should be made available to the global community with associated standardized procedures and well-characterized reagents. A centralized laboratory or “virtual reference facility” consisting of several networked laboratories could update the assay compendium as scientific understanding advances and as methods are optimized. Such a compendium would require sharing of detailed methods, reagents and antigens, immune sera, monoclonal antibodies, and provision or training of staff to perform the tests. One specific urgent need is the development of novel immunoassays to investigate the cellular products which reflect cell-mediated immunity.

2. Standardize clinical trial design and assessment to allow comparison of data and to determine correlates of protection.

Malaria vaccine clinical trials are designed carefully so as to ensure that sufficient data are collected about the vaccine candidate being evaluated to inform subsequent decision-making about its future development. Because vaccine trials require significant financial and human resources, scientists traditionally control costs by collecting

only the data required to measure primary and secondary endpoints. This approach poses two problems. First, definitions and types of endpoints differ among clinical trials, making comparisons among candidates and across trials either difficult or impossible. This is due in part to the need for different case definitions in different epidemiological settings with accompanying different clinical and pathological manifestations. Second, once candidates have moved into clinical development, research is generally focused on measuring protective efficacy, with minimal emphasis on exploring basic research questions that remain, such as elucidating mechanisms of immunity and establishing correlates of protection. Both of these limitations must be addressed to maximize the benefit of trials. In spite of the complexity of malaria presentation, much greater standardization is feasible and should be pursued to increase the ability to compare results across studies.

While not a new idea, standardization would be a change from current clinical trial practice. Standardization of trial procedures and end points, along with appropriate informed consent, will enable researchers to make wider use of trial samples and data sets to establish patterns of correlates of protection. By using a standard set of measurements that all trial results obtained can employ and sharing the results widely, scientists will be able to compare trials in different epidemiological settings with different adjuvants and antigens. Data from both positive and negative controls and standards may offer insights and should be included in data sets. Clinical trial harmonization will also have ethical and regulatory implications.

Even with standard endpoints, comparison of vaccines would still be challenging, given differences in vaccine candidates, in transmission settings, and in the epidemiologies of the populations where the vaccines are evaluated. Standardized end points must be combined with detailed information on trial participants, including age, malaria endemicity, use of individual methods of malaria protection, and genetic background. Studies must reflect the epidemiological diversity of trial sites and should seek to determine immune response by age range and parasite exposure. Care must also be taken to protect human subjects' rights to confidentiality. With clinical trial standardization and standardized assays, scientists could significantly enhance the pursuit of reliable correlates of protection.

3. Use state-of-the-art approaches, including functional genomics, to characterize the biological functions of proteins at the interface of host-parasite interactions and to identify novel potential antigen candidates.

Whereas malaria vaccine researchers have sometimes selected antigens for evaluation in clinical settings based on their cellular interactions, researchers lack a complete understanding of parasite-host interactions to optimally guide these choices. Genomic tools can increase scientists' understanding of the detailed interaction between the parasite and its host. For example, researchers can determine which genes are essential to parasite survival and which are redundant. This insight can allow researchers to identify specific molecules, or parts of molecules, from the parasite that may represent novel immune targets. Achieving a clear understanding of protein function to inform and drive antigen selection represents a new approach that can guide the systematic application of genomic tools. Scientists can apply this understanding to identifying new vaccine concepts.

Work has already begun in this area. Malaria vaccine researchers are just beginning to use new genomic and proteomic technologies. While currently costly, they offer valuable insights into potential new vaccine targets and typically require minimal blood samples. Efforts to use genomic and proteomic technologies should accelerate in pursuit of the 2025 goal. These tools can allow scientists to identify alternative invasion pathways, specify molecules involved in these interactions, and define the function of gametocyte, ookinete, and sporozoite surface proteins. Specific technologies that should be developed and applied to malaria vaccine research include microarray-based tools, targeted mutagenesis, expression profiling, and experimental, high-throughput functional genomic research on humans and on *P. falciparum* parasites from diverse populations.



Photo courtesy of Sarah Ewart

Applying these new tools to the parasite's blood stage, the phase in the parasite's life cycle that presents the greatest scientific complexity, should prove to be particularly productive. While some efforts to consider blood-stage malaria using genomics are underway, these efforts remain somewhat fragmented. A more systematic application of genomics to the erythrocytic stage is needed, as a blood-stage component is likely to be a key part of any highly efficacious vaccine.

Genomic approaches can also help understand the effects of natural genomic diversity (i.e., polymorphism) among parasites and humans. The reasons why parasite and human polymorphisms have co-evolved are unknown but may have important implications on understanding which parasite molecules are critical for disease and the epidemiological correlates of diversity. Pairing research facilities in endemic and non-endemic countries to facilitate information exchange can add structure to laboratory and clinical research interactions focused on assessing polymorphism and its implications for vaccine development.



Photo courtesy of Richard Lord

4. Develop web-based information-sharing tools to strengthen connections between the laboratory and the clinic.

Web-based information-sharing tools should be developed to facilitate data sharing among laboratory and clinical researchers. For example, robust information exchange among laboratory and clinical researchers could facilitate several essential studies into mechanisms of innate and acquired immunity, including cross-trial studies. With

effective information-sharing systems, scientists around the world could exchange immunology data efficiently, shedding light on the immune response and how it varies by epidemiology and age, and on vaccine-induced protection mechanisms.

Information sharing must include processes and procedures for protecting researchers' ability to publish findings in peer-reviewed journals, compete for grants, and pursue other traditional academic rewards. Standards for entering information into shared databases (e.g., results or techniques that are reproducible) are also required to ensure the data are useful and appropriate for subsequent analysis. The Human Genome Project offers lessons for information-sharing methods and funding mechanisms that allow collaboration and data sharing while supporting traditional, healthy, academic competition. The Human Genome Project adopted a process that permitted information sharing within a framework of rules that protected the researcher's ability to later publish the findings. There is also precedent for such collaboration within the malaria community, as evidenced in the *P. falciparum* genome project. Such pre-publication data sharing could accelerate progress in vaccine development by two or three years, the time typically required to publish results. Any new information-sharing process should be credible, provide incentives for participation, and be an avenue for sharing both negative and positive research results that are important for advancing vaccine development.



Photo courtesy of Molly Mort

3 Vaccine Development

Two important new activities can lead to advances in malaria vaccine development:

5. Establish a systematic approach for prioritizing sub-unit vaccine candidates using accepted pre-clinical criteria.
6. Pursue multi-antigen, multi-stage, and attenuated whole-parasite vaccine approaches.

Vaccine development is primarily concerned with choosing specific vaccine candidates, formulating them appropriately, and conducting clinical trials. As is the case with many other diseases, incomplete understanding of malaria immunology and disease mechanisms mandates that scientists follow a largely empirical method for identifying vaccine candidates.

Vaccine development efforts are hindered by five significant hurdles:

- Scientists currently lack an adequate understanding of mechanisms of disease and immunity, or correlates of protection, necessary to rationally select candidates to proceed to clinical trials.
- Evaluation of a vaccine concept from inception to proof-of-concept trial requires many years and millions of dollars.
- There are far more potential malaria vaccine candidates than there is capacity or funding to investigate these candidates in clinical trials.
- Multi-antigen vaccine candidates may offer higher efficacy but cannot be evaluated quickly in the clinic and may be costly to manufacture.
- Whole-parasite approaches may offer very high efficacy, but may not be able to be brought to the scale necessary to meet global demand for a malaria vaccine.

Given these challenges, scientists need a methodology for selecting the most promising vaccine candidates for further evaluation while minimizing unfruitful investments in less promising or redundant approaches. Accordingly, establishing a systematic, rigorous rationale for selecting which sub-unit vaccine candidates to advance to clinical trials is a primary concern in vaccine development. At the same time, because scientists do not know whether sub-unit approaches will be able to offer highly efficacious vaccines, alternative approaches such as whole-parasite and combination vaccines should also be pursued.



Photo courtesy of PATH

5. Establish a systematic approach for prioritizing sub-unit vaccine candidates using accepted pre-clinical criteria.

Malaria researchers have long debated ways of ranking vaccine candidates—a process that requires criteria to organize the myriad opportunities available in the post-genomic era. According to the World Health Organization, there are more than 30 potential malaria vaccine candidates in development. The majority of these are based on recombinant proteins and over one-half consist of a single antigen.⁴ With limited resources available to evaluate these candidates, prioritization is required. A systematic, evidence-based approach for prioritizing vaccine candidates would expedite the progression of promising vaccine concepts along the development pathway and promote greater confidence among scientists and funders that investments are focused on the best candidates.

Pre-clinical ranking criteria might include factors such as:

- Type of immune response induced by the candidate.
- Ability to generate a functional and stable form of the antigen.
- Ability to measure antimalaria immune effector function *in vitro*.
- Potential formulations of the candidate.
- Ability to manufacture and scale up production of the candidate.

Researchers should then apply these and other criteria to rank vaccine candidates, particularly those based on the same antigens, in an objective manner. While this approach may be most helpful for prioritizing antigens, adjuvants, and formulations for sub-unit vaccines, it could be extended to include other vaccination strategies such as vector-based or whole-parasite approaches.

Systematic selection criteria will not guarantee the success of top-ranked candidates. In fact, prioritizing candidates runs the risk of de-prioritizing a candidate that might ultimately offer the best protection. However, in a scientific community with limited resources and correlates of protection yet unknown, developing and continuing to refine a systematic and evidence-based approach to candidate selection can help to focus investments on candidates that appear to be the most promising, given today's best scientific knowledge.

While systematic criteria can be used to inform go/no-go decisions for clinical development, the criteria should not disqualify a candidate altogether. Instead, the criteria could help to focus research on poorly scoring antigens by identifying knowledge gaps, including the biological implications of polymorphic variation in the field. As new insights are gained, antigens can be re-evaluated for their potential. In addition, the prioritization criteria must be regularly reviewed and revised to reflect the most advanced scientific understanding.

⁴ World Health Organization (WHO) Initiative for Vaccine Research, *Portfolio of candidate malaria vaccines currently in development, March 2005*, Geneva: WHO; 2005. Available at http://www.who.int/vaccine_research/documents/en/malaria_table.pdf

6. Pursue multi-antigen, multi-stage, and attenuated whole-parasite vaccine approaches.

Given the complexity of *P. falciparum* and the early stage of many malaria vaccine development efforts, a diversity of vaccine approaches should be pursued. Recently, individual sub-unit vaccine candidates have been the primary research focus and constitute the majority of malaria vaccine concepts. Results from research into sub-unit vaccines to date have led some scientists to believe that these vaccines by themselves may not achieve the highest possible efficacy. These candidates may have to be combined with other candidates to create multi-antigen vaccines. Some scientists believe that such approaches, along with attenuated whole-parasite approaches, may offer the greatest potential to produce highly efficacious vaccines that provide long-term protection in diverse epidemiological settings.

Multi-antigen vaccines, likely targeting different stages in the parasite's life cycle, may confer better protection than a vaccine based on a single antigen. One approach may be to pursue a multi-stage vaccine by combining two partially effective vaccine candidates that target different stages of the parasite's life cycle to achieve greater overall efficacy through additive or synergistic effects. Ultimately, such vaccines may include multiple antigens from the same parasite life-cycle stage in conjunction with antigens targeting other stages. Such an approach may also avoid vaccine failure caused by polymorphic variations in diverse parasite populations. This method introduces higher formulation and production costs and entails more complex interactions between the vaccine and the immune system.



Photo courtesy of Robert C. Thompson

Whole-parasite approaches are not new in vaccine development. Experimental vaccination with attenuated parasites has been shown to offer protection against challenge with malaria parasites. However, vaccines based on attenuated malaria parasites face significant obstacles because they are difficult to characterize and manufacture in large quantities. *In vitro* cultures of sporozoites and a sporozoite challenge model are needed to support further exploration of these concepts. While the obstacles associated with these approaches are significant, new technologies such as genetic attenuation of sporozoites, new methods to generate large numbers of sporozoites, and the completion of a low-dose blood-stage trial in naïve volunteers offer new promise for possible breakthroughs. Improved analytical tools now allow for more complete characterization of whole-parasite vaccine concepts, and human trials using genetically attenuated parasites are needed. While regulatory and safety issues remain, some scientists believe that vaccine candidates using whole-parasite approaches are feasible and merit continued attention because of their potential to demonstrate high efficacy.



Photo courtesy of Siri Wood

4 Key Capacities

Two important and new activities could establish critical capacities needed to accelerate malaria vaccine development:

7. Establish readily accessible formulation and scale-up process development capacity for malaria vaccines.
8. Build and broaden GCP clinical trial capacity in Africa and other malaria-endemic regions to accommodate the growing number of trials required for malaria vaccine development.

While a number of promising malaria vaccine candidates are undergoing various stages of development, the capacity to evaluate them remains limited. Formulation and process development expertise and capacity are primarily concentrated in pharmaceutical companies where, with few exceptions, there is limited investment in malaria vaccine development. Clinical trial human resource and infrastructure capacity in malaria-endemic countries is limited. In order to achieve the goals of the Roadmap process, these key capacities must be developed.

To strengthen the capacity to undertake formulation and process development and to conduct clinical trials, the malaria vaccine community must overcome the following challenges:

- The difficulty many researchers have in accessing adequate process development and formulation capabilities and the most promising adjuvants.
- The imbalance between the growing number of potential malaria vaccine candidates and the small number of GCP clinical trial sites in malaria-endemic regions, which limits the capacity to evaluate these candidates.

Addressing these challenges could enhance the malaria vaccine community's ability to develop efficacious formulations and evaluate them in clinical trials in malaria-endemic regions.

7. Establish readily accessible formulation and scale-up process development capacity for malaria vaccines.

The malaria vaccine community requires additional formulation and process development resources and expertise. Although the malaria vaccine community has strong basic science and pre-clinical expertise, it has much less experience with chemistry, manufacturing, and control issues. Many researchers in the community (who do not work for pharmaceutical companies) lack access to the protein characterization, formulation, and process development capabilities necessary to assess whether those formulations can be economically manufactured in a good



manufacturing practice environment. Further, no single partner currently involved in malaria vaccine development has the required capacity to manufacture and formulate the wide range of vaccine concepts being developed.

Establishing an accessible process development center or set of collaborating research organizations that operate as a “virtual center” would address this challenge. Either approach would most likely represent a partnership among academic, commercial or contract, and government institutions. The center should support rapid sharing of information, help define scope and objectives for any formulation or process development project pursued, and advise on integrating process development and formulation with the larger vaccine development process. Appropriate governance and transparency will be required for this approach to gain widespread acceptance among scientists and funding agencies.

8. Build and broaden GCP clinical trial capacity in Africa and other malaria endemic regions to accommodate the growing number of trials required for malaria vaccine development.

In the absence of a thorough understanding of immune responses to *P. falciparum* and mechanisms of disease, clinical evaluation of vaccine candidates is the only way to measure efficacy and duration of protection. Evaluation of these candidates in malaria-endemic areas provides the most reliable information regarding how the vaccine is likely to perform under conditions of natural exposure. Further, candidates must be evaluated in areas with diverse transmission settings and epidemiologies. Currently, there are few clinical trial sites in Africa that can conduct malaria vaccine trials. In order to accommodate the growing number of candidates proceeding through the pipeline, the malaria vaccine community must strengthen and ensure the sustainability of existing sites while making sure that the sites maintain their relevance for scientific research.

While a number of clinical trial sites already exist in malaria-endemic areas of Africa, few have sustainable business models with staff who can conduct trials under GCP conditions. Multiple sites are required to ensure sufficient capacity in the future. To prepare clinical sites for evaluation of malaria vaccine candidates, they must have reliable funding and well-trained staff. Sites also require local leadership with outstanding project management skills to manage staff and resources and to secure consistent, sustained research productivity and corresponding funding. Each site also requires financial accounting structures and specialized personnel (e.g., certified clinical research coordinators, data management quality assurance, and clinical research monitors). Stronger biomedical ethics capacity is also needed to ensure ethical standards are applied. Viable career development pathways and job security are required to attract and retain investigators and staff to ensure that a critical mass of competent, skilled personnel is available to support these sites in the long term.

In addition to the strength of the site itself, a number of scientific factors affect a site's appropriateness for malaria vaccine trials. Clinical trials with a promising vaccine candidate will eventually need to be conducted in a variety of transmission and epidemiological settings so as to demonstrate the efficacy of the candidate in those settings. Malaria disease burdens near trial sites generally decline over time as interventions, such as insecticide-treated nets, insecticide spraying, and drugs, become more widely used either during the course of clinical trials or through higher than average community education efforts. While this phenomenon is unquestionably positive for local populations, trial sites without significant malaria disease burden are less attractive for malaria vaccine proof-of-concept trials because the sample sizes required to demonstrate the effect of the vaccine become larger and less attainable. Finally, sites must be able to conduct long-term follow up of trial subjects, especially for the purposes of identifying potential secondary effects. Guidelines should be developed to encourage long-term monitoring and assessment of safety and duration of protection. Improving demographic systems that can characterize the studied population and follow subjects for five or six years will enable longer-term monitoring.



Photo courtesy of Sarah Ewart

5 Policy & Commercialization

Three activities represent the highest priorities for addressing malaria vaccine policy and commercialization:

9. Establish and maintain country-level dialogues to facilitate decision-making on malaria vaccine policy.
10. Secure sustainable financing for future procurement of vaccines.
11. Develop novel regulatory strategies to expedite approval while ensuring safety.

In addition to overcoming technical and scientific challenges, the successful delivery of a malaria vaccine requires that policy and commercialization issues be addressed to ensure that people in endemic communities have reliable access to the vaccine in a timely manner once efficacy has been demonstrated. Effective policy and commercialization efforts must address four critical challenges:

- Uncertain regulatory pathways for licensing a vaccine for use primarily in developing nations.
- Incomplete understanding of how and whether countries should introduce malaria vaccines among malaria-control mechanisms and interventions targeting other diseases.
- Reluctance of donors and policy-making bodies to plan for the purchase and deployment of malaria interventions that are still in development.
- Limited market pull for private-sector investments in the development of vaccines targeting some of the poorest populations in the world.

These challenges are not new, but ongoing efforts to address them have been under-funded and sometimes fragmented. More focused efforts can help to send the right signals that will stimulate the vaccine development pipeline today and ease eventual introduction of a vaccine.

9. Establish and maintain country-level dialogues to facilitate decision-making on malaria vaccine policy.

Leaders of malaria-endemic countries will ultimately make decisions about whether to introduce a licensed malaria vaccine, yet there has been limited formal contact regarding malaria vaccines with country leaders to date. By establishing contact with national stakeholders, the malaria vaccine community can explore their decision-making processes in order to ensure that the community will be able to provide the data to support the process. In learning which data are required by decision-makers, the malaria vaccine community will be able

to collect the data during clinical development. Making the necessary data available for decision-making would minimize unnecessary delays in the uptake of a licensed malaria vaccine.

Decision-makers require a better understanding of the impact of a malaria vaccine. Critical data points include an understanding of the malaria disease burden and the effectiveness of existing interventions, the vaccine's potential impact on health, the vaccine's cost-effectiveness and affordability, how the vaccine would be integrated into existing health services, and community perceptions of the vaccine. Some of these data already exist and some will have to be collected. In the absence of rigorous data, some of this insight can be obtained through models. However, existing models must be refined or new models must be developed where these data can be supported and validated with clinical trial information.

As malaria typically occurs alongside other epidemics such as HIV/AIDS and tuberculosis, analyses should be extended to assess malaria interventions alongside those targeting other diseases. At the same time, public-health budgets in most malaria-endemic nations are constrained, disease interventions compete for funds, and the knowledge needed for informed decision-making is incomplete. Country-level dialogues should attempt to address the complex interplay among diseases in diverse epidemiological settings to support informed decision making.

Researchers in the malaria vaccine community should continue to engage with key stakeholders to ensure that preparations are made to consider a future malaria vaccine. These and other country-level dialogues would complement ongoing efforts at the global level to understand and communicate the implications of introducing a malaria vaccine into public-health systems across Africa and other highly endemic regions.

10. Secure sustainable financing for future procurement of malaria vaccines.

Although a malaria vaccine will not be licensed for five to ten years or more, countries and donors should begin to plan for its purchase now. Endemic countries require sustainable, long-term financing mechanisms to ensure that they can acquire malaria vaccines without straining limited public health budgets. When countries become confident that financing will be available, they are more likely to signal strong demand for a malaria vaccine. Sustainable financing and strong country demand will stimulate additional investment in malaria vaccine development by pharmaceutical companies and others.

AMCs, in which procurement agencies enter into binding contracts to purchase vaccines when they become available, represent one financing approach that has received attention in recent years. Finance ministers from the Group of Seven industrialized nations are evaluating AMCs and the potential implementation of a pilot AMC in 2006. If malaria is chosen for this pilot program, specific design work on how to structure the commitment will be required to support pursuit of the 2025 goal and the 2015 landmark.

A related financing tool is the development of a viable pricing model that incorporates the unique costs and benefits of commercializing vaccines that exclusively target diseases of the poor. Pharmaceutical firms currently engaged in vaccine development can help to identify suitable factors for inclusion in such a model (e.g., tiered pricing for different financing scenarios or phases, factoring the value of public relations into pricing, and cost sharing with philanthropic organizations). A successful model could encourage industry participation without compromising corporate fiscal health.

II. Develop novel regulatory strategies to expedite approval while ensuring safety.

Regulatory pathways for vaccines exclusively targeting populations in developing nations are not yet established. The predominant global regulatory agencies (i.e., the US Food and Drug Administration [FDA] and the European Medicines Evaluation Agency) customarily do not license products that are not intended for use in their populations. Many African countries do not have their own established regulatory agencies and, in some cases, national regulatory mechanisms are unclear. Accordingly, regulatory review of a future malaria vaccine may seriously delay the introduction of a malaria vaccine. For these reasons, novel regulatory approaches are needed to expedite vaccine approval and distribution while ensuring that the highest safety standards have been met.

To reduce the unpredictability of the future regulatory pathway of malaria vaccines, regulatory agencies should offer transparent and detailed guidelines describing their processes for consideration, especially for communities—like the malaria vaccine community—who are pursuing the development of products primarily intended for developing countries. At the same time, malaria-endemic countries should establish national policies and regulatory processes. All national regulatory agencies require a range of skills to support effective vaccine licensure and deployment.



Photo courtesy of the David and Lucile Packard Foundation

Strategies to develop and navigate regulatory pathways can rise above the plane of malaria vaccine development. The FDA's Critical Path Initiative is one example of a regulatory agency seeking to work more closely with the pharmaceutical industry to accelerate vaccine and drug development. Partnerships with other vaccine developers may help to spread the cost of developing shared regulatory processes for developing nations among multiple communities, avoid duplicating efforts, and ensure consistency across health interventions.



Photo courtesy of PATH

6 Implementation

The eventual success of the Roadmap depends on the ongoing commitment of all to realize the vision of the process—to develop a preventive malaria vaccine that can save millions of lives.

Developing an effective malaria vaccine is an enormous challenge. This Roadmap, developed with the insights of 230 experts from 35 nations, reflects the global nature of the challenge and the world-wide response required. The Roadmap attempts to organize the malaria vaccine community around a shared vision and goals and identifies 11 priorities that hold great potential for efficiently advancing malaria research. However, the publication of the Roadmap document will accomplish very little without further action. The Roadmap can guide the malaria vaccine community to improve the effectiveness and relevance of individual endeavors while contributing to a larger effort to develop a life-saving product.

The eventual success of the Roadmap depends on the ongoing commitment of all to realize the vision of the process—to develop a preventive malaria vaccine that can save lives. The malaria vaccine community will have to rise above their individual and organizational efforts in order to achieve the landmark of developing a first-generation vaccine by 2015 and the goal of developing a highly efficacious second-generation vaccine by 2025. While there are no guarantees of success, achieving the priorities identified in this Roadmap will help the community to accelerate progress toward the development of a malaria vaccine and to maximize the effectiveness of the resources invested.

Members of the malaria vaccine funders group, each associated with agencies funding malaria vaccine development and themselves contributors to the Roadmap process, have committed to greater coordination, collaboration, and partnership in supporting some of the priorities identified by the Roadmap. Some of these organizations have already begun to work together to address the Roadmap's priorities. A further outcome of the Roadmap process was the recognition of the need for increased commitments from existing donors, combined with funds from new donors, to invest in the priorities identified through this process and realize the goal of the Roadmap by 2025.

With so many lives at stake, the malaria vaccine community should work together to pursue these activities aggressively. There is no time to waste. Millions of children in Africa and other malaria-endemic regions are waiting for an effective malaria vaccine. Scientists know that with sufficient resources and increased collaboration, they can and will develop one. With a renewed commitment and energy from the malaria vaccine community to focus on the priorities outlined in the Roadmap, scientists will be able to accelerate the development of their shared goal: an effective malaria vaccine that can save millions of lives.

A Appendix

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