

**MALARIA VACCINE
TECHNOLOGY ROADMAP**

Draft Vision

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Preface

This draft vision document articulates the long-term goals of the global malaria vaccine community. It will be used to guide subsequent development of a global Malaria Vaccine Technology Roadmap that aims to substantially accelerate development of an effective malaria vaccine. This vision reflects the collective views provided by leading experts from the malaria and vaccine development communities (listed in Appendix B) at a meeting held in October 2004 in Hinxton, England. The meeting was jointly sponsored by the Wellcome Trust and the Bill and Melinda Gates Foundation, and was coordinated by the Malaria Vaccine Initiative, PATH. The subsequent roadmapping process, summarized in Appendix A, will engage the wider malaria vaccine community and expert external advisors.

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Executive Summary

Malaria is a deadly killer that exacts an enormous toll on people in developing countries. An estimated 2.7 million people die of malaria each year and another 300 to 500 million people suffer acute illnesses from the disease. Most of the deaths occur in children under the age of five living in sub-Saharan Africa. Efforts to combat malaria are being pursued on several fronts, including anti-malarial medicines, insecticide-impregnated bed nets, and malaria vaccine research and development. Despite some successes, meaningful progress in subduing the disease is hampered by inadequate health delivery systems, drug resistance, insufficient funding for existing treatment programs, and the complex biology of the parasite, among other obstacles.

The world needs a malaria vaccine to prevent this pernicious disease and to provide sustained health benefits in developing countries. An effective vaccine offers one of the most promising long-term solutions in a complete arsenal of tools for combating malaria. Scientific advances from both within and outside the traditional malaria vaccine community are expanding the number of candidate vaccines and stimulating new research and development. Nevertheless, the malaria parasite presents exceptionally difficult scientific challenges. Developing a safe and effective malaria vaccine remains elusive despite decades of effort.

A new approach is urgently needed to accelerate the development of an effective malaria vaccine to save lives. This requires a commitment by scientists, vaccine developers, policy leaders, and donors to come together to develop a shared vision for a malaria vaccine and create the necessary partnerships to ensure success. The collective expertise, knowledge, and resources of the global malaria community must be coordinated, integrated, and aligned with common long-term goals.

The malaria vaccine community has come together to create a bold vision (see inset) for accelerating the pace of vaccine development. The vision calls for the availability of a vaccine to reduce death and severe illness among young children in sub-Saharan Africa by 2015, and for the availability of a significantly more effective vaccine by 2020.

Malaria Vaccine Vision

By 2015, an effective malaria vaccine will be available to help reduce death and severe illness among young children in sub-Saharan Africa. By 2020, a vaccine with even greater efficacy will be available. This vision will be achieved through unprecedented global coordination and cooperation that will radically accelerate the pace of progress in malaria vaccine research, development, and testing.

This vision specifically focuses on *P. falciparum*. As the most deadly species of malaria, this is deemed the most urgent priority for malaria vaccine research and development. New knowledge gained through this research may contribute to advances in research on other species, such as *P. vivax*, and other areas of vaccine development. The community's vision for radically accelerating the development process opens the door for new vaccine candidates (in addition to RTS,S) to emerge, proceed through clinical trials, and become licensed to begin saving lives.

A series of specific goals support the vision. The two primary goals quantify the effectiveness of the vaccines to be available in 2015 and 2020 (see inset). Associated and interim goals defined in this document clarify expectations and objectives for the malaria vaccine development community.

This vision represents the first step in a collaborative, knowledge-based process known as technology roadmapping. The malaria vaccine community has adopted this process as a tool to define diverse approaches, identify new opportunities and gaps, prioritize critical needs, provide linkages among activities, and establish shared criteria for success. The roadmap will reflect a consensus of global views and provide an evolving, common blueprint for collaborative action by the entire malaria vaccine community. A broad cross-section of the malaria vaccine community and expert external advisors will be invited to participate in the roadmapping review process to enlist diverse perspectives, insights, and creative thinking on productive pathways. By attracting and focusing the right resources on solving the problems that lie in the critical paths to success, the community as a whole can achieve its vision for an effective malaria vaccine.

Primary Goals

By 2015, license a vaccine that can achieve a 50% reduction in malaria deaths and severe illness among young children in sub-Saharan Africa.

By 2020, license a vaccine that can achieve an 80% reduction in malaria mortality and severe illness in sub-Saharan Africa.

1. Introduction

Malaria is an urgent global problem that exacts a terrible price on some of the populations least equipped to address this widespread and powerful disease. It is the fourth largest cause of death in children of developing countries, accounting for 10.7% of such deaths worldwide in 2002 (CDC 2004). Malaria kills an estimated 2.7 million people and causes 300 to 500 million acute illnesses annually (Plotkin and Orenstein 2004). Approximately 90% of malaria deaths occur in sub-Saharan Africa (WHO 2005a), and three-quarters are in young children (CDC 2004). In fact, malaria is the leading cause of death in African children.

The devastation of malaria extends well beyond the harsh physical toll on infected people. Malaria creates an economic drain on local economies as a result of missed work and school days. Malaria-related costs to individuals and families include insecticide-treated mosquito nets, anti-malarial drugs, travel to medical facilities, treatment, and, all too frequently, burial. Governments bear the brunt of costs for the needed health facilities, medication, medical supplies, lost labor/work days, insecticide spraying and distribution, and lost tourism or other economic opportunities. In countries with a heavy malaria burden, the disease may account for as much as 40% of public health expenditures, 30 to 50% of inpatient admissions, and up to 50% of outpatient visits (WHO 2005b). These burdens can significantly impede economic development. The overall economic impact of malaria translates into an estimated 1.3% penalty on the annual economic growth rates of endemic countries (Gallup and Sachs 2001).

Efforts to combat malaria are being pursued on many fronts (see inset). A malaria vaccine, if one were developed, might avoid or alleviate many of the current, ongoing deployment and delivery obstacles by offering relatively long-term protection. However, certain traits of the malaria parasite present exceptionally complex challenges to vaccine development.

Options for Combating Malaria

Existing tools help reduce disease and suffering among populations at risk:

- insecticide-treated nets
- indoor or outdoor residual spraying with insecticides
- other forms of vector control
- anti-malarial drugs

Key challenges to the effectiveness of these tools include the following:

- escalating costs
- growing drug-resistance
- logistics of re-treatment
- pesticide resistance

Malaria vaccines, while not currently available, present an attractive option because of their potential to protect the most vulnerable from becoming ill. They represent an important part of a comprehensive portfolio approach to protecting populations at risk.

Research and development efforts to develop a malaria vaccine are underway around the world, and impressive advances are being achieved. Multiple advanced studies are in progress, the number of potential candidate vaccines is growing, and new tools for understanding interactions affecting the human immune response are emerging from diverse disciplines. Yet, despite these promising efforts, the seriousness of the malaria problem demands a more aggressive, coordinated, and cooperative approach that can finally produce an effective malaria vaccine in the near future. Now, more than ever, the global malaria vaccine community must come together to coordinate its knowledge, capabilities, and resources to move this effort forward.

To facilitate collaboration, the global community is creating a technology roadmap for the development of an effective malaria vaccine. The roadmap is designed to align current R&D efforts, identify critical needs and gaps, and create clear pathways and timelines for developing a viable malaria vaccine by 2015. This vision takes the first step by defining the goals and major scientific challenges that will guide the development of a successful roadmap.

2. Influential Factors

The pace of malaria vaccine development is influenced by a complex set of scientific, technical, political, and economic factors. Many of these factors are interrelated. For example, perceptions and attitudes toward malaria vaccine research and development can be pivotal in shaping political priorities, resource allocation, collaboration, regulation, and markets. These factors, in turn, can significantly expedite or hinder research and development and affect the pace of scientific and technical advances in the field. Understanding the variety of key trends and drivers and their interrelationships is a prerequisite to developing a realistic vision and supporting strategic goals. Some trends will tend to support vaccine development efforts, some will impede efforts, and some may either support or inhibit progress. The malaria vaccine community must consider these trends and their implications to effectively capitalize on opportunities and develop strategies to overcome challenges.

Perceptions and Priorities

The general public is becoming increasingly aware of malaria. Heightened global awareness of health issues in general—and malaria specifically—are a boon to malaria R&D. News coverage of the impacts of infectious diseases and the inequities of access to health care around the globe is increasing pressure for action and creating a humanitarian imperative. Increased international recognition of the need for a malaria vaccine has placed it higher on the global research agenda, concentrating resources and accelerating the pace of research and development. This recognition has also led to increasing R&D capacity in endemic countries and the emergence of global vaccine financing and delivery systems that will be needed once a vaccine enters the market.

Political interest in and support for African issues is relatively high. Some of the wealthier developed countries have exhibited a growing interest in and commitment to Africa. If this trend continues, support for malaria vaccines could increase. However, political tides can be unstable and may again shift away from African health issues during the next decade. The emergence of other infectious diseases could also divert resources away from a malaria vaccine.

Competing priorities could jeopardize donor resources for R&D. Donor and other funding organizations continuously seek to maximize the effectiveness of their resources by reducing waste and eliminating redundancies in research and development. Other priorities, such as defenses against bioterrorism, are likely to compete for the same funds as vaccines. Moreover, despite recent promising results, some individuals in the scientific and funding communities maintain doubts about vaccines as an effective means to control malaria and favor pharmaceuticals or conventional means of intervention.

Developing countries face multiple needs of major consequence. In many disease-endemic countries, malaria control must compete with other high-priority programs. Malaria vaccine research and development is seldom high on the political agendas of malaria-endemic countries, where clinical trials are held.

Public expectations must be treated with sensitivity. The opportunity to publicize future advances and gain public support must be carefully weighed against the risk of raising hopes unrealistically. Malaria vaccine research and development efforts have suffered in the past from inflated expectations, and the community must avoid repeating that scenario. The research and development community may need to find a balance between meeting public-sector expectations of “best efforts” in good science and meeting private-sector expectations of goal-based product development.

Science and Technology

New technologies and knowledge will fuel innovation and advances. Malaria vaccine research and development will benefit profoundly from new knowledge and technologies that are developed either specifically for vaccine research or for related fields, such as proteomics. Of greatest value will be an increased understanding of the human immune response to malaria, the structure and function of the *falciparum* malaria parasite, and the interaction between host and parasite. Such understanding may emerge through improved bioinformatics, research advances in innate and acquired immunity, and emerging research technologies. Novel technologies will aid researchers in their quests to develop vaccines that can improve on natural immunity, ultimately leading to a vaccine that will not only help those who might otherwise perish, but also the millions of people who currently develop natural immunity through ongoing exposure and repeated illness.

Unavailability of predictive models and assays represent key hurdles to candidate vaccine selection and analysis. The lack of predictive models can create major delays in vaccine development. Malaria researchers must rely on an empirical approach to vaccine discovery and testing due to the

lack of known correlates of protection; standardized immunological assays; and a predictive, pre-clinical assay or challenge model. Because these tools are not widely available or standardized among researchers, credible comparisons among methods, assays, and case definitions are difficult or, in many cases, impossible. Finally, progress is slowed by the lack of functional knowledge about antigens and the lack of technologies to measure functional immunity.

The need for regional capacity building is becoming more urgent. The global research and development community's engagement, training, and support of African scientists and infrastructure have been limited, creating a dearth of human resources and capital in endemic countries. Specifically, capacity for field trial sites and investigators capable of meeting standards for good clinical practice (GCP) are limited. In addition, large industrial companies retain nearly all capacity meeting GMP (good manufacturing practice) standards, thus limiting the ability of researchers in the public sector to obtain and use test lots for clinical trials.

Markets and Incentives

Commercial interest in malaria vaccine development is increasing. Industry is showing greater interest in malaria vaccine development as initiatives to generate market "pull" mechanisms gain momentum (e.g., the British government's advance purchase commitment announced in November 2004). Military and other emerging markets in malaria-endemic regions may also generate increased investment. As these trends continue, malaria vaccine researchers in academia and non-profit organizations may increasingly gain interested industrial partners, bringing additional expertise and capabilities to bear on malaria vaccine research and development.

The need to significantly stimulate market forces continues. Many in industry still doubt the potential for a viable malaria vaccine market, questioning the ability of poor countries in which the disease is endemic to absorb the costs of a vaccine. This perception has been compounded by the lack of accurate demand forecasts (one is expected later in 2005). Balancing development costs against long-term benefits has also been problematic, forcing some within the vaccine community to focus on price (rather than the potential solutions) early in the development process. Subunit vaccines are likely to incorporate multiple components, which will increase manufacturing and materials costs.

Non-market forces are also valuable incentives. The global reach of various political, socio-economic, and humanitarian endeavors will propel continued research and development of a malaria vaccine. The Millennium Development Goals established by the United Nations, for

example, provide a strong impetus for this research, both directly (through the sixth goal: combat HIV/AIDS, malaria, and other diseases) and indirectly (through the fourth goal: reduce child mortality). The way in which malaria vaccine R&D is conducted and coordinated may also be influenced by progress in research toward an AIDS vaccine through the global HIV Enterprise model. In addition, the projected population growth in developing countries, where birth rates can be up to 10 times higher than those in the developed world, will increase focus on the need for an effective malaria vaccine.

Collaboration

Community commitment is a powerful accelerator. Vaccine research and development efforts will gain significant momentum and speed if the greater malaria vaccine community succeeds in coming together to define and collectively pursue shared criteria for success. Conversely, an inability to articulate and pursue a common set of goals will slow the rate of progress, result in disjointed research and development, and produce less than optimal results.

Collaborative efforts must creatively break free of traditional barriers.

Funding mechanisms can sometimes fragment the research and development field and inhibit collaboration. Individual researchers may also view joint planning arrangements with reluctance or skepticism, preferring to maintain independence. Intellectual property rights restrict access to existing technologies, assays, models, and adjuvants, preventing researchers from taking advantage of the most advanced tools and knowledge. Such issues and related costs can discourage creative new “players” with innovative approaches from entering the field.

A novel approach to knowledge management and sharing is imperative.

Members of the R&D community tend not to publish negative results, even though they could be extremely helpful to other researchers in down-selecting antigens, concepts, and candidate vaccines. Researchers are also reluctant to test to the point of failure, so work continues on vaccine candidates that may have a low chance of success, at the cost of developing other, potentially more effective and successful products. Limited knowledge sharing also leads to an excessive number of equivocal clinical trials.

Industry can provide a useful, goal-oriented approach.

Lack of a “value chain” or systems approach virtually eliminates the possibility for a succinct or efficient R&D development process for a vaccine. Such systems approaches are used in the

Value Chain Management

Value chain management is the integration and coordination of upstream and downstream activities (from R&D to delivery) to enhance the vaccine development process and speed time to market.

pharmaceutical or biotechnology industries to great benefit, and would likely add considerable value to malaria vaccine development by preventing duplication of development strategies and increasing coordination along the value chain. Application of a goal-oriented approach to malaria R&D can expedite progress, but must also recognize the potential contributions of creative, independent efforts.

Regulatory Environments

Regulations are still evolving. Regulatory requirements on clinical trials for malaria vaccines vary widely among both developed and developing countries. Many regulations are still evolving and, in some cases, appropriate governing bodies have yet to be identified. Various concerns can lead regulators to impose additional requirements on trials, which can increase costs and impede progress. Conversely, technology advances may obviate some steps currently in the clinical path to licensure. Depending on how these regulations develop, they will expedite or inhibit progress toward a malaria vaccine.

In developed nations, particularly in the United States and Europe, regulations and risk-assessments governing pharmaceutical development have become increasingly elaborate, often discouraging clinical research. In other parts of the world, regulatory environments for pharmaceuticals are becoming increasingly uncertain. Furthermore, mechanisms for licensing products useful only to sub-Saharan Africa remain untested.

3. Vision

An effective malaria vaccine is urgently needed to save lives and reduce human suffering. Many members of the malaria vaccine community believe that a vaccine could be developed and made widely available within the next decade. A specific, clear global vision for this vaccine can help to define research and development needs, attract resources, and align diverse efforts to significantly accelerate progress.

A vision identifies where an organization, group, or community should be in the future to best meet the needs of stakeholders. A shared vision is a guiding image of success that serves as a powerful rallying point for the community. A vision should present a “stretch” challenge that, while ambitious, could realistically be achieved within a defined time frame, and it also describes the enhanced functioning of the group to achieve the vision.

The malaria vaccine community has developed a bold vision (see inset) that reflects the urgent need for a vaccine against the most deadly form of malaria. While the community recognizes the vaccine as a global priority, it also fully appreciates the unpredictability inherent in biomedical research and product development—particularly in an area for which correlates of protection are unknown. The uncertainties and complexities associated with vaccine development help focus the vision on bringing an effective vaccine to the point of readiness for deployment. Subsequent vaccine deployment and delivery processes, while essential, will entail separate challenges, solutions, and resources. As a practical matter, however, vaccine deployment is envisioned to coincide with the delivery of other effective malaria prevention and control strategies. The end goal is to save lives and reduce the health and economic burdens imposed by malaria on some of the poorest regions of the world.

Malaria Vaccine Vision

By 2015, an effective malaria vaccine will be available to help reduce death and severe illness among young children in sub-Saharan Africa. By 2020, a vaccine with even greater efficacy will be available. This vision will be achieved through unprecedented global coordination and cooperation that will radically accelerate the pace of progress in malaria vaccine research, development, and testing.

An Urgent Need Demands a Bold Vision

The 2015 goal conveys the urgency of the need for a malaria vaccine and is meant to stimulate innovative approaches to vaccine discovery, development, and

testing. This date does not in any way limit efforts to those vaccine candidates that have already entered early-stage testing. The community's vision for radically accelerating the development process paves the way for new vaccine candidates to emerge, progress through clinical trials, and potentially achieve the vision of making an effective vaccine widely available.

Realistically, malaria cannot be *conquered* by 2015. While the vision calls for an effective vaccine candidate to be available by that year, first-generation malaria vaccines are not likely to be 100% effective in protecting people from the disease. In fact, the scientific complexity of malaria may prevent vaccines alone from ever achieving complete efficacy. Subsequent delivery may introduce complications that will need to be addressed or resolved as they are identified.

Beyond 2015, the vaccine community clearly anticipates the need for continued efforts to develop a more effective and longer lasting vaccine to further reduce the toll of malaria. A second-generation malaria vaccine with greater efficacy and stability should be licensed and available by 2020.

Focus on *Plasmodium falciparum* to Save Lives

The vision specifically focuses on a vaccine against the malaria caused by *P. falciparum*, the most deadly strain of the disease. *P. falciparum* is found predominantly in Africa, but is on the rise in Southeast Asia and elsewhere. The global vaccine community recognizes that other species of the parasite, most notably *P. vivax*, also cause significant health problems in many parts of the world. However, 90 percent of malaria deaths worldwide occur in sub-Saharan Africa—the majority in children under five years of age. By focusing on this most vulnerable population, the vision directs R&D efforts toward alleviating the greatest human suffering caused by the disease.

Vaccines that target *P. vivax* also stand to benefit from pursuit of this vision and the ensuing advances in research on *P. falciparum*. As researchers learn more about the human immune response, clinical trial design, and delivery platforms, this new knowledge may be applied throughout the vaccine development community.

Radical Acceleration Requires Improved R&D Processes

The envisioned radical acceleration of vaccine development will require the extended vaccine community to function in a new, highly coordinated, and sustainable manner. Researchers and developers from the public and private sectors worldwide will work together under a new compact to develop and commercialize an effective malaria vaccine.

Global collaboration among scientific researchers, commercial vaccine developers, donors, and government officials will accelerate malaria vaccine development and dramatically reduce malaria-related health problems. To develop a vaccine as quickly as possible, the malaria vaccine community will place the goal of developing a life-saving vaccine above individual interests. The community will commit the necessary resources to develop an effective vaccine and create new mechanisms for integrating the fruits of current and future efforts. Academia and industry will cooperatively take advantage of improved scientific understanding, rationale for candidate selection, and new coordination mechanisms to collaborate more closely on all phases of vaccine discovery, pre-clinical development, and clinical research.

The pace of scientific discovery will increase as immunologists, epidemiologists, vaccine developers, and clinical researchers align their efforts to answer critical scientific questions defined by the malaria vaccine community.

Cooperative research and development teams and partnerships will bring together experts from diverse disciplines to bring the latest technologies to bear on malaria vaccine efforts. New mechanisms of information exchange and knowledge management will enable scientists to rapidly absorb new findings from clinical trials, producing a robust portfolio of vaccine candidates.

4. Goals

The Malaria Vaccine Vision is supported by a series of specific goals tied to a timeline or schedule. These goals clarify the aims and scope of the vision and will aid in the subsequent mapping of research and development pathways, priorities, and other essential activities to achieve the vision.

Two distinct yet complementary sets of supporting goals have been established to stimulate advances and measure progress. The first set, the *product goals*, articulate desired vaccine characteristics and performance targets to ensure that an effective, licensed malaria vaccine is made available by 2015 and that a vaccine providing greater efficacy and duration of protection is licensed and available by 2020. The second set, the *process goals*, define needed improvements within the malaria community to enhance collaborative efforts and expedite or improve vaccine research, development, and testing processes. Meeting these process goals will inform the selection and evaluation of promising candidate vaccines to accelerate progress in achieving the product goals.

Malaria Vaccine Product Goals

The ultimate outcome of malaria vaccine development will be a dramatic reduction in malaria deaths and the burden this disease places on the public health and economies of endemic regions. The community's primary goals and accompanying targets quantify the impacts on public health:

By 2015, license a vaccine that can achieve a 50% reduction in malaria mortality among children under five years of age in sub-Saharan Africa.

- a 50% reduction in severe and clinical disease
- a 20% reduction in all-cause mortality in sub-Saharan Africa.

By 2020, license a vaccine that can achieve an 80% reduction in malaria mortality in sub-Saharan Africa.

- an 80% reduction in severe and clinical disease

While reducing mortality due to malaria appears straightforward, it is not always possible to isolate malaria as the cause of death. Often, malaria is but one of

several complicating health factors that ultimately lead to death. The target for reducing all-cause mortality addresses the challenge of this metric.

The magnitude of the malaria epidemic demands an urgent response, yet more than 30 years of research and development have not yielded a vaccine against this scientifically complex disease. A partially effective vaccine has the potential to save hundreds of thousands of lives, but rushing a vaccine to the marketplace may eclipse the opportunity to bring a more effective product to market in the near term. In developing a vaccine, the community must therefore balance the need to save lives as soon as possible against the drive to continue improving the efficacy of potential malaria vaccines. Although the cost of a human life cannot be quantified for use in an economic model, the commercialization of malaria vaccines does not make economic sense below a certain minimum efficacy threshold. Recognizing this delicate but real balance, the malaria vaccine community has established minimum efficacy goals for vaccine candidates in 2015 and 2020 (to achieve the vision). These goals also take into account the scientific challenges of the disease and the complexity of the parasites, which render complete protection elusive.

As with most vaccines, the actual public health impact will be lower than suggested by the stated efficacy goals. An analysis to determine the real public health impact based on stated efficacy targets will enable the malaria vaccine community to identify the specific public health benefits of vaccination against malaria caused by *P. falciparum*. Measurement of the benefit will inform subsequent malaria vaccine development efforts, such as those that target *P. vivax*. To define the vaccine's contribution, the analysis should account for other control measures, such as drugs, bed nets, and other interventions considered in overall malaria control and prevention strategies.

Goals for duration of protection, safety, stability, affordability, compatibility with the EPI schedule, and licensure are presented in Figure 1. The intent of these goals is to identify the rate of progress required between now and 2015, and between 2015 and 2020, to achieve the vision. With the exception of licensure, these goals should be pursued in parallel, where feasible, to facilitate rapid advances. Many of these goals can only be quantified within the context of a specific antigen used in a vaccine candidate.

Malaria Vaccine Product Goals

	2005	2010	2015	2020
Efficacy		<ul style="list-style-type: none"> ▶ 2007: significantly improve Phase 2b efficacy 	<ul style="list-style-type: none"> ▶ 2010: step down to infant Phase 2b 	<ul style="list-style-type: none"> ▶ 2015: 50% vs. mortality, severe disease, and clinical disease over 24 months ▶ 2020: 80% vs. mortality, severe disease, and clinical disease over 4 years
Safety	<ul style="list-style-type: none"> ▶ 2005: Develop preclinical toxicology package 		<ul style="list-style-type: none"> ▶ 2015: proven safety and immunogenicity 	
Stability		<ul style="list-style-type: none"> ▶ 2007: prove stability in pre-clinical trials 	<ul style="list-style-type: none"> ▶ 2015: temperature stability 	
Affordability	<ul style="list-style-type: none"> Design scalable manufacturing 	<ul style="list-style-type: none"> Improve yields Reduce cost of goods, particularly adjuvants 		<ul style="list-style-type: none"> ▶ 2020: vaccine is affordable
Compatibility with EPI Schedule			<ul style="list-style-type: none"> ▶ 2015: compatible with EPI schedule 	<ul style="list-style-type: none"> ▶ 2020: compatible with EPI schedule in fewer than three doses
Licensure			<ul style="list-style-type: none"> ▶ 2015: license 1st generation vaccine ▶ 2015: 2nd generation vaccine completes Phase 3 trials 	<ul style="list-style-type: none"> ▶ 2020: license 2nd generation vaccine

Figure 1: Product Goals*

* Goals shown represent a synthesis of goals developed by participants in three separate breakout groups at the Vision Meeting.

Malaria Vaccine Community Process Goals

To radically accelerate the pace of research and development in pursuit of the vision, the malaria vaccine community must come together in new ways. The process of managing and sharing information, coordinating activities, and leveraging resources to achieve shared goals will require fundamental shifts in the way malaria researchers work together. Public-private partnerships have emerged as an important model for cooperation and are likely to play a pivotal role in malaria vaccine research and development.

To help establish a framework for novel collaborations, the malaria vaccine community has defined *process goals* that speak to the research and development process, rather than only to characteristics of vaccine candidates. The assignment of timeframes to process goals will better define the pace of development needed to achieve the vision. *[Editor's Note: As shown below, timeframes were not developed for all process goals during the meeting. Reviewers are asked to please supply target completion dates (or start and stop dates) where needed to enable construction of a timeline or Gantt chart to guide development of the roadmap. We would like this document to reflect your ideas, but we will assign the missing dates if we do not hear from you. Thank you in advance for your feedback.]*

Scientific Discoveries

- *2006*: Identify major mechanisms of defense in humans for blood-stage parasites to guide vaccine discovery, development, and evaluation.
- *2008*: Identify major mechanisms of defense in humans for liver-stage parasites, if any, to guide vaccine discovery, development, and evaluation.
- *Date needed*: Establish challenge models for development of asexual blood stage and transmission-blocking vaccines in humans.
- *Date needed*: Identify and standardize assays to identify and measure correlates of protection and to determine antigen functionality.

Coordination and Collaboration Processes

- *2005*: Establish a directed development program involving collaboration of major donors; secure full and robust funding of coordination efforts.
- *Date needed*: Increase collaboration within the malaria vaccine community, with emphasis on avoidance of unnecessary redundancy.
- *Date needed*: Facilitate procedures to overcome intellectual property barriers in academic and industrial settings.
- *Date needed*: Improve and ensure access to all relevant data through database development, knowledge management, and open access.

- *Date needed:* Develop processes for coordinated project management:
 - Use technology development groups to select products and structure projects, following industry’s models for project management.
 - Engage industry, funding organizations, academia, and others in public-private partnerships.

Clinical Trial Capacity

- *Date needed:* Develop and maintain diverse sites for trials so that vaccines are tested with different transmission intensities.
- *Date needed:* Coordinate and standardize procedures for trials to facilitate cross-trial comparisons.
- *Date needed:* Cultivate development of geographically distributed human resources and expertise to support increasingly varied clinical trials.
- *Date needed:* Coordinate with malaria intervention programs to ensure adequate epidemiological data at trial sites.

Standards and Shared Criteria

- *2006:* Establish shared go/no-go decision criteria to prioritize vaccine candidates. Engage key stakeholders in a “steering” function to help coordinate and guide decision-making along the product development continuum.
- *2007:* Disseminate to the malaria community standardized assays and reference standards to allow comparison of vaccines, including antigen selection and clinical trial results.
- *2009:* Achieve broad acceptance of go/no-go criteria.
- *Date needed:* Make benchmark adjuvants available to investigators.

Funding

- *Date needed:* Fund good manufacturing practice (GMP) production.
- *Date needed:* Secure purchase commitments for the vaccine(s).
- *Date needed:* Fund “gaps” in the overall research and development portfolio.

Landscape Analysis

- *Date needed:* Understand and define the regulatory environment in African nations.
- *Date needed:* Monitor the malaria environment (outbreak statistics, population dynamics, interactions with other diseases) over time to

understand how changes affect the way that public health impacts and cost-benefit measures are judged for a candidate vaccine.

5. Big Questions

Underlying the malaria vaccine development effort is a series of fundamental scientific questions that the vaccine research and development community has been wrestling with for a long time. Collectively identifying and defining these core questions is an essential step toward identifying the critical research activities and resources necessary to find solutions.

Certain traits of the malaria parasite present exceptionally complex challenges to vaccine development efforts. Specifically, the parasite goes through multiple stages of development and exhibits sophisticated immuno-evasive behavior at each developmental stage. In addition, a vaccine would have to meet a variety of public health and practical feasibility criteria related to compatibility with other vaccines, production, reconstitution and storage, dose schedules, and other factors.

Despite these formidable challenges, a malaria vaccine appears ultimately achievable. Causes for optimism include (1) the promise shown by some adjuvants and platform technologies; (2) the recent elucidation of the malaria genome sequence, which may lead to the discovery of more vaccine immunogens; and (3) a growing understanding of how the human host immune response interacts with the parasite.

The community seeks ways to effectively develop, adapt, share, and apply new knowledge and technology to accelerate malaria vaccine development. The Malaria Vaccine Technology Roadmap will create a unified framework that maps malaria vaccine challenges and end points and helps organize cooperative action. To provide a solid starting point for the roadmapping effort, the malaria vaccine community has identified a series of “big questions,” scientific and non-scientific, that represent the most critical and challenging issues in the path to success.

The big questions identified in this section necessarily reflect the complexity of malaria vaccine research and development. Figure 2 presents these big questions in four categories and indicates key linkages among the questions.

- Enhanced Biological Understanding
- Rational Vaccine Design and Selection
- Improved Clinical Capabilities
- Enabling Environment

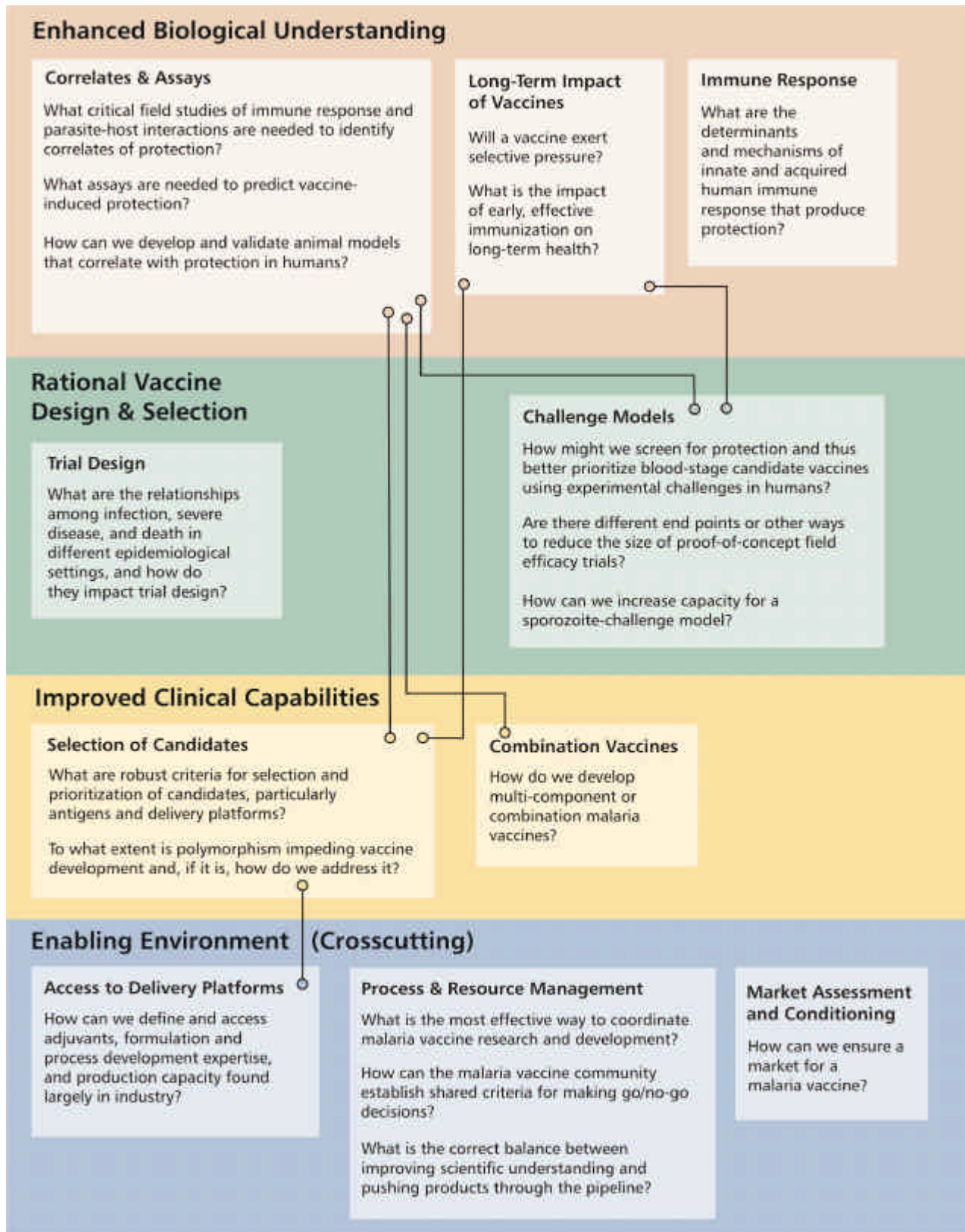


Figure 2: “Big Questions” Are Interrelated

Close relationships are assumed among all “big questions” within a category (or row). The lines between individual big questions indicate particularly strong relationships among questions in different categories. These relationships suggest that knowledge gained in pursuit of one big question could inform other R&D.

Answers to some of these big questions can inform and streamline the research and development process. To the extent possible, these questions should be answered early to expedite subsequent efforts. While some big questions stand in the critical path to success, many can be addressed simultaneously rather than sequentially. A few cannot be fully answered until a vaccine has been marketed, because scientists will need to monitor the impact of vaccination in humans on *P. falciparum* after vaccines have been used over an extended period of time.

Enhanced Biological Understanding

Correlates & Assays

- **What critical field studies of immune response and parasite-host interactions are needed to identify correlates of protection?** In early-phase trials, clinical researchers currently must measure end points that may or may not be indicative of protection. In some cases, clinical trials are deemed inconclusive and results are questioned because end points may not indicate or reflect protection. Because there is limited information on mechanisms of immunity to malaria, investigators must seek correlates that could be used to determine or measure protection. Valid correlates would allow vaccine developers to better manage clinical trials and should greatly accelerate progress in malaria vaccine development.
- **What assays are needed to predict vaccine-induced protection?** The inability to predict protection induced by a particular vaccine or antigen and technology platform further slows vaccine development by forcing investigators to take an empirical, rather than rational, approach. Qualified assays based upon meaningful correlates of protection would allow researchers to predict protection and this would accelerate progress by allowing scientists to focus their research and development on the most protective vaccine candidates in the lab without first taking them through expensive and time-consuming field trials.
- **How can we develop and validate animal models that correlate with protection in humans?** Animal models have greatly aided research and development of many other vaccines. To date, no such models have been shown to correlate to protection against malaria in humans. Models should allow scientists to conduct experiments in animals to determine the potential for vaccine candidates to convey protection. Validated animal models would radically accelerate progress through targeted candidate selection prior to clinical trials.

Long-Term Impact of Vaccines

- **Will a vaccine exert selective pressure?** As vaccines are introduced to populations, a vaccine could exert selective pressure on parasite populations,

resulting in the appearance of vaccine-resistant strains. While the malaria organism does not appear to evolve rapidly, care must be taken to monitor changes to *P. falciparum* over time in vaccinated populations. This will ensure that vaccines remain effective in protecting populations from disease.

- **What is the impact of early, effective immunization on long-term health?** Statistics show that once a child in sub-Saharan Africa reaches five years of age, that child has survived the period over which he or she is most vulnerable to malaria morbidity and mortality. During that five-year interval, a child is likely to have contracted malaria at least once, and this infection begins to build natural immunity that should persist and, assuming additional episodes, strengthen throughout adulthood. As vaccines are introduced to young children and infants, it is as yet unclear if or how immunization will impact this gradual building of natural immunity. Great care must be taken to ensure that vaccination, with appropriate boosting, of young children will impart life-long immunity and not merely postpone severe illness or death until later in life.

Immune Response

- **What are the determinants and mechanisms of innate and acquired human immune response that produce protection?** Malaria vaccine researchers do not yet understand how humans develop immunity to malaria. This lack of understanding requires that the community use time- and resource-intensive clinical research to empirically determine efficacy, and this must be done in the absence of firm theoretical or rational bases for selection of vaccine candidates. Research and development would be greatly accelerated if there were a greater understanding of mechanisms of immunity to, and protection from, malaria, and if biological signals that correlate with protective immunity were known. Defining differences in immune response between two groups exposed to malaria parasites, those protected and those not protected, may identify indicators of protection.

Rational Vaccine Design and Selection

Trial Design

- **What are the relationships among infection, severe disease, and death in different epidemiological settings, and how do they impact trial design?** Clinical trials are resource intensive, requiring significant funding, expertise, and facilities within a clinical test site that, from an epidemiological standpoint, has known and, potentially, predictable, characteristics. Because resources are limited and since clinical trials (particularly latter-phase studies) take years to plan and conduct, the community must perform them in a known environment to reap meaningful information. Understanding the effects of malaria in different epidemiological settings would allow investigators to

optimize trial design and ensure that they obtain the most useful and scientifically meaningful results from each trial.

Challenge Models

- **How might we screen for protection and thus better prioritize blood-stage candidate vaccines through the use of experimental human challenge models?** Even though blood-stage vaccines offer promise, relatively few have progressed to human challenge or early clinical trials, possibly because of hurdles to using challenge models in clinical development. Existing methods for blood-stage challenge may provide meaningful results and aid in understanding risks to human subjects, but to fully explore blood-stage candidates, experimental challenge models are needed to determine immunogenicity and protection. None exist today. Further clinical development must establish an adequate case definition of protection (e.g., absence of parasitemia, absence of pathologic complications, reduction of transmission), one that is appropriate for the conduct of field trials in endemic areas.
- **Are there different end points or other ways to reduce the size of proof-of-concept field efficacy trials?** If a concept for smaller clinical trials were available for early-stage, proof-of-concept studies, the smaller trials would accelerate screening of candidate vaccines and allow for more vaccines to be tested with fewer trial participants required.
- **How can we increase capacity for a sporozoite challenge model?** Studies have shown attenuated sporozoite-based vaccines can confer nearly complete protection. However, the vast majority of research and development is directed at pre-erythrocytic, antigen-based vaccines, with fewer resources directed at sporozoite research and development.

Improved Clinical Capabilities

Selection of Candidates

- **What are robust criteria for selection and prioritization of candidates, particularly antigens and delivery platforms?** Over 100 vaccine candidates or antigens have been reported as being under development. While this number is impressive, scientists are presently developing a relatively small number of candidates. Of these, a few will proceed from basic research through pre-clinical studies, an even smaller number will be evaluated in clinical trials, and a very few will achieve marketing approval or licensure. To progress any candidate, funding must be available, results encouraging, and commercial production feasible. While an influx of funding in recent years has enabled a higher number of vaccine candidates to be evaluated in clinical trials, the malaria vaccine community only receives a fraction of the

funding necessary to conduct clinical trials on all promising vaccine candidates. Criteria for selection and prioritization of candidates would allow the community to focus precious resources on the most promising antigens and candidates, reducing unfruitful lines of research and development.

- **To what extent is polymorphism impeding vaccine development and, if it is, how do we address it?** Polymorphism is a potential problem for any vaccine, yet currently marketed vaccines provide little evidence of this being an actual problem. However, *P. falciparum* is a highly complex organism, certainly as compared to infectious organisms for which vaccines exist. Malaria parasite antigens are polymorphic to elude the immune response, yet not all regions of the parasite chromosome are highly polymorphic. It also appears unlikely that malaria parasites would change rapidly (i.e., over a few years). As a countermeasure to polymorphism, vaccine developers may need to carefully select candidate antigens or regions of an antigen from DNA sequences that are not highly polymorphic. This approach could reduce the impact polymorphism might play in limiting vaccine effectiveness.

Polymorphism

With regard to the malaria parasite, polymorphism refers to the ability of the parasite to slightly change a protein in a particular gene so that the human immune response no longer recognizes the parasite.

Combination Vaccines

- **How do we develop multi-component or combination malaria vaccines?** Many scientists believe that due to the complex life cycle of *P. falciparum*, only a multi-component vaccine will provide maximum efficacy and duration of protection. By including antigens that target both pre-erythrocytic and blood stages, a vaccine would be more likely to elicit resistance to the disease. Ultimately, transmission-blocking approaches may also be included in a malaria vaccine to prevent spread of the disease. However, development of multi-component vaccines is challenging, complex, and costly, because each must incorporate two or more antigens in a single vaccine platform with an adjuvant to be effective against different stages of the parasite. Additionally, potential interactions among antigens must be considered and evaluated. Antigens must therefore be combined to produce a vaccine that is safe, stable, affordable, and, in an immunological sense, without antagonism. Ideally the antigens would be synergistic, leading to higher efficacy than a single antigen vaccine.

Enabling Environment

Access to Delivery Platforms

- **How can we define and access adjuvants, formulation and process development expertise, and production capacity found largely in industry?** To date, it has been difficult to apply the knowledge and experience of the vaccine industry to the production and formulation of candidate malaria vaccines, in part because some information is proprietary. Industry possesses significant resources that could profoundly benefit malaria vaccine research and development, including proprietary adjuvants, expertise in formulation and process development, and manufacturing capacity. Additional capabilities exist in contract research laboratories and academia. Industry's responsibility to generate profits for stockholders outweighs their motivation to divert resources toward malaria vaccine research and development. While biotechnology firms may be more willing to contribute technology and/or expertise to malaria vaccine development, they often require use of their proprietary platform technology or patents. Therefore, academic and non-profit sectors often find access to these resources difficult, complicated, or impossible—hindering overall progress in malaria vaccine development. Efforts must be made to combine the knowledge, skills and experience of the vaccine and biotechnology industries and academia to malaria vaccine development.

Process and Resource Management

- **What is the most effective way to coordinate malaria vaccine research and development?** Acceleration of vaccine development means that members of the malaria vaccine research and development community must find new and better ways to coordinate their efforts. Improved coordination does not mean the community works in a single direction; it is critical that diversity in scientific thinking remains, thus allowing for innovative approaches and possible breakthroughs. Rather, coordination implies a rationalization of all approaches, both “mainstream” and “radical,” without stifling scientific discovery and recognizing that some redundant studies may be appropriate and can be built into the overall malaria research and development strategy. Effective coordination will allow those working on malaria vaccines to have the most complete, up-to-date information to inform their decisions. Coordination will also enable the research community to leverage investments by working together in those areas where cooperative research and development would achieve the maximum scientific gain, reducing unnecessary redundancy of efforts.
- **How can the malaria vaccine community establish shared criteria for making go/no-go decisions?** A difficult aspect of malaria vaccine development is evaluating vast number of possible antigens and vaccine

candidates that could potentially prove to be safe and effective. Cost and time requirements of clinical trials severely limit the number of these antigens that can be intensely investigated. The decision process could be improved. A shared go/no-go decision process would strategically cull antigens and allow the community to focus on those that show the most promise. This, in turn, should greatly add to the overall efficiency and speed of vaccine development. No-go, or termination, criteria may be most important, as their absence leads to long-standing development, and associated expenses.

- **What is the correct balance between improving scientific understanding and pushing products through the pipeline?** With the prospect of saving lives, it is understandable to “push” products to market as quickly as possible. In fact, such efforts to develop a first vaccine is often attained at the expense of acquiring a deeper scientific understanding that could potentially support future development of a “better” vaccine; i.e., one with greater efficacy or duration of protection. Thus, the better vaccine may take longer to reach people who continue to suffer. Pushing an early candidate vaccine to market may save lives, but it could also strain public health budgets while achieving a relatively small impact on public health. This could hinder longer term improvements to the vaccine by eroding support for immunization programs among governments or donors displeased with their previous vaccine experience. Managing this balance between development of an early vaccine or waiting to develop a purported better vaccine will be a difficult, ongoing challenge for the malaria vaccine community.

Market Assessment and Development

- **How can we ensure a market for a malaria vaccine?** Because *P. falciparum* malaria affects some of the poorest regions of the world, most intended users will not have personal resources to purchase a malaria vaccine. The developed vaccine industry has specialized capabilities and expertise that, if brought to bear on malaria vaccine research and development, could significantly accelerate progress and save lives. However, without a sufficient infusion of donor funding, malaria vaccine sales to endemic areas would be limited. To assume the high risk of investing in malaria vaccine development, vaccine industries must have an assured market to enable them to recoup investment in research and development and to make a profit. Assurances from donors to purchase a licensed malaria vaccine and credible signals of demand by governments of malaria-endemic nations may help the vaccine industry to overcome their reluctance to become involved in malaria vaccine development. The malaria vaccine demand forecast to be released later in 2005 may help to build the case for investment in the needed research and development.

6. Looking Forward

This draft vision document is the first step in creating a strategic framework for rallying the malaria vaccine community around shared priorities. Leading experts from diverse fields contributed to its development (See Appendix B). The vision statement, supporting strategic goals, and big questions will guide subsequent identification of research and development priorities, technology pathways, and milestones for the Malaria Vaccine Technology Roadmap.

The Malaria Vaccine Technology Roadmap will reflect a consensus of global views and provide an evolving common blueprint for the entire malaria community. The roadmapping process will continue to engage leading scientists, donors, vaccine developers, and industry leaders from around the globe to identify the salient scientific problems, the most promising technology pathways, and the most productive collaborations to tackle this complex challenge.

Ultimately, the technology roadmap will provide an organizing framework for malaria vaccine challenges and promote cooperative action. It will help researchers understand how their efforts align with and support other research and development activities. The roadmap will also enable donors and other funding organizations to support those roadmap implementation activities that best match their missions while better understanding the contribution their funding makes toward the overall goal.

Technology roadmapping discussions are expected to begin in March 2005 and continue for several months to allow the broadest possible contributions from the malaria vaccine community and from experts outside the community, who may also offer valuable insights to the process. While a final Malaria Vaccine Technology Roadmap document will be published later in 2005, the roadmap will remain a “living” plan for the entire global malaria community and undergo revisions as needed.

The draft vision outlines the strategic framework that will form the foundation for subsequent technology roadmapping discussions. As the malaria vaccine community continues through the process, this draft vision will remain open for comment. To provide comments on this document, please contact Ross Brindle at Energetics, Inc. (rbrindle@energetics.com). The collective contributions of all those interested in malaria vaccine development will strengthen the final roadmap; your ongoing contributions are encouraged.

As a final session at the Malaria Vaccine Technology Roadmap Vision Meeting held in October 2004, participants were encouraged to begin thinking about potential solutions to the big questions that emerged. Table 2 presents their preliminary thoughts; this unrefined information is intended for use as feedstock to the technology roadmapping discussions. Looking ahead, participants at the upcoming Technology Roadmap Workshop may also take note of the key themes developed at the Vision Meeting (see inset). These themes highlight the community's commitment to securing long-term funding for high-risk activities and developing strong yet flexible academic systems and partnerships that facilitate excellence and interdisciplinary approaches.

Key Themes

- Demand excellence in studies
- Interdisciplinary teams are essential
- Strong academic system is needed
- Traditional model does not lead to product development—need incentives for teaming
- Funding organizations need to take risks—malaria vaccine R&D is a long, slow process

Table 2: Possible Solutions to Big Questions

Correlates and Assays

- Establish GLP/GCP immunoassay service center of malaria
- Expand provision of standardized reagents and assays for evaluation
- Fund stock falciparum challenge cultures and other standard reagents, and distribute via MR4
- Develop reliable/validated assays for functional antibodies
- Analyze genotypes appearing sequentially in vaccinated and controls groups
- Create/fund a collaborative network to optimize and standardize immunoassays (ELISA, GIA, ADCI, T-cell, etc.) with capacity to provide standard operating procedures, reagents, statistical analyses, and databases
- Standardize assays and protocols; establish reference labs
- Agree to exchange sera/cells among trials of vaccines based on same antigens
- Make falciparum transgenic rodent parasites
- Focus the world's malaria immunologists to search for correlates of protective immunity of RTS,S in challenge and natural infections
- Prepare a list of potential correlates of vaccine efficacy and ask malaria community to critique the list and refine

Combination Vaccines

- Assess protective efficacy of non-replicating, metabolically active *P. falciparum* vaccine in experimentally challenged and naturally exposed humans
- Develop low-dose, whole-parasite vaccine to circumvent antigen selection difficulties and antigenic polymorphism
- Seriously examine an attenuated vaccine approach
- Test vaccines currently showing partial efficacy together in challenge model
- Evaluate a combination vaccine that has non-overlapping and measurable endpoints, (e.g., RTS,S and transmission blocking)
- Show additive protection as soon as possible
- Study combination blood stage vaccines in model systems and assess in vitro assays to evaluate combinability

Long-Term Impacts of Vaccines

- Set up common "pharmaco-vigilance" database for long-term follow-up

Immune Response

- Introduce RTS,S on broad scale and study impact, correlates, safety, escape, etc.
- Validate existing correlates and develop better ones

Process and Resource Management

- Establish (elect?) a small working group to coordinate vaccine R&D
- Create "bait" for enhanced industrial involvement to access processes, adjuvants, formulation capabilities, and GMP products
- Submit requests to industry for access to adjuvants

Table 2: Possible Solutions to Big Questions (Continued)

Selection of Candidates

- Use bioinformatics as a first screen for candidate antigens
- Rank antigens on a basis of functional structural and immunological knowledge (need firm criteria)
- Create a catalog of all proteins expressed in: sporozoites, early liver stages (irradiated sporozoites), late liver stages, asexual stages (RDNG, Schizont), and gametocytes and gametes
- Develop limiting dilution cell transfer assays for protective responses
- Organize head-to-head comparisons of candidates when feasible
- Improve utility of SCID mouse model for malaria

Challenge Models

- Establish a working group of interested scientists (with funding) to develop blood challenge model
- Test efficacy of the three blood-stage vaccines currently in African trials in a blood-stage challenge
- Use combinations of antigens in challenge models to screen out unpromising candidates
- Develop minimal challenge models to screen faster in the clinics
- Develop/fund central sporozoite challenge center

Trial Design

- Develop multiple banks of frozen parasites
- Set Proof of Concept bar low (lower limit > 0) to avoid eliminating potentially successful candidates too soon (we don't know what endpoints correlate with success)
- Conduct critical analysis of current data on potential proxy measures of clinical disease to be able to conduct smaller efficacy trials
- Hold a consultation on Phase III trial design
- Conduct harmonization meeting on Phase II analysis planning

Policy and Economics

- Develop malaria vaccine advisory group, list all scientists who wish to communicate through it
- Hold WHO-AFRO summit on criteria for adoption (with donors)
- Establish committee to link malaria vaccine development with immunization and malaria control and prevention programs
- Set up a WHO-led coordinating "steering group" to plan and advise on trials (head-to-head, selection criteria, etc.), backed up by significant new funding as incentive
- Create mechanisms to track progress, advances, and setbacks in the field

Delivery Platforms

- Hold a conference specific to adjuvants, process expertise, and capacity from industry
- Establish formulation facility funded by public sector by creating a global platform having access to all adjuvants and formulations
- Fund GSK to evaluate candidate antigens in optimal delivery platforms and develop lead candidates (fastest bang for the buck)

Appendix A:

Technology Roadmapping

Malaria represents a growing threat to vulnerable populations. Current, dispersed research efforts are exploring new vaccines, yet the world health community would welcome increased funding and progress. A collaboratively developed technology roadmap can be a powerful and highly effective tool to stimulate new thinking and approaches, map alternative investigative pathways, coordinate diverse aspects of development, and attract new funding.

A Malaria Vaccine Technology Roadmap Working Group (see Appendix B) was formed to help tailor the technology roadmapping process to the unique needs of the malaria vaccine community. The Working Group defined the scope of the effort and continues to play an important role in guiding the overall process.

The Roadmap development process will engage leading scientists, donors, vaccine developers, and industry leaders from around the globe to identify the salient scientific problems, the most promising technology pathways, and the most productive collaborations to tackle this complex challenge. The collective insights of experts within and outside of the malaria vaccine community will help to align the technical and financial resources of the public and private sectors.

The first step in the roadmapping process is to develop a unified vision that clearly articulates the long-term goals for the future. This document contains the first draft of that vision. It is based on discussions that took place at the Malaria Vaccine Technology Roadmap Vision Meeting, held October 24-26, 2004, at the Wellcome Trust Conference Centre in Hinxton, England. The meeting was jointly sponsored by the Bill and Melinda Gates Foundation and the Wellcome Trust, and was coordinated by the Malaria Vaccine Initiative, PATH. The 35 experts who participated in the meeting (see Appendix B) contributed their insights and expertise, laying out the concepts on which this document is based. Tables summarizing these meeting results may be viewed at www.malariavaccineroadmap.net/summary.html.

Technology roadmapping discussions are expected to begin in March 2005 and continue for several months to allow the broadest possible involvement by the malaria vaccine community and by experts outside the community, who may also offer valuable insights to the process. While a final Malaria Vaccine Technology Roadmap document will be published later in 2005, the roadmap will remain a “living” plan for the entire global malaria community and undergo revisions as needed.

Appendix B:

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Appendix C:

References

- CDC 2004. Centers for Disease Control and Prevention (CDC) website, U.S. Department of Health and Human Services. *Malaria Facts*. (May 2004). Retrieved January 10, 2005, from <http://www.cdc.gov/malaria/facts.htm>
- Gallup and Sachs 2001. Gallup J.L., Sachs J.D. (2001). "The Economic Burden of Malaria," *Am J Trop Hyg* 2001;64 (1,2) S:85-96. Retrieved January 10, 2005, from U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) website, http://www.cdc.gov/malaria/pdf/Gallup_AJTMH_2001.pdf
- Malaria Vaccine Technology Roadmap website. *Vision Meeting Results*. Retrieved January 13, 2005, from <http://www.malariavaccineroadmap.net/summary.html>
- Plotkin and Orenstein 2004. Plotkin S.A., Orenstein W.A. (eds.). (2004). *Vaccines* (Fourth Edition). Saunders Press (Philadelphia, PA). pp. 1283 – 1289. Retrieved January 10, 2005, from <http://www.malariavaccineroadmap.net/background.html>
- WHO 2005a. World Health Organization (WHO), Roll Back Malaria website. *Malaria in Africa*. Retrieved January 10, 2005 from http://www.rbm.who.int/cmcc_upload/0/000/015/370/RBMInfosheet_3.htm
- WHO 2005b. World Health Organization (WHO), Roll Back Malaria website. *Economic Costs of Malaria*. Retrieved January 10, 2005 from http://www.rbm.who.int/cmcc_upload/0/000/015/363/RBMInfosheet_10.htm