

MALARIA VACCINE TECHNOLOGY ROADMAP

Vision Meeting

Summary Results — Draft

November 2004



Sponsored by
The Wellcome Trust
Bill and Melinda Gates Foundation

Organized by
Malaria Vaccine Initiative, PATH

24-26 October 2004
Wellcome Trust Conference Centre
Hinxton, Cambridgeshire, United Kingdom

Please submit comments:
Ross Brindle
Energetics, Inc.
410.953.6239
rbrindle@energetics.com



Table of Contents

INTRODUCTION	1
OPENING SESSION RESULTS	
Table 1. Factors Shaping Malaria Vaccine R&D	3
Table 2. Lessons Learned.....	7
BREAKOUT SESSION RESULTS	
<i>Group A</i>	
Table 3. Vision and Strategic Goals.....	9
Table 4. Key Scientific Challenges	10
Table 5. Big Questions	11
List of Participants.....	12
 <i>Group B</i>	
Table 6. Vision and Strategic Goals.....	14
Table 7. Key Scientific Challenges	16
Table 8. Big Questions	18
List of Participants.....	19
 <i>Group C</i>	
Table 9. Vision and Strategic Goals.....	21
Table 10. Key Scientific Challenges	22
Table 11. Big Questions	23
List of Participants.....	24
CLOSING SESSION RESULTS	
Table 12. Synthesis of Big Questions	26
Table 13. Potential Solutions.....	27

INTRODUCTION

Many promising research efforts to develop a malaria vaccine are underway around the world, and impressive advances are being achieved. Yet, there remains an urgent need to accelerate the pace of progress in creating, systematically evaluating, and optimizing candidate malaria vaccines. A large number of high-level studies are in progress, the number of potential candidate vaccines (combinations of antigens, adjuvants, and platforms) is growing, and new tools for understanding interactions affecting the human immune response are emerging from diverse disciplines. Now, more than ever, better coordination is needed within the global health community to use all new knowledge, developments, and resources efficiently to move this scientific effort forward.

One important step that the malaria community is taking to accelerate vaccine development is to create a Malaria Vaccine Technology Roadmap. 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 Malaria Vaccine Technology Roadmap will reflect a consensus of global views and is intended to serve as a common blueprint for the entire malaria community. It will provide a framework that maps malaria vaccine challenges and end points and helps organize cooperative action. The first step in the roadmapping process is developing a unified vision of where malaria vaccine R&D is heading and shared goals that can guide progress.

This document presents a summary of discussions that took place at the Malaria Vaccine Technology Roadmap Vision Meeting that was held on 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 coordinated by the Malaria Vaccine Initiative, PATH. The purpose of the Vision Meeting was to gather leaders from the malaria vaccine community to create the shared vision and supporting strategic goals that will guide development of a Malaria Vaccine Technology Roadmap. The 35 experts who participated in the meeting also identified key scientific challenges and formulated the “big questions” that must be answered to address the challenges.

The meeting results are being used to create a draft Vision document that will provide valuable input to the technology roadmap. The Vision document will outline the strategic framework that will be used to structure the subsequent Roadmap Workshop and articulate the community’s shared vision and goals.

Unlike other scientific meetings in which participants share research findings and discuss their implications, this meeting was designed to encourage participants to fully explore the challenges and big questions that malaria vaccine research seeks to answer. Interactive discussions took place in general sessions that included all participants and in smaller breakout groups. The breakout groups allowed participants to engage in more intimate and in-depth discussions and ensure that all viewpoints are heard. The results of the general sessions and breakout groups are presented in the body of this document.

Prior to the meeting, a Roadmap Working Group was formed to clarify the scope of the Malaria Vaccine Technology Roadmap as follows:

- The Roadmap will focus on the development of a commercially viable vaccine that targets *P. falciparum*.
- Children under five years of age in Sub-Saharan Africa are the main target population for the Roadmap.

The Roadmap Working Group also developed a candidate vision statement that sought to describe the shared vision of the malaria vaccine community. The challenge for the Working Group was to craft a vision statement that is ambitious, easily understood, appropriate, and achievable. At the workshop, participants offered comments on this vision statement in facilitated discussions (see Tables 3, 6, and 9 for the results of those discussions).

Candidate Vision Statement Discussed At the Vision Meeting

“By 2015, we will have significantly reduced death and illness in young children in sub-Saharan Africa due to the successful development and introduction of an affordable malaria vaccine.”

Vision Meeting Structure

The figure below outlines the conceptual structure of the Vision Meeting agenda and the questions that were explored within each activity.





*Opening Session
Results*

TABLE 1. FACTORS SHAPING MALARIA VACCINE R&D
 (◆ = Factors expected to have strongest influence on malaria vaccine R&D)

SUPPORTS ACCELERATION				
The factors listed in this section are expected to support the acceleration of malaria vaccine R&D in the coming 5-10 years.				
DEVELOPING CAPACITY ◆◆◆◆◆◆◆◆◆◆	SUPPORTING TECHNOLOGIES ◆◆◆◆◆◆◆◆◆◆	INCENTIVES ◆◆◆◆	GROWING AWARENESS ◆◆◆◆◆◆◆◆◆◆	COMMERCIAL DEVELOPMENT ◆◆◆◆◆◆◆◆◆◆
<ul style="list-style-type: none"> • Increased R&D capacity in disease endemic countries • Emerging global vaccine financing and delivery system 	<ul style="list-style-type: none"> • Development of adjuvants/ vaccinology can improve on natural immunity • Advances in toll receptor research and innate immunity • Success of commercialization of other vaccines • Growing emphasis on concepts rather than technology • Better bioinformatics • Systems biology approaches and resulting technologies 	<ul style="list-style-type: none"> • HIV vaccine enterprise may influence how malaria vaccine R&D is conducted/coordinated • Globalization <ul style="list-style-type: none"> – 10 million births in developed countries – 110 million births in developing countries • Impetus of millennium development goals drives activity 	<ul style="list-style-type: none"> • Growing discontent with world health inequities • Increasing international recognition of the importance of malaria • Recent awareness in lay community of the impact of global infectious diseases • Increasing perceived value of vaccines • Placing malaria research high on the development agenda • Economic benefits for governments 	<ul style="list-style-type: none"> • Creation of competitive environment with tangible economic reward for success • Increasing tourism and travel is increasing awareness of malaria and possible tourist market • Industrial capabilities can increasingly be engaged under the right circumstances

SUPPORTS/INHIBITS
The factors listed in this section may support or inhibit malaria vaccine R&D, depending on how they develop or emerge during the next 5-10 years.
<ul style="list-style-type: none"> • Increasing need to limit waste and redundancy in research ◆ • Growing commitment of high-income countries to Africa • Continued limits in clinical research capacity inhibit rapid, optimal testing/learning • Shift of political focus away from/to African health problems can support or inhibit • Other infectious disease threats in “developed” countries can divert resources away from malaria • Alternative malaria interventions may support vaccine R&D if they fail or inhibit vaccine R&D if they succeed • Success of other measures to control malaria may force vaccines to compete for limited funds as other control methods are purchased and deployed • Vaccine trial ethics <ul style="list-style-type: none"> – Must trials provide bet nets and combination therapies? – Can Phase I trials be conducted in developing countries? • Agreement on the main end points for vaccine development • Unknown costs due to regulatory requirements in addition to other costs • Support for investigators to move through trials • Prioritization of translational versus basic research

TABLE 1. FACTORS SHAPING MALARIA VACCINE R&D (Continued)

(◆ = FACTORS EXPECTED TO HAVE STRONGEST INFLUENCE ON MALARIA VACCINE R&D)

INHIBITS ACCELERATION					
The factors listed in this section have the potential to inhibit the acceleration of malaria vaccine R&D in the coming 5-10 years.					
PREDICTIVE ABILITIES ◆◆◆◆◆◆◆◆◆◆	KNOWLEDGE MANAGEMENT AND SHARING ◆◆◆◆◆	EXPECTATIONS & PUBLIC UNDERSTANDING ◆	REGULATIONS ◆◆	INTELLECTUAL PROPERTY ◆◆	OTHER
<ul style="list-style-type: none"> • Lack of predictive pre-clinical assay or model • Lack of immunological assays and correlates of protection • Poor predictive ability of preclinical studies • Inability to make credible comparisons at every level (methods, assays, case definitions, etc.) • Total lack of rationale in product discovery development • Lack of functional knowledge of antigens and of the structure they are in when they perform • Lack of technologies to measure functional immunity • Lack of understanding of immune correlates of protection 	<ul style="list-style-type: none"> • Lack of knowledge and/or will to down-select antigens, concepts, and candidate vaccines • Lack of knowledge management and dissemination of information/results • Temptation to conduct too many equivocal clinical trials, especially to generate political support in endemic countries • Reluctance to do the experiment that kills an antigen • One semi-successful product can inhibit development of other products 	<ul style="list-style-type: none"> • Managing expectations and realities; over-hyping positive results • Needed shift from “best efforts” public sector mindset to goal-based product development mindset • Growing need for partnerships among funders, governments, industry, and researchers to mitigate high risk of malaria vaccine R&D • Leveraging information dissemination channels • Diminishing patience among public 	<ul style="list-style-type: none"> • Increasingly over-elaborate regulation and risk assessment of developed world pharmaceuticals • Untested mechanism for licensing products useful only for sub-Saharan Africa • Changing and uncertain regulatory environment for products not licensed in U.S./Europe first 	<ul style="list-style-type: none"> • IP issues restrict access to technologies (e.g., assays, models, adjuvants, etc.) • Opportunity costs of resolving intellectual property issues limits the ability of new “players” with new ideas or technology to contribute 	<ul style="list-style-type: none"> • Natural immunity takes five years and multiple infections to develop; malaria vaccines must do better • Skepticism that a vaccine is feasible • Excess of arrogance, ignorance; lack of modesty and humility to address difficult questions • Vaccine safety issues • Real costs of full scale development of multiple constructs

TABLE 1. FACTORS SHAPING MALARIA VACCINE R&D (Continued)
 (◆ = FACTORS EXPECTED TO HAVE STRONGEST INFLUENCE ON MALARIA VACCINE R&D)

INHIBITS ACCELERATION – (Continued)					
The factors listed in this section have the potential to inhibit the acceleration of malaria vaccine R&D in the coming 5-10 years.					
LACK OF PRIORITY ◆	SYSTEMS APPROACH ◆◆◆◆	CAPABILITY LIMITATIONS ◆◆◆◆◆◆ ◆◆◆◆◆◆	LIMITED FUNDING ◆◆◆◆◆◆◆◆	BARRIERS TO COLLABORATION ◆◆◆◆◆◆◆◆	MARKET FORCES ◆◆◆◆◆◆◆◆
<ul style="list-style-type: none"> • Conflict of priorities in endemic countries • R&D is not on the political agenda • Anti-vaccine movements in some governments 	<ul style="list-style-type: none"> • Duplication of development strategies • Lack of coordinated efforts to create pharmaceutical or biotechnology-like approach • Lack of a “value chain” or systems approach to solving malaria 	<ul style="list-style-type: none"> • Inadequate human resources/capital in endemic countries, particularly for clinical trials • Lack of sufficient engagement, training, and support of the African research community and infrastructure • GMP test lot capacity is mainly in larger company environment • Limited R&D experience in public sector • Limited public sector formulation capacity • Insufficient GCP-capable field trial sites and investigators 	<ul style="list-style-type: none"> • Insufficient public sector funding • Competing priorities for funding <ul style="list-style-type: none"> – Competition with perceived risk of bioterrorism • Falling productivity of global R&D in “big pharma” endangering public good policies 	<ul style="list-style-type: none"> • Reluctance of potential partners to enter into joint planning • Funding mechanisms fragment the field, inhibiting coordination • View of scientific community and funders regarding drugs and other control methods (e.g., bednets) • Concerns over the likely costs of malaria vaccines in relation to the funds available for health in endemic countries 	<ul style="list-style-type: none"> • Difficulty balancing cost of development and potential benefits • Focus on price (and not solution) too early in process • Perceived lack of market discourages industrial engagement <ul style="list-style-type: none"> – Accurate demand forecasts do not exist • Community perception of value of malaria vaccine in Africa • Subunit vaccines will need to be highly multicomponent, increasing cost out of range of affordability

TABLE 2. LESSONS LEARNED

SCIENTIFIC STUDIES	RESEARCH STRATEGY	CAPACITY BUILDING AND SUPPORTING ANALYSIS	PUBLIC AND POLICY INTERFACES	DESIGN PROCESS AND RESOURCE ALLOCATION	COLLABORATION AND INFORMATION SHARING
<ul style="list-style-type: none"> • We can make the malaria vaccine • Partial immunity to malaria can be achieved • We have learned how to do robust field vaccine trials well • It is not as hard as we think it is • We must form conclusions based on data (i.e., we don't know that single antigen vaccine won't work) • Single antigen subunit vaccines alone are not enough • Subunit paradigm started in 1983; it is a lot more difficult than ever imagined and may never deliver a vaccine • Evaluation of poorly made/characterized product leads to wasted effort (e.g., SPF 66) • Shortage of choice in adjuvants for clinical use • Insufficient invested has been directed at characterizing a successful human response • Better animal models and immunological understanding are needed to facilitate process • Understanding of humans has grown through funding of human research • We don't know what will or won't work; we need to know what we don't know an design studies to answer those questions 	<ul style="list-style-type: none"> • Some major successes are accidents • Too much "herd instinct" driving research • Insufficiently thought out or prepared experiments and trials lead to inconclusive results • Value of long range, multidisciplinary planning/coordination • Need for more structured support, more steering • Need more information and technology sharing to agree on standard reagents and assays for human and animals • Emerging focus on vaccine impact on mortality and not travelers vaccine • This is a public health market, not commercial • An ad hoc empirical approach is unlikely to work for blood stages; systematic approach to validation is required • Need to plan for iterative vaccine development • Technology with multiple applications has higher chance of development • Keep diversity of thinking; form small group with "bizarre" approaches • Select scalable approaches • Lack of systems approach can delay public health impact • Comparison is essential for killing inadequate technology early • The greater the effort to move vaccines into the field, the more we learn towards ultimate goal 	<ul style="list-style-type: none"> • Developing the vaccine is only the start of the solution • Building research infrastructure takes time • The complexity and time lines of vaccine R&D are larger than expected • A variety of skill sets are required for success • There is a poorly understood reluctance to professionally define markets and true costs (among those who can pay) • We sometimes mix assumptions with facts <div data-bbox="745 829 1047 906" style="text-align: center; border: 1px solid black; padding: 5px;"> KEY THEMES </div> <ul style="list-style-type: none"> • Demand excellence in studies • Interdisciplinary teams are essential • Strong academic system is needed <ul style="list-style-type: none"> - Academic model does not lead to product development – need incentives for teaming • Funders need to take risks – malaria vaccine R&D is a long, slow process • Celebrate the handoffs 	<ul style="list-style-type: none"> • It is difficult to balance advertisements of successes with realistic expectations <ul style="list-style-type: none"> - Do not over-hype results (managing expectations) • Impact on lives saved holds more weight than infection; trails are needed to build the case but major barriers exist to doing mortality trials • We have learned how critical the link between clinical research and policy makers and implementers really is • Underestimation of the difficulties, (e.g., Tdr 1375 or WHO 2000) <ul style="list-style-type: none"> - Public perception and possibly scientific arrogance • The right political and strategic context for malaria R&D is important for success • Vaccine development must consider delivery to ensure an effective vaccine can quickly make a public health impact • Canine hookworm vaccine was highly effective but other public perception barriers stopped it; will a malaria vaccine that only treats children be accepted by the public? • Fight the ethicists to address the public health question 	<ul style="list-style-type: none"> • Ensure high-quality products go into high-quality trials (don't skimp) <ul style="list-style-type: none"> - Need decision-making criteria to determine which products to use • It takes enormous focus and resources just to move through Phase IIb clinical trials • Well focused and funded work will lead us to success, e.g., RTS,S • Stop doing underpowered (scientist) and under-funded (funder) experiments • Persistence pays – a systematic approach to development works • Perseverance is not the same as obstinance <ul style="list-style-type: none"> - Investigators should not identify with a specific vaccine candidate • Try to concentrate efforts on limited number of antigens • Be willing to kill failed products • Multi-site studies with all partners engaged have led to quick resolution of policy • The research system has shifted incentives from products to publications, shaping researcher focus; this must be reversed <ul style="list-style-type: none"> - Do funders drive this? 	<ul style="list-style-type: none"> • Limited access to data slows research progress <ul style="list-style-type: none"> - Publish negative data - Publish all results using open access portal - Open access to data can allow for more transparent evaluation, better quality, and improved assessment and decisions • Value of multi-institutional collaboration and data sharing <ul style="list-style-type: none"> - Collaborative efforts have worked - Data, results, knowledge must feed back into the process - Working with partners other than industry is slower and requires more effort for product development • Funding agencies must drive towards multi-component vaccines • We have a tendency to forget our past lessons learned and repeat mistakes • Wins of the "collective" may equal losses for an individual <ul style="list-style-type: none"> - Killing projects means ending someone's funding, creating resistance to collective work and testing to failure • Rewards and incentive structure is insufficient for public sector product development • Conduct multi-center trials with important public health end points (death)

*Breakout Session
Results*

GROUP A

TABLE 3. VISION AND STRATEGIC GOALS – GROUP A

VISION	PROCESS GOALS	PRODUCT GOALS
<p>Revise draft visions statement to read (in italics) <i>By _____, we will have developed at least one malaria vaccine capable of being deployed in young children in sub-Saharan Africa to reduce disease and death.</i></p> <ul style="list-style-type: none"> Establishing a firm date of 2015 places too much emphasis on candidates already in the pipeline such as RTS,S. Accelerating the number of candidates to choose from (more candidates in a shorter time period) should be a goal as well Establishing a firm date too far into the future implies that this is a nearly impossible task and may reduce enthusiasm The word “significantly” in the draft vision has only limited meaning as a metric We need to distinguish between death versus illness as an outcome goal Bringing a vaccine candidate to a deployable state should be the vision rather than focusing on development and introduction Affordability is an implied goal The target population of young children in sub-Saharan Africa is appropriate, but other research avenues should not be overlooked Some feel sub-Saharan Africa should not be the only target population, but all recognize that it is the geographic region that bears the heaviest economic burden 	<ul style="list-style-type: none"> Strengthen and coordinate clinical trial sites Facilitate procedures to overcome intellectual property barriers (academic and industry) Understand and define African regulatory environment Monitor malaria environment Coordinate and collaborate within the malaria vaccine community Establish challenge model for development of asexual stage vaccine in humans Enable rational antigen selection <ul style="list-style-type: none"> Decision-making criteria Comparability across studies Establish criteria for prioritizing of vaccine candidates <ul style="list-style-type: none"> Decision-making metrics 	<p>Notes:</p> <ul style="list-style-type: none"> Clinical trials must be more standardized to accommodate cross trial comparisons. Greater site coordination, including procedures for trials, is needed. This is also a human resource issue related to having adequate expertise geographically distributed to support more and more varied clinical trials. Intellectual property barriers include access to new ideas, sharing of ideas across organizational boundaries, and access to commercially protected assays and antigens. To monitor the malaria environment includes issues such as outbreak statistics, population dynamics, and interactions with other diseases (and their demographic profiles). Monitoring changes over time will affect the way that public health impact over time and cost-benefit measures are judged for any candidate. Emphasizing collaboration and the importance of “not reinventing the wheel” can allow for learning from other vaccine initiatives whenever possible. Not all agree that activities and approaches in HIV vaccine initiatives could be directly imported or adapted for malaria vaccine R&D. <p><u>Safety and immunogenicity</u></p> <ul style="list-style-type: none"> 2005: preclinical toxicology package, extend to Phase Ia and Ib trials 2015: step down into infant trials in Phase IIb 2020: proven safety and immunogenicity <p><u>Stability</u></p> <ul style="list-style-type: none"> 2007: prove stability in pre-clinical trials 2020: temperature stability <p><u>Efficacy against morbidity and mortality</u></p> <ul style="list-style-type: none"> 2007: Significantly improve Phase IIb vaccine efficacy 2012: step down to infant Phase IIb 2015: conduct morbidity trials 2020: prove efficacy against morbidity Allow for natural boosting <p><u>Affordability</u></p> <ul style="list-style-type: none"> 2007: scalable manufacturing 2010: improve yields 2012: reduce cost of goods, particularly adjuvants 2020: vaccine is affordable <p><u>Compatibility with EPI schedule</u></p> <ul style="list-style-type: none"> Less than 3 doses in the EPI schedule by 2020 <p>Notes:</p> <ul style="list-style-type: none"> 2020 was favored over 2015 for developing product goals. Characteristics of what is needed when were more agreed upon by the group than a determination of targets to measure success of any product goal. Many of the product goals are entwined with the process goals. Decision-making metrics and criteria for prioritizing candidates will support determining “efficacy.”

TABLE 4. KEY SCIENTIFIC CHALLENGES – GROUP A

(♦ = MOST CRITICAL CHALLENGE, ● = CRITICAL CHALLENGE)

ANTIGENS (CATEGORY I)	VACCINE DESIGN (CATEGORY I)	ASSAYS (CATEGORY II)	MECHANISMS OF IMMUNITY (CATEGORY II)	CLINICAL TRIALS (CROSS-CUTTING)	MANUFACTURING (CROSS-CUTTING)
<ul style="list-style-type: none"> Antigenic polymorphism of subunit vaccines ♦ Challenge for a whole attenuated parasite vaccine ●● Poor immunogenicity of subunit antigens ● Identification of candidates from VAR gene studies 	<ul style="list-style-type: none"> How to design efficacious vaccine boosted by natural exposure ●●●● Ability of a vaccine to reliably elicit protective response (quantity and quality) ●● Subunit vaccine candidates all selected on basis of antibody efficacy not CMI ● Rational approaches to combination of antigens ● Determinants of antigen/vaccine combinability in multicomponent vaccines Challenge of an anti-toxic vaccine Reduce reactogenicity 	<ul style="list-style-type: none"> Standardized assays of immune response ♦●●● No predictive, pre-clinical assay or model for either screening of newly discovered antigens or for assessment of existing candidate vaccines ●● Application of systems biology tools to malaria vaccine development ●● 	<ul style="list-style-type: none"> Understand mechanisms and determinants of acquired and innate immunity ♦♦♦♦♦ Nature and durability of immunologic memory in malaria ●● MIC and immune responses of different populations (ethnic groups) Basis for poor Ig of malaria antigens (and how to overcome) Pathogenesis of severe disease Immune escape mutants Understand clinical and late immunological consequences of early vaccine protection Ability of material immune response to impede vaccine take in baby Induction of immunity early in life Co-infections (HIV and other parasitic infections) Immune response in infected individuals 	<ul style="list-style-type: none"> Improved understanding of relationship between infection, disease, severe disease, and death ♦●●●●●●● Challenge model for development of asexual stage vaccine in humans ♦●●●●● Design of (and acceptance of the need for) mortality trials ♦♦ Agree on acceptable efficacy criteria for pivotal trials ● Endpoints measurement ● Establish quality systems in clinical trials to improve effective data collection and comparability of results ● Clinical development pathway for combination vaccines The impact of co-infections (HIV and other parasitic infections) on efficacy Critical development pathway (clinical trials) sequence Sustained human capacity capable of GCP/GLP trials Select optimal dose and schedule for candidates for clinical trials Challenge of measuring mild disease/severe disease across sites in Africa 	<ul style="list-style-type: none"> Combining antigens for different life cycle stages ●●●● Immunological interference between antigens Chemical interactions with immune response that would inhibit combinability Determine the places (geographic) where production will take place and any government registration requirements Optimized production system of recombinant products
<p>ADJUVANTS AND FORMULATION (CATEGORY I)</p> <ul style="list-style-type: none"> Lack of human resource expertise ♦ Lack of potent adjuvants for inducing CMI ●● Evaluate process to reach a stable product stored at 5°C 		<p>CORRELATES OF PROTECTION (CATEGORY II)</p> <ul style="list-style-type: none"> Establish humeral and CMI correlates through EPI/existing vaccine trials ●●● Correlates and predictors of protective immunity Animal model predictive of human protection ●●● Understand relation between and the determinants of infection and disease ● <ul style="list-style-type: none"> Mortality Endpoints 			<p>REGULATORY ISSUES (CROSS-CUTTING)</p> <ul style="list-style-type: none"> Unified regulatory procedures in Africa to protect intellectual property rights and registration of products
					<p>RESEARCH AND COMMERCIAL DISCONNECT (CROSS-CUTTING)</p> <ul style="list-style-type: none"> Availability of potent adjuvants outside of industry (availability potentially controlled by commercial interest unwilling to license/share) ● Scalability ● From prime boost to something more feasible
<p>NOTES: The scientific challenges are grouped into two Categories. Category I includes Antigens, Adjuvants and Formulation and Vaccine Design. Category II includes Assays, Correlates of Protection, and Mechanisms of Immunity. The other groups of scientific challenges cut across the two Categories.</p>					

TABLE 5. BIG QUESTIONS – GROUP A

1. What are the determinants and mechanisms of innate and acquired immune responses in humans that determine protection?
2. How can we develop and validate animal models that correlate with protection in humans?
3. From the standpoint of designing efficient clinical trials, what is the relationship between infection, disease, severe disease, and death, especially in different epidemiological settings?
4. How do we develop an experimental human challenge model for asexual blood stage vaccines that is generally acceptable and predictive of efficacy in field trials?
5. To what extent is polymorphism impeding vaccine development and if it is, how do we overcome this?
6. What are robust criteria for selection of candidates, particularly antigens and delivery platforms?
7. How do we ensure the durability of protection following vaccination?
8. Is cell-mediated immunity critical to blood stage efficacy?
9. How do we make platform technologies accessible to the research community?
10. If we need multi-component vaccines, how do we determine how many antigens are required?

List of Participants – Group A

Dr. Pedro Alonso	Hospital Clinic Barcelona
Prof. Fred Binka	Indepth-Network
Dr. Bernard Fanget	Flamel Technologies
Dr. Martin Friede	World Health Organization
Prof. Michael Good	Queensland Institute of Medical Research
Dr. Lee Hall	NIAID, NIH
Dr. Andreas Holtel	European Commission
Dr. Frank Malinoski	Oxxon Therapeutics, Inc.
Dr. Vasee Moorthy	Malaria Vaccine Initiative, PATH
Dr. Regina Rabinovich	Bill & Melinda Gates Foundation
Dr. Mark Walport	The Wellcome Trust
Ms. Sarah Ewart	Malaria Vaccine Initiative, PATH
Dr. Irene Petrick	Pennsylvania State University (Facilitator)

*Breakout Session
Results*

GROUP B

TABLE 6. VISION AND STRATEGIC GOALS – GROUP B

VISION STATEMENTS	PARTNERSHIP STRATEGIES
<ul style="list-style-type: none"> • By 2015 we will have reduced child mortality from malaria by at least 50% through the development of an effective vaccine delivered with other effective malaria control tools. • By 2015 we will deploy a preventative vaccine for malaria as a fundamental element of the control of infection and disease in malaria areas. • By 2015, the united malaria vaccine community and partners will have developed a malaria vaccine which has undisputable potential to significantly reduce death and illness from the disease in young children in Sub-Saharan Africa • Development of a malaria vaccine that will have a major impact on the disease is achievable in the next decade. The roadmap will set out the steps that are needed to do this and develop new partnerships and methods of working that will enormously speed the process. 	<ul style="list-style-type: none"> • We as a malaria vaccine community recognize that we must work collectively to develop a vaccine as quickly as possible. We commit to placing the goal of having a life-saving vaccine above our individual interest. • We will create and commit the necessary resources to develop an effective malaria vaccine by creating a new mechanism for combining the fruits of current and future (short-term) antigen discovery and delivery efforts. This will involve all interested public and private (especially industrial) institutions. • In recognition of the unacceptable burden of malaria, the scientific community of the world in the public and private sectors, in the developed and developing world will create a new compact to implement a shared strategic vision to create and deploy an effective malaria vaccine to all those who will benefit. • The community of scientists, policymakers and funders commit themselves to work effectively together to achieve the development and implementation of an effective and affordable malaria vaccine to prevent death and disease in Africa. • Accelerate malaria vaccine development by addressing the gap between academia and industry by improving the rationale, coordination, collaboration at vaccine discovery, pre-clinical development, and clinical development levels.
DISCUSSION OF DRAFT VISION	<ul style="list-style-type: none"> • <i>For the scientific community:</i> To decrease child mortality we will <ul style="list-style-type: none"> - bring together disciplines - increase opportunities for developing country scientists to have career opportunities in relevant skills areas - harness the latest technologies • <i>For the public and decision makers</i> <ul style="list-style-type: none"> - We are committed to membership funds - We regard it as a global priority to develop a vaccine against fatal malaria as soon as possible. • We envision a new, sustained, highly-coordinated malaria vaccine development effort that includes the entire world community of researchers and developers. This effort will introduce a malaria vaccine within the next two decades that will reduce mortality.
<ul style="list-style-type: none"> • Misses vision of ownership • Dates are a trap • Too broad • Who is it targeting? • Need to improve rationale and collaboration • Implementation <i>not</i> introduction • May turn people away 	

TABLE 6. VISION AND STRATEGIC GOALS – GROUP B *(Continued)*

PROCESS GOALS	PRODUCT GOALS
<ul style="list-style-type: none"> • Identify major mechanisms of defense in humans for each of the parasite stages to guide vaccine discovery, development, and evaluation by 2006 (blood stage) and 2008 (liver stage) • By 2005, establish a directed development program involving collaboration of major donors • By 2007, disseminate to the malaria community standardized assays and reagents to allow comparison of candidate vaccines • By 2006, converge on Go/No-Go decision criteria. By 2009, achieve broad acceptance of Go/No-Go decision criteria. 	<ul style="list-style-type: none"> • By 2015, achieve a 40% reduction of malaria mortality and a 20% reduction of all cause mortality.
GENERAL PROCESS ACTIVITIES (NO DATES)	
<ul style="list-style-type: none"> • Develop alternative pathways involving multiple industrial partners as well as the public sector • Make benchmark adjuvants available • Develop surrogate markers • Develop and maintain diverse sites for trials so that vaccines are tested with different force of infection • Ensure adequate epidemiology coupled to the interventions • Fund GMP production • Coordinate with other interventions 	

TABLE 7. KEY SCIENTIFIC CHALLENGES – GROUP B

(♦ = MOST CRITICAL CHALLENGE, ● = CRITICAL CHALLENGE)

MECHANISMS OF IMMUNITY	UNDERSTANDING ANTIGENS	CLINICAL TRIALS		STRUCTURAL/ INSTITUTIONAL/ ECONOMICS	VACCINE DESIGN
		DESIGNING TRIALS	UNDERSTANDING RESULTS		
<ul style="list-style-type: none"> Understanding the impact of the mother's natural immune status during pregnancy on vaccine efficacy in the infant ● Understanding of infant immune system <ul style="list-style-type: none"> Protection of young children against clinical malaria may lead to reduced natural immunity when they become adults Understanding why immunity decline so fast Determining the mechanisms of immunity (in nature) in humans <ul style="list-style-type: none"> Mechanism of acquiring (and losing) natural immunity to malaria Determining if immunity is mainly a function of more cells Determining if local/regional immunity is important Understanding the immuno-modulatory mechanisms induced during infection that impede the efficacy of a vaccine Does exhaustion occur? Understanding the importance of cross-reactivity 	<ul style="list-style-type: none"> Understanding why malaria antigens are poorly immunogenic How to know if we need to produce more antigens 	<ul style="list-style-type: none"> Empirical exercise: clinical trial is your readout. What level of efficacy? ●● Developing an agreed upon standard set of end points ● Developing the capacity to conduct trials with mortality end points ● Lack of a human blood stage challenge system No data to compare the immunogenicity of "related" vaccine candidates Ascertaining whether someone has died of malaria Lack of methods to compare trials 	<ul style="list-style-type: none"> Understanding how selective pressure of a sub-unit vaccine affects the parasite population structure and might lead to resistance ♦●●●●● Determining how we work together to fully exploit the data we have ● Explaining why vaccines fail <ul style="list-style-type: none"> A) parasite B) host: genetic? Acquired? Circumstantial? Developing alternative assays to estimate parasite burden (LOH, HRD-2, etc.) Understanding the relationship between anti-parasitic and anti-disease (especially anti-fatal disease) efficacy 	<ul style="list-style-type: none"> Overcoming the expected high cost of an effective vaccine ♦● Lack of career structures for local scientists in malarious countries ●● Balance between understanding the science and implementing trials Making academic researchers product driven Lack of scientific capacity in Africa to conduct GCP trials 	<ul style="list-style-type: none"> Designing a vaccine that maintains protective immunity ♦● Developing an approach for attenuated vaccines Devising a strategy for exploiting the genome knowledge in vaccinology Parasite-specific tools receive too little attention Predicting protective immunogenicity Developing "go" criteria for selecting: <ul style="list-style-type: none"> One molecule as candidate An antigen delivery system An adjuvant An antigen combination Developing "no go" criteria to end development Lack of data to indicate minimally what we are shooting for
	<p style="text-align: center;">COMBINATION VACCINES</p> <ul style="list-style-type: none"> Multiple candidate antigens ♦●● <ul style="list-style-type: none"> Designing trials for combinations Combinations likely more effective but are tricky to develop, characterize, and release Devising methods for developing multivalent vaccines (such as VLPs) ● Combinations of vaccine antigens and formulations may lead to antagonism Delivery vehicles/vector 				

TABLE 7. KEY SCIENTIFIC CHALLENGES – GROUP B (Continued)

(♦ = MOST CRITICAL CHALLENGE, ● = CRITICAL CHALLENGE)

ADJUVANTS	MALARIA BIOLOGY	ANIMAL MODELS	VACCINE AND OTHER INTERVENTIONS	HUMAN CORRELATES	PRODUCT & PROCESS DEVELOPMENT
<ul style="list-style-type: none"> • Getting better access to adjuvants ●● • Getting access to formulation capacity ●●● • Understanding of mode of action of adjuvants 	<ul style="list-style-type: none"> • Understanding determinants of severe malaria and death from malaria – uncertainty about correlation of clinical malaria to more severe form ● • Determining if HIV infection will undermine protective effects of malaria vaccine • Better defining the interaction between blood stage antigens in RBC invasion – Redundancy • <i>P. Falciparum</i> (et al.) as “residents” are well-poised to escape human immune response • Understanding the importance of (a) parasite (virulence) and (b) host (susceptibility) diversity, and parasite-host combinations that may be particularly dangerous • Understanding the potential influence of entomological inoculation rate (ETR) on vaccine efficacy • Understanding how vaccines affect parasite populations 	<ul style="list-style-type: none"> • Absence of immunogenicity model reflecting human immune response ● • Lack of interest in improving models that could save years of development ● • Absence of easy relevant animal models • Lack of coherence between in vitro and in-vivo models 	<ul style="list-style-type: none"> • Difficulty in evaluating vaccine efficacy as other interventions (ITNs, IPT) are introduced ● • Finding a niche for a disease-ameliorating malaria vaccine in the context of integrated control effluents 	<ul style="list-style-type: none"> • Absence of established correlates of protection ♦♦♦♦●●●● <ul style="list-style-type: none"> – Importance of improving predictive assays • Discovering pathogenic mechanisms that allow chemical correlates of clinical disease • Validation of models based on clinical findings • Incorporation of correlates in efficacy trials prospectively • Determining efficacy in the recent RTS,S trial due solely to the adjuvant (enhancing immunogenicity of natural infections)? • Understanding the (molecular) basis for RTS,S failures in the recent trial in Mozambique 	<ul style="list-style-type: none"> • Developing criteria for making go/no-go decisions ● • Stability – can this be achieved ● • Insufficient knowledge in the community on process development • Adaptation to genome-wide Ag numbers • Lack of market understanding in technical decision making • Ability to make a malaria vaccine affordable by process engineering or other strategies, given the severe economic constraints

TABLE 8. BIG QUESTIONS – GROUP B

<i>CORRELATES OF PROTECTION</i>	<i>ANTIGENS</i>	<i>OTHER</i>
<ul style="list-style-type: none"> • What are the correlates of the protection? • What are the critical studies of the immune response and other host and parasite factors that should be done in the context of vaccine field trials in search of correlates of protection? 	<ul style="list-style-type: none"> • How do we choose the best antigens? • How can antigens be combined in vaccines <ul style="list-style-type: none"> – Safety – Without antagonism – Affordability 	<ul style="list-style-type: none"> • Will a vaccine exert selective pressure? • Will new adjuvants/vehicles <ul style="list-style-type: none"> – Be available – Be efficacious for most candidate antigens or combinations thereof
<i>MECHANISMS OF IMMUNITY</i>	<i>ACCELERATING VACCINE DEVELOPMENT</i>	
<ul style="list-style-type: none"> • What is the mechanism of immunity? • What is different about the immune response in naturally immune people as opposed to people who have not yet acquired preventive immunity? – 	<ul style="list-style-type: none"> • How do we define and access <ul style="list-style-type: none"> – adjuvants, – process development expertise – formulation expertise – capacity that are found largely in industry? • How do we balance between scientific understanding and moving products through the pipeline? • How do we establish shared criteria for making go/no-go decisions? 	

List of Participants – Group B

Prof. Peter Beverley	Edward Jenner Institute for Vaccine Research
Dr. Ted Bianco	The Wellcome Trust
Dr. Carter Diggs	US Agency for International Development
Dr. Pierre Druilhe	Institut Pasteur
Dr. Marie-Paule Kieny	World Health Organization
Dr. Richard Klausner	Bill & Melinda Gates Foundation
Dr. Pascoal Mocumbi	European & Developing Countries Clinical Trials Partnership
Prof. Malcolm Molyneux	Malawi-Liverpool-Wellcome Trust Research Programme
Dr. Melinda Moree	Malaria Vaccine Initiative, PATH
Prof. Sarah Rowland-Jones	Medical Research Council
Dr. Alan Shaw	Merck & Co., Inc.
Prof. Peter Smith	London School of Hygiene and Tropical Medicine
Mr. Jack Eisenhauer	Energetics, Inc. (Facilitator)

*Breakout Session
Results*

GROUP C

TABLE 9. VISION AND STRATEGIC GOALS – GROUP C

COMMENTS ON DRAFT VISION	PROCESS GOALS	PRODUCT GOALS
<p>Revise to read (revisions in <i>italics</i>): “<i>To radically accelerate malaria vaccine R&D so that by 2015, we will have substantially reduced death and severe illness in young children in sub-Saharan Africa due to the successful development and introduction of a malaria vaccine.</i>”</p> <p><u>Vision statement revisions</u></p> <ul style="list-style-type: none"> • “Affordable” is implied • Changed “significantly reduce” to “substantial” to avoid implication that we only seek statistically significant results • Consider adding “to introduce to infants...” <p><u>Key points to be included in supporting text</u></p> <ul style="list-style-type: none"> • Continue to introduce better vaccines after 2015 • Process/community aspect and improvements • The vaccine contributes to public health • Caveats needed to properly manage expectations • Exclusion of <i>P. vivax</i> may upset some in the community – include explanation of why it is excluded and how <i>P. vivax</i> vaccines will benefit from the roadmap activities <p><u>Comments on 2015 date</u></p> <ul style="list-style-type: none"> • A vision statement with a defined time frame will help to push development • This vision implies a 4X speed increase compared to RTS,S, which is a good goal • Absent radical acceleration, the 2015 date implies focus on candidates that have been tested today (i.e., RTS,S), which may be too limiting 	<ul style="list-style-type: none"> • Create a means to coordinate and guide decision-making along the product development continuum (involving key stakeholders in a “steering” function) • Secure full and robust funding of coordination efforts • Improve and ensure access to all relevant data through database development, knowledge management, and open access • Optimize and standardize methodology and reagents used for evaluation • Build greater global capacity for clinical trials • Secure a purchase commitment for the vaccine being produced <p><u>Notes</u></p> <ul style="list-style-type: none"> • Establish means for comparability (from antigen selection to endpoint) • Identify needed assays: <ul style="list-style-type: none"> – Required for growth (KO) – Correlate of protection – Function of antigen • Establish ridged/systematic criteria for target validation to modify targets rather than kill them • Establish needed tools: <ul style="list-style-type: none"> – Blood-stage challenge model – Transmission blocking • Establish means for head to head comparison of clinical trials • Build capacity for conducting clinical trials in endemic regions • Develop process for coordinated project management <ul style="list-style-type: none"> – Which product? – How to do it? – Could be a technology development group that relies on an industry model – Improved decision making with go/no-go criteria at each stage – Engage industry, funders, academia, and others in public-private partnerships • Funding “gaps” in portfolio management 	<p>Product goals were developed for the first-generation vaccine that will be available in 2015 to meet the vision and the second-generation vaccine that would offer higher efficacy and be available after 2020.</p> <p><u>Efficacy vs. mortality</u></p> <ul style="list-style-type: none"> – 2015: 50% over 24 months (from last dose) – 2020+: 80% over 4 years <p><u>Efficacy vs. severe disease</u></p> <ul style="list-style-type: none"> – 2015: 50% over 24 months – 2020+: 80% over 4 years <p><u>Efficacy vs. clinical disease</u></p> <ul style="list-style-type: none"> – 2015: 50% over 24 months – 2020+: 80% over 4 years <p><u>Other vaccine product goals</u></p> <ul style="list-style-type: none"> • Compatible with EPI distribution and schedule [0,2,3,4,9,15-18 months; several options] • Boostable for older kids <p><u>Licensure and Commercialization</u></p> <ul style="list-style-type: none"> • 2015: 1st generation licensed • 2015: 2nd generation finishes Phase III trials • 2020: 2nd generation licensed <p><u>Notes</u></p> <ul style="list-style-type: none"> • As with most vaccines, the public health impact will be lower than stated efficacy goals. The public health impact should be quantified through cost-effective analysis that also takes into account other control measures. This will allow the malaria vaccine community to identify the specific public health impact of vaccination.

TABLE 10. KEY SCIENTIFIC CHALLENGES – GROUP C

(◆ = MOST CRITICAL CHALLENGE, ● = CRITICAL CHALLENGE)

CORRELATES OF PROTECTION AND MODELS	ANTIGENS	MECHANISMS OF IMMUNITY	CLINICAL TRIALS	ASSAYS
<ul style="list-style-type: none"> Establish vaccine-specific and attainable immunological correlates of protection ◆◆●●●● Identify the best methods for testing vaccine combinations ●●● Develop predictive animal models ●● <ul style="list-style-type: none"> More reagents and funding for non-human primate models Correlate non-clinical studies with clinical results 	<ul style="list-style-type: none"> Set firm criteria for antigen prioritization and validation (particularly for blood-stages) ◆◆●●●● Understand whether two partially effective, different-stage vaccines can synergize for greater overall efficacy ◆◆●●● Lack of novelty in antigen pipeline ●● Address structure-function issue of highly validated antigens ● Systematically map the gene expression of difficult life-cycle stages of <i>P. falciparum</i> Develop strategy for combining antigens to build on RTS,S trial results Incomplete antigen (target) discovery Exploit new technology <ul style="list-style-type: none"> Mine the genome Chip technology Antigen selection has been driven by ability to model protection and the study of natural immunity, not on fundamental understanding of the immune response (particularly in the case of blood stage), possibly leading to the selection of sub-optimal antigens Assess prospects of PFMP-1 vaccine 	<ul style="list-style-type: none"> Understand whether protective immunity is based on memory or on long-lasting, low-level antigen presence to stimulate constant protective levels of antibody. If the latter, focus development on delivery strategies that can maintain low-level antigen presence ●●●●● Understand the basis of incomplete protection in natural settings ●●●● Understand the short duration of RTS,S efficacy ●● Understanding protection in the two systems that meet the vision criteria: naturally acquired immunity and irradiated sporozoites ● Establish way to measure duration of efficacy 	<ul style="list-style-type: none"> Clinical trial capacity bottleneck ●●●●● Make trials smaller for proof-of-concept (different end points) ◆● Establish blood stage challenge ● Scale of equivalence trials makes them challenging to conduct ● Test duration of efficacy with T-cell inducing vaccines ● Establish clinical trial designs for small-scale field efficacy testing Lack of understanding of how long researchers must follow up with trial participants <ul style="list-style-type: none"> Look for delay in peak, emergence of more robust parasite Need surveillance mechanisms Move candidate faster into humans Define end points of trials in animals and humans 	<ul style="list-style-type: none"> Understand information current assays provide and determine whether new assays are needed ●●●●●● Optimize/standardize and then validate the predictive nature of GIA, ADCI, ISI, Aotus, and orthology models ● Improve lab assays to read out clinical trial results to guide development Establish cell-mediated immunity (CMI) reference center Develop and qualify meaningful assays for constructs
BIOLOGICAL TOOLS				NON-SCIENTIFIC CHALLENGES
<ul style="list-style-type: none"> Develop in-vitro culture of sporozoites ● Establish frozen sporozoite challenge model to allow any lab in the world to do challenge studies ● Effectively cryo-preserve gametocytes Develop better culture for liver stage parasites Make available and validate master seed lots for four or more isolates of <i>P. falciparum</i> to conduct challenges 		<ul style="list-style-type: none"> Improve access to formulation capabilities for public sector efforts ◆◆◆◆●●● Make an irradiated sporozoite vaccine practical ◆ Minimize manufacturing cost of multi-component vaccines Ensure preclinical work is done on clinical-grade material 	<ul style="list-style-type: none"> Create vaccine delivery systems that induce optimal immunity to multiple targets ●● Limited available adjuvants Understand immune mechanisms of antigenic targets 	<ul style="list-style-type: none"> Establish central community body to help overcome regulatory and other non-scientific barriers that can slow progress ●●●● <ul style="list-style-type: none"> Regulations vary, some places are more problematic Large vaccine companies can help if there is adequate return on investment Establish method for securing many more volunteers for challenge studies

TABLE 11. BIG QUESTIONS – GROUP C

SCIENTIFIC BIG QUESTIONS	NON-SCIENTIFIC BIG QUESTIONS
<ul style="list-style-type: none"> • How can we prioritize antigens for clinical evaluation? Can useful criteria be set? <ul style="list-style-type: none"> – Can we make an in-vitro assay that predicts clinical immunity? – Are there basic science indicators or research tools that allow us to down-select? • What assays are needed to predict vaccine-induced protection? <ul style="list-style-type: none"> – Answering this question will allow for more, smaller Phase 1b trials – Assays will likely be trial specific • How do we develop vaccine systems for multi-component malaria vaccines? <ul style="list-style-type: none"> – Does this strategy work? If so, how do we deliver the vaccine? – Can we combine different stage vaccines with limited efficacy to get high overall protection (i.e., are there synergies)? – How can we improve access to formulation capabilities for the public sector? • How can we screen for protection and prioritize blood-stage candidates using experimental challenges in humans? • How can we make field efficacy trials smaller for proof-of-concept? <ul style="list-style-type: none"> – “Small” = 30-50+ participants – Are there different end points that should be measured? – Can we use teams to build trial capacity in endemic regions? – Can we improve trial design and standardize for ease of comparison? 	<ul style="list-style-type: none"> • What is the most effective way to coordinate malaria vaccine research and development? • How can we ensure there will be a customer for our vaccine?

List of Participants – Group C

Dr. Ripley Ballou	GSK Biologicals
Dr. Brendan Crabb	The Walter and Eliza Hall Institute of Medical Research
Dr. Filip Dubovsky	Malaria Vaccine Initiative, PATH
Prof. Brian Greenwood	London School of Hygiene and Tropical Medicine
Prof. Adrian Hill	University of Oxford
Dr. Stephen Hoffman	Sanaria
Dr. Douglas Holtzman	Bill & Melinda Gates Foundation
Dr. Steven Reed	Infectious Disease Research Institute
Dr. Zarifah Reed	WHO – Initiative for Vaccine Research
Dr. Kevin Reilly	Independent Consultant
Dr. Michael Roy	SAIC
Dr. Val Snewin	The Wellcome Trust
Mr. Ross Brindle	Energetics, Inc. (Facilitator)



*Closing Session
Results*

TABLE 12. SYNTHESIS OF BIG QUESTIONS

CHALLENGE MODELS	TRIAL DESIGN	LONG-TERM IMPACTS OF VACCINES	DELIVERY PLATFORMS	PROCESS AND RESOURCE MANAGEMENT	IMMUNE RESPONSE	SELECTION OF CANDIDATES	CORRELATES AND ASSAYS
<ul style="list-style-type: none"> • How do we develop an experimental human challenge model for asexual blood-stage vaccines that is generally acceptable and predictive of efficacy in field trials? • How can we screen for protection and prioritize blood-stage candidates using experimental challenges in humans? • How can we increase capacity for a sporozoite challenge model? 	<ul style="list-style-type: none"> • From the standpoint of designing efficient clinical trials, what is the relationship between infection, disease, severe disease, and death, especially in different epidemiological settings? • How can we make field efficacy trials smaller for proof-of-concept? Are there different endpoints? 	<ul style="list-style-type: none"> • Will a vaccine exert selective pressure? • How do we ensure the durability of protection following vaccination? • What is the impact of early, effective immunization on long term health? 	<ul style="list-style-type: none"> • How do we define and access adjuvants, process development expertise, formulation expertise, and capacity that are found largely in industry? <div data-bbox="800 812 1031 885" style="text-align: center;">POLICY AND ECONOMICS</div> <ul style="list-style-type: none"> • How can we ensure there will be a customer for our vaccine? 	<ul style="list-style-type: none"> • What is the most effective way to coordinate malaria vaccine research and development? • How do we establish shared criteria for making go/no-go decisions? • How do we balance between improving scientific understanding and pushing products through the pipeline? 	<ul style="list-style-type: none"> • What are the determinants and mechanisms of innate and acquired immune responses in humans that determine protection? • What is different about the immune response in naturally immune people as opposed to people who have not yet acquired protective immunity? 	<ul style="list-style-type: none"> • What are robust criteria for selection and prioritization of candidates, particularly antigens and delivery platforms? • To what extent is polymorphism impeding vaccine development and, if it is, how do we overcome this? <div data-bbox="1493 803 1724 876" style="text-align: center;">COMBINATION VACCINES</div> <ul style="list-style-type: none"> • How can antigens be combined in vaccines safely, affordably, optimally, and without antagonism? Which antigens should we use? • How do we develop vaccine systems for multi-component malaria vaccines? 	<ul style="list-style-type: none"> • What assays do we need to predict vaccine-induced protection? • How can we develop and validate animal models that correlate with protection in humans? • What are the critical studies of the immune response and other host and parasite factors that should be done in the context of vaccine field trials in search of correlates of protection?

TABLE 13. POTENTIAL SOLUTIONS TO BIG QUESTIONS

CHALLENGE MODELS	TRIAL DESIGN	LONG-TERM IMPACTS OF VACCINES	POLICY AND ECONOMICS	SELECTION OF CANDIDATES	COMBINATION VACCINES	CORRELATES AND ASSAYS	
<ul style="list-style-type: none"> 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 Develop/fund central sporozoite challenge center Use combinations of antigens in challenge models to screen out unpromising candidates Develop minimal challenge models to screen faster in the clinics 	<ul style="list-style-type: none"> Set Proof of Concept bar low (LL>0) to avoid eliminating potentially successful candidates too soon (we don't know what endpoints correlate with success) Develop multiple banks of frozen parasites Hold a consultation on Phase III trial design Conduct harmonization meeting on Phase II analysis planning Conduct critical analysis of current data on potential proxy measures of clinical disease to be able to conduct smaller efficacy trials 	<ul style="list-style-type: none"> Set up common "pharmaco-vigilance" database for long-term follow-up 	<ul style="list-style-type: none"> Develop a malaria vaccine advisory group and list of 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 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Assess protective efficacy of non-replicating, metabolically active <i>P. falciparum</i> 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 	<ul style="list-style-type: none"> 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 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 Analyze genotypes appearing sequentially in vaccinated and controls groups 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 Agree to exchange sera/cells among trials of vaccines based on same antigens Develop reliable/validated assays for functional antibodies 	
	DELIVERY PLATFORMS	<ul style="list-style-type: none"> 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) 					
	IMMUNE RESPONSE	<ul style="list-style-type: none"> Introduce RTS,S on broad scale and study impact, correlates, safety, escape, etc. Validate existing correlates and develop better ones 					PROCESS AND RESOURCE MANAGEMENT
							<ul style="list-style-type: none"> Create "bait" for enhanced industrial involvement to access processes, adjuvants, formulation capabilities, and GMP products Submit requests to industry for access to adjuvants Establish (elect?) a small working group to coordinate vaccine R&D