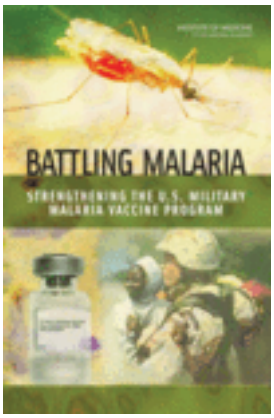

Battling Malaria: Strengthening the U.S. Military Malaria Vaccine Program

Committee on U.S. Military Malaria Vaccine Research - A Program Review, Patricia M. Graves, Myron M. Levine, Editors

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STRENGTHENING THE U.S. MILITARY MALARIA VACCINE PROGRAM

Patricia M. Graves, Myron M. Levine, Editors

Committee on U.S. Military Malaria Vaccine Research:
A Program Review

Medical Follow-Up Agency

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Walter E. Brandt, The PATH Malaria Vaccine Initiative, Bethesda, Maryland
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Allan J. Saul, Malaria Vaccine Development Unit, National Institutes of Health, Rockville, Maryland

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Adel Mahmoud**, M.D., Ph.D., president of Merck Vaccines, Merck & Co., Whitehouse Station, New Jersey. Appointed by the National Research Council and Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

Malaria, the febrile illness caused by the protozoa *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* transmitted via the bites of infected female *Anopheles* mosquitoes, remains a cardinal endemic public health problem in much of the less developed world. Most fatal cases of malaria are caused by *P. falciparum* and occur in sub-Saharan Africa. Malaria also constitutes a significant threat for nonimmune travelers from industrialized countries who visit (even for short periods) developing world settings where malaria transmission is ongoing; such travelers include U.S. military personnel. For more than a century malaria has posed a serious threat to U.S. military personnel both in large-scale conflicts involving large numbers of troops deployed in endemic areas for extended periods (e.g., the Vietnam conflict) and in small-scale operations. Indeed, this risk was brought home starkly in 2003 when 80 of 290 members of a Marine expeditionary force deployed to Liberia (28 percent) developed *P. falciparum* malaria; 40 were so ill that they required evacuation, and several had to be admitted to intensive care. Regrettably, the increasing prevalence of drug-resistant *Plasmodium* strains makes chemoprophylaxis much less reliable.

Scientific and biotechnological breakthroughs in the 1970s and 1980s generated widespread optimism that malaria vaccines could become a reality in the foreseeable future to provide protection for troops prior to their deployment to high-risk areas. The military has somewhat special needs for a malaria vaccine compared to pediatric populations in endemic areas. Consequently, this has been one instance where the military research establishment has had to achieve a high degree of self-reliance,

while nevertheless coordinating, wherever possible, with global malaria vaccine development efforts.

During the past two decades there have been two highly productive malaria vaccine research programs located within the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Center (NMRC). Whereas there has been considerable collaboration, cooperation, and sharing of resources and reagents by the highly committed and productive staffs of both programs, there has also been a considerable degree of duplication of core facilities, business and regulatory affairs units, and clinical trial processes. There have been divergence of strategies and sometimes direct competition (e.g., by partnering with different vaccine companies to attain access to similar viral vectors). Recognizing the great complexity and expense of the mission to develop a malaria vaccine for the U.S. military in an era of scarce resources, the Department of Defense (DoD) considered it a propitious moment to request the Institute of Medicine (IOM) to convene an expert committee to review all aspects of the DoD malaria vaccine research program. The relocation in 2000 of the WRAIR and NMRC programs to the same building has also provided an opportunity for collaboration and cooperation that did not exist when the programs were physically separate.

Within its overall remit, the committee was asked to identify barriers to achieving success and to make specific recommendations of how to overcome barriers, streamline the program, and improve chances for success. Towards this goal, the IOM convened a committee with experts in malaria biology, industrial and public-sector vaccine development, immunology, basic and clinical vaccinology, regulatory affairs, and knowledge of military preventive medicine, deployments, and procedures. The findings of the committee are summarized in this report. The report also contains a series of specific recommendations, which if followed, the committee believes, will significantly improve the likelihood of successful development and licensure of a first-generation malaria vaccine and will create a knowledge base to allow accelerated development of a subsequent second-generation malaria vaccine. The committee emphasized the need to overhaul the management structure of the DoD malaria vaccine enterprise to utilize existing resources in a more rational manner, and the need for a significant infusion of additional core support to the malaria vaccine development enterprise. If these fundamental changes can be implemented, the committee is optimistic that the mission of developing and licensing a safe and efficacious malaria vaccine for protecting U.S. military personnel can be accomplished.

Myron M. Levine
Chair

Acknowledgments

Despite their considerable knowledge and experience, the members of this Institute of Medicine committee could not have completed their task without the cooperation of the USAMRMC and MIDRP staff, especially Dr. Moshe Shmuklarsky and COL David Vaughn, who responded quickly and helpfully on many occasions to requests for information and clarification. The scientific staffs of WRAIR and NMRC, under the leadership of COL Gray Heppner and CAPT Tom Richie, willingly and comprehensively shared their scientific results and plans openly with the committee during the first meeting and were responsive to later requests for further information or explanation. Thanks are also due to Dr. Filip Dubovsky who provided information on the global malaria vaccine effort. We are especially grateful to Hellen Gelband of the IOM for knowledgeable and constructive input to the report at all stages.

This study was managed, coordinated, and documented by Dr. Rick Erdtmann and myself with assistance from IOM staff members Reine Homawoo and Pamela Ramey-McCray. However, there were many other staff members at the National Academy of Sciences who assisted with this study, especially Bronwyn Schrecker, Clyde Behney, and Susanne Stoiber. Andrea Cohen kept us on track with our budget, Tyjen Tsai helped move the report through the production process, Kristen Gilbertson provided invaluable help with references and formatting the report, and Lois Joellenbeck gave useful advice. The copyeditor, Mark Goodin, did excel-

lent and careful work. We also thank Katie Friedell of the Beckman Center in Irvine, Calfornia, for help with meeting arrangements. We are very grateful to all of these people for their efforts.

Patricia M. Graves, Ph.D.
Consulting Scientist

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Abbreviations and Acronyms

AFMIC	Armed Forces Medical Intelligence Center
AFRIMS	Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand
AIBS	American Institute of Biological Sciences
AMA	apical membrane antigen
AVP	acquisition of vaccine production
BMF	biological master file
BUMED	Bureau of Medicine and Surgery (U.S. Navy)
BWD	biological warfare defense
CAPT	captain
CDD	capability development document
CDMRP	congressionally directed medical research program
CG	commanding general
CI	confidence interval
COL	colonel
CRADA	cooperative research and development agreement
CSI	congressional special interest
CSP	circumsporozoite protein
DALY	disability adjusted life years
DoD	Department of Defense
EPA	Environmental Protection Agency

FDA	Food and Drug Administration
FTE	full-time equivalent
FY	fiscal year
GEIS	global emerging infections surveillance
GMP	good manufacturing practice
GOCO	government-owned, contractor-operated
GSK	GlaxoSmithKline
HSRRB	Human Subjects Research Review Committee
HURC	Human Use Research Committee
IAA	interagency agreement
ICGEB	International Centre for Genetic Engineering and Biotechnology
IND	investigational new drug
IRB	institutional review board
JTF-MV	Joint Task Force—Malaria Vaccine
LSA	liver-stage antigen
MAJ	major
ME-TRAP	multiple epitope—thrombospondin-related adhesion protein
MIDRP	Military Infectious Diseases Research Program
MPL	monophosphoryl lipid A
MSP	merozoite surface protein
MVA	modified vaccinia Ankara
MVI	Malaria Vaccine Initiative
NAMRU	Naval Medical Research Unit
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMRC	Naval Medical Research Center
ONR	Office of Naval Research
ORD	operational requirements document
PfEMP	*P. falciparum* erythrocyte membrane protein
POM	program objective memorandum

R&D	research and development
RAP	rhoptry-associated protein
RESA	ring-infected erythrocyte surface antigen
SBIR	Small Business Innovation Research
SBRI	Seattle Biomedical Research Institute
SG	surgeon general
SSP	sporozoite surface protein
TRAP	thrombospondin-related adhesion protein
USAID	U.S. Agency for International Development
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRAA	U.S. Army Medical Research Acquisition Activity
USAMRIID	U.S. Army Medical Research Institute for Infectious Diseases
USAMRMC	U.S. Army Medical Research and Materiel Command
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

Summary

The Department of Defense (DoD), through the commanding general of the U.S. Army Medical Research and Materiel Command (USAMRMC), asked the Institute of Medicine (IOM) to conduct a programmatic review of the military *Plasmodium falciparum* malaria vaccine research and development program.

All four species of the genus *Plasmodium* that cause human malaria present a threat, but *P. falciparum* is the most severe and important. The complex life cycle of *Plasmodium* (including development in humans and in mosquito vectors) presents a wide array of potential vaccine targets. Vaccines against any of three stages—the preerythrocytic, blood, or transmission stages—are possible. The committee restricted its deliberations to *P. falciparum* malaria, which is the current focus of the military's malaria vaccine program, and to vaccines against the preerythrocytic and blood stages.

THE MALARIA THREAT TO THE U.S. MILITARY

Malaria has affected almost all military deployments since the American Civil War and remains a severe and ongoing threat. Current prevention methods for malaria (repellents and impregnated uniforms/mosquito nets) in forces deployed to endemic areas are inadequate, and compliance with chemoprophylaxis is incomplete. In Liberia in 2003, there was a 28 percent attack rate in Marines who spent a brief period ashore, and half of the 80 Marines affected had to be evacuated by air to Germany. This

costly and dangerous episode reinforced the fact that a vaccine would be the best method of averting the threat of malaria given the likely increasing number of deployments to high-risk areas. Therefore the DoD should markedly enhance its research and development efforts to produce malaria vaccines suitable for military needs. The large investment (at least $300 million) that is required to give a high likelihood of success in producing a vaccine in the next 10 years needs to be acknowledged and planned for.

MALARIA VACCINE RESEARCH AND DEVELOPMENT IN THE U.S. MILITARY

Malaria vaccine research and development is carried out at the Walter Reed Army Institute of Research (WRAIR), the Naval Medical Research Center (NMRC), and at DoD laboratories overseas in Kenya, Thailand, Indonesia, Peru and Egypt . Management coordination of these activities is the responsibility of the tri-service Military Infectious Diseases Research Program (MIDRP) which is under the direction of USAMRMC. The malaria vaccine research and development programs at these institutions are referred to jointly in this report as the MIDRP Malaria Vaccine Program.

Malaria Vaccine Progress to Date

The MIDRP Malaria Vaccine Program is a large proportion of the global effort and has been involved in about half of all the vaccine candidates that have been or are currently in development, including several of the candidates that have progressed to clinical efficacy trials in endemic areas. The Malaria Vaccine Program has unique capabilities not readily available elsewhere, such as the well-defined sporozoite challenge model and the pilot GMP (good manufacturing practices) production facility.

Early experiments with irradiated sporozoite vaccines were encouraging, providing a measure of protection against infection. However, the generation of both antibody and cellular protective responses with subunit vaccines has proved challenging, with many failed leads and disappointments. Gene-based (DNA) vaccines have not yet fulfilled their early promise generated by results in small animal models, although progress is being made. The most encouraging recent breakthrough was the development at WRAIR of the viruslike particle RTS,S with a particular adjuvant AS02A (in collaboration with GlaxoSmithKline [GSK]).

The USAMRMC has a mandate to develop a malaria vaccine as part of its mission to protect the U.S. military against naturally occurring infectious diseases. The military's vaccine needs differ from those of popula-

tions living in endemic areas but are quite similar to the needs in the civilian traveler market. Ideally, a high level of efficacy against infection is required for a relatively short period of time (e.g., 6 months). The most likely scenario is a "first-generation vaccine" that is a valuable adjunct to chemoprophylaxis, followed by development of an "ideal" vaccine that could be used alone for malaria prevention. A first-generation vaccine providing about 60 percent protection against clinical disease (with a lower limit of 30 percent for the 95 percent confidence interval around the 60 percent point estimate of efficacy) for 6 months is regarded as useful. A second-generation "ideal" vaccine, which could be used to replace the routine use of chemoprophylaxis, would have to provide greater than 95 percent protection against infection over a longer time period.

No vaccine candidates are currently in development that are likely to meet the military requirements for a first-generation vaccine in the next 5 to 10 years. A more realistic target date for availability of a licensed vaccine (even with more resources) is 2015–2020.

The program to develop a malaria vaccine for U.S. military personnel should focus on (and have the capacity to conduct) clinical efficacy trials in immunologically naïve military personnel (off and on chemoprophylaxis) in endemic areas, for which the field sites currently maintained by the DoD are a critical resource. Suggestions for the design and size of the trials necessary to demonstrate the suggested efficacy for the first-generation vaccine are provided in Appendix C to this report.

Research on all three main malaria vaccine development strategies—gene-based (e.g., DNA, plasmid, or viral vector vaccines), protein-based, and attenuated sporozoite approaches—should be continued. However, as research progresses, the number of candidate products must be limited by dropping those that perform less well. The MIDRP Malaria Vaccine Program should aggressively move into clinical trials to test specific vaccine products, and select two to three leads at phase 1 and one at phase 2 for each strategy. For protein-based and gene-based strategies, the focus should be on specific vaccine products that combine the lead antigens (CSP, SSP-2/TRAP, LSA-1, AMA-1, and MSP-1) including their use in heterologous prime-boost combinations.

Given the limited time available for this review, the committee did not wish to give more detailed specific advice other than to narrow the focus to a smaller number of candidate antigens. Despite having extensive expertise in all scientific aspects of the program, the committee concluded that instead of offering one-time advice on specific antigens or approaches, it would be more productive to recommend a structure and process for ongoing review and decision making about the scientific direction of the work.

PROGRAM INTEGRATION

The DoD malaria vaccine research has been conducted by WRAIR and NMRC, with the former focusing on recombinant proteins and the latter on gene-based approaches. Previously located separately, these two agencies moved to occupy the same building in the year 2000. There is no scientific justification for maintaining these separate programs. Whereas there has been considerable collaboration, cooperation, and sharing of resources and reagents by the highly committed and productive staffs of both programs, there has also been divergence of strategies as well as a considerable degree of duplication of core facilities, business and regulatory affairs units, and clinical trial processes.

The current cumbersome, inefficient, and complex management structure and processes imposed by two separate programs constitute very critical barriers to progress. An inadequate advisory structure and project management process also impede effective strategic planning.

Accordingly, the MIDRP Malaria Vaccine Program should be integrated into a unified organizational entity (Joint Task Force for Malaria Vaccine [JTF-MV]) that spans the spectrum and life cycle of responsibilities: epidemiological/threat assessment, research and development, advanced product development, clinical trials, licensure, manufacture, technology transfer, procurement, maintenance of manufacturing practice standards, and regulatory compliance.

The JTF-MV should be a single organizational and legal entity led by a scientific director appointed by the commanding general of the USAMRMC. The JTF-MV should have sufficient staff assigned to it to deal with business and regulatory affairs and avoid future intellectual property conflicts and other issues. A scientific advisory board should be constituted to conduct external review and advise on long-term objectives. The annual proposal cycle should be replaced with a more programmatic approach to project management.

Two previous external committees have recently reviewed DoD vaccine programs. The first was an independent panel of experts that submitted a report titled *DoD Acquisition of Vaccine Production* to the deputy secretary of defense in December 2000. Subsequently an IOM committee tasked with assessing vaccine policies for naturally occurring infectious diseases produced *Protecting Our Forces*, a report edited by Lemon et al (IOM, 2002). Both these committees recommended organizational changes similar to those proposed here, although they have encompassed the vaccine program more generally rather than just malaria. Implementation of the current recommendations should be assured by the establishment of a malaria vaccine program transition team for the period required to carry out the JTF-MV reorganization and constitution of the scientific advisory board.

NEED FOR INCREASED RESOURCES

Malaria remains a major problem for U.S. military personnel deployed to endemic areas, a threat that is not diminishing in importance with time. Therefore the DoD program to develop a malaria vaccine compatible with the needs for protecting U.S. military personnel should be fully supported. To increase the likelihood of achieving the current goals for a first-generation vaccine and to test the limited number of vaccine candidates described above will require a several-fold increase in the current malaria vaccine development budget by 2010, with continuation at that level to at least 2015.

RECOMMENDATIONS

A list of the committee's recommendations is provided in Box S-1, which follows.

BOX S-1
RECOMMENDATIONS

The Malaria Threat and Need for a Vaccine

Recommendation 2.1: The DoD should markedly enhance its research and development efforts to produce malaria vaccines suitable for DoD needs. Malaria is a severe ongoing threat for U.S. military personnel deployed to malaria-endemic areas of the world, and current malaria prevention and control methods are indisputably inadequate.

Recommendation 2.2: The DoD should formally acknowledge the high cost of developing any new vaccine and the fact that the MIDRP Malaria Vaccine Program is severely underfunded in relation to the goal. To increase the probability of success, this discrepancy needs to be rectified.

The U.S. Military Malaria Vaccine Research and Development Program—Scientific Aspects

Recommendation 4.1: For a first-generation vaccine, a level of 60 percent efficacy (with a lower limit of 30 percent for the 95 percent confidence interval around the 60 percent point estimate of efficacy) against the *clinical effects* of *P. falciparum* would be a useful adjunct to chemoprophylaxis for military use. Nevertheless, research to develop a more effective second-generation vaccine that can be used in the absence of chemoprophylaxis and that would confer a much higher level of efficacy against *infection* should continue.

continued

BOX S-1 Continued

Recommendation 4.2: Small, carefully designed and executed clinical efficacy trials involving U.S. military personnel (or other groups of immunologically naïve, nonmilitary personnel) off chemoprophylaxis (initial proof of principle studies) or on chemoprophylaxis (later study) should be carried out to assess the efficacy of the leading MIDRP Malaria Vaccine Program candidate in field sites in endemic areas. In this regard, field sites currently maintained by the DoD in Africa are a critical resource.

Recommendation 4.3: Research on all three main malaria vaccine development strategies—gene-based (e.g., DNA, plasmid, or viral vector vaccines), protein-based, and attenuated sporozoite approaches—should be continued. However, as research progresses, the number of candidate products must be limited by dropping those that perform less well. The MIDRP Malaria Vaccine Program should aggressively move into clinical trials to test specific vaccine products, and select two to three leads at phase 1 and one lead at phase 2 for each strategy. For protein-based and gene-based strategies, the focus should be on specific vaccine products that combine the lead antigens (CSP, SSP-2/TRAP, LSA-1, AMA-1, and MSP-1) including their use in heterologous prime-boost combinations.

Recommendation 4.4: Finding correlates for protection *in humans* relevant to each of the above vaccine strategies should be a research priority.

Recommendation 4.5: The MIDRP Malaria Vaccine Program should continue research on human immune processes and responses to malaria. The current incomplete understanding of the mechanisms of protective immunity to malaria in humans constitutes a barrier that impedes malaria vaccine development.

Organization and Management of the Program

Recommendation 5.1: The MIDRP Malaria Vaccine Program, currently composed of two separate entities—WRAIR and NMRC, should be integrated into a unified organizational entity (Joint Task Force for Malaria Vaccine [JTF-MV]) that spans the spectrum and life cycle of responsibilities: epidemiological/threat assessment, research and development, advanced product development, clinical trials, licensure, manufacture, technology transfer, procurement, maintenance of manufacturing practice standards, and regulatory compliance.

Recommendation 5.2: The JTF-MV should appoint one scientific director, reporting to the commanding general of the USAMRMC, to provide joint direction and accountability for the program. The scientific director must have operational authority and budgetary as well as scientific control.

Recommendation 5.3: The JTF-MV should organizationally incorporate an industry/business model and be constituted as a single legal entity (able to share proprietary data) that would simplify the external contracting process, including cooperative research and development agreements, interagency agreements, and other contracts. The JTF-MV must include team members with specialized expertise in business and regulatory affairs. Although these individuals would be located in the existing business and regulatory affairs units, adequate staffing for these tasks must be assigned to the JTF-MV in order to avoid or minimize future intellectual property conflicts and other issues.

Recommendation 5.4: The JTF-MV program for vaccine development should have an external senior expert advisory group (scientific advisory board) that conducts yearly face-to-face meetings to provide external review and evaluation of the scientific program, and also gives ongoing advice in a timely manner. The scientific advisory board can assist the program to set clear and appropriate objectives (defined up front), with benchmarks of progress. Draft terms of reference for the scientific advisory board are found in Appendix E.

Recommendation 5.5: The annual proposal cycle should be replaced with a more programmatic and directed approach to project management under the newly reorganized JTF-MV. The MIDRP sets the annual budget and long-range objectives (with input from the scientific advisory board), and implementation is by the JTF-MV with a longer (approximately 3 year) time horizon for projects.

Recommendation 5.6: A malaria program transition team (led by a program manager with a strong business/industry background who reports to the commanding general of USAMRMC) should be established to carry out the JTF-MV reorganization and constitution of the scientific advisory board and assist with recruitment of a highly qualified JTF-MV scientific director. This transition team will be disbanded once the reorganization is in place.

continued

BOX S-1 Continued

Recommendation 5.7: A workforce plan must be developed and implemented by the JTF-MV. This plan should include training and budgeting for the next generation of scientists in the military program, ways to improve recruitment and retention of civilians and foreign nationals, and succession planning to ensure availability of required staff in 5–10 years time. The DoD should respond to the lack of sufficient depth of human resources to carry through current objectives with increased resources to carry out the workforce plan.

Recommendation 5.8: Sufficient funding should be made available to support the infrastructure to produce pilot-lot formulations of MIDRP malaria vaccine candidates in-house at the pilot production plant at Forest Glen (an invaluable part of the MIDRP Malaria Vaccine Program). Although pilot lots of all candidate vaccines cannot be made at Forest Glen, the ability to prepare certain candidates removes a major obstacle that would otherwise impede the program.

Recommendation 5.9: A formal economic analysis would be helpful in order to clarify current costs of malaria (both *P. falciparum* and *P. vivax*) prevention, treatment, and case management. This economic analysis would reveal the direct (monetary) and indirect (lost work time) costs that would be averted by both a first-generation vaccine (to be used in conjunction with chemoprophylaxis) and a second-generation vaccine (to replace chemoprophylaxis).

Recommendation 5.10: Given that malaria remains a major problem for U.S. military personnel deployed to endemic areas and this threat is not diminishing in importance with time, the MIDRP program to develop a malaria vaccine compatible with the needs for protecting U.S. military personnel should be fully supported. To increase the likelihood of achieving the current goals for a first-generation vaccine and to test the limited number of vaccine candidates described above will almost certainly require a several-fold increase in the current malaria vaccine development budget by 2010, with continuation at that level to at least 2015.

1

Introduction

THE REVIEW PROCESS AND INPUTS

The Department of Defense (DoD), through the commanding general of the U.S. Army Medical Research and Materiel Command (USAMRMC), requested the Institute of Medicine (IOM) to conduct a programmatic review of the *Plasmodium falciparum* malaria vaccine research and development program. The USAMRMC seeks to pursue a world-class program aimed at developing effective vaccines against malaria in military personnel deployed to malaria endemic regions.

The DoD-funded research is coordinated within the USAMRMC by the Military Infectious Disease Research Program (MIDRP). These agencies strive to protect the U.S. military against naturally occurring infectious diseases via the development of Food and Drug Administration (FDA)-approved drugs, vaccines, and diagnostics and Environmental Protection Agency (EPA)-approved vector control systems. Malaria vaccine research in the DoD takes place at the Walter Reed Army Institute of Research (WRAIR), the Naval Medical Research Center (NMRC), and at overseas laboratories. The malaria vaccine research and development programs at these institutions are referred to jointly in this report as the MIDRP Malaria Vaccine Program. The MIDRP Malaria Vaccine Program coordinates its efforts to develop a vaccine meeting the military's special needs with a wider global effort to develop a vaccine against malaria.

The IOM formed a review committee of 11 subject matter experts with collective expertise in malaria vaccine research, parasite immunology, malarial biology, clinical trials and regulatory affairs, industrial and

public-sector vaccine development, biologic products research and development (vaccinology), military research and development programs, tropical medicine, and public health.

The task statement presented to the committee was as follows:

1. Determine whether the DoD malaria vaccine research and development program is scientifically sound and able to achieve the vaccine program objectives within specified timelines. Assessments will include research and development strategy, management, budget, research staff (size and capabilities), research equipment, communications, and identification of potential barriers impeding research progress.

2. Given that significant barriers are identified, recommend how to overcome them.

3. Identify the major strategic goals and timelines based on the material received and presentations made by the DoD's program representatives, and recommend ways and means to improve the likelihood of achieving them. This may include, as appropriate, recommendations for an optimal configuration of program elements.

4. Recommend any additional studies or actions that the DoD malaria vaccine program could undertake to enhance its program, including the timing and priority of such efforts.

The IOM committee convened twice in person and twice by teleconference during the period of the 6-month study. Their first meeting lasted 2.5 days, and the committee reviewed in detail the MIDRP malaria vaccine research and development program, its historical development, its current research efforts and budget, and its goals and objectives as presented by key MIDRP research staff. The USAMRMC also posed additional questions that it wished the IOM to address. An outside presenter (Dr. Filip Dubovsky of the Malaria Vaccine Initiative [MVI]) was also invited to give a global nonmilitary perspective. The IOM committee convened a closed session to deliberate and outline the programmatic review findings and proposed recommendations. At the second meeting, the committee reviewed a draft report and prepared its findings and recommendations. The committee report was subject to external peer review, in accordance with the usual IOM procedures, prior to final approval for release.

The committee was able to build on some earlier work, including a 1996 IOM workshop report entitled *Vaccines Against Malaria: Hope in a Gathering Storm* that was prepared for a consortium of federal and private

sponsors (IOM, 1996). The following three findings reached by the participants of the 1996 workshop are especially pertinent to this review: (1) malaria is still the most prevalent vector-borne disease in the world, (2) a malaria vaccine is feasible, and (3) the high cost of vaccine development dictates a coordinated strategy and a need to focus on a limited number of options (IOM, 1996).

The committee also reviewed the recent Malaria Vaccine Technology Roadmap (Roadmap, 2006), produced by a broad consensus process, with funding from the Bill and Melinda Gates Foundation and the Wellcome Trust. The Malaria Vaccine Technology Roadmap is a draft guide produced by the international community of researchers devoted to the development of an effective malaria vaccine. The roadmap identifies major barriers that need to be overcome in order to advance the development of an effective vaccine and recommends strategic priorities and approaches.

The timetable of meetings for the IOM study committee was as follows:

- First meeting: January 23–25, 2006, at Silver Spring, Maryland
- Teleconference: February 15, 2006
- Second meeting: February 22–23, 2006, at Irvine, California
- Teleconference: March 14, 2006

SCOPE AND ORGANIZATION OF THE REPORT

All four species of human malaria (*P. falciparum, P. vivax, P. ovale,* and *P. malariae*) present a threat. The potentially fatal *P. falciparum* is the most severe and important, although *P. vivax* causes debilitating disease and is common in many areas outside Africa. Vaccines can be developed from any of three possible stages of malaria—the preerythrocytic, blood, or transmission stages. This report focuses on the first two of these stages. The transmission stage type of vaccine is not a current active area of research in the MIDRP Malaria Vaccine Program. Although potentially effective in reducing transmission levels and hence new infections, this strategy is less useful for immediate individual protection on arrival in an endemic area. As requested by USAMRMC, the committee restricted its deliberations to *P. falciparum* malaria—the current focus of the MIDRP Malaria Vaccine Program—and to vaccines against the preerythrocytic and blood stages.

A list of recommendations is provided in Box S-1. The report is divided into five chapters and has nine appendixes. Chapter 1, the current chapter, is the Introduction, describing how this study came about, the charge to the committee, and the processes by which the committee went about its task. Chapter 2 describes the magnitude of the malaria problem in the world and the threat this presents to the military. Data on

the extent and effect of malaria in past military deployments are given, and the case for a vaccine is presented. The final section reviews the cost and time needed to have a high likelihood of producing an effective vaccine. Chapter 3 presents basic information on malaria and the rationale for vaccine development. The scientific background on vaccine development is necessary to place the current MIDRP Malaria Vaccine Program research in context and assess its scientific validity. The chapter also describes the scientific barriers to malaria vaccine development that have been identified. The status of current vaccine candidates and description of the MIDRP Malaria Vaccine Program's contributions to the global vaccine effort are given. Chapter 4 describes the scientific aspects of the MIDRP Malaria Vaccine Program. In particular, the committee's opinions on the desirable characteristics for a first-generation and later-generation vaccines are spelled out, together with advice on requirements for pivotal licensure track trials to demonstrate the recommended level of efficacy. An overview of current work on vaccines is then presented together with the committee's overall assessment and recommendations concerning the scientific aspects of the program. Chapter 5 is concerned with the organization and management of the program. The committee's recommendations for reorganizing and streamlining are presented here. Reference is made to previous reports on the DoD vaccine acquisition process. This chapter also discusses the adequacy of human resource and financial commitments to the program.

Appendix A is a tabulation of previous clinical *P. falciparum* vaccine trials. Appendix B gives the existing DoD requirements for a malaria vaccine. Appendix C provides plans for possible field trials testing malaria vaccines in nonimmune adult volunteer subjects deployed to (military personnel) or recruited to spend time in (civilians) endemic areas. Appendix D is a listing of patents granted to the program. Appendix E is a draft charter for a scientific advisory board. Appendix F gives the recommendations of a previous IOM report on DoD vaccine related issues. Appendix G gives the recommendations of a previous committee of independent experts who advised the DoD on vaccine acquisition and production. Appendix H gives the agenda of the open meeting held in January 2006, and Appendix I contains biosketches of the IOM committee and staff members.

2

The Malaria Threat and Need for a Vaccine

GLOBAL MALARIA PROBLEM

Malaria is an infection caused in humans by four species of the *Plasmodium* genus of parasitic protozoans (*P. falciparum, P. vivax, P. ovale,* and *P. malariae*) that are transmitted by many species of anopheline mosquitoes. *Plasmodium falciparum* is the most widespread and also the most serious form. Recent estimates of the annual number of clinical malaria cases worldwide range from 214 to 397 million (WHO, 2002; Breman et al., 2004), although a higher estimate of 515 million (range 300–660 million) clinical cases of *P. falciparum* in 2002 has been proposed (Snow et al., 2005). Annual mortality (overwhelmingly from *P. falciparum* malaria) is thought to be around 1.1 million (WHO, 2002; Breman et al., 2004). Malaria deaths are believed to account for 3 percent of the world's total disability adjusted life years (DALYs) lost, and 10 percent of DALYs in Africa (Breman et al., 2004). In developing countries malaria is currently believed to be the third most common cause of death among children less than 60 months of age, after deaths from respiratory infections and diarrheal diseases.

Almost half of the world's population lives in areas where they are exposed to risk of malaria (Hay et al., 2004), and the increasing numbers of visitors to endemic areas are also at risk. Residents of endemic areas develop clinical immunity to the disease through repeated exposure, but the immunity wanes rapidly once a resident leaves the endemic area. However, this immunity takes years to develop, and adults in endemic areas have frequent infections though they rarely suffer symptoms. Pregnant women experience renewed susceptibility, especially during the first

pregnancy. Thus the burden of the disease in highly endemic areas falls mainly on young children and pregnant women. Malaria also significantly increases the risk of childhood death from other causes (Snow et al., 2004).

The amount spent worldwide on malaria research and development is not commensurate with its contribution to the global burden of disease. The Malaria R&D Alliance (2005) estimated that in 2004, malaria accounted for about 46 million DALYs lost but that only US$288 million was spent worldwide for research and development. This amounts to only about US$6.20 per DALY. This is significantly lower than the amounts spent per DALY on tuberculosis (TB) ($10.88) and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) ($24.26) in 2004.

MILITARY MALARIA PROBLEM

This will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease.

—General Douglas MacArthur, 1943

Malaria has persisted as a formidable problem—indeed a veritable scourge—for the U.S. military throughout its history. Tables 2-1 and 2-2 show lists of major U.S. military actions, deployments, or overseas exercises in which malaria posed a meaningful threat. Some actions involved

TABLE 2-1 Major U.S. Military Actions, Deployments, or Overseas Exercises in Locations with a Malaria Threat

Location	Year	Threat	Morbidity and Mortality
Civil War (Union)	1861–1865	*P. vivax* *P. falciparum*	1.3 million cases, 10,000 deaths[a]
Panama Canal	1904–1914	*P. vivax*, *P. falciparum*	1906 malaria rate 1263/1000/year 1913 malaria rate 76/1000/year[b]
WWI	1914–1918	*P. vivax*	Estimated 5000 cases overseas 1917: 7.5/1000/year in United States[c]
WWII	1939–1945	*P. falciparum*, *P. vivax*	600,000 cases mostly in Pacific theater. In some areas of South Pacific malaria rates were 4000/1000/year (4 cases per person per year) (Downs et al., 1947)

TABLE 2-1 Continued

Location	Year	Threat	Morbidity and Mortality
Korean War	1950–1953	*P. vivax*	Malaria rate 611/1000/year 3000 cases in troops returning to United States[d]
Vietnam War	1962–1975	*P. falciparum*, *P. vivax*	100,000 cases[e] 1.7/1000 case fatality rate Hospital admissions 27/1000/year 1965 malaria rate for U.S. Army forces: 98/1000/year 1970: 2222 cases (mostly *P. vivax*) treated in United States
Panama	1988–1989	*P. falciparum*	Action primarily in Panama City
Persian Gulf	1991	*P. vivax*	Few cases in northern Iraq, Kurdish area
Somalia	1992–1994	*P. falciparum*, *P. vivax*	48 cases; 243 cases in forces on return home[f] (CDC, 1993)
Nigeria	2001	Chloroquine-resistant *P. falciparum*	Special forces 7 cases (2 deaths) in 300 men
Afghanistan	2003	*P. vivax*, chloroquine-resistant *P. falciparum*	8 cases in 725 Ranger task force members[g] (Kotwal et al., 2005)
Liberia	2003	*P. falciparum*	U.S. marines 80/290 (28% attack rate) with 40 Marines evacuated by air to Germany
Iraq War	2003–	*P. vivax*	Few cases

[a] Records for the Confederate forces were difficult to find (probably not kept). One example in South Carolina was 42,000 cases in 18 months in 1862–1863. (Malaria was endemic in the United States until the late 1940s).

[b] 1913 malaria rate drop was due to control measures enforced by Colonel Gorgas.

[c] Malaria rate for troops training and/or garrisoned in southern states.

[d] In troops returning home there were at one point 629 cases/week.

[e] Some operational areas were intense: Ia Drang Valley (1966) malaria rate 600/1000/year, equivalent of 2 maneuver battalions rendered inoperative.

[f] In Bardera in 1993 where malaria is hyperendemic: 53/490 cases in Marines.

[g] Attack rate (June–September 2002) 52.4/1000/year.

TABLE 2-2 Other Limited U.S. Military Actions/Deployments (Actual or Standby) in Locations with a Malaria Threat (1990 Onward)

Area	Country
Africa	Kenya, Tanzania, Sierra Leone, Uganda, Cameroon, Zambia, Sudan, Ethiopia, Gambia
Asia	Indonesia/East Timor, Papua New Guinea, Solomon Islands, Malaysia, Thailand, Cambodia, Laos, India, Pakistan, Bangladesh, Myanmar, Sri Lanka
Middle East	Iran, Syria, Turkey, Saudi Arabia, Yemen
Americas/ Caribbean	Panama, Honduras, Colombia, Brazil, Peru, Guatemala, Nicaragua, Haiti, Dominican Republic

NOTE: Increasing multidrug resistant *P. falciparum* throughout Africa and prevalent in Asia. Increase in chloroquine-resistant *P. vivax*—Papua New Guinea, Irian Jaya (Indonesia), Solomon Islands, India, Thailand (borders), and Brazil.

U.S. forces on standby but not deployed. Nonetheless, the malaria threat was present. Where possible, malaria casualty data are included. Notably, since the Vietnam War, U.S. military actions abroad have (with the exception of the Iraqi operations) been increasingly smaller, shorter, more intense and in geographic areas with significant malaria threats (Tables 2-1 and 2-2). To use a preventive medicine phrase, the malaria problem is most often "local and focal," as was the experience for U.S. Marines in Liberia in 2003.

Prior to World War II, malaria caused significant morbidity and mortality in the American Civil War and Spanish-American War and threatened U.S. strategic interests in Panama. At the end of World War I malaria was a problem in U.S. troops at home that were garrisoned and training in southern states. During this period the U.S. Army Medical Department distinguished itself through the leadership of three remarkable individuals: MAJ George Sternberg, MAJ Walter Reed, and MAJ William Gorgas. Their combined successes (especially Gorgas in Panama) led to today's U.S. military operational malaria strategy: control, prevent, and treat (Ockenhouse et al., 2005).

During World War II this basic malaria strategy was put to the test of global warfare. Unfortunately, vector control has limited application on the rapidly changing battlefield (although the introduction of dichlorodiphenyltrichloroethane [DDT] in 1944 was a late success [Harper et al., 1947]). Treatment was problematic given the shortage of quinine that

persisted until the introduction of Atabrine (quinacrine) in 1943–1944, after which prophylaxis became a possibility. Prevention was limited to personal countermeasures (topical repellents and bed nets) as there was no malaria vaccine.

The strategic shortage of quinine caused by the Japanese blockade and intelligence that German scientists had developed new synthetic antimalarial drugs (Sontochin and Resochin) influenced the U.S. military and Allies to focus on antimalarial drug discovery and development. A program for chemotherapeutic research was launched in the United States in 1941 that involved strong collaboration between the armed services, scientific institutions, university laboratories, and pharmaceutical firms (WHO, 1986). Too late for the World War II effort, this exceptionally coordinated alliance produced an arsenal of new antimalarial drugs that included chloroquine, primaquine, and pyrimethamine. Over the next 20 years many experts, military and civilian, came to believe that the world malaria situation could be controlled and that malaria could even be eradicated. This confidence was supported by the success of primaquine to treat relapsing *P. vivax* malaria in U.S. troops returning home from the Korean War.

In 1960 resistance to chloroquine was reported in South America and Southeast Asia. Soon cases of chloroquine-resistant *P. falciparum* malaria were being reported in U.S. military personnel in South Vietnam. A new generation of antimalarial drugs was needed to protect and treat U.S. forces. The U.S. Army Research Program on Malaria was launched in 1963 as part of the Walter Reed Army Institute of Research (WRAIR) (WHO, 1986). By 1974, 26 new drugs (or combinations) had been developed, 11 completing clinical trials, with mefloquine as the flagship response to chloroquine-resistant *P. falciparum*. Fansidar (sulfadoxine/pyrimethamine) became available when it was licensed in the United States in 1983, but it was little used by the military for prophylaxis because of the risk of adverse effects and because of the availability of mefloquine in the late 1980s. While mefloquine was arduously moving through Food and Drug Administration (FDA) approval in 1989, *in vitro* resistance was reported by Army scientists working in Thailand. Soon reports of clinical failures occurred and by the mid-1990s clinical failure rates reached 50 percent in Southeast Asia.

In the early 1970s, pioneering clinical trials by academic investigators (Clyde, 1975) supported by the U.S. Army Medical Research and Materiel Command (USAMRMC) and Naval Medical Research Center (NMRC) investigators directly collaborating with academic investigators (Rieckmann et al., 1979) showed that immunization of volunteers with hundreds of bites of irradiated mosquitoes protected the subjects from challenge with infected *Anopheles*. Seizing the initiative from these early insights, in the

early 1980s, both the WRAIR and NMRC had nascent productive malaria vaccine efforts. This work focused on understanding mechanisms of protective immunity in human and animal models. Then the specter of rapidly evolving multidrug-resistant *P. falciparum* malaria combined with advances in parasite culture and molecular biology converged in the malaria vaccine community to produce the first human recombinant circumsporozoite protein (CSP) and synthetic peptide malaria vaccines (Ballou et al., 1987; Herrington et al., 1987). These early clinical trials were followed by a resurgence of interest in the irradiated sporozoite immunization model and a search for immunologic correlates of protection. The stage was set, and both the WRAIR and NMRC programs began in earnest to work on development of a military vaccine (Heppner et al., 2005; Richie and Saul, 2002).

In 2003, the critical need for a military malaria vaccine and newer antimalarial drugs to overcome escalating multidrug-resistant *P. falciparum* and problems with mefloquine toxic side effects was dramatically illustrated when a Marine expeditionary unit deployed 290 men ashore in Liberia on a peacekeeping mission in 2003. In 2 weeks the Marine expeditionary unit suffered a 28 percent *P. falciparum* attack rate (80/290 men) with 40 Marines evacuated by air to the military regional medical center in Landstuhl, Germany. One must anticipate that operational scenarios similar to the Marine expeditionary unit in Liberia will continue to occur elsewhere in Africa and in other malarious regions of the world.

Currently troops sent to endemic areas are expected to take malaria prophylactic drugs as instructed and to use personal protective measures such as mosquito nets and insecticide-impregnated uniforms. Compliance with chemoprophylaxis is notoriously low, especially when concerns about adverse effects surface and the risks of malaria are not well understood (as in Liberia in 2003). The rapid emergence of malaria drug resistance and the dwindling number of options for chemoprophylaxis make this a risky strategy to rely on. Personal protective measures are not 100 percent effective on their own, and insecticide resistance is an additional threat to the continued effectiveness of impregnated materials. Both chemoprophylaxis and mosquito net availability depend on supply chains that may not be fully operative in combat and emergency deployment situations.

A highly effective vaccine for U.S. forces that could be given to personnel before their departure for a malaria endemic region is a much needed solution and would be much more reliable than the partially effective methods of chemoprophylaxis and personal protection.

Recommendation 2.1: The Department of Defense (DoD) should markedly enhance its research and development efforts to produce

malaria vaccines suitable for DoD needs. Malaria is a severe ongoing threat for U.S. military personnel deployed to malaria-endemic areas of the world, and current malaria prevention and control methods are indisputably inadequate.

COST AND TIME NEEDED TO PRODUCE A VACCINE

Assuming that a successful vaccine can be developed and produced, what are the likely costs of this task? These were estimated in a 2000 report from an independent committee of experts chaired by Franklin Top, M.D., that was convened to make recommendations on improving the DoD acquisition process for vaccines (Top et al, 2000). The report, *Department of Defense Acquisition of Vaccine Production* (referred to here as the "Top report") examined the feasibility of vaccine production for defense against biological agents, but the findings are also relevant to naturally occurring diseases. They included cost estimates for vaccine development and production, and some summary findings of this report are reproduced in Table 2-3.

The research and development costs estimated by the Top report for discovery through production and licensure of a single vaccine were $300 to $400 million, in year 2000. It is estimated that clinical trials represent 30–40 percent of the total vaccine development cost. The additional costs listed in Table 2-3 represent what would be required if the DoD were actually to produce a number of vaccines in-house (estimated by this report at 8 different vaccines, requiring human resources of approximately 2,500 skilled individuals). The concept here for a government-owned, contractor-operated facility is for full vaccine production, not just pilot-lot production.

The estimates of the Top report are compatible with those of Greco who used a $300 million estimate, of which the majority ($210 million)

TABLE 2-3 Industry Benchmark Cost Estimates for Vaccine Production

Element	Cost/Product (in $ millions)
Research and development	300–400
Facility capital costs	370 initial[a]
Additional production, labs, and support	75–115[b]
Manufacturing operations and maintenance	30–35 per year

[a] First three vaccines.
[b] For each vaccine beyond initial 3 to 4.
SOURCE: Top et al., 2000.

was needed for the late development phase (Greco, 2004). The average time required for new vaccine development was estimated at 10 years (Struck, 1996).

By far, the two major direct costs in a decade-long vaccine development program that results in licensure of a final product are the clinical trials (mainly phase 2 and 3) and the construction and furbishing of a manufacturing facility where the vaccine can be produced following licensure. Depending on the specific vaccine, considerable costs early on may also be expended in process development to learn how to manufacture the vaccine in an economic and consistent manner. The biologics license application submitted to the FDA contains extensive information characterizing the product and summarizes the safety, immunogenicity, and efficacy data from well-designed clinical trials. The application also contains information documenting that the manufacturing processes result in a product that is consistent in relevant characteristics and in the clinical acceptability and immunogenicity of different lots. The biologics license application also describes the features of the facility that will manufacture the vaccine. The costs of constructing and furbishing a manufacturing facility vary greatly from one vaccine to another. This depends not only on the characteristics of the specific vaccine but also on the maximal number of doses that the facility is expected to produce.

In summary, the estimated cost to achieve a high likelihood of development of a successful new vaccine ranges upward from a minimum of $300 million, spent over at least 10 years. Although the cost and time commitments to produce a vaccine seem enormous, these have to be balanced against the current expenses for prevention and treatment of malaria and the ineffectiveness of current prevention and control methods leading to high casualty numbers in many deployments (see Table 2-1).

Recommendation 2.2: The DoD should formally acknowledge the high cost of developing any new vaccine and the fact that the Military Infectious Diseases Research Program (MIDRP) Malaria Vaccine Program is severely underfunded in relation to the goal. To increase the probability of success, this discrepancy needs to be rectified.

3

Malaria Vaccines

The complex *Plasmodium* life cycle is summarized in Figure 3-1. Infection is initiated by inoculation of sporozoites from an infected anopheline mosquito. In humans the parasite undergoes cycles of replication in the liver (exoerythrocytic cycle) and in the blood (erythrocytic cycle). The sporozoites and liver stages are cumulatively referred to as the preerythrocytic stages.

For protection of individuals, studies of experimental and naturally acquired immunity provide a solid rationale for the feasibility of a malaria vaccine that can target either preerythrocytic (sporozoite and liver) stage or asexual erythrocytic blood stages of the parasite, or both. While both types of vaccine would also reduce transmission, it is also theoretically feasible to protect communities by high coverage with vaccines that would generate immune responses to sexual stages in the blood of humans and that would then interfere with completion of the life cycle when anophelines consume the blood of such vaccinated humans. However, the latter type of vaccine is not immediately useful for individual protection as would be required by the Department of Defense (DoD).

Vaccines based on the preerythrocytic stages usually aim to prevent infection completely, whereas blood-stage vaccines aim to reduce (and perhaps eventually eliminate) the parasite load once a person has been infected, thus alleviating the clinical symptoms. However, vaccines acting at the preerythrocytic stage may also reduce the severity of the subsequent blood infection. This could occur by reduction in the number of parasites emerging from the liver into the blood or by delaying the initiation of the

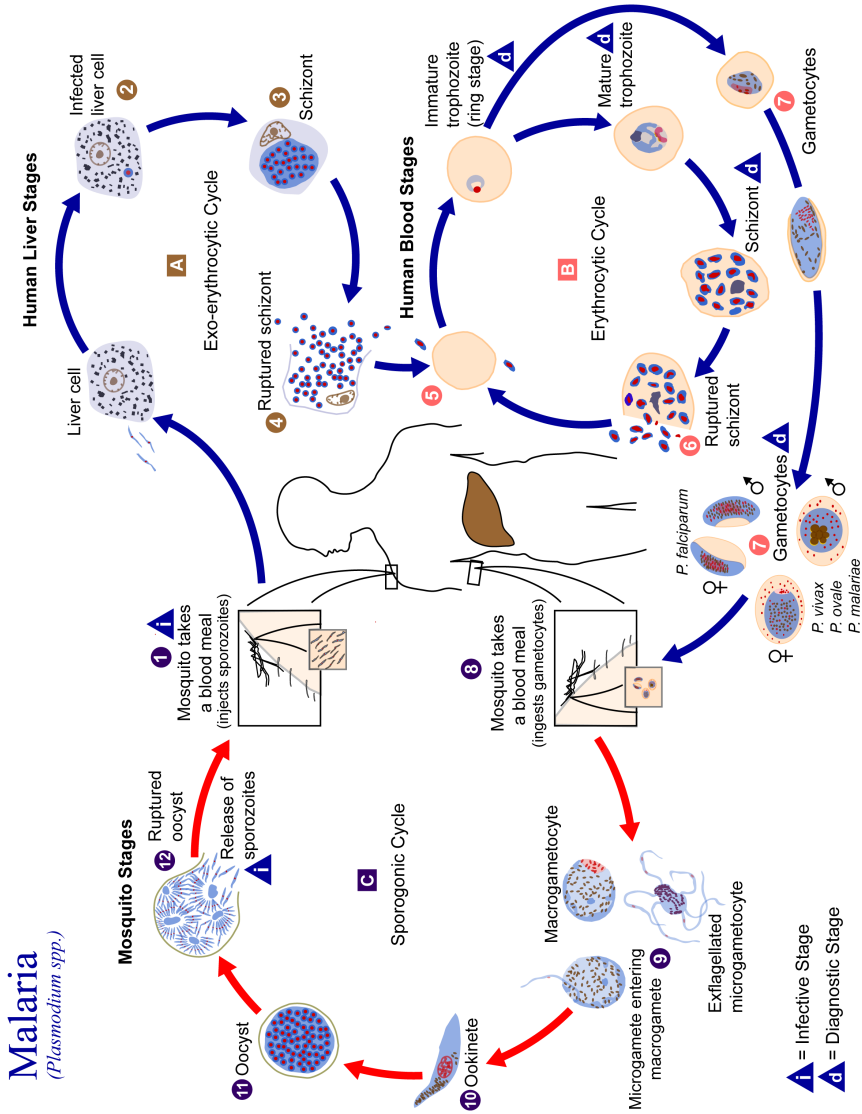


FIGURE 3-1 The malaria life cycle.

The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host (1). Sporozoites infect liver cells (2) and mature into schizonts (3), which rupture and release merozoites (4). (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks or even years later.) After this initial replication in the liver (exoerythrocytic schizogony A), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony B). Merozoites infect red blood cells (5). The ring-stage trophozoites mature into schizonts, which rupture releasing merozoites (6). Some parasites differentiate into sexual erythrocytic stages (gametocytes) (7). Blood-stage parasites are responsible for the clinical manifestations of the disease.

The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal (8). The parasites' multiplication in the mosquito is known as the sporogonic cycle C. While in the mosquito's stomach, the microgametes penetrate the macrogametes and generate zygotes (9). The zygotes in turn become motile and elongated (ookinetes) (10) and invade the midgut wall of the mosquito where they develop into oocysts (11). The oocysts grow, rupture, and release sporozoites (12), which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle (1).

SOURCE: CDC, 2002.

blood-stage infection thereby allowing the immune system additional time to mount effective immune responses.

It is generally agreed that a vaccine effective against both preerythrocytic and asexual blood stages would be ideal to protect individuals at high risk. However, inclusion of multiple antigens in a vaccine complicates its development: intellectual property issues must be addressed, clinical trials must assure that there is no interference among the antigens, and the cost is increased. Nevertheless, there is ample evidence from an array of bacterial and viral vaccines (e.g., various multivalent infant combination vaccines including diphtheria-pertussis-tetanus, measles-mumps-rubella-varicella, 7-valent pneumococcal conjugate, etc.) that there is precedent for developing effective vaccines containing multiple antigens.

SPECIFIC MILITARY NEEDS WITH RESPECT TO A MALARIA VACCINE

The committee was asked to consider whether the military malaria vaccine requirements were different from those in other populations. The answer is a qualified yes. For the military it would be ideal to prevent infection (parasitemia) completely, but it is certainly necessary to achieve a high level of protection from the debilitating clinical effects of malaria (Table 3-1). A relatively short duration of protection is acceptable (approximately 6 months). For children in highly endemic areas, on the other hand, complete protection from infection may not be essential; a vaccine that reduces clinical and severe malaria by half would be extremely useful. However, the duration of protection for children in endemic areas needs to be at least one year, given the difficulty of delivering booster doses. Nevertheless, it is conceivable that a vaccine meeting military needs could also have a significant public health impact.

The needs of the tourism/traveler market are quite similar to those of the military (Table 3-1). One difference is that most civilian travelers may not require even as long as 6 months protection—a shorter period may be acceptable as long as efficacy is high. A short initial schedule would also be desirable for travelers, but less critical for the military where basic training of several weeks to months occurs before deployment.

For all needs (military, public health, and civilian travelers), *P. vivax* is less of an urgent problem than the potentially fatal *P. falciparum*. This committee was asked to consider only the *P. falciparum* vaccine program, as it is the most severe and urgent problem. However, prevention of the clinical debilitation of *P. vivax* and other malaria species is also critical to the military as a second priority.

TABLE 3-1 Malaria Vaccine Needs in Different Groups

	U.S. Military Personnel	Typical Civilian Traveler	High-Risk Populations in Malaria Endemic Areas
Primary goal	High-level protection against infection (or clinical disease[a]) in nonimmune adults	High-level protection against infection (or clinical disease) in nonimmune adults	Prevent disease and death in young children[b]
Minimum duration of efficacy	6 months	6 months	13–18 months
Rapid onset of protection	Yes (after booster)	Yes	Not necessarily
Able to be boosted by natural infection	Desirable but not essential	Desirable but not essential	Yes
Compatible with current childhood immunization schedules	No	No	Preferably
Short initial schedule	Desirable but not essential	Yes	Preferably
Lack of interference with other vaccines	Yes (other predeployment vaccines)	Yes (other pretravel vaccines)	Yes (other childhood vaccines)

[a]Although protection from clinical disease is most important, protection against infection as well as against clinical disease would also eliminate potential risk of transfusion malaria.

[b]The level of protection required has been estimated by the Malaria Vaccine Technology Working Group, a recently formed consensus group (Roadmap, 2006). The goals and timelines are as follows: for a first-generation vaccine, protective efficacy of more than 50 percent against severe disease and death (licensure 2015); for a second-generation vaccine, more than 80 percent protection against clinical disease and death (licensure 2025).

MALARIA VACCINE DEVELOPMENT

Development of any new vaccine is a difficult task, and the malaria parasite is even more challenging because of its complex life cycle and antigenic complexity. As with any complex new vaccine (e.g., HIV, tuberculosis), there will be a long list of potential vaccine antigens and formulations in the early stages; this list is expected to be whittled down to a few better prospects during the development process. Potential vaccine constructs may be eliminated because they turn out not to be protective, because they cannot be reliably produced, because the companies developing them do not have sustained interest, or because of safety issues with either the antigens or the formulations (e.g., adjuvants).

Malaria vaccines under development include attenuated whole organisms, recombinant proteins, peptides, and gene-based (DNA or viral vector) vaccines, using a variety of adjuvants. A fairly recent development is the prime-boost strategy, which involves a combination of different antigen delivery systems encoding the same epitopes or antigen (for example naked DNA followed by DNA in a viral vector), delivered at an interval of a few weeks apart.

The following section briefly describes the history of research and development on malaria vaccines, including the identification of important malaria antigens and understanding of immunogenicity, much of which was done by Military Infectious Diseases Research Program (MIDRP) Malaria Vaccine Program researchers. The following information illustrates the depth of experience in the MIDRP Malaria Vaccine Program and their collaborators as well as the fact that current promising candidates have emerged from a long and sustained effort over the last 30 years (Appendix A).

Prelicensure vaccine trials in humans progress in step-by-step fashion under regulatory supervision. The trial stages are defined here according to Levine et al beginning with phase 1 (dose-finding, preliminary safety, and initial immunogenicity studies) (Levine et al., 2002). These are followed by phase 2 (larger-scale safety and immunogenicity and sometimes preliminary assessments of efficacy [e.g., via experimental challenge studies]) and phase 3 trials (large-scale studies to assess efficacy under conditions of natural challenge and to gather additional information on safety).

Preerythrocytic Stages

Attenuated Sporozoites

Early studies in the 1960s demonstrated high levels of protective immunity following immunization with radiation-attenuated sporozoites in

experimental rodent and primate models (Nussenzweig and Nussenzweig, 1989). Protection was sterile in that no blood-stage parasites were demonstrable in the blood of immunized hosts challenged with viable sporozoites. Protection was also stage specific, as the sporozoite-immunized animals remained fully susceptible to challenge with blood-stage parasites. Hallmark early studies in humans demonstrated that sterile immunity could be obtained in volunteers immunized by frequent exposure to large numbers of irradiated mosquitoes infected with *P. falciparum* or *P. vivax* (Clyde, 1990; Rieckmann, 1990). Protection was species specific and strain cross-reactive in that volunteers immunized by exposure to the bites of irradiated *P. falciparum*-infected mosquitoes were protected against multiple strains of *P. falciparum* from diverse geographical areas, but not against *P. vivax*. These findings were confirmed in later studies carried out by the University of Maryland and the Naval Medical Research Center (NMRC) in which 95 percent of volunteers exposed to a minimum of 1,000 bites from irradiated mosquitoes infected with *P. falciparum* were protected for periods of up to 9 months (Herrington et al., 1991; Hoffman et al., 2002).

Circumsporozoite Protein

The early identification of target antigens was based on recognition by sera and cells of protected volunteers and experimental hosts immunized with attenuated sporozoite vaccine. The first antigen identified by serological screening was a major surface antigen of the sporozoite, the circumsporozoite protein (CSP),[1] and this protein was the first malaria parasite to be cloned and sequenced in *P. knowlesi*, followed soon thereafter by *P. falciparum* (Dame et al., 1984; Ellis et al., 1983; Enea et al., 1984). The sequences showed a prominent feature of the CSP: It contains a large number of repeats of a short amino acid sequence (NANP in *P. falciparum*). CSP remains a primary vaccine candidate, either alone or in combination with other preerythrocytic- or erythrocytic-stage antigens, in vaccine development programs of the Walter Reed Army Institute of Research (WRAIR) and the NMRC, as well as at other institutions (WHO, 2005).

Mechanisms of immune protection that target the CSP include both antibody and cellular responses. Based on the demonstration in rodent and primate models that high antibody titers against CSP repeats correlated with protection (Zavala et al., 1985), early *P. falciparum* vaccine efforts focused on generation of strong humoral immunity. The first phase 1 and

[1]The acronym CSP was also used to describe the circumsporozoite precipitin reaction, encountered when sera from volunteers immunized with irradiated sporozoites were exposed to sporozoites expressed from the salivary gland of mosquitoes.

2 trials (see Appendix A) tested efficacy of *P. falciparum* CSP expressed as a recombinant protein R32tet32, comprising 32 repeats of the tetramer NANP expressed in tandem with 32 amino acids from the bacterial tetracycline resistance gene translated out of frame (Ballou et al., 1987). Further studies used a synthetic peptide-protein conjugate $NANP_3$-TT, comprising three copies of the NANP repeat conjugated to tetanus toxoid as carrier (Herrington et al., 1987). Challenge of a small number of volunteers immunized with the alum adjuvanted subunit vaccines provided the first demonstration that antirepeat antibodies were protective in humans *in vivo*, but vaccine efficacy was limited by overall low titers. Subsequent clinical trials by WRAIR examined CSP repeats using various conjugates including fusion with 81 amino acids from a nonstructural protein of influenza (R32NS1), adjuvanted with monophosphoryl lipid A(MPL)/ cell wall skeleton of *Mycobacterium phlei* and squalene (Hoffman et al., 1994), and R32 fused to Tox A (Fries et al., 1992). These different conjugates increased antibody titers but did not significantly increase protection.

In addition to antibody responses, cellular responses to CSP were found to play a critical role in protection (Aggarwal et al., 1990; Romero et al., 1989; Sadoff et al., 1988; Weiss et al., 1988). In irradiated sporozoite rodent models, the role of antibody and cells differed depending on malaria species and strain of mouse (Doolan and Hoffman, 2000). Cellular responses are multifaceted, but a primary immune mechanism is the production of interferon that targets the intracellular hepatic exoerythrocytic forms (Ferreira et al., 1986; Schofield et al., 1987a). Interferon gamma, produced by CD4+ or CD8+ T cells elicits nitric oxide production in the infected cell that destroys the hepatic-stage parasites (Mellouk et al., 1991; Seguin et al., 1994). A number of CD4+ and CD8+ T-cell epitopes were identified in the N and C terminus of the CS protein (Nardin and Nussenzweig, 1993), several of which overlapped polymorphic regions of the *P. falciparum* CS protein (Good et al., 1989).

A phase 2 trial of recombinant *P. falciparum* CSP containing CD4+ and CD8+ T cell epitopes, but no NANP repeats, administered in liposomes/ MPL/alum did not demonstrate any protection (Heppner et al., 1996). This implies that a combination of antirepeat antibody and cellular responses may be required for vaccine efficacy in humans, as suggested by studies in the sporozoite immunized rodent model (Schofield et al., 1987b; Rodrigues et al., 1993). Such vaccines would provide a multipronged approach with antibody eliminating most if not all of the infectious sporozoite inoculum and cellular responses, mediated by inhibitory cytokines or direct cytotoxicity, targeting the remaining intracellular exoerythrocytic forms in the liver. Recombinant full-length CSP, however, was poorly immunogenic in phase 1 trials using alum as adjuvant, indicating that antigen format was important (Herrington et al., 1992).

RTS,S Vaccine and the Effect of Adjuvant

The most successful approach to improve immunogenicity of CS subunit vaccines was provided by WRAIR in collaboration with GlaxoSmithKline (GSK). A multimeric antigen was constructed by fusing the CSP repeats and C terminus to hepatitis B virus surface antigen (HBsAg). Notably, the recombinant CS protein-HBsAg hybrid monomers (RTS) when coexpressed in yeast cells with native hepatitis B surface antigen monomers (S) spontaneously formed viruslike particles, a vaccine preparation termed RTS,S.

Most importantly, it was found that a specific adjuvant was critical to vaccine efficacy, as protection was obtained only with RTS,S formulated in a potent adjuvant developed by GSK comprising a combination of MPL and QS21 in an oil in water emulsion (Garcon et al., 2003). This vaccine formulation elicited sterile immunity in a proportion of both malaria-naïve volunteers and malaria-experienced adults in the Gambia (Bojang et al., 2001; Kester et al., 2001; Stoute et al., 1997, 1998).

Gene-Based and Prime-Boost Approaches

DNA vaccines and viral vectors were amongst the vaccine delivery systems that appeared promising for the generation of CS-specific cellular immunity, and in some initial studies in small animals this goal was achieved (Rodrigues et al., 1994, 1997, 1998; Sedegah et al., 1994). However, clinical trials of these candidate vaccines when used alone or in repeated homologous boosting regimes have been disappointing, with low levels of antibody and minimal protection (Le et al., 2000; Wang et al., 1998).

Recent years have seen the development of immunization strategies using a combination of different antigen delivery systems encoding the same epitopes or antigen, delivered at an interval of a few weeks apart. This sequential immunization approach with different vectors is known as *heterologous prime-boosting* and is capable of inducing greatly enhanced and persistent levels of CD8+ T cells and Th1-type CD4+ T cells compared to homologous boosting (Anderson et al., 2004; Li et al., 1993; Sedegah et al., 1998). Recently in murine malaria models, different strains of adenovirus have also been shown to be promising candidates for this approach (Ophorst et al., 2006). Efforts to boost RTS,S-primed responses with the recombinant modified vaccinia Ankara (MVA) virus expressing CSP, or vice versa, did not increase vaccine efficacy (Dunachie and Hill, 2003).

Erythrocytic Stages

A rationale for blood-stage vaccines is provided by the naturally acquired immunity that develops by adulthood in people living in endemic areas. Passive transfer of immune serum from adults to children was shown to decrease parasitemia and clinical disease (Cohen et al., 1961; Edozien, 1961; Sabchareon et al., 1991).

The potential targets of blood-stage immunity include a highly polymorphic antigen on the surface of erythrocytes, PfEMP-1, as well as antibodies that target polymorphic merozoite antigens known to play a role in invasion of erythrocytes, such as MSP-1 and AMA-1.

Many studies ranging from phase 1 to phase 3 have been done with a synthetic polymer, termed SPf66, which contains peptides derived from the amino acid sequences of three *P. falciparum* merozoite proteins found to be protective in the *Aotus* monkey model (Patarroyo et al., 1987). Clinical trials in adults and children in South America, Africa, and Southeast Asia failed to demonstrate reproducible levels of protection against infection or clinical disease (results are summarized in Appendix A, Table A-3).

More recently, phase 2 clinical trials of a combination vaccine composed of MSP-1, MSP-2, and RESA, a ring-infected erythrocyte surface antigen expressed on erythrocytes, demonstrated a 62 percent reduction in parasite density with a lower prevalence of parasites expressing the MSP-2 allele found in the vaccine (Genton et al., 2002).

Multiantigen Multistage Approaches

A multistage vaccine would be expected to reduce the sporozoite inoculum and hepatic stages as well as block merozoite invasion of erythocytes, thereby reducing or eliminating clinical disease. A vaccine that also included different allelic forms of polymorphic antigens would also reduce the potential for selection of strain-specific responses.

The scientists at WRAIR were among the first to test a multistage vaccine composed of a recombinant vaccinia virus, NYVAC 7, engineered to express CSP and six additional antigens derived from sporozoite/liver and blood stages. These included sporozoite/liver-stage antigen SSP-2/TRAP,[2] important in parasite targeting to host cells and motility (Sultan et al., 1997), LSA-1, a parasite protein expressed only in the liver (Hollingdale

[2]SSP-2 (sporozoite surface protein-2) and TRAP (thrombospondin-related adhesion protein) were independently discovered as sporozoite stage and sporozoite/erythrcytic stage antigens, respectively, and subsequently shown to be identical. Accordingly, the term TRAP/SSP-2 or SSP-2/TRAP is often used as a way of referring to the antigen. The latter is used here.

et al., 1998); and MSP-1 and AMA-1 expressed in the invasive merozoite stage. Despite the ability of the vaccine to elicit antibody and cellular immune responses to these antigens, only 1 out of 35 volunteers was protected (Ockenhouse et al., 1998). See Appendix A.

In efforts to increase efficacy of RTS,S-induced immunity the CSP-based vaccine has been combined with a preerythrocytic-stage antigen (SSP-2/TRAP) or blood-stage antigen (MSP-1). However, in the experimental challenge model, RTS,S protective efficacy was not increased by a combination of RTS,S + MSP-1, and immunization with RTS,S + SSP2/TRAP resulted in reduced vaccine efficacy (Heppner et al., 2005; Heppner, 2006).

The multistage vaccine approach adopted by the NMRC focused initially on DNA plasmid vaccines. NMRC was first to study immunogenicity of a CSP DNA plasmid malaria vaccine in human volunteers showing the ability to elicit strong CD8, but poor CD4 and antibody responses (Wang et al., 1998). Efforts to boost CSP DNA-primed responses with RTS,S were not successful (Epstein et al., 2004; Wang et al., 2004). Strong support for the potential of multistage DNA vaccines, however, was provided by studies in the *P. knowlesi*/rhesus model (Rogers et al., 2001). Immunization with four plasmids encoding full-length *P. knowlesi* CSP, SSP-2/TRAP, AMA-1, and MSP-1_{42} followed by poxvirus boost elicited significant levels of sterile protection and control of parasitemia in rhesus monkeys (Rogers et al., 2002). In human volunteers phase 1 and 2 trials of MuStDO5, a mixture of DNA plasmids encoding five preerythrocytic-stage proteins, CSP, SSP-2/TRAP, LSA-1, LSA-3 (a second liver-stage antigen expressed also in sporozoites), and PfExp1 (an exported liver-stage antigen found in parasitophorous vacuoles), have been carried out. Although the vaccine elicited positive CD4+ and CD8+ T-cell responses, no antibody or protection against challenge was obtained in the immunized volunteers (Wang et al., 2005), indicating that nonfalciparum animal models can be very misleading in predicting results with falciparum immune responses and/or protection in humans. Recent studies have demonstrated immune interference by certain antigens within the combination and these findings have been used to down-select antigens and identify the most promising combination, termed *CSLAM* (CSP, SSP-2/TRAP, LSA-1, AMA-1, MSP-1) for further studies (Sedegah et al., 2004).

A clinical trial of ME-TRAP, a multiple epitope construct, containing T- and B-cell epitopes from several preerythrocytic-stage antigens linked to SSP2/TRAP and delivered as a DNA prime followed by a boost in the MVA viral vector, failed to show protection in malaria-exposed volunteers (McConkey et al., 2003; Moorthy et al., 2004b). However this is still a highly active area of research with different combinations of viral vectors being investigated (Webster et al., 2005).

SCIENTIFIC BARRIERS TO MALARIA VACCINE DEVELOPMENT

Insufficient Knowledge of Malaria Biology

A major scientific barrier to developing malaria vaccines is insufficient knowledge about the malaria parasite, especially parasite polymorphism and antigenic variation. It must be acknowledged that most current vaccines were developed without extensive knowledge of this variability. However, most vaccines for simpler organisms are not as challenging as malaria. At present there are no FDA-approved vaccines for organisms more complex than viruses and bacteria, although some other parasite vaccines are in development.

The sequencing of the malaria genome has helped to accelerate the study of different variants of important target antigens, but it is not clear which antigens or how many allelic variants of each will be needed in a vaccine. Despite the large number of parasite antigens, most research focuses on a few long-known antigens out of the approximately 5,000 genes present in the malaria genome. Understanding parasite population structure and antigenic variation in nature requires lengthy and difficult field and laboratory studies, some of which are currently underway by other groups.

Lack of Understanding of Protective Immunity

A second major problem is the lack of understanding of the mechanisms of immune protection from malaria (Good, 2001). Most vaccines are established based on examples of naturally acquired immunity, and there are not good examples of complete immunity to the disease in nature that can be used as a model. Despite the fact that there is an established challenge model of protection against preerythrocytic stages, there is still no fundamental understanding of why certain people are protected and others not. Romero et al (1989) demonstrated the characteristics of T cells in the mouse that confer immunity, and the results of Kryzch et al (1995) tended to confirm these findings, but in general these results cannot be clearly reproduced in human challenge studies.

Although some work has suggested that protection in adult volunteers immunized with RTS,S correlated with presence of high antirepeat antibodies and CD4+ T cells (Lalvani et al., 1999) and with low numbers of CD8+ T cells detected by intracellular cytokine staining (Sun et al., 2003), generally trials conducted either with experimental challenge (Kester et al., 2001; Stoute et al., 1997, 1998) or natural challenge (Alonso et al., 2005; Bojang et al., 2001) have not demonstrated clear immune

correlates of protection. Either the assays or reagents being used are not sophisticated enough, or there is a fundamental unrecognized immune process involved.

Inadequate Animal Models

There is considerable uncertainty about how well animal research models reflect human immunity. The lack of a good animal model is reflected in the fact that the WRAIR and NMRC programs are in conflict: WRAIR scientists apparently do not believe the *Aotus* model to be useful on the path to a vaccine (Heppner et al., 2001), whereas NMRC uses it (among several other animal models) as a means for evaluating potential antigens. The use of many different animal models in preclinical studies precludes direct comparison of similar vaccine constructs being developed by WRAIR and NMRC, such as adenovirus 35 versus adenovirus 5 viral vectors.

Poor Definition of Outcomes

Lack of clear definition of desired outcomes (prevention of infection, clinical disease, and severe disease) contributes to confusion about the best approach to developing a malaria vaccine. Even with defined outcomes in particular animal model systems, it is often not clear how well protection in these model systems correlates with success in humans.

The Malaria Vaccine Technology Roadmap

Many of these barriers are of long standing, having been recognized in an earlier Institute of Medicine (IOM) report on malaria vaccines (IOM, 1996) and also by the Malaria Vaccine Technology Roadmap Working Group (Roadmap, 2006), a collaborative process sponsored by Malaria Vaccine Initiative (MVI), the Bill and Melinda Gates Foundation, WHO, and the Wellcome Trust, in which the MIDRP Malaria Vaccine Program scientists fully participated. Overcoming these barriers forms the rationale for the list of top 10 priorities produced by the roadmap committee, with priority initiatives 1 through 7 being of direct relevance to MIDRP Malaria Vaccine Program vaccine efforts (Table 3-2). The MIDRP Malaria Vaccine Program could contribute significantly by developing jointly agreed criteria about the appropriateness of different animal models and outcome measurements in order to assist the global community in defining joint go/no-go criteria for vaccine candidates.

TABLE 3-2 Top 10 Priority Initiatives for Malaria Vaccine Development According to the Malaria Vaccine Technology Roadmap

Category	Priority Initiative	Detail
Advancing Science	1. Improved understanding of parasite-host interactions	Use new technologies in genomics, proteomics, and other disciplines to study parasite biology and parasite-host interactions to enhance scientific understanding of the human immune response induced by *P. falciparum*.
	2. Correlates of protection	Identify and validate correlates of protection, which would greatly expedite vaccine design.
	3. Standardized assays and reagents	Develop standardized "tool kits" of validated assays, reagents, and operating procedures to enable comparison of results from models, field trials, and other experiments.
	4. Process development capabilities	Improve access to robust process development and GMP pilot-lot manufacture to accelerate the clinical testing of promising vaccine candidates.
	5. Standardized trial end points	Clearly define standard end points and measurement methodologies for use in clinical trials. Producing comparable field metrics can extend the value of clinical trials beyond the efficacy of a particular vaccine candidate.
Improving Processes	6. Shared go/no-go criteria	Develop a common set of measurable criteria, linked to the strategic goals, to guide scientific and investment decisions at various stages along the entire vaccine development process.
	7. Increased and sustained clinical trial capacity	Increase the capacity of endemic regions to provide ample, epidemiologically diverse sites with good clinical practice capability to support planned clinical trials.
	8. Balanced global portfolio	Create a structured process to help guide and manage a balanced global portfolio of malaria vaccine research and development to focus global and local investments on the most critical needs.
Shaping Policies and Commer-cialization	9. Novel regulatory and introduction strategies	Develop innovative regulatory strategies to prepare endemic countries and global bodies to evaluate a future malaria vaccine. Early attention to regulatory processes can avoid delays and allow a smooth transition to diminish the special challenges of deploying a malaria vaccine, including effective integration with existing intervention strategies.
	10. Innovative financing mechanisms	Pursue innovative financing mechanisms that are supported by nation-level decision-making processes to stimulate market pull and ensure a viable market in endemic countries.

SOURCE: Roadmap, 2006.

DEPARTMENT OF DEFENSE SCIENTIFIC CONTRIBUTIONS TO THE GLOBAL MALARIA VACCINE RESEARCH EFFORT

A long-standing commitment to malaria research, including crucial drug development research mentioned above, has led the MIDRP Malaria Vaccine Program labs to the forefront of malaria vaccine development. Some of the highlights of the basic research from the last 40 years include being one of the first laboratories in which malaria parasites were cultured (Haynes et al., 1976), the development of automated and standardized culture techniques and growth inhibition assays (Desjardins et al., 1979; Haynes et al., 2002), and the establishment of routine mosquito infections from cultured parasites (Chulay et al., 1986).

Expertise in immunology and monoclonal antibody production at WRAIR was crucial to the success of cloning and sequencing the CSP gene (Dame et al., 1984). Particular expertise was developed in identifying (by antibody selection from a *P. falciparum* expression library) and sequencing several merozoite surface antigens that are recognized by neutralizing antibodies, including MSP-1 and MSP-2 (Lyon et al., 1986; Thomas et al., 1990). Important conformational targets on MSP-1 recognized by inhibitory antibodies and containing T-cell epitopes were identified (Krzych et al., 1995; Lyon et al., 1997), as well as the discovery of both inhibitory and blocking epitopes (Uthaipibull et al., 2001) on the MSP-1_{42} portion of the molecule, leading to redesign of this vaccine candidate.

Sequencing of the CSP gene led directly to the first recombinant protein vaccine R32tet32 and its subsequent modifications (Ballou et al., 1987), which are described in more detail above and in Appendix A. The MIDRP Malaria Vaccine Program researchers also demonstrated the importance of the CSP central repeats in generating protective antibodies as well as the necessity for cell-mediated immune responses in protection, with target epitopes in the CSP C-terminal region (Aggarwal et al., 1990; Malik et al., 1991; Sadoff et al., 1988). This information was crucial in designing the RTS,S vaccine antigen.

In more recent years the MIDRP Malaria Vaccine Program, especially the NMRC, have played a major role in the successful effort to sequence the complete *P. falciparum* genome and the subsequent complete sequencing of other malaria species (Carlton et al., 2002; Gardner et al., 2002a,b).

The current capability of the MIDRP Malaria Vaccine Program labs to carry out *P. falciparum* sporozoite challenge trials is unparalleled in the world; they have by far the most experience in carrying out these experimental challenge trials. Sporozoite challenge for *P. vivax* vaccine trials (using mosquitoes infected from gametocyte carriers rather than culture) is also available at the Armed Forces Research Institue of Medical Sciences (AFRIMS). The other unit that was self-sufficient for many years in the

1980s and 1990s in performing multiple sporozoite challenges of volunteers was the Center for Vaccine Development of the University of Maryland School of Medicine, which maintained a dedicated insectary of mosquitoes infected with a cloned *P. falciparum* strain (CVD-1) (Davis, 1994; Herrington et al., 1988). It is only very recently that any other academic labs have taken on the task of *P. falciparum* experimental challenge. For example, during the past five years, the University of Oxford has performed multiple challenge studies using mosquitoes reared at Imperial College, London, United Kingdom (Webster et al., 2005); WRAIR assisted in setting up the initial Oxford challenge trials. The University of Nijmegen, the Netherlands, has also recently completed one small sporozoite challenge trial for a CSP peptide vaccine (Genton et al., 2005).

In addition to the ability to conduct human clinical trial challenges, the MIDRP Malaria Vaccine Program labs have contributed immensely to standardizing animal models of malaria, including the *P. yoelii*/mouse model, the *P. knowlesi*/rhesus model, and the *P. falciparum*/*Aotus* model. Development of an additional *P. knowlesi* model in natural rhesus hosts in Indonesia is in progress.

Notably, the MIDRP Malaria Vaccine Program has been involved in development and testing of three of the seven *P. falciparum* vaccine candidates that have progressed as far as phase 2 trials in endemic areas (Appendix A, Table A-3). The most promising one at present is RTS,S. Of the others that have reached the stage of human clinical trials in endemic areas, four ([$NANP_3$]-tetanus toxoid, R32toxA, CSP-NANP/5.1, and SPf66) are no longer being considered as candidates; MSP-1/MSP-2/RESA (combination B) is dormant; and ME-TRAP DNA and recombinant viral vector heterologous prime-boost vaccines are still being evaluated.

WRAIR scientists played a significant role in clarifying the efficacy of the SPf66 vaccine. Much effort and many field trials were devoted to testing the efficacy of non-GMP pilot-lot formulations of this peptide vaccine after initial promising results from South America. Independent manufacture and testing of the vaccine with assistance of WRAIR eventually contributed to the view that SPf66 conferred insufficient protection to warrant further development or routine use.

STATUS OF CURRENT VACCINE CANDIDATES

Figure 3-2 summarizes the current status of the most important *P. falciparum* vaccine antigens being considered and demonstrates the level of MIDRP Malaria Vaccine Program involvement in the worldwide effort. Constructs with which the MIDRP Malaria Vaccine Program is involved are shown as solid lines. Only trials of *P. falciparum* preerythrocytic, blood-stage and multistage vaccine candidates are included in Figure 3-2;

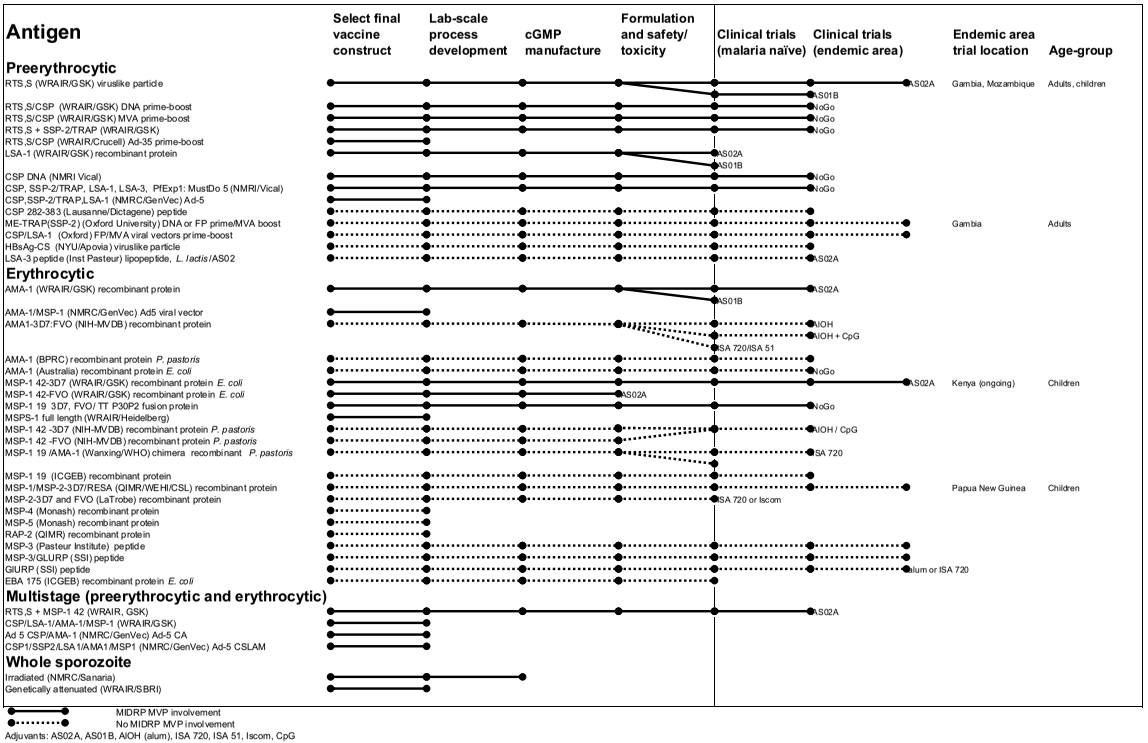


FIGURE 3-2 Current global *P. falciparum* vaccine development showing the developmental stage reached and the extent of MIDRP Malaria Vaccine Program involvement.
SOURCES: F Dubovsky, D Vaughn, DG Heppner, T Richie, personal communications, January 23, 2006; WHO, 2005.

transmission-blocking antigens and *P. vivax* vaccines are beyond the scope of this review. Several reviews describe the trials in more detail (Ballou et al., 2004; Graves and Gelband, 2003; Moorthy et al., 2004a; Richie and Saul, 2002; Targett, 2005). More details about individual vaccine constructs are given in Appendix A, which lists the constructs and trials that have been conducted according to the type of trial (safety and immunogenicity trials only [Table A-1], and trials with experimental [Table A-2] or natural [Table A-3] challenge) and the parasite stage involved (preerythrocytic, erythrocytic, and multistage, respectively).

It can also be seen from Figure 3-2 that the MIDRP Malaria Vaccine Program is involved in the development of about half of the vaccine candidates that have not yet reached phase 2 trials but are under active development. These include some of the most advanced constructs that have achieved investigational new drug filing including MSP-1, AMA-1 and LSA-1 recombinant proteins with AS02A and AS01B adjuvants. The MSP-1 vaccine is currently in clinical efficacy trials in Kenya.

Because of the importance of RTS,S to the MIDRP Malaria Vaccine Program's current strategy, we summarize the results of randomized studies in endemic areas in Figure 3-3. Four randomized efficacy trials of RTS,S have been conducted: one trial of RTS,S in nonimmune adults used artificial challenge with infected mosquitoes (Kester et al., 2001), one trial was with adult men followed over two malaria seasons in the Gambia (Bojang et al., 2001), and two cohorts of children aged 1–4 years in Mozambique were followed for up to 18 months (Alonso et al., 2004, 2005).

Figure 3-3 shows efficacy as estimated by three different outcomes: new malaria infection, clinical malaria, and severe malaria. Initial estimates of RTS,S efficacy in completely preventing *infection* from the trials at WRAIR were about 50 percent (Kester et al., 2001; Stoute et al., 1997). This level of efficacy was not borne out in a trial in adults in the Gambia in the first season after immunization, although there was 71 percent increase in time to first infection in the first 9 weeks after immunization (Bojang et al., 2001). However the efficacy of RTS,S against *clinical episodes of malaria* was high (63 percent reduction, 95 percent confidence interval [CI]: 18–93 percent) in the second year after immunization, after a booster dose (Bojang et al., 2001).

Two cohorts of children 1–4 years of age in Mozambique (one of which received chemotherapy to clear infections before follow-up) were partially protected by RTS,S for up to 18 months after immunization (Alonso et al., 2004, 2005) (Figure 3-3). Although the protection against new malaria *infection* (assessed in cohort 1) over a six month period was low (9 percent, 95 percent CI: 1–16 percent), the efficacy against *clinical malaria* was 30 percent (95 percent CI: 11–45 percent) over a six month period and remained at this level for up to 18 months (efficacy 35 percent, 95 percent

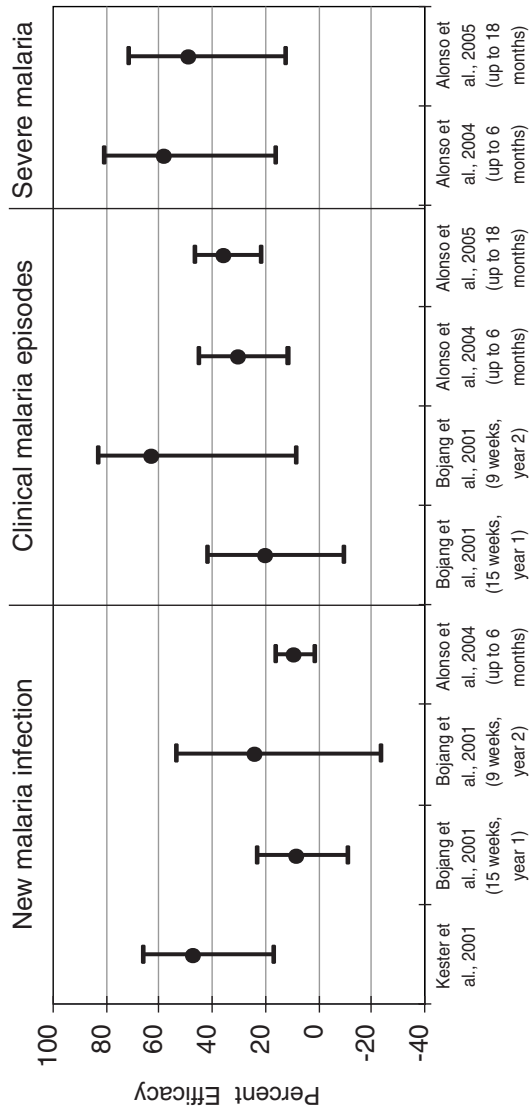


FIGURE 3-3 Results of randomized controlled trials of efficacy of RTS,S vaccine against new malaria infection, clinical malaria, and severe malaria.
SOURCE: Modified from Graves and Gelband, 2003, using data from papers cited.

CI: 22–47 percent). It was encouraging that RTS,S also showed significant protection against *severe malaria* in children, estimated at 58 percent (95 percent CI: 16–81 percent) in the first six months and 49 percent (95 percent CI: 12–71 percent) over an 18 month period (Alonso et al., 2004, 2005). No significant safety issue associated with RTS,S vaccines was found, although the frequency of some local and systemic adverse effects (e.g., injection site pain, malaise) was increased compared to placebo (Bojang et al., 2005). Protection was not limited to the CSP variants used to make the vaccine (Alloueche et al., 2003).

4

The U.S. Military Malaria Vaccine Research and Development Program—Scientific Aspects

MALARIA THREAT

Malaria presents a serious medical threat to U.S. military capability for operations in any environment where malaria is endemic—specifically, the developing tropical and subtropical regions of the world. This includes essentially all of Africa, most of Southeast Asia, much of India, Pakistan and Bangladesh, parts of Central Asia and the Middle East, parts of South America, and most of Central America. Many of these regions are characteristically politically and economically unstable with brittle infrastructures and often social unrest. Current malaria countermeasures include drug prophylaxis and treatment, vector control and personal protection efforts (topical repellents, clothing, and bed nets)—but no vaccine.

Prophylactic malaria drugs are currently the major preventive measure for military personnel. The Department of Defense (DoD) continues to produce new such drugs, including, most recently, tafenoquine. However, there are serious issues around the effective use of antimalarial drugs that include increasing multidrug resistance to *P. falciparum* (Asia and Africa) and *P. vivax* (Asia), problems with compliance both in terms of personal discipline and concerns over possible toxic side effects, and potential logistical failures. Consequently, a malaria vaccine that protects military personnel against infection and severe disease, although requiring a long and expensive research and development commitment to bring the product to Food and Drug Administration (FDA) approval, affords

the most cost-effective, safest, and least encumbering solution to the malaria threat.[1]

Department of Defense Mandate for a Malaria Vaccine

The U.S. Army was designated by Congress (1982) as the lead agent for infectious disease research. Renewed emphasis on the importance of vaccines and other countermeasures was given in Executive Order 13139 (1999) directing that "It is the policy of the United States government to provide our military personnel with safe and effective vaccines, antidotes, and treatments that will negate or minimize the effects of these health threats." These health threats include diseases endemic to an area of operations, such as malaria.

Under the direction of the U.S. Army Medical Research and Materiel Command (USAMRMC), the tri-service Military Infectious Diseases Research Program (MIDRP) coordinates malaria vaccine research and development at the Walter Reed Army Institute of Research (WRAIR), the Naval Medical Research Center (NMRC), and at DoD laboratories overseas in Kenya, Thailand, Indonesia, Peru, and Egypt.

MALARIA VACCINE REQUIREMENTS

The current requirements for a malaria vaccine (Appendix B) are formulated in a U.S. Army operational requirements document dated March 13, 1997, which has now expired and is due to be replaced. Although the current requirements were prepared under the auspices of the Army, the requirements are no different for the Navy and Marines. The requirements are used to guide the MIDRP Malaria Vaccine Program through the vaccine research and development process, including aiding in the decision process of when to move a product to advanced development.

The current requirements are expressed in terms of "development threshold" and "development objective," but the consequences of a product reaching either of these benchmarks was not clear. In addition, the requirement for efficacy was subject to different interpretations since it did not distinguish between prevention of infection, clinical attacks, or severe malaria.

Rather than attempting to interpret and revise the military requirements using the same terminology as in the operational requirements

[1]Initial Capabilities Document for Infectious Disease Countermeasures, DoD Division of Combat Development and Doctrine, AMEDD Center and School, Fort Sam Houston, Texas, 2005.

document, the committee opted to express its views about the desirable targets for a malaria vaccine in terms of two types of vaccine, a "first-generation vaccine" and an "ideal" vaccine (Table 4-1). The former would be a vaccine worth using by the military in addition to chemoprophylaxis, while the latter represents the most desirable vaccine in all characteristics and could be used to replace the routine use of chemoprophylaxis.

The desired levels of protection specified in Table 4-1 (60 percent for a first-generation vaccine and at least 95 percent for a second-generation vaccine) represent the consensus Delphian judgment of the committee members based on their expert opinion and by analogy with other diseases for which vaccines are being developed. For the first-generation vaccine, there is no objective criterion justifying the level of 60 percent—it represents what the committee felt would likely be useful in addition to chemoprophylaxis.

Vaccine development often follows a "generational" process whereby the first vaccine licensed and marketed is not fully effective, but is later replaced with a second-generation vaccine with greater efficacy, a different schedule, a different target age-group, and/or better safety. This has occurred for example with the *Haemophilus influenzae* type b (Hib), pertussis, pneumococcal, and hepatitis B vaccines. This adjunctive strategy is very

TABLE 4-1 Important Characteristics of a First-Generation Malaria Vaccine and a Later-Generation Ideal Vaccine

Characteristic	First-Generation Vaccine	Ideal Vaccine
Species	*P. falciparum*	All malaria species
Efficacy end point	Clinical disease	Blood-stage infection
Level of vaccine efficacy[a]	60%	≥95%
Duration of protection	6 months	3 years
Immunization schedule	Reasonably rapid, convenient, and compatible with concurrent other vaccines	Rapid, convenient, and compatible with concurrent other vaccines
Chemoprophylaxis still required	Yes	No

[a]The proposed levels are intended as point estimates. The lower limit for the first-generation vaccine might be of the order of 30–40 percent, by analogy with what is regarded as potentially useful for seasonal influenza and HIV.

likely to be the scenario for malaria vaccines given the difficulty of producing an initial vaccine with high efficacy. Achievement of the first-generation vaccine should not lead to the cessation of further vaccine development, given the importance of malaria to the military and the continuing need for chemoprophylaxis with the first-generation vaccine.

P. falciparum is a more important target than other malaria species. Because it seems unlikely that the same vaccine would protect against multiple species of *Plasmodium*, more than one vaccine may be needed. Although it would not be the most desirable outcome, one could envisage a situation in which there is a vaccine that is more than 95 percent effective against *P. falciparum*, but prophylaxis is still needed because there is not yet such a vaccine against *P. vivax*.

The generational approach is similar to that recommended for a public health-oriented vaccine as proposed by the Malaria Vaccine Technology Roadmap Working Group (Roadmap, 2006). The consensus of the roadmap working group was that the goal for a first-generation public health-oriented vaccine is 50 percent efficacy, lasting for a year or more, against severe disease and death in children under 5 years (by 2015). The goal for a second-generation vaccine is 80 percent efficacy, that lasts longer than 4 years, against clinical disease and death.

Recommendation 4.1: For a first-generation vaccine, a level of 60 percent efficacy (with a lower limit of 30 percent for the 95 percent confidence interval around the 60 percent point estimate of efficacy) against the *clinical effects* of *P. falciparum* would be a useful adjunct to chemoprophylaxis for military use. Nevertheless, research to develop a more effective second-generation vaccine that can be used in the absence of chemoprophylaxis and that would confer a much higher level of efficacy against *infection* should continue.

CLINICAL TRIALS TO TEST EFFICACY OF A FIRST-GENERATION MALARIA VACCINE

The MIDRP Malaria Vaccine Program has the goal of licensing a "U.S. military/travelers" vaccine that might not have relevance for preventing disease in indigenous pediatric populations in malarious areas. A series of carefully designed clinical trials executed in a step-by-step fashion move a vaccine candidate incrementally towards licensure. Phase 1 trials preliminarily examine the vaccine candidate's safety and immunogenicity in small numbers of healthy adults. These early phase 1 trials detect adverse reactions that occur at high frequency and provide an initial glimpse of whether the candidate elicits relevant immune responses.

Subsequent phase 2 trials that assess the vaccine in increasingly larger numbers of subjects are typically placebo controlled to better measure the rate of adverse events versus background complaints. For vaccines that will ultimately target infants or young children, phase 1 and 2 trials must be undertaken in progressively younger subjects until the target age is reached. If a vaccine candidate combines several distinct antigens, each of which may independently contribute to protection, phase 2 studies must document that immune responses are elicited to all the component antigens.

For some vaccines such as candidate malaria vaccines, it is possible to obtain preliminary assessments of the efficacy of the vaccine by performing experimental challenge studies at late phase 1 as well as early phase 2. In performing experimental malaria challenges, vaccinated and control subjects are each exposed to the bites of five insectary-reared mosquitoes infected with *P. falciparum*. These challenge trials are critical to selection of effective preerythrocytic vaccine candidates.

Large-scale randomized controlled phase 3 efficacy trials remain the "gold standard" for demonstrating the efficacy of a vaccine to prevent the disease under natural conditions of exposure. In general, prelicensure phase 3 trials are expensive, logistically demanding, require multiple years to complete, and are subject to the vagaries of year-to-year variation in disease incidence. Phase 3 trials represent the ability of a vaccine to protect under "idealized conditions" where there is a pristine cold chain, analyzed subjects have received full dosage of vaccine, and case detection is intensive.

Once the clinical acceptability, safety, and immunogenicity of the leading vaccine candidate (see following sections on various candidates) have been successfully demonstrated in phase 2 trials and its efficacy documented in several experimental challenge studies in U.S. subjects exposed to insectary-reared *Anopheles*, it is appropriate to transition the vaccine to phase 3 efficacy field studies. These phase 3 field efficacy studies, if they can be accomplished, are key to licensure.

Given the crucial importance of providing a clear path to licensure for a potential vaccine, the committee concluded that it was appropriate to discuss their view of the feasibility of undertaking such daunting key studies within the DoD system. In contrast, the various other clinical trials, including phase 1 and 2 safety and immunogenicity trials, Phase 2 experimental challenge model studies, and assessment of the large-scale safety and immunogenicity testing of three production lots of the vaccine are generic and well within the capability of the MIDRP Malaria Vaccine Program testing infrastructure.

The MIDRP Malaria Vaccine Program investigators have long held the view that it may be possible to perform phase 3 trials in which cohorts of malaria-naïve adult subjects from the U.S. military or other immuno-

logically naïve adult populations might be immunized with the experimental malaria vaccine or a control vaccine prior to being sent to endemic areas of very high seasonal *P. falciparum* transmission (Brown et al., 1994; Sherwood et al., 1996). The initial type of study to be carried out in U.S. adults brought to such a malaria "hot spot" for several months would be a rigorous test of the vaccine's ability to confer 60 percent efficacy compared to a control vaccine. Some examples of a control vaccine that would confer an independent benefit upon the control subjects include a quadrivalent meningococcal conjugate or rabies vaccine; this benefit for the control subjects would be important from the bioethical perspective. During the high transmission period (usually 3–5 months in duration) the subjects would be kept under intensive clinical surveillance using active case detection to identify cases of *P. falciparum* malaria. For ethical reasons, physicians, nurses, corpsmen, and other health care providers would accompany the subjects to the field area to assure prompt and vigorous therapy.

For many years, DoD researchers have maintained a field site in Western Kenya where the dynamics of transmission during high season are such that 89 percent of semi-immune adults developed clinical *P. falciparum* malaria during the 5-month peak period of transmission (January through May) (Sherwood et al., 1996). In Western Kenya, approximately 100 percent of immunologically naïve older infants and toddlers develop confirmed clinical malaria during high season. It is expected that in the absence of compulsive rigorous chemoprophylaxis, approximately 100 percent of immunologically naïve U.S. adults would develop clinical malaria if they spent several months at this site during peak transmission season. The extremely high attack rates of malaria that occur in susceptibles in such an area suggest that phase 3 efficacy trials could be conducted with numbers of subjects that would be logistically feasible while maintaining close clinical supervision.

Because the point estimate of efficacy expected of the vaccine is relatively low (i.e., only 60 percent), it would be important to design the trial to include a rigorous lower limit of efficacy. A lower limit of 30 percent for the 95 percent confidence interval (CI) around the 60 percent point estimate of efficacy is recommended.

The committee considered two types of trials in nonimmune U.S. adults living temporarily in a malaria endemic area—without and with prophylaxis. Details of such proposed studies are given in Appendix C. The MIDRP Malaria Vaccine Program investigators working at AFRIMS in conjunction with Royal Thai Army rangers established the feasibility of carrying out an efficacy trial of a malaria vaccine in (semi-immune) volunteers who were not given chemoprophylaxis when sent to a field area of high malaria transmission (Brown et al., 1994). The precedent for this

type of study was also established with volunteers from the Colombian Army who participated in an efficacy evaluation of SPf66 vaccine (Amador et al., 1992).

Preliminary calculations were performed in order to assess the sample sizes necessary for such trials. The assumptions were that the malaria attack rate would be 70 percent (without chemoprophylaxis) and that the vaccine efficacy is 60 percent (with a lower limit of 30 percent for the 95 percent CI around the 60 percent point estimate of efficacy). The estimates in Appendix C show that the sample sizes required are reasonable: approximately 400 persons (200 per group) would be needed to give 90 percent power of detecting such an effect for initial trials without chemoprophylaxis. In trials with chemoprophylaxis, it was assumed that 10 percent would fail to take it; thus 4,000 persons would be needed for these trials in order to have 400 persons for the analysis.

Because of the investment made heretofore in maintaining field sites and conducting trials in Africa, such as in Western Kenya and in Ghana, a first-generation malaria vaccine that conferred 60 percent efficacy for 6 months would constitute a product that could be successfully evaluated for efficacy in prelicensure phase 3 trials both without and with chemoprophylaxis. These suggestions are not intended to minimize in any way the daunting challenge that would be faced by the MIDRP Malaria Vaccine Program in having to enroll the large number of U.S. subjects necessary to carry out the large phase 3 efficacy trial in Africa under recommended chemoprophylaxis. On the other hand, this major logistical challenge can be overcome by allocation of sufficient resources and by making such a trial a high priority.

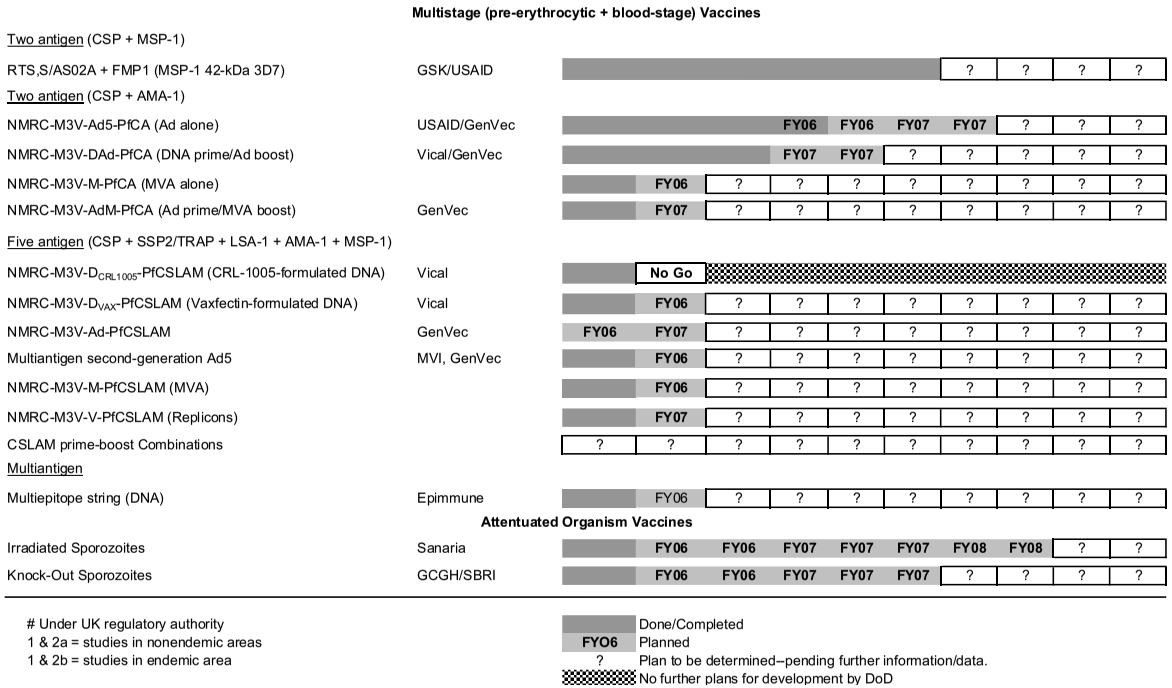
Recommendation 4.2: Small, carefully designed and executed clinical efficacy trials involving U.S. military personnel (or other groups of immunologically naïve, nonmilitary personnel) off chemoprophylaxis (initial proof of principle studies) or on chemoprophylaxis (later study) should be carried out to assess the efficacy of the leading MIDRP Malaria Vaccine Program candidate in field sites in endemic areas. In this regard, field sites currently maintained by the DoD in Africa are a critical resource.

CURRENT AND PLANNED SCIENTIFIC PROGRAM

Table 4-2 shows the very large program of different constructs currently being tested by the MIDRP Malaria Vaccine Program, as well as the partners involved and projected time lines. The particular categories of antigens or constructs will be briefly discussed.

TABLE 4-2 Portfolio of Candidate Malaria Vaccines Under Development by the MIDRP Malaria Vaccine Program

Candidate Vaccines	Partners	Research	Pre-clinical develop-ment	GMP Prod	IND Filing	In Adults 1a	In Adults 2a	In Adults 1b	In Adults 2b	In Children 1b	In Children 2b
Sporozoite-Based Vaccines											
RTS,S/AS02A	GSK										
RTS,S/AS01B	GSK									FY07	FY08
Adenovirus35 CS	Crucell/NIAID					FY06					
Ad35CS+RTS,S/AS01B Prime/Boost	Crucell/GSK/NIAID				FY06	FY07	FY07	?	?	?	?
PfCSP DNA / MVA CSP (MVA.CSO) Prime/Boost	NIAID/Oxford U.			#	FY06	#	#	FY06	?	?	?
RTS,S/AS02A + MVA CS	GSK/Oxford/WRAIR			#	#	#	No Go				
RTS,S/AS02A + DNA CS	GSK					No Go					
RTS,S/AS02A + TRAP	GSK						No Go				
Liver-Stage Vaccines											
LSA-1/3D7 (FMP011)/AS02A	GSK/MVI				FY06	FY06	FY06	?	?	?	?
LSA-1/3D7 (PMF011)/AS01B	GSK/MVI				FY06	FY06	FY06	?	?	?	?
Next-generation Antigens		FY06	FY07	?	?	?	?	?	?	?	?
Blood-Stage (asexual) Vaccines											
MSP-1 = Merozoite Surface Protein											
MSP-1 42-kDa 3D7 (FMP1)/AS02A	GSK/USAID/MVI										
MSP-1 42-kDa FVO (FMP010)/AS01B	GSK/USAID				FY06	FY06	?	FY06	?	?	?
MSP-1 42-kDa FVO (FMP010)/AS02A	GSK/USAID				FY06	?	?	FY06	?	?	?
AMA-1 = Apical Membrane Antigen											
AMA-1 3D7 (FMP2.1)/AS02A	GSK/USAID/MVI						FY06			FY06	FY07
AMA-1 3D7 (FMP2.1)/AS01B	GSK/USAID/MVI				FY06	FY06	FY06	?	?	?	?
AMA-1 FVO (FMP009)/AS02A	GSK/USAID				FY06	FY07	?	FY07	?	?	?
AMA-1 FVO (FMP009)/AS01B	GSK/USAID				FY06	?	?	FY07	?	?	?



SOURCE: Heppner, 2006; Richie, 2006; Vaughn, 2006

RTS,S

The WRAIR group has a strongly focused research and development strategy with an emphasis on the RTS,S recombinant protein preerythrocytic vaccine with GlaxoSmithKline (GSK) adjuvants. This continues a line of research that began 20 years ago after the sequencing of the circumsporozoite protein (CSP) and the preparation of the first recombinant proteins at WRAIR. Current efforts to improve immunogenicity and protective efficacy of RTS,S focus on new adjuvant formulations, comparing oil in water MPL/QS21 (AS02A) with a MPL/QS21 liposome formulation (AS01B), heterologous prime-boosts using naked DNA or viral vectors expressing CSP to boost RTS,S responses, and multistage antigen combinations (Ballou, 2005; Heppner et al., 2005). Direct comparisons of AS01B and AS02A are required and in progress with certain contructs, but constraints imposed by commercial partners limit some comparisons of the RTS,S/AS02A or AS01B constructs with and without particular viral vectors.

Recombinant Proteins

Other current WRAIR efforts focus on expressing recombinant blood- and liver-stage proteins, including MSP-1, AMA-1, and LSA-1 in *E. coli* with the correct conformation to elicit inhibitory antibodies. This is a particular challenge as both inhibitory and blocking antibody have been shown to develop following immunization and infection (Nwuba et al., 2002). To address these concerns both WRAIR and NMRC are developing growth inhibition assays to measure functional antibodies. Clinical trials are planned or in progress for all three antigens, and the intention is to assess the immunogenicity and efficacy of each separately before deciding whether to include them in a multicomponent vaccine.

For MSP-1, early studies of MSP-1_{19} conjugated to tetanus toxoid showed poor immunogenicity in immunized volunteers (Keitel et al., 1999), and therefore efforts have focused on MSP-1_{42}, which contains additional T-cell epitopes. Combinations of two alleles (FVO/3D7) are planned for both MSP-1 and AMA-1 in order to overcome potential problems with polymorphism and strain specificity of vaccine-induced immunity. Both blood-stage antigens will be tested with AS02A adjuvant and AS01B formulations in fiscal year 2006–2007. These approaches are similar to those that are planned by the National Institutes of Health (NIH) with their *Pichia pastoris*-expressed MSP-1_{42} 3D7/FVO and AMA-1 C1 (FVO/3D7) in phase 1 trials (Malkin et al., 2005). However, the MIDRP Malaria Vaccine Program is more advanced in the phase 2 trial process for the 3D7 forms of MSP-1.

Gene-Based Vaccines and Prime-Boost Approaches

The NMRC group is focused on gene-based vaccines with a wide-ranging and diverse program. They are pursuing several specific strategies of DNA-based constructs. These revolve around the group of sequences known as *CSLAM* (CSP, SSP-2/TRAP, LSA-1, AMA-1, MSP-1) that were down-selected from a much larger group of DNA sequences previously included in the earlier MuStDO5 vaccine, which failed to show immunogenicity in human trials in the U.S. Antigen interference is suspected as part of the reason for that failure, and therefore noninterfering antigens were selected based on data from animal models.

The following are the specific subunit approaches:

- Plasmid DNA (five plasmids each encoding one of the CSLAM antigens) in collaboration with Vical, using novel adjuvants such as Vaxfectin, either alone or as prime for subsequent boost for viral constructs (below)
- Adenovirus 5 vectors in collaboration with GenVec, with two to five antigen sequences (CSLAM or some of its constituent antigens) used in DNA priming and vector boosting
- Poxvirus vectors used in a similar way to adenovirus 5 vectors and containing the same antigens
- Virus replicon particles in collaboration with Alphavax
- Viral priming followed by recombinant protein boosting, in collaboration with the NIH Malaria Vaccine Development Unit and WRAIR
- Multiepitope vaccines (T- and B-cell epitopes in viral vectors that bind to multiple HLA types, removed from surrounding unnecessary sequences) in collaboration with EpiImmune

The NMRC has immediate plans for a phase 1 clinical trial of the adenovirus 5/CSP + AMA-1 construct in U.S. volunteers in the near future, followed by trials of different prime-boost combinations of DNA and adenovirus 5 constructs for CSP/AMA-1.

The WRAIR scientists have also been investigating heterologous prime-boost regimens, in which different immunogens are used for prime versus boost, to further optimize immune responses. WRAIR is collaborating with Crucell and GSK in exploring use of Ad35 virus expressing CSP to boost RTS,S primed responses (although these studies are contingent on resolving intellectual property issues of both companies). Vaccinia-based prime-boost strategies are also being considered but are not proving to be successful.

The above description summarizes the aspects of research, particularly those funded directly by MIDRP Malaria Vaccine Program, that were

described to the committee. The program has been very effective in generating additional funds for research that may have different emphases.

Antigen Discovery Using Genomics and Proteomics

In addition to focusing on empirically defined antigens, both WRAIR and NMRC have initiated antigen discovery programs using genomics and/or proteomics. NMRC has extensively explored algorithms and new methods to identify and express potential candidates for preclinical studies. At least one new preerythrocytic antigen (AgX) recognized by cells from sporozoite-challenged volunteers has been identified by these methods. Exploration of the parasite transcriptome has led to the identification of critical genes required for hepatic-stage development, and deletion of these genes has provided genetically attenuated parasites for vaccine development.

Attenuated Sporozoites

The use of genetically or radiation-attenuated sporozoites as a military vaccine is being pursued (Mueller et al., 2005). WRAIR scientists are collaborating on a genetically attenuated sporozoite approach under a Gates Foundation Grand Challenges in Global Health grant with the Seattle Biomedical Research Institute. The radiation-attenuated sporozoite strategy is being pursued by a private company, Sanaria, founded by a former NMRC director, with National Institute of Allergy and Infectious Diseases (NIAID) support and strong links to the NMRC (Hoffman et al., 2002). Attenuated sporozoite vaccines would provide a multistage vaccine without the need to identify relevant antigens, and although the logistical and regulatory challenges of this approach are significant, the high vaccine efficacy of attenuated sporozoite vaccines merits efforts to test these vaccines in phase 1 and 2 trials.

Planned Clinical Trials

To summarize the status of current vaccine candidates, ongoing and pending clinical trials are listed in Table 4-3.

OVERALL ASSESSMENT OF SCIENTIFIC PROGRAM

The committee noted the impressive scientific program and achievements and the unparalleled opportunities provided by the availability of the human sporozoite challenge model. The work has resulted in hundreds of publications in the peer-reviewed scientific literature. From 2001

TABLE 4-3 Current and Pending MIDRP Malaria Vaccine Program Clinical Trials

Lead Agency	Construct	Objective	Site	IRB Approved
WRAIR	MSP-1/AS02A	Safety, immunogenicity in immune 1–5-year-olds[a]	Kenya	Yes
WRAIR	MSP-1/AS02A	Efficacy in immune 1–5 year-olds[a]	Kenya	Yes
WRAIR	AMA-1/AS02A	Safety, immunogenicity in immune adults[b]	Mali	Yes
WRAIR	RTS,S	Efficacy AS02A vs. AS01B in naïve adults	United States	Yes
WRAIR	RTS,S	Safety, immunogenicity AS02A vs. AS01B in immune adults	Kenya	Yes
WRAIR	LSA-1/AS02A	Safety, immunogenicity, efficacy in naïve adults	United States	Pending
WRAIR	LSA-1/AS01B	Safety, immunogenicity, efficacy in naïve adults	United States	Pending
NMRC	Ad Pf CA	Safety, immunogenicity, efficacy in naïve adults	United States	Pending

[a]These trials funded by the Malaria Vaccine Initiative for a pediatric vaccine goal.
[b]Funded by NIAID.

to 2005 alone, WRAIR scientists contributed to 149 papers and NMRC scientists to 147 papers on malaria vaccine-related studies, the largest number for any MIDRP program area. Since 1990, the NMRC malaria vaccine program has had six patent applications approved and WRAIR has had eight (see Appendix D). One additional WRAIR patent is expected to be assigned a patent number in the next few months, giving a total of nine from WRAIR. The MIDRP Malaria Vaccine Program has also been successful in leveraging additional funds and has had very successful collaborations.

The research funded by the MIDRP Malaria Vaccine Program has been enormously beneficial to the overall global vaccine effort. Highlights include the success in clinical trials with RTS,S, the expansion of activities beyond preerythrocytic vaccines to include erythrocytic antigens in multi-stage vaccines (both protein and gene based), the advanced production of these antigens to good manufacturing practices (GMP) standards, and the advances in gene-based prime-boost technologies with combination vaccines in animal models. Progress on the genetically and irradiated-attenuated sporozoite vaccine strategy is also very encouraging.

However there is concern over the large number of vaccine candidate constructs currently under evaluation, with numerous external partners involved. Lack of financial independence sometimes puts the partners in control. The pathway from preclinical research to clinical trials for the numerous gene-based products is sometimes not clear. In some cases the partners appear to be excessively influencing the research agenda while simultaneously imposing restrictions on what can be accomplished. For example, the use of two different adenovirus vectors needs to be reconciled, as do the two adjuvants being used by GSK. Head-to-head efficacy comparisons of constructs and vectors from different commercial partners are unlikely to occur and may not be necessary in any case. Other decision methods such as standardized comparative immunogenicity tests could be used to narrow the scope.

Increased focus on a smaller number of potential constructs is required, but the program lacks a prospective process or objective criteria for down-selection of candidates. Performance should be evaluated by established humoral and cellular immune response assays in a reference laboratory if possible, and additionally for blood-stage candidate vaccines by a functional immune response assay such as the merozoite growth inhibition assay. Development of these mutually agreed upon criteria should be the responsibility of Joint Task Force for Malaria Vaccine (JTF-MV) discussed below. Down-selection criteria should utilize all available information from the rapidly progressing HIV vaccine field to assess vaccine delivery platform leads.

The committee noted that increased focus on fewer candidate antigens and constructs does not imply decreased funding as development of even one of the current constructs will require a greatly increased budget. Maintaining a larger number of constructs is likely to lead to failure to complete development or to delay substantially the development of candidates.

From the information presented, the committee felt that there is no vaccine candidate yet available that is likely to meet the military requirements (even the suggested revised requirements) in the next 5 to 10 years. The likelihood of eventual success appears to be high, but a more realistic target date for availability of a licensed *P. falciparum* vaccine (even with more resources) is 2015–2020.

Recommendation 4.3: Research on all three main malaria vaccine development strategies—gene-based (e.g., DNA, plasmid, or viral vector vaccines) protein-based, and attenuated sporozoite approaches—should be continued. However, as research progresses, the number of candidate products must be limited by dropping those that perform less well. The MIDRP Malaria Vaccine Program

should aggressively move into clinical trials to test specific vaccine products, and select two to three leads at phase 1 and one lead at phase 2 for each strategy. For protein-based and gene-based strategies, the focus should be on specific vaccine products that combine the lead antigens (CSP, SSP-2/TRAP, LSA-1, AMA-1, and MSP-1) including their use in heterologous prime-boost combinations.

Recommendation 4.4: Finding correlates for protection *in humans* relevant to each of the above vaccine strategies should be a research priority.

Recommendation 4.5: The MIDRP Malaria Vaccine Program should continue research on human immune processes and responses to malaria. The current incomplete understanding of the mechanisms of protective immunity to malaria in humans constitutes a barrier that impedes malaria vaccine development.

After thorough review of the MIDRP Malaria Vaccine Program in order to understand the current situation and the program's quality, the committee concluded that it is crucial to narrow the focus to a smaller number of candidate antigens. Given the limited time available for this review, the committee did not wish to give more detailed specific advice other than that given above and in Recommendation 4.3. Despite having extensive expertise in all scientific aspects of the program, the committee concluded that instead of offering one-time advice on specific antigens or approaches, it would be more productive to recommend a structure and process for ongoing review and decision making about the scientific direction of the work.

5

Organization and Management of the Program

PROGRAM MANAGEMENT

Malaria vaccine research in the Department of Defense (DoD) takes place at the Walter Reed Army Institute of Research (WRAIR), the Naval Medical Research Center (NMRC), and the overseas laboratories. The laboratories in Kenya and Thailand are subordinate units of WRAIR, and laboratories in Indonesia, Peru, and Egypt are subordinate units of NMRC. The DoD-funded research is coordinated within the U.S. Army Medical Research and Materiel Command (USAMRMC) by the Military Infectious Disease Research Program (MIDRP). The relationships between the program elements (USAMRMC, MIDRP, NMRC, WRAIR) are shown in Figure 5-1.

Within MIDRP there are four research areas and 11 program areas, one of which is program area F—malaria vaccine research. This is further subdivided into four task areas:

- Task F: Malaria vaccine research
- Task 6A: Protein-based vaccines
- Task 6B: DNA-based vaccines
- Task A1: *P. vivax* vaccines.

The first three task areas are the subject of this program review. In general, projects fall under Task F if they are core activities or relate to either antigen discovery, basic understanding of the malaria parasite (e.g., genetic diversity), or the immune response to it in humans and animals.

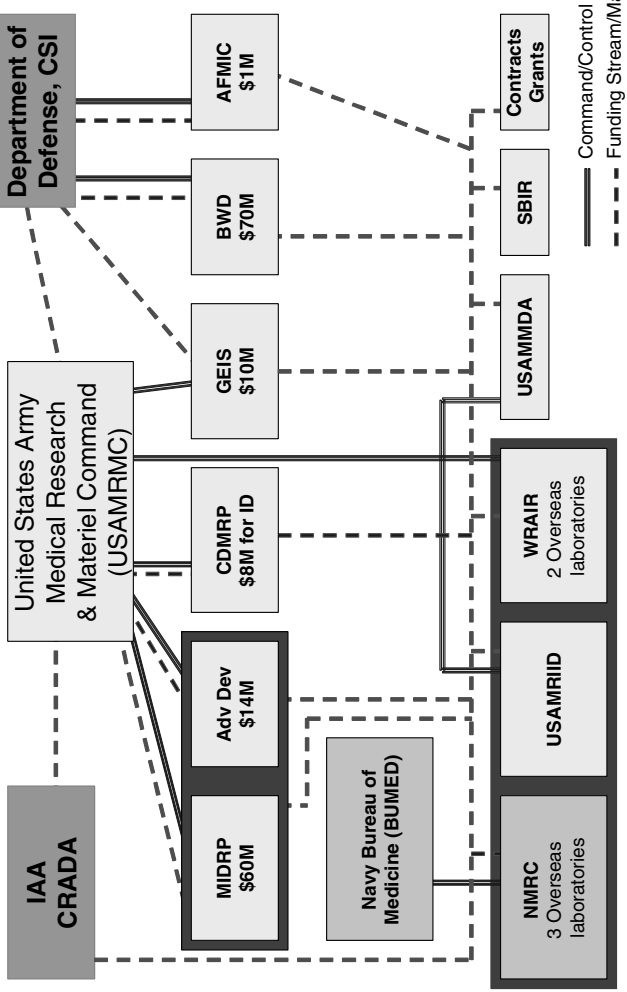


FIGURE 5-1 Military infectious diseases research program working relationships.
NOTE: IAA: interagency agreement; CRADA: cooperative research and development agreement; CSI: congressional special interest; MIDRP: Military Infectious Disease Research Program; Adv Dev: advanced development; CDMRP: congressionally directed medical research programs; GEIS: Global Emerging Infections Surveillance; BWD: Biological Warfare Defense; AFMIC: Armed Forces Medical Intelligence Center; USAMRIID: U.S. Army Medical Research Institute for Infectious Diseases; USAMMDA: U.S. Army Medical Materiel Development Activity; SBIR: Small Business Innovation Research.
SOURCE: Vaughn, 2006.

However, some basic and innovative research including new antigen discovery appears under tasks 6A and 6B as well. Task areas 6A and 6B are relatively new divisions within program area F, and the distinctions are still fluid. Task 6A essentially covers work carried out under the auspices of WRAIR, and 6B covers NMRC-specific projects; Task F is intended to cover joint activities. Within each task area there are three to five subsidiary objectives.

Several specific aspects of program management are discussed in the following sections, noting particularly the programmatic barriers that are impeding progress. Significant reorganization is then suggested in order to overcome these barriers.

Project Management Structure

DoD intramural funds are distributed through MIDRP by a proposal application and funding process with an annual cycle (although some core activities such as sporozoite production and GMP production are automatically renewed and are not subject to review each year). Currently, the objectives and their justifications under each task area are developed by a joint steering committee between WRAIR and NMRC that meets four times per year, mainly to manage the project proposal and approval process. The objectives for each task are described in written research plans distributed on the MIDRP website in order to solicit proposals.

Investigator-initiated proposals are written and submitted by objective, first as preproposals and then, if merited, as full proposals. In MIDRP as a whole, for fiscal year (FY) 2007 a large number (225) of new preproposals and 135 new full proposals were submitted, of which 72 new projects will be funded. The total is 116 funded projects since there are also 13 core projects and 31 multiyear projects. A subset of the total proposals submitted for FY2007 are for malaria vaccines: 42 preproposals and 28 full proposals, of which 14 will be funded, together with 3 core and 5 multiyear projects (total 22 for malaria vaccines). Each year the amounts of funds approved for WRAIR and NMRC projects are approximately equal.

External and onsite review by the American Institute of Biological Sciences (AIBS) occurs in order to review the steering committee prioritization of the proposals; however, MIDRP and the steering committee are not obligated to follow the AIBS recommendations. After prioritization, projects above the funding cutoff are approved. Senior Army and Navy investigators intimated that the quality of the AIBS reviews was erratic, and reviewers' comments were not always helpful. In contrast, they lauded the broader type of review offered by a U.S.

Agency for International Development (USAID) committee that reviewed work supported by that agency through the DoD. That committee, which includes individuals with considerable product development experience, was considered to provide more helpful practical guidance.

The project management structure imposes several programmatic barriers. Although improved over earlier iterations, the structure seems cumbersome and inflexible and sometimes obstructive to the flow of work. A large number of competing proposals does not allow the program to be managed with a comprehensive investment and down-selection strategy. The application process and and outside review leads to a heavy administrative burden, and the whole process of application, review, and approval takes over a year from start to finish. There is a lack of focus in an extremely diverse and ambitious scope of work, with unrealistic expectations and a constant pressure to move forward even if not directly towards the goals. An inadequate advisory structure is a barrier to effective strategic planning.

IRB Approval Process for Clinical Trials

Separate institutional review boards (IRB) at WRAIR and NMRC must approve clinical trials followed by a second IRB at the level of the Surgeon General (the Human Subjects Research Review Board (HSRRB) review, see Figure 5-2). These two levels are in addition to local IRB approval at the site of external trials (e.g., Mali, Kenya) and any necessary review by external funding agencies or partners (NIH, GSK, etc.).

The requirement for dual ethical and sometimes also scientific review at WRAIR/NMRC as well as HSRRB (in addition to partner and local IRBs) often adds complexity, cost, and time to a necessarily lengthy process. Facilitation of IRB review in a streamlined way with a short time line is needed.

Business and Intellectual Property Issues

The thrust to develop a vaccine that combines multiple antigens and constructs has led to many intellectual property challenges. Commercial interests are often reluctant for their proprietary constructs to be combined or compared with those of competitors. The committee was not shown current agreements between MIDRP Malaria Vaccine Program and commercial partners, and hence is unaware of the restrictions imposed. The procedures for initiating new partnerships seem convoluted, lengthy, and obscure, with separate systems in WRAIR and NMRC. They no doubt discourage new external partnerships from developing.

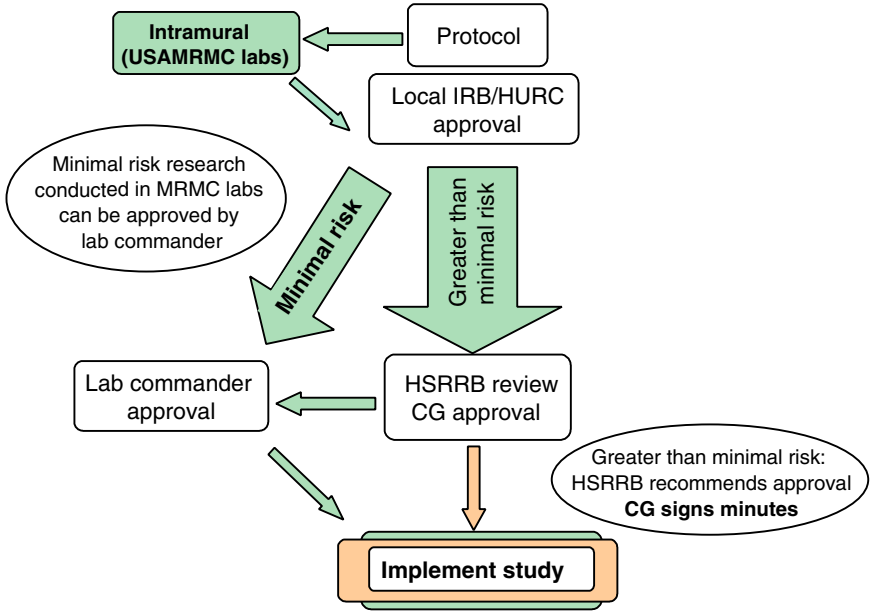


FIGURE 5-2 Process of USAMRMC approval to conduct human subjects research.
NOTE: Excludes additional local and partner IRBs.
SOURCE: Heppner, 2006; Richie, 2006; Vaughn, 2006.

Communication and Resource Sharing

The committee formed the impression that although individual investigators in the two groups (WRAIR and NMRC) communicate informally, there could be much greater interchange and sharing of knowledge, especially at higher management levels. This is despite the fact that there is convergence in the approaches and antigens on which the two groups are now focusing for first-generation vaccines. Both also have discovery efforts in place for second-generation vaccines as well as collaboration with (separate) partners for whole-parasite approaches.

Duplication of core facilities such as flow cytometry, genomics, and immunological assays is inefficient and creates a barrier to standardization of techniques and assays. Although some activities are shared, such as the GMP pilot production facility, opportunities for increased sharing of facilities were noted that should aid standardization and increase pace of progress.

PROGRAM REORGANIZATION

Military malaria vaccine research and development is currently conducted by the U.S. Army (WRAIR) and U.S. Navy (NMRC) in two essentially independent programs nominally coordinated by the MIDRP (USAMRMC) at Ft. Detrick, Maryland. The committee recognized the commitment and energy of the malaria vaccine research groups at WRAIR and NMRC, the strong leadership they have received, and their good intentions to cooperate with each other. Notably, the MIDRP Malaria Vaccine Program has been scientifically productive in spite of a diffuse and cumbersome management structure and inadequate funding that impairs the program's ability to accomplish the malaria vaccine mission. Moreover it has a limited staff, "one-deep" in some critical areas and subject to assignment for clinical duties.

Although the competition between the separate programs at WRAIR and NMRC creates a healthy tension, the programs appear overextended at present. Supporting two independent vaccine development programs is not sustainable, nor is such an approach consistent with business and industry best practices. In industry, although there may be several candidate products in the pipeline, it is unusual to carry two separate products forward simultaneously beyond the early stages of product development, such as following preclinical studies or phase 1 clinical trials.

The committee recognizes the inherent complexity in the DoD's centralized oversight for research and development and acquisition of military vaccines, which was extensively spelled out in a previous Institute of Medicine (IOM) report (IOM, 2002), but the committee considers the number of organizational units unnecessarily complex and seemingly incongruous. This situation is made even more difficult by the USAMRMC's divisions of vaccine research and development (MIDRP), advanced development (U.S. Army Medical Materiel Development Activity [USAMMDA]), and contracting (U.S. Army Medical Research Acquisition Activity [USAMRAA]).

Now that the WRAIR and NMRC are colocated in the same building, there is little justification for the perpetuation of separate malaria vaccine efforts. In making recommendations for reorganization, the committee urges USAMRMC to focus on the goal (a malaria vaccine) and develop structures that will help achieve that goal, rather than a new structure for its own sake. Of course, to do nothing should not be an option.

The committee notes that the concept of reorganization for the malaria vaccine program and MIDRP could be viewed within the theme of U.S. military transformation. Transformation refers to the broad changes the U.S. military must make in its structure, culture, and doctrine to meet the emerging threats challenging our nation in this century. Placed in this con-

text, reorganization of the malaria vaccine program is an opportunity for the MIDRP/USAMRMC to think differently about enabling the program's capability to address the current and future challenge of the malaria threat. Experimentation has been a tradition of the U.S. military's approach to an ever-changing strategic environment. At the level of the MIDRP there is an opportunity to experiment with the malaria vaccine program as a pilot project that integrates the WRAIR and NMRC programs in a joint operation. Success in reorganizing the approach to malaria vaccine development could serve as an example for other infectious disease program areas.

Recommendation 5.1: The MIDRP Malaria Vaccine Program, currently composed of two separate entities—WRAIR and NMRC, should be integrated into a unified organizational entity (JTF-MV) that spans the spectrum and life cycle of responsibilities: epidemiological/threat assessment, research and development, advanced product development, clinical trials, licensure, manufacture, technology transfer, procurement, maintenance of manufacturing practice standards, and regulatory compliance.

Recommendation 5.2: The JTF-MV should appoint one scientific director, reporting to the commanding general of the USAMRMC, to provide joint direction and accountability for the program. The scientific director must have operational authority and budgetary as well as scientific control.

This recommendation does not in any way imply criticism of the current outstanding leadership at WRAIR and NMRC. The search committee for this position should be constituted by MIDRP with assistance from a malaria program transition team (see below in Recommendation 5.6). Recruitment for this high-level scientific and managerial position should consider outstanding individuals from both inside and outside the military. The scientific director must be physically located in the WRAIR/NMRC building (as opposed to the U.S. Army Medical Research Institute for Infectious Diseases at Fort Detrick) in order to provide hands-on management.

Recommendation 5.3: The JTF-MV should organizationally incorporate an industry/business model and be constituted as a single legal entity (able to share proprietary data) that would simplify the external contracting process, including cooperative research and development agreements, interagency agreements, and other con-

tracts. The JTF-MV must include team members with specialized expertise in business and regulatory affairs. Although these individuals would be located in the existing business and regulatory affairs units, adequate staffing for these tasks must be assigned to the JTF-MV in order to avoid or minimize future intellectual property conflicts and other issues.

Recommendation 5.4: The JTF-MV program for vaccine development should have an external senior expert advisory group (scientific advisory board) that conducts yearly face-to-face meetings to provide external review and evaluation of the scientific program, and also gives ongoing advice in a timely manner. The scientific advisory board can assist the program to set clear and appropriate objectives (defined up front), with benchmarks of progress. Draft terms of reference for the scientific advisory board are found in Appendix E.

Recommendation 5.5: The annual proposal cycle should be replaced with a more programmatic and directed approach to project management under the newly reorganized JTF-MV. The MIDRP sets the annual budget and long-range objectives (with input from the scientific advisory board), and implementation is by the JTF-MV with a longer (approximately 3 year) time horizon for projects.

PREVIOUS REPORTS ADDRESSING DOD VACCINE DEVELOPMENT AND ACQUISITION

Three recent expert panels have considered the issue of vaccine development and production in the U.S. military. First, an independent committee of experts chaired by Franklin Top, MD, was convened to make recommendations on improving the DoD acquisition process for Biological Defense Program vaccines that could also include vaccines for the (endemic) Infectious Disease Program. Their report (the Top report) was previously mentioned in Chapter 1 in relation to cost estimates (Top et al., 2000). Subsequently, in 2002 an IOM committee tasked with assessing vaccine policies for naturally occurring infectious diseases produced a report *Protecting Our Forces* edited by Lemon et al. (IOM, 2002). Although the subsets of diseases emphasized by these two committees were different, both committees pointed out that the vaccines produced for both naturally occurring diseases and biowarfare agents would be used in the same way. The IOM report also noted that vaccines of both types (e.g., adeno-

virus types 4 and 7 and certain biowarfare agents) may have insufficient demand to be marketed to the general public. Therefore, the report recommended that vaccines for both types of diseases be considered jointly in the acquisition process. Although the *Protecting Our Forces* report was focused on the U.S. Army, their conclusions are highly pertinent to the overall MIDRP Malaria Vaccine Program (IOM, 2002).

The summary recommendations of these two committees are reproduced in Appendixes F and G. It is important to note that both committees recommended rather sweeping reorganization of vaccine research and development and acquisition processes within MIDRP and the DoD, none of which has yet been implemented. For example, the first recommendation of the *Protecting Our Forces* report was as follows (IOM, 2002):

> Combine all DoD acquisition responsibilities under a single DoD authority that includes the entire spectrum of responsibility—from potential threat definition through research and development, advanced product development, clinical trials, licensure, manufacture, procurement, and continued maintenance of manufacturing standards and regulatory compliance.

Similarly, the Top report recommended "changes in DoD policy and organization, legislation, and statutory commitments" as well as to "combine programs from discovery to production" (Top et al., 2000). It was recommended that the DoD acquisition program for all vaccines (biowarfare agents and naturally occurring diseases) be managed as an acquisition category 1 program under a government-owned, contractor-operated vaccine production facility. The Top report generated cost estimates (see Chapter 1) and facility design plans for completing vaccine production for major threats in-house, suggesting that a facility with a 25-year life cycle and producing eight vaccines would require $3.2 billion and a staff of approximately 2,500 people.

A third report, *Giving Full Measure to Countermeasures*, dealing with biodefense vaccines also supported the Top report (IOM, 2004). The 2004 IOM report recommended giving vaccines and drugs very high visibility as a separate program in the DoD hierarchy at the assistant secretary level in order to compete for funds more effectively.

The Top report said that there should be "accountable, lean DoD management structure." A similar recommendation was made by the IOM *Protecting Our Forces* report (IOM, 2002):

> Ensure that there is an effective, ongoing senior advisory group—one providing perspectives from both within and outside of DoD—to assess program priorities and accomplishments, to act as a proponent for vaccines and other infectious disease countermeasures, and to maintain active relationships with current science and technology leaders in academic, government, and corporate sectors.

Although these recommendations referred to overall vaccine development, they are very applicable to the MIDRP Malaria Vaccine Program. They reinforce the current committee's recommendations for major reorganization of the WRAIR/NMRC programs into a JTF-MV, for the formation of a scientific advisory board, and for the streamlining of the prioritization and research proposal approval process into a truly joint programmatic approach. Optimally, the JTF-MV would be a hybrid organization incorporating the best and most relevant features of both military and business organization.

Recommendation 5.6: A malaria program transition team (led by a program manager with a strong business/industry background and reporting to the commanding general of the USAMRMC) should be established to carry out the JTF-MV reorganization and constitution of the scientific advisory board and assist with recruitment of a highly qualified JTF-MV scientific director. This transition team will be disbanded once the reorganization is in place.

HUMAN RESOURCE COMMITMENTS

The numbers of full-time equivalent (FTE) staff dedicated to malaria vaccine research and development in the U.S. is currently 70 at WRAIR and 32 at NMRC. At WRAIR the great majority (60) of these FTEs are in the Department of Immunology. In addition there are 140 FTE staff (mostly support staff) at the United States Army Medical Research Unit in Kenya (USAMRU-K), 8.5 at the Armed Forces Research Institute of Medical Sciences in Thailand (AFRIMS), 8.8 at the Naval Medical Research Unit (NAMRU)-2 in Indonesia, 1 at NAMRU-3 (Egypt), and 3.2 at NMRC-D (Peru).

Figures 5-3 (WRAIR) and 5-4 (NMRC) show the breakdown by staff level (senior scientists, other scientists, technicians, and support staff) in each relevant department or overseas unit. Of the senior scientific staff, 63 percent were based in the United States at NMRC or WRAIR.

Table 5-1 indicates the salary source breakdown for staff in each institution (shown separately for the U.S. labs and overseas labs). Overall in the United States, 17 percent of staff were active-duty military, 13 percent government civilian employees, and 70 percent contract or other.

The above charts and table show that the current programs are dependent on very small numbers of individuals (fewer at NMRC than WRAIR). The committee noted with concern the lack of depth in the program. Experienced staff members are stretched very thin, and programs are affected if personnel are sent to or volunteer for active duty in conflict

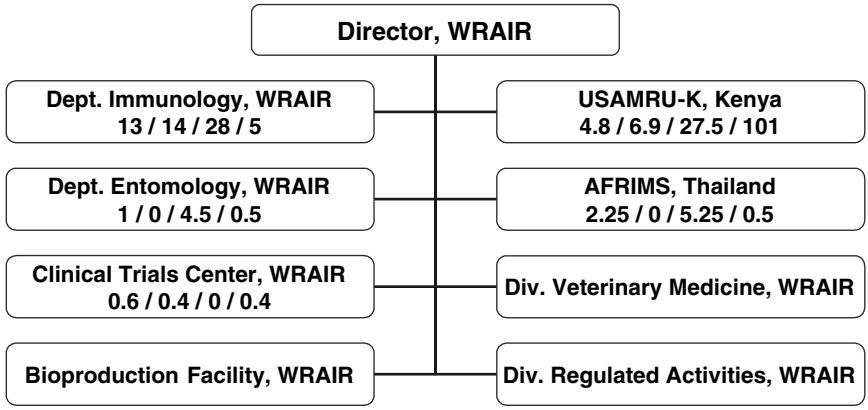


FIGURE 5-3 WRAIR organizational elements involved in the malaria vaccine research and development program and key personnel (expressed in full-time equivalent) dedicated to the malaria vaccine effort.
NOTE: Numbers in each box represent FTEs as follows: senior scientist / other scientist / technician / support staff. If no numbers are given, there are no staff dedicated to the malaria vaccine program.
SOURCE: Vaughn, 2006.

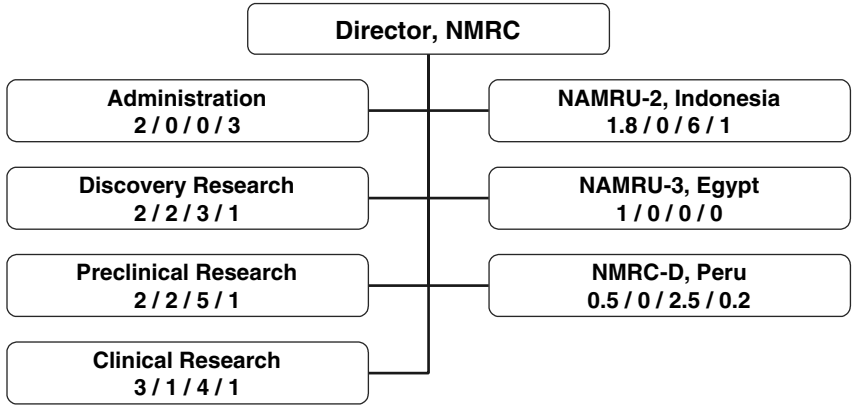


FIGURE 5-4 NMRC organizational elements involved in the malaria vaccine research and development program and key personnel (expressed in full-time equivalent) dedicated to the malaria vaccine effort.
NOTE: Numbers in each box represent FTEs as follows: senior scientist / other scientist / technician / support staff.
SOURCE: Vaughn, 2006.

TABLE 5-1 Numbers of FTE Staff in Different Categories in United States and Overseas Labs

	Government, military	Government, civilian	Contract	Other	Total
WRAIR labs	10	11	45	2	68
NMRC labs	7	2	23	0	32
Total United States labs	17	13	68	2	100
Army overseas	5	6	139	1	151
Navy overseas	2	5	6	0	13
Total overseas	7	11	144	1	164

situations. The long-term future of the malaria vaccine research and development program is compromised by the lack of perceived career enhancement opportunities. The ability to attract and retain military and civilian scientists requires appropriate promotion rewards and incentives.

Recommendation 5.7: A workforce plan must be developed and implemented by the JTF-MV. This plan should include training and budgeting for the next generation of scientists in the military program, ways to improve recruitment and retention of civilians and foreign nationals, and succession planning to ensure availability of required staff in 5–10 years time. The DoD should respond to the lack of sufficient depth of human resources to carry through current objectives with increased resources to carry out the workforce plan.

FINANCIAL COMMITMENT

The DoD's internal funding for malaria vaccine research and development is channeled mainly through MIDRP, which oversees all infectious disease research. The MIDRP's overall budget for all diseases was about $40 million in 2005, which is a significant decline from a peak of over $50 million in 1998 ($64 million in real [inflation-adjusted] terms). Although a slight rise to over $45 million is projected in the MIDRP's overall research and development budget over the period 2006 to 2011, this represents a stable or declining trend in real terms.

A limited amount of additional funds are released through additional channels (USAMMDA) when a promising vaccine product enters the advanced development process. However, this represents only 10 percent or less of the MIDRP total.

The MIDRP intramural budget for malaria vaccine research rose from $5.5 million in 1994 to a peak of over $10 million in 2001 (Figure 5-5). This was approximately one-quarter of the total MIDRP budget at that time. After a steep decline in malaria vaccine funding, down to $7 million in 2003, the amount increased slightly in 2004 and 2005 to about $8.5 million. In 2004, the overall amount spent by the DoD on malaria vaccines from both internal and external sources was $22.9 million (Malaria R&D Alliance, 2005). The MIDRP malaria vaccines budget is projected to remain stable at this level through 2011 (as is the overall MIDRP budget), effectively declining in real terms to below the 1994 level (Figure 5-5).

For comparison of malaria vaccine spending with other malaria research and development, MIDRP spent a larger amount (almost $12 million in 2004) on antimalarial drug discovery and development and a smaller amount on vector control research (almost $2 million in 2004). Considering all aspects, malaria research requires about half of the MIDRP's research budget.

It should be noted that these amounts do not include the salaries of military personnel; however this category of staff constitutes less than 20 percent of the total staff involved (see Table 5-1).

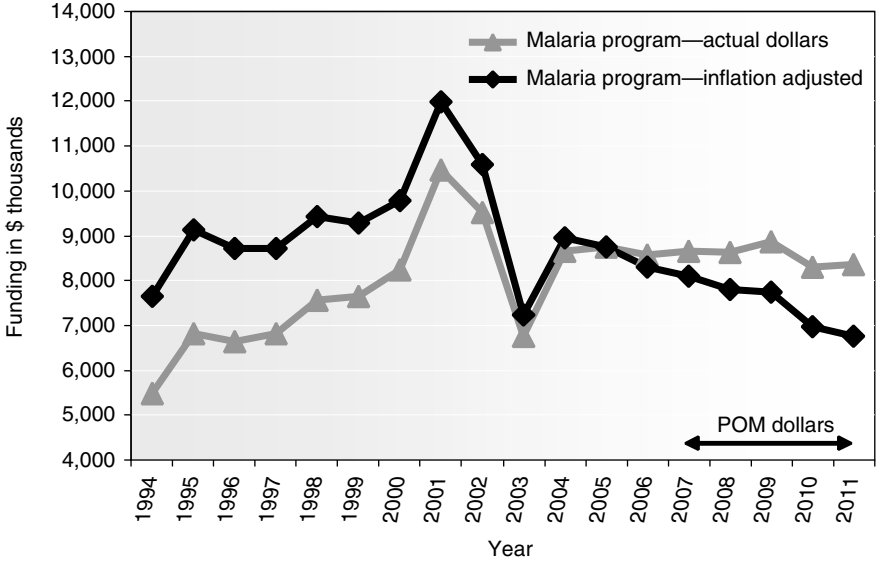


FIGURE 5-5 MIDRP funding for malaria vaccine research, 1994–2011 (projected).
NOTE: Baseline year is 2005, using Biomedical Research and Development Price Index.
SOURCE: Vaughn, 2006.

Because the DoD is a recipient of funds from other organizations, notably USAID, NIAID, and the Gates Foundation, WRAIR and NMRC independently manage funds that at least triple the intramural total.

Worldwide, it was estimated that $323 million was spent on malaria research and development (including drugs, vaccines, vector control, and diagnostics) in 2004 (Malaria R&D Alliance, 2005). About one-quarter of this total (approximately $80 million) was spent on malaria vaccine research and development. Thus with a contribution of over $9 million in 2004, DoD is a significant contributor to the world's malaria vaccine research and development effort in financial as well as scientific terms (see above).

Notwithstanding the DoD's major financial contribution, the amount spent by MIDRP on malaria vaccine research and development falls far short of the required amount to bring even one vaccine product to licensure, which was estimated above to cost upwards of $300 million at the very least, and probably much more (see Table 2-3).

It appeared to the committee that lack of funding was dictating suboptimal decision making—for example, the selection by NMRC of only two of the CSLAM antigens rather than the full set of five for the first clinical trials of the DNA-adenovirus prime-boost approach. The committee's opinion was that limiting the vaccine in this way was not fully capitalizing on previous research and was reducing the chances of success. There are other technical challenges, such as purification and production of large quantities of GMP proteins for clinical trials and licensure, that can also be overcome given sufficient resources and access to facilities.

The Forest Glen GMP pilot production facility is crucial to the program as it overcomes the barrier of producing sufficient material for phase 1 and phase 2 trials of certain antigens. It enables the program to produce in-house many potential antigens and constructs for screening. Currently the facility produces recombinant proteins but could produce certain other potential types of candidate vaccines. The facility time available to the malaria program is currently limited by the need to support the facility by contracting out to other groups.

At present, it is not envisaged that the Forest Glen GMP pilot production facility would produce the material for pivotal phase 3 licensure track trials of the vaccine. Careful planning and costing for the transition from in-house production to a larger-scale facility for phase 3 trials is needed. Ideally, the large-scale manufacture facility that would prepare the phase 3 material would be the site of manufacture of the vaccine postlicensure. External collaboration with industry will almost certainly be required, but such must be carefully managed to enable the DoD to achieve its primary goals.

The overseas laboratories are important sites for planning and carrying out field trials, studying naturally acquired immunity, and training. The funding of the overseas laboratories under the new management structure must be carefully considered during the transition.

It is clear that if the MIDRP Malaria Vaccine Program is to produce a malaria vaccine, a large increase in funding will be necessary. Military needs for a vaccine are unique and specific, and will not be met by others. Although the program has done an impressive amount of work with the relatively small budget available, and has been able to leverage significant outside funding, the overall amount available is not sufficient for advanced development of even one candidate antigen.

Recommendation 5.8: Sufficient funding should be made available to support the infrastructure to produce pilot-lot formulations of MIDRP malaria vaccine candidates in-house at the pilot production plant at Forest Glen (an invaluable part of the MIDRP Malaria Vaccine Program). Although pilot lots of all candidate vaccines cannot be made at Forest Glen, the ability to prepare certain candidates removes a major obstacle that would otherwise impede the program.

Recommendation 5.9: A formal economic analysis would be helpful to clarify current costs of malaria (both *P. falciparum* and *P. vivax*) prevention, treatment, and case management. This economic analysis would reveal the direct (monetary) and indirect (lost work time) costs that would be averted by both a first-generation vaccine (to be used in conjunction with chemoprophylaxis) and a second-generation vaccine (to replace chemoprophylaxis).

Recommendation 5.10: Given that malaria remains a major problem for U.S. military personnel deployed to endemic areas and this threat is not diminishing in importance with time, the MIDRP program to develop a malaria vaccine compatible with the needs for protecting U.S. military personnel should be fully supported. To increase the likelihood of achieving the current goals for a first-generation vaccine and to test the limited number of vaccine candidates described above will almost certainly require a several-fold increase in the current malaria vaccine development budget by 2010, with continuation at that level to at least 2015.

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Appendix A

Vaccine Trials

TABLE A-1 Phase 1 Trials of Malaria Vaccines That Did Not (or Have Not Yet) Progressed to Phase 2

Type of Vaccine	Vaccine Details	MIDRP Involvement	Results	References
Preerythrocytic Vaccines				
CSP recombinant	VaxSynCSA: full-length CSP, baculovirus expressed/alum	No	Minimally immunogenic (n = 20)	Herrington et al., 1992
	CVD 908-rCSP: CSP expressed in attenuated *Salmonella*	No	Immunogenic to 3/10 participants	Gonzalez et al., 1994
DNA based	CSP-DNA	NMRC	Good cellular but no antibody responses (n = 20)	Le et al., 2000; Wang et al., 1998
DNA prime/ protein boost	PfCSP DNA/RTS,S AS02A boost	NMRC	Antibody, CD4 and CD8 T cells	Epstein et al., 2004
Synthetic peptide	MAP1NYU: PfCSP-repeats/ alum/QS21	No	Good antibody responses	Nardin et al., 2000
	PfCSP-repeats + T-cell epitopes + Pam3Cys polyoxime	No	Good antibody and CD4+ T-cell responses	Nardin et al., 2001
Viruslike particle	ICC-1132: HBcAg + CSP repeats + T-cell epitopes	No	Antibody, CD4+ T cells	Nardin et al., 2004; Oliveira et al., 2005

Erythrocytic Stage Vaccines

Peptide	MSP-3/alum or ISA 720	No	Antibody, T cells, interferon	Audran et al., 2005
Recombinant protein	MSP-1/MSP-2 conjugated to diphtheria toxoid	No	Good antibody response; hypersensitivity to diphtheria toxoid	Ramasamy et al., 1995
	MSP-1/P30P2: two allelic forms of $MSP1_{19}$ plus tetanus toxoid T-cell epitopes	WRAIR	Good antibody response in 14/32	Keitel et al., 1999
	AMA-1C (3D7 and FVO forms), *Pichia pastoris* expressed	No	Good antibody response to both forms	Malkin et al., 2005
	AMA-1/ISA 720	No	Low antibody (vaccine instability)	Saul et al., 2005

TABLE A-2 Phase 2 Trials of Malaria Vaccines Using Experimental Challenge of Adult Volunteers from Nonendemic Areas

Type of Vaccine	Vaccine Details	MIDRP Involvement	Results	References
Preerythrocytic Vaccines				
Irradiated sporozoites	Whole parasites	University of Maryland/ NMRC/ WRAIR	95% protection after > 1000 bites	Clyde, 1975; Herrington et al., 1991; Hoffman et al., 2002; Rieckmann et al., 1979
Synthetic peptide	$NANP_3$-tetanus toxoid	No	1/3 protected	Herrington et al., 1987
	CSP 102 (282-383): CSP C-terminus/ alum or ISA 720	No	No protection	Genton et al., 2005; Lopez et al., 2001
CSP recombinant	R32tet32 (FSV1): CSP repeats/alum	WRAIR	1/6 protected	Ballou et al., 1987
	R32toxA: CSP repeats/ *Pseudomonas* toxin A	WRAIR	1/3 protected	Fries et al., 1992
	R32NS1-81: CSP repeats + 81aa flu A nonstructural protein in MPL/squalene/ mycobacterial cell wall	NMRC/ WRAIR	2/11 protected	Hoffman et al., 1994

	Repeatless form: CSP N- and C-terminus/liposomes/MPL/alum	WRAIR	0/15 protected	Heppner et al., 1996
Viruslike particle	RTS,S: HBsAg/CSP repeat and C-terminus + adjuvant: 1. alum vs alum/MPL 2. MPL vs oil-in water vs oil-in water/MPL/QS21 3. oil-in-water/MPL/QS21 (AS02)	WRAIR	 1. 0/6 and 2/8 protected 2. 1/8, 2/7, and 6/7 protected 3. 18/41 protected	 Gordon et al., 1995 Stoute et al., 1997, 1998 Kester et al., 2001
	ICC-1132/I SA 720 HBcAg + CSP repeats and T-epitopes	Oxford/Apovia (WRAIR provided sporozoites)	No protection (0/11) following single immunization	Walther et al., 2005
Erythrocytic Stage Vaccines				
Recombinant protein	MSP-1, 2/RESA (combination B) with montanide ISA720 (blood-stage challenge)	No	0/12 protected	Lawrence et al., 2000
Multistage Vaccines				
Peptide/recombinant	CSP $NANP_{19}$/5.1(Exp-1)	No	0/13 protected	Sturchler et al., 1992
Recombinant protein	CSP/MSP-2 (combination A)/alum	No	0/33 protected	Sturchler et al., 1995

continued

TABLE A-2 Continued

Type of Vaccine	Vaccine Details	MIDRP Involvement	Results	References
DNA plasmids	MuStDO5: CSP, SSP-2/TRAP, LSA-1, LSA-3, Exp-1	NMRC	0/31 protected	Wang et al., 2005
Recombinant virus	NYVAC-7: CSP, SSP-2/TRAP, LSA-1, MSP-1, SERA, AMA-1	WRAIR	1/35 protected	Ockenhouse et al., 1998
Heterologous prime-boost	RTS,S AS02A/CSP MVA or CSP MVA/RTS,S AS02A	Oxford/ WRAIR	No increase in vaccine efficacy compared to RTS,S	Dunachie et al., 2006
	RTS,S AS02A/SSP-2/TRAP	WRAIR	Decreased vaccine efficacy compared to RTS,S	Walsh et al., 2004; Heppner, 2006
	RTS,S AS02A/MSP-1_{42}	WRAIR	No increase in vaccine efficacy compared to RTS,S	Heppner et al., 2005; Heppner, 2006
	ME-TRAP DNA/MVA and ME-TRAP fowlpox/MVA	No	20% protection	Bejon et al., 2005; Keating et al., 2005; Webster et al., 2005

TABLE A-3 Summarized Results of Randomized Phase 2 Human Malaria Vaccine Trials Using Natural Challenge Conducted to Date (December 2005)

Vaccine Type	Vaccine Details	MIDRP Involvement	Trials and Results	References
Preerythrocytic Vaccines				
Synthetic peptide	CSP (NANP)3-TT	No	One trial Burkina Faso, no effect	Guiguemdé et al., 1990
Recombinant protein	CSP R32toxA	WRAIR/ AFRIMS	Two trials (Thailand, Kenya), no effect	Brown et al., 1994; Sherwood et al., 1996
Viruslike particle	RTS,S	WRAIR	One trial with adults in the Gambia: weak protection against clinical malaria in first year, boosted in second year to 63%. Two trials in children in Mozambique: weak protection against infection, 26% against clinical malaria, 56% against severe malaria. (see Figure 3-3)	Alonso et al., 2004, 2005; Bojang et al., 2001
Heterologous prime-boost	ME-TRAP DNA/MVA	No	One trial in adults (the Gambia), no effect	Moorthy et al., 2004

continued

TABLE A-3 Continued

Vaccine Type	Vaccine Details	MIDRP Involvement	Trials and Results	References
Erythrocytic Stage Vaccines				
Recombinant protein	MSP-1/MSP-2/ RESA (combination B)	No	One trial in Papua New Guinea children: reduction in parasite density 49%; reduction in incidence of infections of MSP-2/3D7 (as in vaccine). No effect on clinical malaria	Genton et al., 2002
Multistage Vaccines				
Peptide/ recombinant	CSP $NANP_{19}$/ 5.1(Exp-1)	No	No cases in either trial group	Reber-Liske et al., 1995
Synthetic peptide	SPf66	Limited WRAIR participation in three trials	10 trials: little effect in Africa (4 trials) or Asia (1 trial), weak effect in S America (5 trials)	Acosta et al., 1999; Alonso et al., 1994; Amador et al., 1992; Bojang et al., 1997, 1998; D'Alessandro et al., 1995; Leach et al., 1995; Masinde et al., 1998; Nosten et al., 1996; Noya et al., 1994; Sempertegui et al., 1994; Urdaneta et al., 1998; Valero et al., 1993, 1996

APPENDIX A REFERENCES

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Appendix B

Current Requirements for a Malaria Vaccine

The current requirements for a *Plasmodium falciparum* vaccine are formulated in a U.S. Army Operational Requirements Document (ORD) dated March 13, 1997, which has now expired and will be replaced by a Capability Development Document (CDD) that is currently (January 2006) in draft. Although these documents have been prepared under the auspices of the U.S. Army, the requirements are no different for the Navy and Marines. The table below shows the requirements as they stand in the expired ORD and the draft CDD.

TABLE B-1 Current Operational Requirements for a *P. falciparum* Malaria Vaccine

Attribute	Development Threshold	Development Objective
Efficacy	80% protection	90% protection
Time to protection	Within 14 days	Within 7 days
Duration of protection	At least 1 year	At least 2 years
Shelf life	At least 2 years	At least 3 years
Dosing schedule	Protection will be attained after two doses	Protection will be attained after one dose

Appendix C

Suggested Design of Trials for Testing Malaria Vaccines in Nonimmune Adults Visiting Endemic Areas

A total of three critical phase 3 trials of efficacy is envisioned. All three trials would be randomized (at the level of the individual subject), controlled, and double blind (or blinded observer). In the two initial small trials, the subjects, under close clinical supervision, would not take concomitant chemoprophylaxis. In the third study, the participants would be given chemoprophylaxis, but it is assumed that at least 10 percent of them would not take it. Clinical supervision would still be provided. In this way the study would be analogous ethically to experimental challenge studies where subjects who do not take chemoprophylaxis are exposed to the bites of five *Anopheles* mosquitoes infected with *P. falciparum*.

TRIALS IN THE ABSENCE OF CHEMOPROPHYLAXIS

In the initial two small phase 3 efficacy studies in Western Kenya (or perhaps Ghana or Indonesia), the subjects would be entirely dependent on the accompanying medical staff to provide prompt diagnosis of malaria, to initiate optimal specific therapy, and to maintain follow-up to avoid complications. During these two relatively small initial efficacy trials, the opportunity would be taken to collect sera and peripheral blood mononuclear cells from the subjects at baseline and at various time points thereafter to perform measurements of serum antibodies and cell-mediated immune responses. If the vaccine proves efficacious, the hope would be to identify immunologic correlates of protection.

To have 90 percent power to detect a statistically significant differ-

ence (alpha = 0.025, single tail) in the attack rate for clinical malaria in vaccinees versus controls (based on estimated 60 percent vaccine efficacy and a lower limit of 30 percent for the 95 percent confidence interval [CI]), the trial would have to be large enough to allow detection of a total of 160 confirmed *P. falciparum* clinical malaria cases.

Some assumptions for design of the trials without chemoprophylaxis include the following:

- At least 70 percent of the U.S. control subjects will develop clinical malaria during approximately 5 months of stay in peak transmission season. (It is recognized that this is likely a conservative estimation as the attack rate in controls is more likely to approach 100 percent).
- Because of the remoteness of the geographic location, the duration of local exposure (approximately 5–6 months) and the other demands of participating in an intensive, complex vaccine trial, a dropout rate (loss to follow-up) of up to 18 percent must be expected.

A total of 164 analyzable subjects per group is needed to have 90 percent power to detect a significant difference (alpha = 0.025, single tail) if the expected attack rate in controls is 70 percent and expected vaccine efficacy is 60 percent (with a lower limit of 30 percent for the 95 percent CI). If 200 subjects are randomly allocated to the malaria vaccine group and 200 to the control group, with 18 percent loss to follow-up, at the end of the study there will remain approximately 164 vaccine and 164 control subjects available for analysis. At the expected attack rate, this would yield about 115 confirmed *P. falciparum* cases among the controls and about 46 cases among the vaccinees (60 percent proportionate reduction); the 161 cases in this scenario would provide the total of 160 cases needed to address the primary aim. With these results as an example, the 95 percent CI around the 60 percent point estimate of vaccine efficacy would be 43 percent lower limit and 72 percent upper limit.

If this first phase 3 efficacy trial in subjects not under cover of chemoprophylaxis is successful, the committee proposed that a corroborating trial of identical design be carried out one season later. This trial would provide a second opportunity to collect clinical specimens in the search for immunologic correlates of protection.

TRIALS IN THE PRESENCE OF CHEMOPROPHYLAXIS

If the corroborating phase 3 trial not under chemoprophylaxis also yields positive results, it would be appropriate for the Military Infectious Diseases Research Program (MIDRP) Malaria Vaccine Program to undertake a much larger phase 3 trial with 10 times as many subjects in the

vaccine and control groups, all of whom would be issued standard military chemoprophylaxis. Although subjects would be recommended to take chemoprophylaxis, there would be no systematic direct supervision of subjects taking their daily medication. Rather this would be left to the discretion of the individual subject, recognizing that in real-life conditions, a variable proportion of military personnel deployed to sites of known malaria risk do not take chemoprophylaxis in a reliable way. Accordingly, in a conservative assumption, 10 percent of the study subjects would fail to take chemoprophylaxis for sufficiently extended periods so that these subjects would be equivalent in risk to the nonprophylaxed subjects of the preceding two efficacy trials.

Thus, if 2,000 enrolled subjects were randomly allocated to receive the maturing candidate vaccine and 2,000 others to the control group, by the end of the study, despite some expected dropouts and loss to follow-up, approximately 1,640 analyzable subjects would be available in each group. Of these, because of random allocation, one would expect about 164 "nonchemoprophylaxed" subjects to be available for analysis in each group. Among the 1,640 analyzable control subjects, one would expect to detect around 115 cases of *P. falciparum* malaria (70 percent attack rate among the 164 controls who did not adhere strictly to chemoprophylaxis). One would also expect to detect 46 cases of *P. falciparum* malaria in the vaccine recipients (60 percent proportionate reduction); this constitutes a total of 161 cases between the two groups. The limits of the 95 percent CI around the 60 percent point estimate of vaccine efficacy, as in the previous example, would be 43 percent (lower limit) and 72 percent (upper limit) around the point estimate of efficacy.

Appendix D

Patents

Since 1990, the Naval Medical Research Center (NMRC) and the Walter Reed Army Institute of Research (WRAIR) malaria vaccine programs have had six and eight patents granted, respectively. One further WRAIR patent is expected to be assigned a patent number in the coming months. The titles of approved patents are listed below.

NMRC PATENTS GRANTED TO DATE

U.S. Patent Issue No. 5,095,093 on March 10, 1992
Title: Protective four amino acid epitope against *Plasmodium vivax* malaria
Inventors: Hoffman, Charoenvit, and Jones

U.S. Patent Issue No. 5,198,535 on March 30, 1993
Title: Protective malaria sporozoite surface protein immunogen and gene
Inventors: Hoffman, Charoenvit, Hedstrom, Khusmith, and Rogers

U.S. Patent Issue No. 5,599,543 on February 4, 1997
Title: Protective four amino acid epitope against *Plasmodium vivax* malaria
Inventors: Hoffman, Charoenvit, and Jones

U.S. Patent Issue No. 5,814,617 on September 29, 1998
Title: Protective 17 kDa malaria hepatic and erythrocytic stage immunogen and gene
Inventors: Hoffman, Charoenvit, Hedstrom, and Doolan

U.S. Patent Issue No. 6,066,623 on May 23, 2000
Title: Polynucleotide vaccine protective against malaria, methods of protection and vector for delivering polynucleotide vaccines
Inventors: Hoffman, Hedstrom, and Sedegah

U.S. Patent Issue No. 6,399,062 on June 4, 2002
Title: Murine monoclonal antibody protective against *Plasmodium vivax* malaria
Inventors: Charoenvit, Hoffman, and Beaudoin

WRAIR PATENTS GRANTED TO DATE

U.S. Patent Issue No. 4,906,564 on March 6, 1990
Title: Antigenic determinants recognized by antibodies obtained using a pathogenic agent or derivative thereof that presents a restricted set of antigens
Inventors: Lyon, Chulay, Thomas, Howard, Weber

EUROPEAN PATENT OFFICE Patent Issue No. 0192626 on July 29, 1992
Title: Malaria circumsporozoite vaccine
Inventors: Ballou, Gross, Hockmeyer, Young

GERMAN Patent Issue No. P3686178.2 on July 29, 1992
Title: Malaria circumsporozoite vaccine
Inventors: Ballou, Gross, Hockmeyer, Young

SOUTH AFRICAN Patent Issue No. 86/0874 on December 30, 1996
Title: Malaria circumsporozoite vaccine
Inventors: Ballou, Gross, Hockmeyer, Young

U.S. Patent Issue No. 6,310,046 on October 30, 2001
Title: Sequestrin of *Plasmodium falciparum*
Inventors: Duffy, Ockenhouse

U.S. Patent Issue No. 6,541,815 on November 4, 2003
Title: Sequestrin
Inventors: Duffy, Ockenhouse

U.S. Patent Issue No. 6,855,322 on February 15, 2005
Title: Isolation and purification of *P. falciparum* merozoite protein-142 vaccine
Inventors: Lyon, Angov

U.S. Patent Issue No. 7,029,685 on April 18, 2006
Title: *Plasmodium falciparum* AMA-1 protein and uses thereof
Inventors: Lanar, Dutta, Ware, Nair

Appendix E

Scientific Advisory Board for DoD Malaria Vaccine Research and Development Program (Draft Charter)

The following represents an indicative charter for the proposed scientific advisory board. The final document should be drawn up by the program management together with the transition team during the reorganization into the Joint Task Force for Malaria Vaccine (JTF-MV). It should include consideration of whether additional technical advisory groups are needed in addition to this board.

PURPOSE

The Institute of Medicine (IOM) committee strongly recommends establishment of a scientific advisory board (SAB), under the executive agency of the U.S. Army Medical Research and Materiel Command (USAMRMC), to serve as senior advisors to the Military Infectious Diseases Research Program (MIDRP) Malaria Vaccine Program.

AUTHORITY

Commanding general, USAMRMC.

FUNCTION

The SAB shall act to guide high-level decision making on issues related to the accomplishment of the MIDRP malaria vaccine mission. Functions include the following:

- Advise the proposed transition team charged with planning and implementing the malaria vaccine research and development program reorganization into the JTF-MV.
- Assess military vaccine research and development program priorities and accomplishments.
- Act as a center of strong advocacy for a protective vaccine as the primary countermeasure to the malaria threat.
- Provide credible expert perspective from both within and outside the Department of Defense (DoD).
- Maintain active relationships with current science and technology leaders in the academic, government, and corporate/industry sectors.

STRUCTURE

The SAB shall consist of at least seven members. The chair shall be appointed by the commanding general from among the members. To obtain the best advice possible, the members and the chair shall be selected on the basis of eminence in medical research with a broad range of expertise in microbiology, parasitology, epidemiology, infectious diseases, malaria, clinical trials, regulatory affairs, and vaccine research and development. None of the members shall be on active duty status, though retired members who are otherwise qualified and can represent a balanced perspective on the Army and Navy approaches to vaccine development should be invited to participate. Members' backgrounds should represent a variety of areas such as: the Department of Health and Human Services, the National Institutes of Health, the Food and Drug Administration; academia and industry; the Gates Foundation and the Malaria Vaccine Initiative; and retired DoD or military personnel.

Members shall be invited to serve for time periods of two to three years, with overlap of rotating members to ensure continuity and ongoing responsibility and scientific oversight. In addition, the board should provide vaccine research and development expertise to advise the commanding general of the USAMRMC on how best to restructure the MIDRP Malaria Vaccine Program in the context of various resource options that may be available to maximize the likelihood of successful vaccine(s) development in the near future (i.e., in 5–10 years).

Nonvoting members with broad experience and detailed knowledge of the MIDRP Malaria Vaccine Program should be available and present during the advisory board meeting(s) to answer questions and clarify issues concerning the MIDRP Malaria Vaccine Program. Several nonvoting members can be proposed, such as the MIDRP research area director and consultants.

MEETINGS

The board will meet at a time and location designated by the commanding general of the USAMRMC. Meetings will be conducted and records of the proceedings kept. The board members will determine a set of recommendations agreed upon by a majority vote. A quorum for the conduct of business shall consist of a majority of members. The approved recommendations will be provided to the commanding general of the USAMRMC. Minutes and/or audiovisual records of the board meeting will be included in the board's reports. All participants must agree to statements of confidentiality and nonconflict of interests.

COMPENSATION

Board members will receive reimbursement for travel-related expenses.

DELIVERABLES

To be formulated.

TERMINATION DATE

To be determined.

Approved _____
Commanding General, MRMC

Appendix F

Recommendations of the IOM Report *Protecting Our Forces*[1]

COMMITTEE RECOMMENDATIONS

Organization, Authority, and Responsibility

The committee recommends that the Department of Defense:

1. Combine all DoD vaccine acquisition responsibilities under a single DoD authority that includes the entire spectrum of responsibility—from potential threat definition through research and development, advanced product development, clinical trials, licensure, manufacture, procurement, and continued maintenance of manufacturing practice standards and regulatory compliance.
2. Consolidate infrastructure, funding, and personnel for DoD acquisition programs for biodefense and naturally occurring infectious disease vaccines.
3. Ensure that there is an effective, ongoing senior advisory group—one providing perspectives from both within and outside of DoD—to assess program priorities and accomplishments, to act as a proponent for vaccines and other infectious disease countermeasures, and to maintain active relationships with current science and technology leaders in academic, government, and corporate sectors.

[1]IOM (Institute of Medicine). 2002. *Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military.* Washington, D.C.: The National Academies Press. P. 133.

Program and Budget

The committee recommends that the Department of Defense:

4. Provide budget resources commensurate with the task.
5. Actively encourage the development, distribution, and use of a well-defined and validated research priority-setting mechanism, which could involve prioritized, weighted lists of infectious disease threats and formal scenario-planning exercises. To do so requires infectious diseases surveillance and the collection and synthesis of epidemiologic information.
6. Include programming goals that ensure greater strength and continuity in the science and technology base across the full spectrum of infectious disease threats, including research related to the epidemiology of infectious diseases, the nature of protective immunity, and both early and advanced vaccine product development.
7. Leverage DoD research efforts by building greater interactions and an effective formalized coordinating structure that links DoD research to vaccine development activities carried out by the Department of Health and Human Services and other public and private groups.

Manufacturing

The committee recommends that the Department of Defense:

8. Work toward manufacturing arrangements that ensure consistent vaccine availability by addressing long-term commitment, predictable volumes and prices, indemnification, and intellectual property issues. These arrangements should include consideration of vaccine-specific, government partnerships with individual private manufacturers, a private manufacturer consortium, and government-owned, contractor-operated vaccine-production facilities.

Regulatory Status of Special-Use Vaccines

The committee recommends that the Department of Defense:

9. Vigorously seek a new paradigm for the regulation of special-use vaccines that remain in Investigational New Drug status with the Food and Drug Administration without reasonable prospects of licensure under current rules, ensuring demonstration of the safety and efficacy of these products commensurate with their anticipated use.

Appendix G

Executive Summary and Recommendations of the DoD Report *Acquisition of Vaccine Production*[1]

EXECUTIVE SUMMARY

By memorandum dated July 20, 2000, the deputy secretary of defense tasked the director of defense research and engineering and the assistant secretary of defense for health affairs to jointly contract with a private organization or panel of experts to conduct a comprehensive study of the Department of Defense (DoD) acquisition of vaccine production. The study was to focus on review of the following areas:

- Vaccines to protect service members against biological warfare threats as well as infectious diseases
- A comparison of current department efforts with best business practices in the biologics industry, and if or how the department can leverage the best aspects of the private-sector programs from industry
- A determination of whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures
- The development of recommendations for how the department should best develop and oversee a vaccine production program

[1]Top FH Jr., Dingerdissen JJ, Habig WH, Quinnan GV Jr., Wells RL. 2000. DoD Acquisition of Vaccine Production. Report to the Secretary of Defense by the Independent Panel of Experts, Dec 2000. In DoD, 2001. *Report on Biological Warfare Defense Vaccine Research and Development Programs.* Washington, D.C.: Department of Defense. [Online]. Available: http://www.acq.osd.mil/cp/bwdvrdp-july01.pdf [Accessed May 3 2006].

An independent panel of experts was established and assessed the DoD's acquisition of vaccine production requirements and ongoing programs, management, and acquisition processes against U.S. vaccine industry best practices.[1] The panel found that:

- Biowarfare and endemic diseases are proven high-consequence threats to military operational effectiveness.
- Vaccines are the lowest risk, most effective protection; they enable force projection and are superior to antibiotics or other treatments.
- The DoD's current acquisition of vaccine production approach is insufficient and will fail.
- A new approach can make this program work.

The size and scope of DoD vaccine requirements for force protection are exceptionally large. The DoD requires new vaccines to protect against 15 or more biowarfare and endemic diseases. By comparison, vaccines licensed for use in the United States protect against about 20 diseases, and Merck & Co., Inc. manufactures nine licensed vaccines. The size and scope of the DoD program is too large for either the DoD or industry alone. A combined, integrated approach drawing on industry, DoD, and national scientific strengths and assets is essential. The DoD needs to consolidate and integrate its vaccine research, development, and acquisition programs for biowarfare defense and endemic disease protection. Success requires a tailored acquisition model and infusion of technically qualified staff at all levels. A joint program executive officer must have responsibility and authority for the program and report to a designated vaccine acquisition executive who reports to the undersecretary of defense (acquisition, technology and logistics). The DoD vaccine acquisition program should be managed as an Acquisition Category I program and—on an eight-vaccine scale—requires a $3.2 billion research and development program. A government-owned and contractor-operated vaccine production facility is an essential element of the DoD program. The DoD senior leadership must meet with and solicit industry support for its vaccine requirements.

TABLE G-1 Summary of the Top Report[a] Findings and Recommendations by Deputy Secretary of Defense Focus Areas

Focus Area	Findings	Recommendations
1—Vaccines to protect service members against biological warfare threats as well as infectious diseases.	Vaccines for biological warfare defense and protection against endemic diseases are essential enablers of force projection.	Combine programs from discovery to production.
2—A comparison of current Department efforts with best business practices in the biologics industry, and if/how the Department can leverage the best aspects of the private sector programs from industry.	Current Department efforts do not meet industry best practices: • Diffuse management and fragmented lines of responsibility • Inadequate scientific oversight • Inadequate program integration from discovery through licensure • Inadequate resources to meet goals	Adopt integrated approach utilizing: • Management and development skills of industry • Accountable, lean DoD management structure • Strong technical guidance and personnel • Government-owned, contractor operated (GOCO)
3—A determination of whether the DoD program requires acquisition processes unique from normal departmental acquisition procedures.	Vaccine acquisition processes are different from weapons system acquisition processes and success requires different procedures.	• Strong technical input imperative — Workforce — Management • Stable, long-range funding for vaccine life cycle • Reprogramming authority
4—The development of recommendations for how the Department should best develop and oversee a vaccine acquisition production program.	DoD acquisition of vaccine production management practices are generally contrary to industry best practices.	• Combined, integrated industry acquisition model • Focused and streamlined organization • Segregated, Office of Secretary of Defense-sponsored funding • Incentivized industry involvement (with GOCO) • DoD, Executive Branch, and congressional support to remove impediments and provide necessary incentives

[a]See footnote 1.

Appendix H

Open Meeting Agenda

COMMITTEE ON DOD'S MALARIA VACCINE RESEARCH—A PROGRAM REVIEW

January 23–25, 2006
Courtyard by Marriott
8506 Fenton St.
Silver Spring, MD 20910
Tel 301-589-4899
Meeting Room

AGENDA

Meeting Objectives

- Obtain perspectives from DoD on the malaria threat to the force
- Review DoD's *P. falciparum* malaria vaccine research program
- Review nonmilitary malaria vaccine efforts
- Develop initial findings and recommendations regarding DoD's Program

Monday, January 23, 2006

Closed Session

8:00	Bias and Conflict Discussion Susanne Stoiber Executive Director, Institute of Medicine

Open Session

9:00	MIDRP Welcome COL David Vaughn, MC Director, Military Infectious Disease Research Program Fort Detrick, Maryland
9:15	Chairman's Remarks and Introductions
9:30	MIDRP and Malaria Program Overview and Review of Committee Charge COL David Vaughn
10:30	Break
11:00	Overview Malaria Vaccine Development Dr. Filip Dubovsky Scientific Director, Malaria Vaccine Initiative
12:00	Lunch
1:00–5:15	Program Review—Protein-based vaccine strategy
1:00	Objectives and Strategy COL Gray Heppner
1:30	Progress towards an RTS,S-Based Vaccine by Year 2010: New Adjuvants, Antigens, and Vectors • Status of RTS,S/AS02A COL Gray Heppner • Adjuvant AS01B: RTS,S/AS02A vs. RTS,S/AS01B COL Kent Kester • GMP Pf Antigens MSP-1, AMA-1, and LSA-1 Dr. Evelina Angov • Adenovirus 35 with circumsporozoite protein Dr. Ann Stewart

2:50	Break
3:00	Clinical Trials of an RTS,S-Based Vaccine COL Gray Heppner
3:30	Future Vaccines • Antigen Discovery COL Chris Ockenhouse • Vivax COL Chris Ockenhouse • Attenuated Knock-out COL Gray Heppner
4:00	Building the RTS,S-Based Vaccine • One Allele or Two? COL Chris Ockenhouse • The role of molecular analyses • Making Development Earlier COL Chris Ockenhouse • The potential microarrays • Assays of Immune Response Dr. Ann Stewart • From robust to validated
4: 30	Barriers from Proof of Concept to Licensure COL Gray Heppner • Funding • Industrial Partners • Licensure Trials
5:00	Discussion
6:30–8:30	Committee Dinner at Redrock Canyon Restaurant, Silver Spring, Maryland

Tuesday, January 24, 2006

Open Session

8:00–12:30	Program Review—DNA-based vaccine strategy
8:00	Objective, Background & Rationale CAPT Tom Richie
8:30	Program History CAPT Tom Richie
8:50	Functional Elements & Activities • Overview CAPT Tom Richie • Discovery Research Dr. Denise Doolan • Target Antigens • Immune Mechanism
9:50	Break (30 minutes) • Preclinical Research Dr. Denise Doolan • Preclinical Development Dr. Denise Doolan • Regulatory Affairs Ms. Gail Levine • Clinical Trials LCDR David Regis
11:05	Clinical Development Plan CAPT Tom Richie
11:30	Barriers to Progress CAPT Tom Richie
12:00	Attenuated Sporozoite Vaccine CAPT Tom Richie
12:30	Lunch

Closed Executive Session

1:30	Discussion of the DoD program including review of questions posed by the sponsor about the Vaccine Program
5:30–5:45	Chairman's time
6:30–8:30	Dinner at hotel, local restaurant of choice OR evening working session

Wednesday, January 25, 2006

*Closed Executive Session**

8:00–12:00 Structured discussion of the DoD malaria vaccine research program

- Clarify gaps or missing information
- Finish discussions regarding key program questions
- Develop initial findings and recommendations
- Establish second meeting date to review report draft.

* An open portion of this meeting was posted from 9:00–9:45 and will be honored if needed.

Appendix I

Committee and Staff Biographies

COMMITTEE MEMBERS

MYRON M. LEVINE, M.D., (Chair) is the director of the Center for Vaccine Development at the University of Maryland School of Medicine and is head of the Division of Geographic Medicine in the Department of Medicine. He is also visiting professor in the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, and the Faculdad de Medicina, Universidad de Medicina, Universidad Peruana Cayetano Heredia, Lima, Peru. He received a B.S. from the City University of New York, M.D. from the Medical College of Virginia, and a D.T.P.H. with distinction from the London School of Hygiene and Tropical Medicine. Dr. Levine is a member of numerous international advisory committees including the WHO Vaccine Advisory Committee and the Advisory Board to the Center for Clinical Vaccinology and Tropical Medicine, Oxford University, and was a member of the working group of the Global Alliance for Vaccines and Immunization during its tenure. He has received prestigious research and other awards including the Albert B Sabin Gold medal award and is holder or coholder of seven patents. Dr. Levine was elected to the Institute of Medicine in 1995

GRAHAM V. BROWN, M.B., B.S., F.R.A.C.P., M.P.H., Ph.D., a physician, is James Stewart Professor of Medicine at the University of Melbourne, Australia and heads the Department of Medicine at the Royal Melbourne and Western hospitals. He is also head of the Victorian Infectious Diseases Service of the Royal Melbourne Hospital and

interim director, Nossal Institute of Global Health. Previously he held positions at the Walter and Eliza Hall Institute of Medical Research and was head of the Division of Infection and Immunity. He received his M.B.B.S. (first class honors in Medicine) and Ph.D. from the University of Melbourne, and M.P.H. from Harvard University. In addition to his clinical expertise in tropical medicine and infectious diseases, Dr. Brown was a member of the team that developed combination B vaccine and protocols for the first phase 2 clinical trial of a blood-stage malaria vaccine in Papua New Guinea in 1998. He is author or coauthor of 187 publications. Dr. Brown was formerly a member of the Strategic Advisory Council of the Bill and Melinda Gates Children's Vaccine Program. He currently serves on numerous advisory boards including the Malaria Vaccine Advisory Committee of WHO and the Scientific Consultants Group of the USAID Malaria Vaccine Development Program.

MICHAEL F. GOOD, M.D., Ph.D., is director of the Queensland Institute of Medical Research (QIMR), Brisbane, Australia, an institution with a longstanding major focus on tropical diseases (especially malaria) and vaccine research. QIMR has conducted Phase 1 and Phase 2 malaria vaccine trials with partners in Papua New Guinea and collaborates extensively with the biotechnology industry. Prior to his appointment as director in 2000, Dr. Good was director of the Cooperative Research Centre for Vaccine Technology at QIMR. Dr. Good received his B.Sc. and M.D. from the University of Queensland and Ph.D. from the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, after which he undertook postdoctoral training followed by a visiting scientist position in the Laboratory of Parasitic Diseases at the NIH (1985–1988). Dr. Good has an outstanding research record with over 220 publications, and he has been awarded the prestigious Fulbright and Neil Hamilton Fairley Fellowships. He is the immediate past president of the Association of Australian Medical Research Institutes. His major contributions and research interests lie in the areas of immunity, immunopathogenesis and vaccine development for malaria and group A streptococcus/rheumatic fever.

DAVID C. KASLOW, M.D., is chief scientific officer of Vical Inc., where he oversees research and development, including discovery, clinical, regulatory and quality functions for Vical's pharmaceutical product candidates for infectious diseases and cancer based on patented gene delivery technology. Dr. Kaslow has an outstanding research career during which he has led research groups at the National Institutes of Health and at Merck & Co., with extensive experience in vaccines and malaria. He received a B.S. in biochemistry from the University of California, Davis, and M.D. from University of California, San Francisco, followed by a fellowship in

human genetics at Johns Hopkins. He joined NIH in 1986 where he held senior research positions including head of Recombinant Protein Development Unit, head of Malaria Vaccine Development Unit and head of the Molecular Vaccine Section in the Laboratory of Malaria Research. From 1999 he was senior director of vaccine research and then head of the Department of Vaccine Research and Technology at Merck & Co. Dr. Kaslow is the author or coauthor of 122 scientific papers and 22 review articles/book chapters, and holds or coholds 13 patents.

MARGARET A. LIU, M.D., is vice chair of Transgene, SA and a visiting professor at the Karolinska Institute in Stockholm, Sweden. She is a pioneer in the area of DNA vaccines, author or coauthor of 128 publications and the inventor for six issued patents. She was formerly the senior adviser in vaccinology for the Bill and Melinda Gates Foundation, vice-president of vaccines research and gene therapy at Chiron Corporation, and senior director of virus and cell biology at Merck & Co. She is currently chair of the Scientific Advisory Group of the International Vaccine Institute (in Seoul) and a scientific advisor for the AIDS Vaccine Advocacy Coalition. She is also a former member of the European Developing Country Clinical Trials Partnership Board (based in The Hague), the WHO Initiative for Vaccine Research Vaccine Advisory Committee, and the Global Alliance for Vaccines and Immunization R&D Task Force during its tenure. Dr. Liu received her B.A. (summa cum laude) in chemistry from Colorado College and her M.D. from Harvard Medical School. Dr. Liu was named one of "The 50 Most Important Women Scientists" by *Discover* magazine in November 2002.

GARY J. NABEL, M.D., Ph.D., is director of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases, NIH. Prior to this appointment in 1999, he was professor of internal medicine and of biological chemistry at the University of Michigan in Ann Arbor, and a Howard Hughes Medical Institute Investigator. Dr. Nabel's expertise is in the area of viral gene expression, vaccines and gene transfer therapy. He has made important contributions to knowledge of gene regulation and immune system activation in the HIV virus, and to DNA-based vaccine research for HIV and other diseases. Dr. Nabel graduated magna cum laude from Harvard and completed the M.D./Ph.D. program there in 1982. His subsequent positions include director of the Center for Gene Therapy and co-director of the Center for Molecular Medicine at the University of Michigan in Ann Arbor. He has received the American Society for Biochemistry and Molecular Biology Amgen Scientific Achievement award and has served on several NIH advisory committees

including the NIAID AIDS Vaccine Research Advisory Committee. Dr Nabel was elected a member of the Institute of Medicine in 1998.

ELIZABETH NARDIN, Ph.D., is associate professor in the Division of Molecular Medicine at the New York University (NYU) School of Medicine, which has a strong focus on malaria biology and vaccine development. Her research interests lie in the mechanisms of T-and B-cell mediated vaccine-induced immunity to malaria parasites, especially the preerythrocytic stages, with an emphasis on development and testing of synthetic peptide malaria vaccines. Her research has included Phase 1 and Phase 2 trials of novel peptide and recombinant vaccine constructs, and development of innovative efficacy testing systems for challenge trials. She received her M.S. from New York University and Ph.D. in parasitology from the NYU School of Medicine, Department of Microbiology, followed by a postdoctoral fellowship in the Department of Pathology. Dr. Nardin was recipient of the Irma T Hirshi Trust Career Scientist Award during 1992 to 1997. She has served as grant reviewer for several international and national organizations including the National Institute of Allergy and Infectious Diseases Tropical Medicine and Parasitology Study Sections and most recently the Clinical Research Study Section.

N. REGINA RABINOVICH, M.D., M.P.H., directs the Infectious Diseases Division of the Bill & Melinda Gates Foundation's Global Health Program. Dr. Rabinovich obtained her M.D. at Southern Illinois University. Her training includes clinical pediatrics at the University of North Carolina [UNC)], epidemiology at UNC and the National Institute of Allergy and Infectious Diseases [NIAID], and a M.P.H. at UNC. She spent 11 years at the NIAID where she served as chief of the Clinical and Regulatory Affairs Branch of the Division of Microbiology and Infectious Diseases, and oversaw a network of extramural units that tested vaccines and drugs in the United States. During her tenure, the units completed large multi-center trials of pertussis and influenza vaccines, as well as phase I trials of new technologies and vaccines such as malaria and rotavirus. She became director of the PATH Malaria Vaccine Initiative in 1999, creating and leading a team to advance development of malaria vaccines for children in endemic countries. Dr. Rabinovich received NIH Awards for her contributions and advocacy for vaccine research and the Children's Vaccine Initiative. She has participated in review panels for the NIH and the Institute of Medicine, and serves on international advisory boards including the Medicines for Malaria Venture, INDEPTH, AMANET and the Institute of One World Health.

ALAN R. SHAW, Ph.D., is currently the president and chief executive officer of VaxInnate, a biotechnology company making vaccines that incorporate activators of the innate immune system. Prior to this, he was the executive director of Virus & Cell Biology at Merck Research Laboratories, and was responsible for all aspects of live virus vaccine research, as well as technical aspects of development and production. He was also responsible for research and early development of recombinant protein-based vaccines. Dr. Shaw has been instrumental in the development of Varivax, ProQuad®, RotaTeq®, Gardasil®, the zoster vaccine Zostavax®, as well as numerous early-stage experimental vaccines. Prior to joining Merck, Dr. Shaw worked on vaccines for hepatitis B and *Plasmodium falciparum* as well as cytokines, cell trafficking and natural inhibitors of interleukin-1 at Biogen, SA in Geneva, Switzerland. Dr. Shaw received a B.A. from Rice University, a M.S. in molecular biology from the University of Texas at Dallas, and a Ph.D. in molecular biology at the Medical College of Ohio. He had postdoctoral fellowships at the International Institute of Cellular Pathology in Brussels and The Rockefeller University. Dr. Shaw is the past chairman of the International Federation of Pharmaceutical Manufacturers Association Biologicals Committee and a part-time member of the faculty at Temple University.

H. KYLE WEBSTER, Ph.D., has had a distinguished military career with 27 years experience primarily at the Walter Reed Army Institute of Research, including 11 years (1981–1991) as chief of the Department of Immunology and Parasitology at the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand. While in Thailand, he directed the first military malaria vaccine trial. He retired as chief, Department of Parasitology at the Walter Reed Army Institute of Research in Washington, D.C. in 1993, and has since worked in senior positions in industry in the United States and Asia for Becton Dickinson, most recently including vice-president for strategic initiatives (2001–2005). Dr Webster was educated at Georgetown University (B.Sc., Ph.D. with distinction) and at the Stanford University/National University of Singapore International Executive Business Program. He is author or coauthor of 162 publications on basic and applied aspects of infectious diseases and immunology, especially on malaria including diagnostics as well as drug and vaccine development. He currently works as an independent consultant in malaria and infectious diseases.

KATHRYN C. ZOON, Ph.D., is the acting director of the Division of Intramural Research, NIAID, NIH, and deputy director for planning and development of the Division of Intramural Research of NIAID. Previously

she was the principal deputy director of the Center for Cancer Research at the National Cancer Institute of the NIH. She served as the director of the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, and was a member of the NIH Scientific Directors from 1992 to 2003. Dr. Zoon was the director of the Division of Cytokine Biology in CBER, 1988-–1992 where she directed the research and review of cytokines, growth factors, and cellular products. She received her B.S. degree, *cum laude*, in chemistry from Rensselaer Polytechnic Institute and her Ph.D. in biochemistry from The Johns Hopkins University. Dr. Zoon is the author of over 100 scientific papers and has received numerous awards, including the Meritorious Executive Rank Award 1994 for revitalizing and reorganizing the CBER and several DHHS Secretary's Awards for Distinguished Service (1998–2005) while at the FDA. Dr. Zoon was elected to the Institute of Medicine in October 2002.

STUDY STAFF

PATRICIA M. GRAVES, M.S.P.H., Ph.D., is the consulting scientist and senior editor. A graduate of Cambridge University, the London School of Hygiene and Tropical Medicine (Ph.D.) and the University of Colorado (M.S.P.H.), she is a specialist in the epidemiology and control of vector-borne diseases, especially malaria and filariasis. She currently works as an independent consultant for national and international scientific and overseas aid organizations. Previously she conducted laboratory and field research on malaria at the National Institutes of Health, the London School of Hygiene and Tropical Medicine, the Papua New Guinea Institute of Medical Research and the Queensland Institute of Medical Research, Australia. She is honorary fellow at the Liverpool School of Tropical Medicine and an author and editor for the Cochrane Collaboration Infectious Disease Group.

FREDERICK (RICK) ERDTMANN, M.D., M.P.H., is Director of the Medical Follow-up Agency of the Institute of Medicine at the National Academies. He attended medical school in Philadelphia where he earned his M.D. degree from Temple University School of Medicine, and holds a M.P.H. from the University of California at Berkeley. He completed a residency program in general preventive medicine at Walter Reed Army Institute of Research in 1975, and is board certified in that specialty. Dr. Erdtmann's assignments with the Army Medical Department include chief of the preventive medicine services at Fitzsimons Army Medical Center, Frankfurt Army Medical Center in Germany, and Madigan Army Medical Center. He also served as division surgeon for the Second Infantry Division in Tongduchon, Korea. He later served as deputy chief of staff

for clinical operations within DoD's TRICARE Region 1, prior to assuming hospital command at Walter Reed Army Medical Center in March 1998. Following that he was assigned to the Office of the Surgeon General as the Deputy Assistant Surgeon General for Force Development. In 2001, following 30 years of commissioned military service, Dr. Erdtmann joined the National Academies as Director of the Medical Follow-up Agency and also serves as Director of the Board on Military and Veterans Health.

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