EXTERNAL EVALUATION OF THE USAID MALARIA VACCINE DEVELOPMENT PROJECT

PROJECT NUMBER: 936-6001

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ACRONYMS

3D7	*Plasmodium falciparum* Clone 3D7 (from Isolate NF54)
AA/GH	Assistant Administrator for the Bureau for Global Health, USAID
AIDS	Acquired Immunodeficiency Syndrome
AMA	Apical Merozoite Antigen
BIO	Biotechnology Industry Organization
CA	Cooperative Agreement
CDC	Centers for Disease Control and Prevention
CRADA	Cooperative Research and Development Agreement
CSP	Circumsporozoite Surface Protein
DOD	Department of Defense
FVO	*Plasmodium falciparum* Vietnam-Oak Knoll strain
FY	Fiscal Year
GH	Bureau for Global Health, USAID
GSK	GlaxoSmithKline
HIDN	Office of Health, Infectious Diseases and Nutrition, USAID
HIV	Human Immunodeficiency Virus
IAA	Interagency Agreements
IND	Investigational New Drug
IPR	Intellectual Property Rights
IRB	Institutional Review Board
kDa	Kilodalton
MIDRP	Military Infectious Diseases Research Project
MSP	Merozoite Surface Protein
MOU	Memorandum of Understanding
MVDP	Malaria Vaccine Development Program
MVI	PATH Malaria Vaccine Initiative
NGO	Non-governmental Organization
NIAID	National Institute for Allergy and Infectious Diseases
NIH	National Institutes of Health
NMRC	Naval Medical Research Center
PATH	Program for Appropriate Technology in Health
R&D	Research and Development
SCG	Scientific Consultants Group
USAID	United States Agency for International Development
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

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EXECUTIVE SUMMARY

The evaluation of the USAID Malaria Vaccine Development Program (MVDP) assesses its accomplishments over the past decade. The Malaria Vaccine Development Project (936-6001), originally authorized from 1992 until 2002, has been extended until 2003.

USAID has supported malaria vaccine development for over 35 years. MVDP was created in the late 1960s in response to the termination of the Malaria Eradication Program. In the early years of the MVDP program, its work was based on an academic model, focusing on basic research. In recent years, MVDP has been much more involved in building a pipeline from early preclinical vaccine development, through the regulatory process, and to clinical and field testing of vaccine candidates.

MVDP is a major contributor to malaria vaccine development on a global level. It has developed close partnerships with other groups involved in malaria vaccine development in both the public and private sectors, including the Walter Reed Army Institute of Research, the Naval Medical Research Center, the National Institutes of Health, Maxygen, the Centers for Disease Control and Prevention, the Malaria Vaccine Initiative, and several Australian programs.

The evaluation of MVDP was carried out from December 2002 through March 2003, and was structured to define the following:

- Progress made, as well as acceleration of progress.
- USAID's current and future unique role/niche in the development of malaria vaccines.
- Ways to improve the program in the future.

Overall, the evaluation concludes that MVDP has been exceptionally successful over the past few years, and has leveraged funds quite effectively. It is clear that MVDP is a key player in the global malaria vaccine development effort. It has created for itself a unique niche as a “catalyst” and “problem-solver” by virtue of its combination of expertise, flexibility, and close monitoring of the changing needs in the field of malaria vaccine development. MVDP has been able to fund key targeted areas which were intended to speed vaccine candidates that would not have been funded by any other entity through the pipeline. This has enabled MVDP to assume a leadership role, and to have tremendous influence over the rapidly accelerating progress of malaria vaccine development.

FINDINGS AND CONCLUSIONS

Importance of the Project

The importance of preventing death and serious disease from malaria in children and in pregnant women in developing countries *cannot be overstated*. Malaria not only has a profound effect on health, but it also has a major impact on the economic development and political stability of endemic areas. In its 2001 report, the Commission on Macroeconomics and Health of the World Health Organization reported that a small number of conditions, including malaria, are so widespread and debilitating, that they can destabilize economies and entire political systems.

The impact of malaria has grown in recent years, despite longstanding treatment and prevention programs. There was consensus among both malaria experts and experts from other fields that, ultimately, the most effective way to control malaria (i.e., prevent death and severe disease) will be to develop a vaccine that is effective in vulnerable populations, particularly children and pregnant women in endemic areas. In addition, it is predicted that in the long run, a vaccine will be much more cost-effective than reliance on current control measures.

Success of the Project

The evaluation team was struck by the glowing praise, and by the uniformity of opinion that MVDP has been *extraordinarily* successful in its mission to move vaccines to the clinic and field for proof of principle as soon as possible. Further, over the past few years, progress in malaria vaccine development has accelerated dramatically, and it was generally felt that MVDP has played a critical role in creating this momentum. MVDP has leveraged funds well, and it has not only achieved major visibility for USAID, but it has also assumed a vital role in maintaining a focus on developing vaccines that will protect populations living in endemic regions.

Elements contributing to MVDP's success include:

- Its expertise in malariology, and its strong goal-directed, product-oriented focus;
- Its ability to communicate effectively, and to work very closely with partners;
- Its flexibility;
- Its exceptionally talented and dedicated Scientific Consultants Group; and
- Its ability to identify other appropriate experts.

It is clear from interviews that had MVDP never existed, several promising malaria vaccine candidates would not be nearly as far along in the development process as they are today, or that these vaccine candidates would never have been developed at all.

Accomplishments

MVDP has established a unique role or niche for itself as a catalyst and as a problem-solver. This role has enabled it to act as a key player and leader in the malaria vaccine field. MVDP is unique among funding entities in that its staff has a thorough understanding of the whole spectrum of malaria vaccine development issues. MVDP also is unique because it has been more flexible, and it has been able to act more quickly than have other funders. Also no other funder has been able to work as swiftly, or had the ability to fund relatively small, but essential facets of larger projects.

MVDP has played an important role in getting several vaccine candidates ready for testing in the field. Its objective, over the past several years, has been to move vaccines to the clinic and field as quickly as possible for proof of principle. Specifically, MVDP support has directly, or indirectly, enabled the work on the Merozoite Surface Protein (MSP1) and the Apical Merozoite Antigen (AMA1) vaccine candidates to move from early preclinical development to clinical trials.

MVDP has achieved a very well-balanced portfolio consisting of projects at different phases of malaria vaccine development, and projects involving different kinds of vaccine candidates. The investment choices were felt to be good ones.

Continuation of the Program

Although the momentum has been building rapidly, there is still so much to be done. Even given unlimited resources, the global effort to get a malaria vaccine licensed and into widespread use in developing countries is predicted to need at least another 10 years. Since MVDP is relatively small in terms of funding and staff, the evaluation team specifically inquired whether USAID should give its malaria vaccine development funds to a larger program. There was agreement that since MVDP has carved out such an importantly positive and unique role in the malaria vaccine development that MVDP should be kept as a separate entity within USAID.

One of the most compelling reasons that MVDP should continue its work is that there are so many potential candidate antigens available for testing today. If this work is not continued, there is a very great risk that progress on important MVDP-supported candidates, such as MSP1 and AMA1, will either be slowed or discontinued for lack of funding and/or for lack of outside expert guidance provided by MVDP.

There was no question that MVDP's goals and direction are in complete accord with USAID's mission of sustainable public health and equitable economic growth throughout the world. In fact, this effort is probably best located with USAID, so as to take advantage of its global health leadership role. It was also noted that since vaccines are considered to be the best prevention measure to control malaria, it would be short-sighted of USAID to discontinue MVDP.

Lessons Learned

The MVDP, like other public and private entities, needs to be more aggressive in pursuing formal agreements with its partners, in order to ensure that if a successful vaccine were developed with its funding, the vaccine would be made available to the populations that need it.

There is no question that progress toward the goal of getting effective malaria vaccines to children and pregnant women in developing countries is *severely* hindered by a lack of resources.

Progress is jeopardized as a result of limited staffing, both of the MVDP and of its partners. The recent re-deployment of several key members of the Walter Reed Army Institute of Research (WRAIR) staff involved in MVDP projects, to responsibilities related to a national emergency, highlights the importance of being able to be responsive and flexible. This issue is made more acute because there is a general lack of depth in staffing and resources throughout the malaria vaccine development field.

RECOMMENDATIONS

General Recommendations

It was *strongly* recommended that USAID's Malaria Vaccine Development Program be continued and, if at all possible, expanded. Everyone agreed that the MVDP has played a key role, and that its financial and expert support of promising projects is critical to maintaining this momentum. MVDP's flexibility and astute investment insight have allowed it to leverage its funds exceptionally well.

There was a consensus that, although USAID contributes a relatively small proportion of the global malaria vaccine development budget, its financial contribution is *very important*. It was noted that this area is so severely under-funded, that the loss of *any* resources would be detrimental to the overall effort, and could markedly slow the process of getting a malaria vaccine to the field. There was concern from experts in malaria, as well as from experts in other fields, such as international health and infectious diseases, that a termination of the MVDP could send a message to the world that USAID was ignoring what considered by most to be the best strategy for controlling malaria in developing countries in the long run.

Although most interviewees acknowledged USAID's fiscal constraints, they repeatedly requested that we include a recommendation for substantially more funding for MVDP in this report.

Options for Future Activities

Rapid progress in malaria vaccine development has necessitated a reevaluation of MVDP's priorities. Although there was a consensus that current efforts be maintained,

two additional categories of options were proposed for consideration, namely, those options that can be supported at the current funding level, and those options representing critical unmet needs that could be addressed only if MVDP were to receive a significant increase in resources.

Continuation at Current Funding Level

The following recommendations apply if the funding level for the MVDP remains at approximately the current level.

1. **Ensure portfolio balance**. MVDP should continue to invest in a diversified portfolio instead of re-focusing its resources more narrowly on only one or two specific areas of product development.

2. **Coordinate with other malaria vaccine developers.** MVDP has been successful in its efforts to coordinate its activities with other malaria vaccine developers, and this should continue, in order to help ensure synergy, prevent duplication of effort, and thereby speed product development.

3. **Develop more robust partnerships.** There was consensus that MVDP should devote more effort in the future to securing formal, written agreements with its partners, particularly those in the private sector, in order to permit more effective long-term planning, to more clearly delineate roles and responsibilities, to better protect intellectual property rights, and to ensure optimal program implementation.

4. **Pursue other preclinical lines of investigation.** The MVDP staff should continue to fund select preclinical projects that have a direct bearing on product development, because this strategy has the potential of speeding up delivery of vaccine to the field.

5. **Build capacity.** The MVDP cannot assume a major role in field site capacity building at its current level of funding. That said, it was felt that if the MVDP's staff identifies a specific critical need that would keep the pipeline open, including the field testing of specific vaccine candidates, it should have sufficient flexibility to use its resources to fill it.

Continuation at an Increased Funding Level

The following are unmet needs that MVDP could consider funding if its budget increased:

1. **Increase participation in coordination efforts.** With additional staff, MVDP could be more supportive of not just national, but also international efforts by WHO and others in convening stakeholder meetings on a regular schedule to facilitate planning and help speed progress. The agenda could be expanded to address a broad array of timely topics, including how to raise more funds for the global malaria vaccine development effort. *Pursue other preclinical lines of investigation.* The MVDP could

get involved in much more expensive preclinical pursuits than it currently can fund. These could include a more aggressive evaluation of potentially useful antigens and platforms, validation of key assays, and a more intense focus on the development of correlates of immunity.

2. **Build capacity.** With sufficient increases in funding, there are several ways that MVDP could gain more control over field site evaluation. The two recommendations for MVDP activities to build capacity include:

   - Field site capacity. It is highly desirable that MVDP be given more resources, so that it can become involved with building capacity as it moves vaccines into field studies. There is a need to prepare existing and new sites to handle the projected number of field trials that will be needed to establish vaccine safety, immunogenicity, and proof of concept in the near future. Strengthening local capacity will contribute to other vaccine development initiatives, as well as to sustainable public health programs.

   - Training programs. One important recommendation that would also further USAID's mission of sustainable development, is that the MVDP develop a program to identify and train talented investigators from developing countries.

3. **Other problem-solving opportunities.**

   - Foster agreements. MVDP could not only obtain advice on fostering agreements to protect its intellectual property rights, but it could also establish models, and provide consultation for its partners to help them protect their interests and to ensure that program implementation has well-defined milestones.

   - Ensure public acceptance. It was noted that there is a vital need to educate the public to help gain acceptance and manage expectations, both for conducting field studies and for the eventual widespread use of a vaccine.

   - Deal with special problems. It was strongly suggested that the MVDP be given more resources to help partners deal with special problems that present barriers to getting vaccines to the field. A good example is MVDP's providing resources, such as an MVDP staff member, who could expedite the Investigational New Drug (IND) submission process. No other funder could support this function, even though it could help eliminate a major obstacle to getting a vaccine from the bench to the field.

4. **Achievement of a major milestone.** It was agreed that if a vaccine candidate suddenly emerged from proof of concept clinical trials as exceptionally likely to significantly reduce morbidity and mortality from malaria in children and pregnant women in developing countries—it would be vital that MVDP funding be dramatically increased.

Staffing needs. It is important to note that the MVDP staff already are functioning very efficiently and accomplishing much more than would normally be expected, so it is not realistic to expect them to embark on new activities without more help. Therefore, if MVDP is given more resources, it will be imperative that it also have more personnel to meet new requirements.

Scientific Consultants Group

It was felt that the Scientific Consultants Group (SCG) should continue to function in the same capacity as it has in the past. In addition to its two annual meetings, there was consensus that the MVDP staff should continue to call on individual members of the SCG to provide expert advice on an ad hoc basis.

Succession

USAID needs to ensure qualified succession to the current MVDP leadership. The MVDP has only two staff members; the loss of either, but particularly the Director, would seriously jeopardize the future of the entire program. To ensure a successful continuation of the MVDP, the program should be better coordinated with other Agency malaria efforts, so that future staffing requirements can be developed over time. It was noted that the wealth of new opportunities afforded by recent advances (particularly as vaccine candidates enter clinical testing), makes this the perfect time to enlist additional staff in accordance with new technical requirements. It is crucial that any new staff have a strong scientific background and be well-grounded in malariology in order to enable the MVDP to maintain its leadership role in malaria vaccine development.

I. INTRODUCTION

OBJECTIVE

The objective of this evaluation was to assess the accomplishments of the United States Agency for International Development (USAID) Malaria Vaccine Development Program (MVDP) over the past decade. The goals were to:

- Evaluate progress made, and identify the potential for acceleration, as a predictor of future progress and investment potential;
- Define USAID's current and future unique role/niche in the development of malaria vaccines; and
- Identify ways to improve the program in the future.

PROJECT BACKGROUND

History

USAID has supported malaria vaccine development for over 35 years. MVDP was created in the late 1960s' in response to the termination of the Malaria Eradication Program. Its history can be divided into four phases:

- 1966-74. Focus on single center research and development with the objective of developing a malaria vaccine.
- 1974-79. Establishment of a network of partners and a variety of research approaches to cellular (sporozoite & merozoite) vaccines based on the academic model.
- 1980-88. Use of molecular approaches and the performance of a clinical trial of New York University's peptide vaccine at the University of Maryland's Center for Vaccine Development.
- 1988-present. Focus on products and a progression to clinical trials.

Authorization

When it was authorized in 1992, the Malaria Vaccine Development Project No: 936-6001 consolidated the efforts of two earlier projects: the Malaria Immunity and Vaccine Research Project (931-0453), and the Malaria Field Trials Project (936-5967). It should be noted that all of these *projects* have been part of the Malaria Vaccine Development *Program.*

The MVDP is currently authorized under a document termed a project paper. This document allows for a wide variety of activities related to vaccine development. The current project (936-6001), originally authorized until 2002, and has been extended until 2003.

Focus

The MVDP's goal is to speed the development of vaccines, in order to protect children and pregnant women from death and from serious disease in malaria endemic areas. In recent years, the MVDP has focused on building a pipeline from early preclinical vaccine development, through the regulatory process, and to clinical and field testing of vaccine candidates. To achieve its aims, the MVDP has pursued the three main areas of development that currently show the most promise for getting effective vaccines to the field. These involve:

- Production and testing of protein subunit vaccines;
- Evaluation of new platform technologies for vaccine development and adjuvant formulations; and
- Development of vaccine strategies to overcome strain variability and the emergence of escape mutants.

Operations

Operationally, the MVDP is located within the Infectious Diseases Division of the Health, Infectious Diseases and Nutrition (HIDN) Office in the Bureau for Global Health of USAID. It is staffed by one full-time, in-house contractor (Carter Diggs, Senior Technical Advisor) and one full-time, off-site contractor (Lorraine Soisson, Technical Advisor).

Funding

The project authorization is $116,000,000, and expenditures have totaled $59,750,277. As can be seen in Figure 1, funding for the MVDP reached its peak in 1985, at over $13 million. It then dropped precipitously from 1993 to 1995, and began to increase slightly beginning in 1998, and was $4.7 million in 2002.[1] This makes MVDP a major contributor to malaria vaccine development on a global level, ranking just below the NIH, the PATH Malaria Vaccine Initiative (MVI), and the Department of Defense (DOD).[2]

To put the MVDP funding in perspective within USAID, it is useful to compare it to funding for the overall malaria program. The budget for all malaria projects at USAID

[1] See Figure 1, Appendix F, "MVDP Budget 1979-2002."
[2] See Figure 2, Appendix F, "Malaria Vaccine Research and Development (R&D) Expenditures: All Donors Worldwide."

has grown from over $20 million in 1999, to more than $60 million in 2002.[3] During that period, the relative proportion devoted to malaria vaccine development has shrunk from over 10 percent to approximately 6 percent.

Partners

The global malaria vaccine development effort involves numerous stakeholders.[4] The MVDP has established good working relationships with these organizations. In addition, as it has made the transition from basic discovery in academic institutions to a widely diversified portfolio focused on moving vaccines quickly to proof of principle - MVDP has developed close partnerships in both the public and private sectors. It has employed a variety of mechanisms to move funds to implementers, ranging from informal negotiations and sub-agreements, providing flexibility, to more formal contracts, cooperative agreements (CAs), and interagency agreements (IAAs).[5] Some of the MVDP's partners are as follows:

- **Walter Reed Army Institute of Research.** The focus of the Walter Reed Army Institute of Research (WRAIR) is on developing, producing, and performing clinical and field evaluations of protein subunit vaccines. WRAIR is working in collaboration with GSK (GlaxoSmithKline) and the Malaria Vaccine Initiative (MVI) of the Program for Appropriate Technology in Health (PATH). In 2003, the MVDP will provide 21 percent of the total budget for the United States Army's malaria vaccine development work at the WRAIR.[6]

- **Naval Medical Research Center.** The Naval Medical Research Center (NMRC) has pursued DNA-based strategies in the past, and currently is working on advanced vaccine construction and formulations, including pox and adenovirus vectored vaccines (in collaboration with Genvec), and replicons (in collaboration with Alphavax). In 2003, the MVDP will provide 12 percent of the total budget for the NMRC's malaria program.[7]

- **NIH.** Currently, the MVDP is funding a project conducted by NIH and by Maxygen involving a proprietary technology termed "molecular breeding." Previously, the MVDP has provided considerable support to collaborative efforts with NIH. Examples include Phase I testing of an early blood stage vaccine formulation and of the Circumsporozoite Surface Protein (CSP) multiple antigen peptide (in collaboration with New York University). The MVDP has also provided initial funding for the creation of the National Institute for Allergy and Infectious Diseases (NIAID) Malaria Vaccine Development Unit.

[3] See Figure 3, Appendix F, "USAID Malaria Funding Trends."
[4] See Figure 4, Appendix F, "Institutions Involved in Malaria Vaccine Development."
[5] See Figure 5, Appendix F, "USAID MVDP Cluster of Partnerships."
[6] See Figure 6, Appendix F, "US Army Malaria Vaccine Budget FY 03."
[7] See Figure 7, Appendix F, "Naval Medical Research Center Malaria Program Budget FY 03."

- **Maxygen.** As noted above, the MVDP is providing support for the collaborative project between NIH and Maxygen, using Maxygen's proprietary "molecular breeding" technology. The goal is to develop a vaccine targeted against a specific hypervariable asexual stage antigen. The technology is designed to overcome this hypervariability. This work has the promise of overcoming strain variability and the emergence of escape mutants.

- **Centers for Disease Control and Prevention.** The MVDP has an agreement with the Centers for Disease Control and Prevention (CDC) to study vaccine candidates resulting from these three strategies in non-human primates.

- As noted above, **MVI** is collaborating with WRAIR in evaluating protein subunit vaccines in field trials.

- **Australian Programs.** The MVDP has supported the Australian program through the funding of RAP2 studies at the Queensland Institute of Medical Research and the CDC, as well as early evaluation of Merozoite Surface Protein-4 (MSP-4) at Monash University. In addition, it supported the early development of a field trial site in Papua New Guinea.

EVALUATION METHODOLOGY

This evaluation was carried out by a five-member team from November 2002, through February 2003. The full scope of work can be found in Appendix A.

First, the evaluation team conducted a thorough review of documents related to the MVDP, and to malaria vaccine development. See Appendix C for a list of documents and publications reviewed. The team then reviewed the MVDP's activities, operations, and management together with the MVDP staff and with other knowledgeable USAID personnel. Because of the importance of public-private partnerships to the MVDP, the evaluation team leader attended a two-day conference, "The Partnering for Global Health Forum 2002," presented by the Biotechnology Industry Organization (BIO) and the Bill and Melinda Gates Foundation. Finally, the team interviewed cooperating partners, funders of malaria vaccine development projects, and other experts in the fields of malaria and malaria vaccines, vaccine development, international maternal and child health, and intellectual property rights. See Appendix B for a complete list of persons interviewed.

Interviews were conducted either in person or by telephone. The length of the interviews ranged from a few minutes to over two hours, depending on the specific background and experience of the person interviewed. The interviews centered around three main categories of inquiry (See Appendix D for a complete list of interview questions):

- Is the project important? Has it been successful? What has it accomplished?
- Should the MVDP continue?
- If it should continue, what kinds of activities should it pursue in the future?

This report is organized into two key parts. Section II represents the evaluation team's findings and conclusions, and includes a review of: 1) the importance of developing a malaria vaccine; 2) the success of the project; 3) the MVDP's accomplishments since 1992; 4) the rationale for continuing the program; and 5) lessons learned.

Section III contains the evaluation team's recommendations for the MVDP's future activities. These include: 1) general recommendations as to how the MVDP should proceed; 2) options for projects that the MVDP could pursue, if its funding remains at its current level; 3) options for projects it could undertake, if its funding level were substantially increased; 4) the future role of the Scientific Consultants Group (SCG); and 5) the importance of developing a successor to the MVDP's leadership from within the program.

II. FINDINGS AND CONCLUSIONS

IMPORTANCE

Health

The importance of preventing death and serious disease from malaria in children and pregnant women in developing countries cannot be overstated. An estimated 300 to 500 million people are infected with this disease each year, and 2 to 3 million die.[8] Severe disease, such as cerebral malaria, often results in permanent disability.

Those at the highest risk of dying or of developing serious long-term damage are people who have not developed immunity to the organism, and those with decreased immunity. These groups include travelers, young children, pregnant women, and people who once lived in endemic regions, but are no longer routinely exposed to the infection.

Economic Impact

In addition to its profound effect on health, **malaria has a major impact on the economic development and political stability of endemic areas.** In its 2001 report, the Commission on Macroeconomics and Health of the World Health Organization (WHO) reported that a handful of conditions, including malaria, tuberculosis, and HIV/AIDS, are so widespread and debilitating that they are capable of destabilizing economies and entire political systems.[9] Between 1960 and 1994, they found that a high infant mortality rate from diseases like malaria was one of the key "predictors of State failure through coups, civil war, and other unconstitutional changes in regime". In contrast, they found that when infant mortality rates decreased, birth rates also fell, and economic growth followed. They concluded that:

> Disease control is one of the most important causal factors in a country's transition from a pattern of high mortality, high fertility, and low economic growth, to a pattern of low mortality, low fertility, and high economic growth.

Role of Malaria Vaccines

Malaria is a re-emerging disease. Its impact continues to grow despite several decades of treatment and prevention programs. The resurging threat from malaria stems from several factors, the most important of which are: the growing problem of parasite resistance to currently available drugs; and the decreasing ability of the public health infrastructure in many endemic regions to keep up with the local need for drugs and vector control (e.g., bed nets and insecticides). The consensus was that, ultimately, the most effective way to control (e.g., prevent death and severe disease) malaria will be to

[8] World Health Organization. *Weekly Epidemiological Record of the World Health Organization.* 1996, 71:(3):17.
[9] World Health Organization, Commission on Macroeconomics and Health. *Macroeconomics and Health: Investing in Health for Economic Development.* December, 2001.

develop a vaccine that is effective in vulnerable populations, particularly children and pregnant women in endemic areas. In addition, it is predicted that, in the long run (future decades), a vaccine will be much more cost-effective than reliance on current control measures.

SUCCESS OF THE PROJECT

This is a very exciting time **in malaria vaccine development, and the MVDP has been a key player.** The first question asked by the evaluation team in interviews was: "Has the MVDP been successful over the past few years?" The response was a resounding and enthusiastic "yes!" The evaluation team was struck by the glowing praise, and the uniformity of opinion that the MVDP has been *extraordinarily* successful in its mission to move vaccines to the clinic and field for proof of principle, as quickly as possible. Several prominent individuals were puzzled that we even bothered to ask this question, since they felt that the MVDP's contributions had been so important.

Over the past few years, **progress in malaria vaccine development has accelerated dramatically, and the MVDP is felt to have played a critical role in** creating this momentum, despite the fact that some other organizations have contributed more funding.[10] The MVDP has maintained the focus of vaccine development on vulnerable populations in endemic countries. Most of those interviewed mentioned how well the MVDP has leveraged its money. Many alluded to the MVDP's getting a tremendous "bang for its buck." It was apparent that the current MVDP leadership has achieved major visibility for USAID, despite its small budget, but interviewees discounted the idea that its financial contributions merely bought USAID "a seat at the table". All agreed that the MVDP has assumed a vital role in maintaining a focus on developing vaccines to protect individuals living in endemic regions—in contrast to other partners whose internal missions were more oriented to the travelers' or the military market. In addition to keeping attention focused on people with the greatest need, the MVDP also has helped accelerate progress by helping partners better focus their resources on more promising aspects of their projects (e.g., the Navy's program), and by helping speed the Investigational New Drug (IND) process.

The MVDP has leveraged its resources well. There was strong consensus that the superb performance of its staff on a number of fronts afforded the MVDP a degree of influence that was clearly disproportionate to its level of funding. Elements contributing to this success include:

- **The MVDP staff has a solid understanding of malariology, and has maintained exceptional goal-directed, product-oriented focus**. These factors have enabled it to repeatedly identify crucial gaps or barriers to getting the product to the field, and to create for itself a unique niche as a catalyst and problem-solver.

[10] See Figure 2.

- **The MVDP has been able to communicate effectively and to work very closely with partners and funding organizations alike.** Its ability to work so well with the various stakeholders has enabled it to help insure that the efforts of the different groups are complementary, and not duplicative.

- **The MVDP is extraordinarily flexible,** permitting it to help its partners to rapidly shift direction, if projects proved not to be as fruitful as anticipated, or if promising new projects arose. This flexibility has permitted the MVDP to make faster progress toward its goal of getting vaccine to the clinic and field, and it has minimized waste of resources.

- **The MVDP has created an exceptionally talented and dedicated Scientific Consultants Group**, and it uses this resource quite effectively.

- **The MVDP has been very successful at identifying appropriate experts** (drawn from staff, Scientific Consultants Group members, and others in the field) to help its partners optimize their resources.

It is clear from interviews that if the MVDP had never existed, several promising malaria vaccine candidates would not be nearly as far along in the development process as they are today, or that they would never have been developed at all.

ACCOMPLISHMENTS

Unique Role/Niche

The MVDP has established a unique role or niche for itself as a catalyst and a problem-solver. Its role has enabled it to be a key player and leader in the malaria vaccine field. The MVDP is unique among funding entities in that its staff has a thorough understanding of the whole spectrum of malaria vaccine development issues. The MVDP also is unique because it has been much more flexible in its ability to allocate funds to relatively small parts of larger endeavors that no one else could fund. Further, it has been able to act much more quickly than have other funders. This combination of expertise, flexibility, and prompt action has enabled it to accurately pinpoint relatively small, but key, investment opportunities, to rapidly step in to keep promising projects on track, and to help initiate new projects without delay. It has kept some very large programs from being terminated.

An example of the MVDP's action to provide support for key activities was its identifying that—the lack of expertise and staff submissions of Investigational New Drugs (INDs) was an important barrier to moving vaccine candidates through the pipeline, from early development to clinical testing. Once the MVDP provided support for its partners, the IND process accelerated dramatically. The MVDP also stepped in to fund trials using FVO in Aotus monkeys, in order to provide proof that this promising candidate could afford protection. Further, the MVDP's support enabled work on the exciting project on molecular breeding to be initiated by Maxygen and by the NIH..

Without the MVDP's support, this project would not have been feasible, and the strategy that has the most potential to overcome the very serious problems of strain variability and the emergence of escape mutants would not have been pursued.

It was repeatedly noted that the MVDP has a remarkable ability to make a relatively small budget go a long way, by successfully identifying strategic projects that are vital to keeping the pipeline flowing. It was clear from all those queried, that USAID funding for malaria vaccine development does not merely ensure USAID a "seat at the table," but it has empowered the MVDP to fill an absolutely critical niche in malaria vaccine development.

Working Relationships

The MVDP has worked extremely effectively with its partners. Partners have noted that the MVDP is always on top of the rapidly changing field of malaria vaccine development, and is exceptionally responsive when there is a need to promptly change direction based on new findings. This is due, in large part, to the MVDP's close monitoring of its projects—by holding regularly scheduled meetings to review progress, and by maintaining open lines of communication with its partners at all times.

The MVDP differs from other funding organizations in that, in most cases, it has much more flexibility in its ability to re-allocate resources promptly when necessary.

Although there is no formal coordination among the donors who fund malaria vaccine development, it is clear that the MVDP is well-respected. Other donors felt that it was very important for USAID to be involved in long-term solutions, as well as in immediate malaria control programs. They had high praise for the MVDP's work, and for its cooperative attitude. Several cited the importance of the role it has played in stimulating communication among the various funders, both within the U.S. and internationally.

Specific Achievements

The MVDP has played an important guiding role in getting several vaccine candidates ready to be tested in the field.[11] Its objective, over the past several years, has been to move vaccines to the clinic and field as quickly as possible, for proof of principle. To achieve this goal, the MVDP has built a pipeline for vaccine evaluation. Specifically, it has provided the guidance and resources to help:

- Identify target antigens, constructs, and vaccine formulations;
- Select a team to refine planning, and to implement;
- Develop processes for pilot production;

[11] For an excellent review of malaria vaccine development, see: James, Stephanie and Louis Miller. "Malaria vaccine development: Status report." *Nature Medicine, Special Focus: Malaria*, 9-13, 2000.

- Produce clinical grade vaccines;
- Develop and implement a regulatory plan;
- Evaluate safety, immunogenicity and efficacy in preclinical, clinical and field studies; and
- Seek correlates of efficacy.

Interviewees **noted the importance of the MVDP's simultaneous investments in several different promising vaccine venues,** in a parallel development approach. The rationale is that it will take many years to determine whether or not an individual candidate will eventually prove to be safe and effective in the field. If vaccine candidates are developed in a linear fashion, or one at a time, excellent candidates may never be tested, or their testing could be delayed many years.

The MVDP has focused mainly on *Plasmodium falciparum*, and on blood stage approaches, but also has been working on a combination of approaches. The MVDP's strategy has pushed several promising candidates along swiftly, especially Merozoite Surface Protein 1 (MSP1) and Apical Merozoite Antigen 1 (AMA1). The MVDP's investment in basic preclinical work paid off and also its investment in helping partners with a regulatory plan which helped and speeded progress with Investigational New Drug (IND) submission. Currently, there are several vaccine candidates ready for IND submission and field testing.

Specifically, the MVDP's support has directly, or indirectly, enabled the following:

<u>MSP1</u>

- Recruitment of a molecular biologist at WRAIR in 1995;
- Initiation of process development at WRAIR;
- Development of a process for production of MSP1 in *E. coli;*
- Collaboration between WRAIR and GSK for vaccine formulation;
- Production of the first GMP lot;
- Performance of an initial Phase I trial at WRAIR that demonstrated safety and immunogenicity;
- Performance of a Phase IIa trial at WRAIR, in combination with RTS,S in 2001;

- Performance of Aotus monkey trials using FVO immunogen, that suggested allele specific protection;

- MVI supported field trials in Kenya in 2002, with Phase I trials in children scheduled for 2003;

- Initiation of NIH supported Phase Ib field trials in Mali in 2003; and

- IND Preparation and Submission.

AMA1

- Production of the ectodomain of 3D7 in *E. coli;*

- Formulation of a vaccine with GSK adjuvant;

- Demonstration that sera from immunized rhesus monkeys inhibits parasite growth *in vitro*;

- IND preparation and submission (imminent); and

- Performance of Phase I trial at WRAIR in early 2003.

Current Portfolio

The MVDP has achieved a very well-balanced portfolio in that it has invested in a variety of key, but diverse projects, ranging from clinical trials (MSP1 and AMA1) to early, but promising discovery (Maxygen). Interviewees felt that these projects were good choices for USAID resources. One of the reasons its investments are so evenly dispersed is that the MVDP has been intimately involved in the development of each of the elements listed above. It has not only provided funding, but also key expert input. The MVDP's current portfolio consists of the following:

Downstream

Downstream activities at the Walter Read Army Institute of Research include production, and clinical and field evaluation of investigational vaccines, as well as the development of assays for clinical evaluation (WRAIR, GSK, and MVI collaboration). The vaccines being tested include the following activities:

- MSP1

    - Field trials in Kenya and Mali;

    - Evaluation of processing inhibition, as a correlate/surrogate of protection;

- Additional Merozoite Surface Protein (MSP) vaccines in the pipeline, including the 42 kilodalton (kDa) *Plasmodium falciparum* Vietnam-Oak Knoll (FVO), and full length 3D7 and FCB1 MSO1 molecules.

- AMA1

  - Phase I studies at WRAIR;
  - FVO in the pipeline.

Midstream

Midstream activities are being performed at the Naval Medical Research Center (NMRC) and include:

- Pox and adenovirus vectored vaccines (in collaboration with Genvec);
- Replicons (in collaboration with Alphavax).

Upstream

Upstream activities facilitate the application of promising new technologies to the development of malaria vaccines - an opportunity that, without MVDP input, would likely be lost, due to a perceived lack of profitability by the biotechnology industry. These efforts are currently focused on an innovative approach to solving the problem of antigenic variation, through molecular breeding (polyimmunogenic EMP1 vaccines). These studies are being performed by Maxygen and by the National Institute for Allergy and Infectious Diseases (NIAID) Malaria Vaccine Development Unit.

Scientific Consultants Group

The MVDP has developed an excellent Scientific Consultants Group (SCG). The SCG meets twice a year to review all MVDP activities. In addition, the MVDP staff calls on individual members of the SCG periodically for expert advice. There was strong agreement that input from this group has been invaluable to the MVDP partners, and that it is an important resource to the field of malaria vaccine development. There also was consensus that the SCG currently is functioning quite well, and that the MVDP staff are using it effectively. Although some recommended an expanded role for this group, including its approval of new projects funded by MVDP, and its provision of more direct project oversight - it was felt that such oversight would limit the MVDP's flexibility, and therefore its effectiveness. In addition, although the members of the consultant group clearly enjoyed participating at the current level of activity, only a few said that they could devote more time to MVDP. That said, the consultant group members volunteered that, since the MVDP staff had been respectful of their time and had always approached them about appropriate issues, they remained quite willing to be called upon for help on an ad hoc basis in the future.

CONTINUATION OF THE PROGRAM

Everyone interviewed agreed that there were vital reasons for the MVDP's work to continue, since it played such a unique and critical role in malaria vaccine development. **Any decrease in current funding,** particularly the elimination of a program that has been as effective as the MVDP, **could delay the availability of a malaria vaccine** by many years.

Although momentum has been building rapidly, there is still so much to be done that even given unlimited resources, the global effort is predicted to need more than another 10 years to get a malaria vaccine licensed and into widespread use in developing countries.

Since the MVDP is relatively small in terms of funding and staff, the evaluation team specifically inquired whether USAID should provide its malaria vaccine development funds to a larger program such as to NIH or to PATH Malaria Vaccine Initiative (MVI), rather than keeping the MVDP within the Agency. There was agreement that the MVDP has formed such an important and unique role for itself that the entire field of malaria vaccine development benefits by keeping it as a separate entity housed within USAID. The MVDP's in-house expertise, in combination with its flexibility to fund small projects that no one else could support, have made it unique in its ability to quickly identify and overcome barriers to moving vaccine candidates through the pipeline.

Availability of Many Promising Candidates

One of the most compelling reasons that the MVDP should continue its work is that **there are so many potential candidate antigens available for testing today.** There was strong agreement that currently identified plasmodium antigens are very viable vaccine candidates. Although scientific advances, such as genomic sequencing, may introduce new vaccine ideas, it is imperative that work on currently available candidates continue. Moreover, ongoing clinical evaluation of these candidates has already, and will continue to provide an understanding of human immunity that is critical to malaria vaccine development, and which is unavailable by any other means. If this work is not continued, there is a very great risk that progress on important candidates will either be slowed or discontinued, for lack of funding and/or outside expert guidance from the MVDP.

Maintaining Momentum

There has never been a more important time to keep up the momentum in the field of malaria vaccine development. Recent scientific breakthroughs have accelerated discovery to almost dizzying proportions, providing enormously exciting candidates for testing. Currently, there are more promising malaria vaccine candidates ready for the IND process than there are resources to push them through the pipeline. It is imperative that several avenues of investigation be pursued simultaneously, so that if, in the end, a particular candidate is not proven to be safe or effective, years will not be lost as another

candidate is developed. Also, since work in malaria vaccines is highly specialized - if a given line of inquiry is not adequately funded, it is highly likely that the investigators will move on to other projects. Even small decreases in funding could seriously jeopardize the recent highly accelerated pace of malaria vaccine discovery and development.

Lost Opportunities

If the MVDP is not continued, several key avenues of progress will be in jeopardy. These include work with the Walter Read Army Institute of Research on Merozoite Surface Protein (MSP1) and on Apical Merozoite Antigen (AMA1) projects; and with the Naval Medical Research Center on new vaccine formulations; and with NIH and with Maxygen, on the exploration of ways to create vaccines that can overcome strain variability and the emergence of escape mutants. Specifically, clinical and field testing of vaccines that already has been developed (e.g., MSP1 and AMA1) will stop. Also, if the MVDP does not continue to support IND submissions, several excellent vaccine candidates may never be tested, because other funders do not provide resources for this kind of support.

Relevance to USAID Priorities

There was no question that the **MVDP's goals and direction were in complete accord with and support of USAID's mission** of sustainable public health and equitable economic growth throughout the world. In fact, this effort is probably best located with USAID, so as to take advantage of its global health leadership role. It was noted that since vaccines are widely considered to be potentially the best prevention measure to control malaria, it would be short-sighted of USAID to discontinue the MVDP. In addition, the loss of the MVDP's influence in maintaining a focus on vaccines for children in endemic areas, could risk a shift back to emphasis on "traveler's" vaccines by the private sector and/or the military, thereby creating the potential for the magnifying of the effective loss.

Funding

Even though **the MVDP** contributes only small amounts of funding compared with other organizations such as NIH and MVI, it has become not only relevant, but **essential, to maintaining the accelerated pace of malaria vaccine development by its wisely leveraging those funds.** It has assiduously selected small, but key, facets of projects that keep the development pipeline open. Examples include: the MSP1 field trial in Kenya, the AMA1 Phase I trial that will take place in early 2003, and support for IND submission for MSP1 and AMA1 candidate vaccines.

It was clear that no one interviewed suggested that the MVDP alone should shoulder the burden of bringing to a reasonable level the funding for malaria vaccine development. However, those interviewed widely agreed that it was unfortunate that such a talented team had such limited resources at its disposal. This report, in the "Recommendations:

Continuation at a higher fund level" section below, contains several specific options as to how the MVDP could utilize increased funds. In brief, these options include:

- Convening international stakeholders;
- Pursuing additional preclinical lines of investigation;
- Building capacity by improving currently existing field sites, and creating a training program for investigators from developing countries;
- Helping partners protect intellectual property rights; and
- Working to help ensure public acceptance of vaccine trials, and the vaccine itself, once it becomes available for general use in endemic areas.

If a particular vaccine candidate were to appear to have striking potential for relatively near-term use in the field on a large scale (e.g., a major breakthrough), experts agree that it would be prudent to provide increased funding to accelerate its development and validation—even if this were to require a diversion of funding from the treatment and traditional prevention (e.g., bed net) programs, to vaccine production and administration—since a vaccine has such great potential to decrease morbidity and mortality from malaria.

LESSONS LEARNED

Agreements with Partners

The **MVDP's position is weak with regard to some private sector collaborators,** because it has not negotiated binding agreements to ensure that, if a successful vaccine were developed with its funding, it would be made available to the populations that need it. This fact had already been recognized by the MVDP staff prior to the onset of this evaluation, and they had begun to develop strategies to address the situation. It should be noted that this problem is not unique to the MVDP; and other public-private partnerships are struggling to develop workable solutions that guarantee access to vaccines developed under such partnerships. However, it was agreed that it is important for the MVDP to promptly seek a remedy to this situation.

Continuity of Funding

There is no question that **progress toward the end game of getting effective malaria vaccines to children and pregnant women in developing countries is severely hindered by a lack of resources.** Currently, there are more promising vaccine candidates in the pipeline than can be tested, because of a lack of funding.

Ability to React to Unexpected Problems

Limited staffing, both of the MVDP and of its partners, **jeopardizes progress.** The recent redeployment of several key members of the WRAIR staff, involved in MVDP projects, to responsibilities related to a national emergency, highlighted the importance of the ability to be responsive and flexible. This issue is made more acute, because there is a general lack of depth in staffing and resources throughout the malaria vaccine development field. This is a serious problem that, if not addressed in the near future, could lead to significant, and potentially years of delays.

IV. RECOMMENDATIONS

GENERAL RECOMMENDATIONS

Continuation of the Program

It was *strongly* recommended that the **MVDP be continued and, if at all possible, expanded.** This is an exciting time in malaria vaccine development, because progress is accelerating rapidly. Everyone agreed that the USAID's Malaria Vaccine Development Program (MVDP) has played a key role in this progress, and that its financial and expert support of promising projects is critical to maintaining this momentum. The MVDP's in-house expertise, flexibility, and astute investment insight have allowed it to leverage its funds exceptionally well, to fill a unique niche as a catalyst and as a problem-solver, and to maintain its leadership role in malaria vaccine development (see Accomplishments above).

Operations

It was clear from the interviews that the **MVDP is being managed extraordinarily well at the present time.** The MVDP staff has shown excellent judgment and management skills. It was recommended that the strategic allocation of resources should remain a staff function, since this management feature has worked so well in recent years.

Impact on the Global Malaria Vaccine Development

There was consensus that, even though **USAID** contributes a relatively small proportion of the global malaria vaccine development budget, its **financial contribution is very important.** It was noted that this area is so severely under-funded, that the loss of *any* resources would be detrimental to the overall effort, and could markedly slow the process of getting a malaria vaccine to the field. In particular, since the MVDP has leveraged its financial contributions so effectively, and funded small projects that no one else could - discontinuing this program would have a disproportionately negative impact. Furthermore, several of those interviewed suggested that if the MVDP were terminated, it could send a message to the world that USAID was ignoring the best strategy for controlling malaria in developing countries.

Funding Level

There was a **broad plea** from those outside the Agency, **for USAID to fund the MVDP at a substantially higher level.** Although most interviewees acknowledged USAID's fiscal constraints, they repeatedly requested that we include this recommendation in this report.

They cited several compelling reasons:

- **The need is great.** The long-term impact of controlling malaria in the developing world would be enormous in both health and economic terms, and vaccination is by far the most promising means to this end.

- This is a vital time to invest in malaria vaccine development, because **progress has accelerated so dramatically in recent years.** Continuing support is essential to field test the current vaccine candidates, to maintain the development pipeline, and to ensure eventual delivery of a final product. Markedly increased support would speed the availability of a malaria vaccine.

- **The MVDP has been influential** in ensuring that malaria vaccine development efforts remain focused on children and pregnant women in developing countries, and not just on more potentially lucrative markets, such as travelers and the military.

- **The transition of vaccine development from the laboratory to the field costs much more than early basic development** and many activities that are now needed to keep promising candidates moving through the pipeline are too expensive for the MVDP to tackle at its current funding level. Although current funding will enable it to continue to make forward progress through strategic partnerships, there is no doubt that the process would move much faster if it had a substantially higher infusion of resources.

- **The MVDP has clearly demonstrated its ability** to leverage its financial and expert resources well beyond expectations, over the past few years.

OPTIONS FOR FUTURE ACTIVITIES

Rapid progress in malaria vaccine development has necessitated a re-evaluation of the MVDP's priorities. Although there was consensus that current efforts be maintained, several additional options were proposed for consideration. These options are divided into two categories: those that can be supported at the current funding level, and those critical unmet needs that could be addressed, if the MVDP were to receive a significant increase in resources.

Continuation at the Current Funding Level

The following recommendations apply, if the funding level for the MVDP remains at approximately the current level.

1. **Portfolio balance.** MVDP should continue to invest in a diversified portfolio, instead of re-focusing its resources more narrowly on only one or two specific areas of product development. There was consensus that the MVDP's portfolio was quite well-balanced, and that it should continue to operate much as it has in recent years, so

that it could continue to be proactive and flexible. These traits have enabled it to leverage its funds successfully, and to fill the niche of "catalyst" and "problem-solver," and to become a leader in the field. The MVDP has been able to identify and to act rapidly to fill crucial gaps in a variety of on-going projects, to help kick-start new initiatives, and to ensure that promising pursuits continued to move swiftly through the pipeline. Narrowing its scope would limit its flexibility and could curtail vital projects, thus resulting in delays in the entire field of malaria vaccine development.

2. **Convening national stakeholders.** The MVDP is uniquely positioned to be a convener, particularly at the national level. It already has been playing an important role in facilitating communications and in informally convening U.S. stakeholders in malaria vaccine development. It clearly has worked closely and effectively with other groups. It is well-respected, not only because it has filled such an important niche, but also because it is perceived as being neutral, in that its only goal is to get malaria vaccine to children and pregnant women in developing countries. Although there was a strong opinion that no one organization could, or should assume the leadership role per se in the malaria vaccine development effort, there was consensus that the MVDP could perform a convening function that would help ensure synergy, prevent duplication of effort, and thereby speed product development.

3. **Protecting intellectual property rights.** There was consensus that the MVDP should devote more effort in the future to securing formal, written agreements with its partners, particularly those in the private sector. These agreements would guarantee that intellectual property and products developed with the MVDP's support will be available for use in developing countries, whether or not the partner ends up using them. It was acknowledged that, as a government agency, the MVDP most likely will not be able to strike exactly the same kinds of partnerships with industry, as have private entities, such as the Gates-funded PATH MVI. That said, it was still felt that the MVDP's approach to collaborations, in general, should be similar to that elucidated in "PATH's Guiding Principles for Private Sector Collaboration,"[12] which addresses:

   - Transfer of a technology developed or owned by PATH;
   - Support by PATH for the development of a collaborator's product; and
   - Support by PATH for introduction of a collaborator's product.

These principles include a definition of roles, responsibilities, and expectations, as well as the recognition of private sector needs such as:

- The legitimate need of the private sector to pursue a profit, in order to ensure a sustainable supply of the product.

- Recognition of the full range of costs necessary from product development to commercialization.

[12] See Appendix E for the full document " PATH's Guiding Principles for Private Sector Collaboration."

It is also important that agreements provide a clear guidance for decision-making, including pre-established milestones and go/no go criteria for each phase of the project.

There are several ways in which the MVDP could obtain the necessary legal, business, and intellectual property rights (IPR) expertise. Using the USAID's in-house legal staff was not considered to be a good option, since the in-house staff would have very limited time to spend on the MVDP, due to other pressing USAID demands. It was suggested that the MVDP either bring someone on staff to work exclusively on its legal issues, or that it develop an outside contractual arrangement for the required advice, on an as-needed basis. The latter option was felt to be the most viable.

However as it acquires the expertise, the MVDP needs to develop a continuous relationship, so that the consultant fully understands its goals, as well as its needs and preferences. In addition, in order to keep products moving swiftly through the pipeline, the MVDP *must* have ready access to such advice at all times.

It also will be important for the MVDP to obtain advice from within the government, due to the special requirements of specific public institutions. It was strongly recommended that the MVDP seek expert advice from other government entities that have more experience than does USAID with technology transfer and intellectual property rights protection issues relating to vaccines. In particular, several interviewees noted the vast experience of the NIH with issues related to vaccines and to other biologicals.

4. **Pursuing other preclinical lines of investigation.** The MVDP should continue to fund select preclinical projects that have a direct bearing on product development, because this strategy has the potential to speed delivery of vaccine to the field. The MVDP should be encouraged to continue to look for new technologies that would further accelerate vaccine development and support their application to malaria. The MVDP should distribute funds just as it has over the past several years, case by case, based on an identified need for enabling technologies. Potential lines of inquiry could involve replicons, adjuvants, and correlates of immunity.

5. **Building capacity.** The MVDP cannot assume a major role in field site capacity building at its current level of funding**.** That said, it was felt that if the MVDP's staff identified a specific critical need that would keep the pipeline open, including the field testing of specific vaccine candidates, it should have sufficient flexibility to use its resources to fill it.

Continuation at Increased Funding Level

Funding for the malaria vaccine development effort throughout the world is woefully inadequate to meet the need, and this lack of funding is *severely* impeding progress. Since the current leadership of the MVDP has clearly done a remarkable job in achieving maximum "bang for the buck," it was strongly felt that this program would have an even more dramatic impact on the field, in most likely speeding the availability of vaccines by a matter of years, if it were given significantly increased resources.

The following are unmet needs that the MVDP could consider funding, if its budget increased:

1. **Enhanced participation in coordination efforts.** With additional staff, the MVDP could be more supportive of international efforts by WHO and others, in convening stakeholder meetings on a regular schedule to facilitate planning and to help speed progress. The agenda could be expanded to address a broad array of timely topics, including how to raise more funds for the global malaria vaccine development effort.

2. **Pursuing other preclinical lines of investigation.** The MVDP could get involved in much more expensive preclinical pursuits than it currently can fund. These could include a more aggressive evaluation of potentially useful antigens and platforms, the validation of key assays, and a more intense focus on the development of correlates of immunity.

3. **Building capacity.** The MVDP could gain more control over the field site evaluation of vaccine candidates. The major emphasis of the MVDP is on product development and testing, but it currently is not funded at a level that permits it to really push leading vaccine candidates through field testing, without cobbling together extensive collaborations. This leaves it with less control over the direction of the work. With sufficient increases in funding, there are several ways that the MVDP could gain more control over field site evaluation. This would not only be highly desirable from the perspective of malaria vaccine development, but it would also support other USAID development efforts.

    - **Field site capacity. It is highly desirable that the MVDP be given more resources, so that it can become involved with building capacity,** as it moves vaccines into field studies. The huge need for building field site capacity for testing new vaccine candidates was addressed by most people interviewed. Overall, most agreed that there will be a need to prepare existing and new sites to handle the projected number of field trials that will be needed to establish vaccine safety, immunogenicity, and proof of concept in the near future.

Some of the expensive projects noted included developing laboratory capacity, improving record keeping (including computerized databases), performing baseline studies of incidence and severity of disease, training local investigators and other personnel, and ensuring the availability of appropriate investigational review board (IRB)/ethics committee review. It was noted that such local capability strengthening has the potential to contribute to the development of vaccines to combat other infectious diseases important to the region, as well as to enhance the local medical and scientific infrastructure in ways that would contribute to sustainable public health programs.

- **Training programs. A relatively small investment in training would go a long way toward building capacity.** One important recommendation that would also further USAID's mission of sustainable development, is that the MVDP

develop a program to identify and train talented investigators from developing countries. It was noted that such a training program could provide sustainability for malaria vaccine development efforts. Several prominent experts in the field, including some members of the Scientific Consulting Group, have indicated a strong interest in helping the MVDP implement such a program.

4. **Other problem-solving opportunities.**

- **Agreements.** The MVDP could not only obtain advice on formulating agreements to protect its intellectual property rights, but it also could establish models, and provide consultation for its partners. Examples would include providing guidance on what issues should be addressed in each contract (e.g., who has the rights to the intellectual property in the developing world, versus developed countries like the United States), and as to what would constitute reasonable expectations for the public and private sectors respectively in each collaboration.

- **Ensuring public acceptance.** It was noted that there is a vital need to educate the public, so as to help gain public acceptance and to manage public expectations. In the short-term, there is a very real issue of getting local support for conducting field studies. In the long term, once a malaria vaccine is ready for widespread use, there will be a need to provide the public with sufficient information to ensure that the vaccine is accepted. The interviews suggested that the MVDP does not currently have the staff or the expertise to pursue public education at this point in time. However, given more staff and resources, it could work with others at USAID, and with local health ministries, to help ensure good participation in field trials, and to gain eventual acceptance of vaccines, once they are available for widespread use.

- **Dealing with special problems.** It was strongly suggested that the MVDP be given more resources to help partners deal with special problems that present barriers to getting vaccine to the field. Examples include the sudden and unexpected manpower issues that arose recently, when several key members of the WRAIR malaria vaccine development team were detained to deal with the current national emergencies related to terrorism and possible war. It was felt that, in order to ensure that the pipeline continues to flow, the MVDP should be able to help support personnel who are urgently needed to continue clinical trials.

There are several mechanisms that it could employ, including providing funding for contractors or additional personnel. In addition, it was noted that since the MVDP staff (Lorraine Soisson) has been so effective at expediting the investigational new drug (IND) process, the hiring of more MVDP personnel, or the provision of resources for partners to hire such personnel, to deal with other regulatory and clinical trial coordination issues, would be invaluable to expediting the availability of vaccines.

5. **Achievement of a major milestone.** It was agreed that if a vaccine candidate suddenly emerged from proof of concept clinical trials, as exceptionally likely to significantly reduce morbidity and mortality from malaria in children and pregnant women in developing countries - it would be vital that the MVDP's funding be increased dramatically (probably by at least an order of magnitude). This funding would be needed to complete pivotal licensure studies, and to introduce the approved vaccine through existing or through new distribution networks.

6. **Staffing needs.** It is important to note that the MVDP staff already are functioning very efficiently and are accomplishing much more than would normally be expected; therefore, it is not realistic to expect them to embark on new activities without more help. Therefore, if the MVDP is given more resources, it will be imperative that it also have more personnel to meet new requirements.

SCIENTIFIC CONSULTANTS GROUP

It was felt that **the SCG should continue to function in the same capacity** as it has in the past. The two meetings per year were felt to be appropriate, and necessary. In addition, there was consensus that the MVDP's staff should continue to call on individual members of the SCG to provide expert advice on an ad hoc basis.

SUCCESSION

USAID needs to ensure a qualified succession to the current MVDP leadership. The current success of the MVDP depends on a staff of only two people. Both individuals' work is clearly excellent, but the loss of either person, particularly the senior technical advisor, would seriously jeopardize the future of the entire program. Since the MVDP is so important to the global malaria vaccine development effort, and since its operations are so complex, it was strongly recommended that USAID take measures *now* to shore up this vulnerability, by grooming a successor to its leadership. To ensure the successful continuation of the MVDP, it should be better coordinated with other Agency malaria efforts, so that future staffing requirements can be better developed over time.

It was felt that the optimal solution would be the addition of an additional staff member, and that either the new hire or the other current staff member serves as deputy to the senior technical advisor. It was noted that the wealth of new opportunities afforded by recent technical advances (particularly as vaccine candidates enter clinical testing), makes this the perfect time to enlist additional staff to handle the rapidly increasing workload. It is crucial that this individual have a strong scientific background and be well-grounded in malariology, so as to enable the MVDP to maintain its leadership role in malaria vaccine development. In this regard, the advisability of maintaining the current level of scientific expertise within the MVDP administrative staff is emphasized as being critical to the provision of appropriate oversight for this extremely technical program. It was suggested that USAID could employ any of a number of hiring mechanisms to fill this position, including a contractual agreement.

APPENDICES

A. SCOPE OF WORK

B. REFERENCES

C. PERSONS CONTACTED

D. INTERVIEW QUESTIONS

E. PATH's GUIDING PRINCIPLES FOR PRIVATE SECTOR COLLABORATION

F. FIGURES

APPENDIX A

SCOPE OF WORK

SCOPE OF WORK

Evaluation of the Malaria Vaccine Development Project: Project Number: 936-6001

I. Title

Activity: Evaluation of the Malaria Vaccine Development Project 935-6001

Contractor conducting the Evaluation: Monitoring, Evaluation, and Design/Assessment Support (MEDS) HRN-I-99-000002-00.

II. Objectives of the Evaluation

1. To review USAID's current and potential future role/niche in the development of malaria vaccines.
2. To assess progress made and in particular, rate of acceleration of progress as a predictor of future progress and thus investment potential
3. To glean lessons from the project experience that can be used to improve a follow-on program.
4. To obtain expert opinion on how strategy and implementation planning can be improved in a follow-on activity.

The primary audience of the evaluation will be USAID/GH Malaria Vaccine Development Project staff. In addition, the results will be shared with USAID/GH senior staff, and AA/GH.

III. Background

During more than 35 years, USAID has supported efforts in malaria vaccine development, first focusing on discovery in academic institutions and, later, on more downstream development, largely in collaboration with partners in the public sector. The current Malaria Vaccine Development Project (936-6001), the subject of this evaluation, continues the work previously performed under the Malaria Immunity and Vaccine Research Project (931-0453) and the Malaria Field Trials Project (936-5967). The Malaria Vaccine Development Project, authorized in 1992, consolidated the efforts of these two earlier projects. The overall program is referred to as the Malaria Vaccine Development *Program (MVDP).*

The USAID MVDP focus is on vaccines to protect children and pregnant women in endemic areas from severe disease and death. Currently, the three major elements of the Project are: (1) a protein subunit vaccine approach with the Walter Reed Army Institute of Research in collaboration with the PATH Malaria Vaccine Initiative (MVI); (2) DNA-based vaccine efforts with the Naval Medical Research Center; and, (3) an approach to

the creation of broad spectrum vaccines through a proprietary technology termed "molecular breeding" with Maxygen, Inc. and NIH. In addition, an agreement with CDC provides for non-human primate studies supporting the three major elements.

Previously, the project has provided considerable support to collaborative efforts with NIH (Phase I testing of an early blood stage vaccine formulation and of a CSP multiple antigen peptide with New York University, as well as initial funding of the NIAID Malaria Vaccine Development Unit). The MVDP has also supported the Australian program through funding of RAP2 studies at the Queensland Institute of Medical Research and CDC, early evaluation of MSP-4 at Monash University, and the earlier development of a trial site in Papua New Guinea.

III. STATEMENT OF WORK

A. MEDS

The Monitoring, Evaluation and Design/Assessment Support Project (MEDS) will provide the following technical and logistical support to complete a final evaluation through a “desk review” of program and other documents, and interviews with selected individuals.

Specifically, MEDS will:

1. Carry out necessary preparation activities for the evaluation, including but not limited to the following:
    a. Recruit consultants
    b. Gather background materials for the team, including:
        - The project paper
        - The project authorization document
        - A summary of project agreements and outputs (from CTO)
        - Selected agreement documents and reports (from CTO)
        - Any other relevant background information and documentation.

2. Organize a Team Planning Meeting with consultants and USAID. The purpose of the meeting is to: introduce consultants; provide a background briefing; produce a detailed work plan; develop a draft outline of evaluation report; develop preliminary evaluation questions and tools; develop a list of contacts to be interviewed; and determine how USAID will be kept informed of activities and make necessary approvals.

3. Provide facilitator and rapporteur of meetings

4. Organize meetings/interviews with selected contacts. (See Attached list of contacts.)

5. Manage and advise the evaluation team.

6. Submit a final draft (four copies) of the report to USAID staff.

7. Incorporate any necessary changes into the draft and submit a final version (6 copies) to the evaluation team chair for approval.

8. Submit approved report to USAID.

B. The External Review Team

The External Review Team will:

1 Review MVDP activities, accomplishments, operations, and management.

2. Conduct interviews, either by phone or written communications with staff of MVDP collaborating partners, key USAID staff, and selected external experts/key informants working in malaria vaccine development.

3 Document the results in a report.

4 Conduct a debriefing for USAID.

IV. Deliverables

1. A detailed work plan with deliverable dates (to be produced at the team planning meeting).

2. A data collection plan and data collection tools.

3. A fully edited, ready for distribution, final evaluation document. The full contents of the document will be decided based on the team planning meeting

V. Team Composition

Team Leader: The Team Leader (TL) will be responsible for managing a team of part-time team members in a comprehensive review of the MVDP and for the preparation of the evaluation report. S/he will be responsible for the overall organization of the report and the presentations. S/he will be the chief liaison with USAID. The TL will provide guidance to other team members, assign appropriate tasks, and ensure timely completion of specific tasks, as well as the entire assessment. S/he should have extensive experience in team leadership and a strong technical grounding in malaria vaccine development. Previous team leadership is a prerequisite for this position. The TL must be able to provide technical, as well as administrative leadership to the team. S/he should consult with USAID contacts (listed below) regularly throughout this exercise to ensure progress

is sound and key SOW issues are being addressed. Although the TL should have a solid technical background, his/her strengths should accentuate the management skills and experience required in the SOW.

Malariologist: Must have training and/or experience in general malariology and/or malaria control and/or clinical management of malaria. Must be at the doctoral level or equivalent. Training/experience in vaccine development is a positive additional qualification.

Vaccine Development Specialist: Must have experience in the development of vaccines in government or industry. Expertise in malariology is a positive additional qualification.

USAID Team Member: This USAID staff member must have either malaria vaccine development or immunology experience.

VI. Illustrative Evaluation Questions

The following are illustrative of the questions the evaluation is intended to address:

6. USAID's Role/Niche in Malaria Vaccine Development

- What is the relevant importance of MVDP contributions to malaria vaccine discovery and development?
- How does the MVDP differ from other programs funding malaria vaccine development? Are any differences positive or negative?
- How synergistic/complementary is MVDP with other efforts?
- Given the historical role of the MVDP, is this role critical going forward?
- Given the changing funding environment for malaria vaccine development, is MVDP's current role still relevant?

7. Project Performance

- What have been MVDP's specific contributions to advancing the development of malaria vaccines? Can the importance of these contributions be quantified? If MVDP had not been in existence, what would be the difference in the current stage of malaria vaccine development?
- Have MVDP activities achieved their anticipated strategic results? What components did not achieve their targets and why?

8. Project Implementation/Management

- How effective has USAID been in coordinating its MVDP partners?
- How has USAID exercised technical and programmatic oversight and management with respect to MVDP implementation?
- Has peer review been used effectively and appropriately?

- How were project priorities set? What was the decision making process for MVDP? Was it effective and efficient?
- Have the implementation agreements/instruments been appropriate for achieving the intended results? Given the increasing role of private sector entities, are there more responsive, effective and efficient implementation mechanisms that USAID should consider? For example, should the MVDP become a "virtual" vaccine development entity (modeled on corporate models of public companies of virtual clinical development/manufacturing/sales/marketing companies) eg. The Medicines Company and others.
- How effective has USAID been in monitoring project implementation?
- How effective has USAID been about coordinating with other donors?
- What aspects, in retrospect, could have been performed better?
- Were there missed opportunities for USAID investment?

9. Future Interactions with the Private Sector

- Does the MVDP need to change its mode of interaction with corporate entities given the current and future economic, regulatory and investment climate? If so, how?
- Although MVDP assumes that there will be a commercial market for malaria vaccines, what should USAID's future strategy include to respond to the possibility that malaria vaccines my have to be manufactured, introduced, and distributed by the public sector? Is it still valid to assume the private sector funding for scale up and final process development of licensed products is probable?
- What are the intellectual property issues that USAID should consider in designing the follow-on project? What are the implications of these considerations on possible implementation mechanisms?
- What is USAID's future role in influencing private sector investment in malaria vaccine development? What mechanisms would be effective for USAID to achieve continued and enhanced private sector involvement?

VII. Evaluation Schedule

September 2002

30 September	Agree on SOW, recruit consultants, gather background materials

October 2002

22 October	Team Planning Meeting at the MEDS office
23 October - 6 Dec	Reading and interviews

December 2002

10 December	Team deliberation and drafting of report

16 December	Team Debriefing to USAID
20 December	Final draft report submitted to USAID

January 2003

10 January	USAID provides feedback on report to MEDS
17 January	Final report submitted to Team Chair for approval
24 January	Approved report submitted to USAID

VIII. Relationships and Responsibilities

In addition to providing consultants, MEDS will provide all technical administrative, logistical, and secretarial support required for completion of the Scope of Work. Technical directions from USAID will be as follows:

Carter Diggs	202 712 5728	cdiggs@usaid.gov
Irene Koek	202-712-5403	ikoek@usaid.gov

Address:
GH/NH/EH
RRB 3.07.013
Washington, DC 20523

VIII. Work week

The contractor is authorized up to a five-day workweek with no premium pay.

APPENDIX B

REFERENCES

REFERENCES

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APPENDIX C

PERSONS INTERVIEWED

PERSONS INTERVIEWED

CASE WESTERN RESERVE UNIVERSITY

Chandy John
Assistant Professor of Pediatric Infectious Diseases and Geographic Medicine
School of Medicine

James Kazura
Chief, Division of Geographic Medicine
Director, Center for International Health
Professor of Medicine and International Health
School of Medicine

Karen Olness
Professor of Pediatrics, Family Medicine, and International Health
Director, Rainbow Center for International Child Health
School of Medicine

Fred Robbins
University Professor Emeritus
School of Medicine
Nobel Laureate
Former president, Institute of Medicine of the National Academy of Sciences
Former USAID MVDP Scientific Consultants Group chairman

MAXYGEN

Volker Heinrichs, Staff Scientist

Russell Howard, Chief Executive Officer

Christopher Locher, Staff Scientist III, Vaccine Development

Robert Whalen, Principal Investigator

NATIONAL INSTITUTES OF HEALTH

Lee Hall
Chief, Malaria Vaccine Development Section
Parasitology & International Programs Branch
Division of Microbiology & Infectious Diseases
NIAID

Carole Long
Head of Immunology
Malaria Vaccine Development Unit
NIAID
Member, USAID MVDP Scientific Consultants Group

Louis H. Miller
Head, Malaria Vaccine Development Unit
NIAID

Frank Neva
Head, Clinical Parasitology Unit
Laboratory of Parasitic Diseases
NIAID
Member, USAID MVDP Scientific Consultants Group

Allan Saul
Head, Antigen Development
Malaria Vaccine Development Unit
NIAID/LPD

NAVY

Daniel Carucci
Captain, United States Navy
Chief, Malaria Program
Naval Medical Research Center

OTHERS

Graham Brown
James Stewart Professor of Medicine
Department of Medicine (RMH/WH)
University of Melbourne
Royal Melbourne Hospital
Victoria, Australia
Member, USAID MVDP Scientific Consultants Group

Filip Dubovsky
Scientific Director
Malaria Vaccine Initiative, PATH

Marie Freire
Chief Executive Officer
Global Alliance for TB Drug Development

Dan M. Granoff
Senior Scientist
Children's Hospital Oakland Research Institute (CHORI)

Brian Greenwood
London School of Hygiene and Tropical Medicine

Laura Guay
Makerere University-Johns Hopkins Research Collaboration
Johns Hopkins University

David Kaslow
Scientific Director
Vical, Inc.

Samuel Katz
Chairman Emeritus, Dept. of Pediatrics
Duke University Medical Center
Former member, USAID MVDP Scientific Consultants Group

Kevin Marsh
Director, Wellcome Trust Research Laboratories
Kilifi, Kenya
Member, USAID MVDP Scientific Consultants Group

Melinda Moree
Director
Malaria Vaccine Initiative, PATH

Regina Rabinovich
Director, Infectious Diseases Program
The Bill and Melinda Gates Foundation
Former Director, Malaria Vaccine Initiative, PATH

Peter Reeve
Member, USAID MVDP Scientific Consultants Group

Harry Rozmiarek
Professor and Chief
Laboratory of Animal Medicine
University Veterinarian
University of Pennsylvania
Member, USAID MVDP Scientific Consultants Group

Jerald Sadoff
Co-Chair, USAID MVDP Scientific Consultants Group

William P. Weidanz
Professor and Chairman
Dept. of Medical Microbiology
University of Wisconsin School of Medicine
Member, USAID MVDP Scientific Consultants Group

Richard Wilder
Sidley, Austin, Brown & Wood
Washington, DC

USAID

Dennis Carroll
Infectious Diseases Team Leader
USAID/GH/HIDN

Carter Diggs
Senior Technical Advisor, MVDP
USAID/GH/HIDN

Mary Ettling
Infectious Diseases Advisor
USAID/GH/HIDN

Richard Greene
Director, HIDN
USAID/GH/HIDN

Irene Koek
Chief, Infectious Diseases Division
USAID/GH/HIDN

Steve Landry
Immunization Advisor
USAID

Lorraine Soisson
Technical Advisor/MVDP
USAID/GH/HIDN

WALTER REED ARMY INSTITUTE OF RESEARCH

Gray Heppner
Lieutenant Colonel, U.S. Army
Chief, Department of Immunology
Department of Immunology

David Lanar, Department of Immunology

Jeffrey Lyon, Department of Immunology

Chris Ockenhouse, Department of Immunology

APPENDIX D

INTERVIEW QUESTIONS

INTERVIEW QUESTIONS

United States Agency for International Development
Malaria Vaccine Development Project

I. Accomplishments

- Has MVDP been successful?
  - Why or why not?
- What has it accomplished to date?
- What would have happened if it had never existed? -- Where would malaria vaccine development be today without MVDP?
- Has there been any acceleration of progress? -- Has its work been gaining momentum?
- What are its strengths?
- What are its weaknesses?
  - Are there things it can do better?
  - Are there things it can/should be doing that it isn't?
- Does it have a unique role/niche?
  - If so, how would you describe it?
  - How does its work compare with that of other organizations? (e.g., MVI, NIH, Military, etc.)?
- How has MVDP worked with you?
  - How could it better help you?
- How effectively has MVDP worked/coordinated with other donors?
- How effective has MVDP been in monitoring project implementation?
- Has MVDP been responsive to the changing needs of its partners?

II. Should MVDP continue? – Go/No go

- Will its work be finished in the near future?
- Is there any compelling reason to continue?
  - Is this a critical time to continue to maintain momentum?
  - Is there something it must jump on right away or risk losing the opportunity?
- What will happen if it does not continue?

III. If MVDP should continue, what should it do? Do you see its unique niche/role changing?

- Should MVDP's efforts be focused or consist of a variety of efforts?
- Should it continue as is? (e.g., upstream, midstream and downstream portfolio)
- Should it support other kinds of activities to overcome barriers to getting to the end game—getting malaria vaccines to the people? (e.g., scientific, legal, coordination, clinical, social, etc.)
- Other scientific endeavors – how far upstream should MVDP position itself?
  - New vaccine candidates
  - Adjuvants
  - Correlates of immunity
  - Replicons
  - Exploring other new technologies
- Should MVDP try to fit in better with USAID's development mission?
  - Help build field site capacity
  - Help with social marketing (e.g., ensuring the vaccine is accepted once it is ready)
- Should MVDP assume a formal coordinating role? (e.g., convene meetings, help assure synergy of efforts)
  - Can malaria vaccine development efforts be coordinated?
  - If so, who should assume the coordinator role? (USAID MVDP, WHO, MVI, etc.)
- Should MVDP assume a public policy/advocacy role? (e.g., help inform policy makers and the public of the importance of this work in an effort to get more funding for MVDP and/or other malaria vaccine development efforts)
- Should MVDP provide legal resources to help generate agreements? Does MVDP have a role here? If so, what?
  - Public private partnerships (PPP) – legal assistance to protect intellectual property rights (IPR) in best interests of public health
  - Help develop formal agreements with MVI, military, NIH, etc. Are these necessary?
- Should MVDP provide resources to help with clinical trials? (e.g., clinical investigators to help test new military vaccines in human subjects)
- **What else could/should MVDP be doing?**

IV. Funding – At MVDP's current level of funding, can it still be relevant? (especially compared with higher levels of funding from NIH and MVI)

- Is MVDP funding optimal?
- If not, what is the optimal level?
- How can MVDP better use its resources?
  - Who can it partner with to leverage its resources better? (e.g., PPPs)
- What are other options/sources for funding for MVDP? For all malaria vaccine development efforts?
- Are there milestones that MVDP must reach in order to get substantial increases in funding?
  - If so, what are they?

V. What other comments do you have?

APPENDIX E

PATH'S GUIDING PRINCIPLES FOR PRIVATE SECTOR COLLABORATION

PATH's Guiding Principles for Private Sector Collaboration

Introduction

PATH's mission is to improve health, especially the health of women and children. To achieve its mission, PATH identifies, develops, and applies appropriate and innovative solutions to public health problems, particularly in low-resource settings. Collaboration—including collaboration with the private sector—is a key element in PATH's approach.

PATH's goal for private sector collaboration is to achieve maximum sustainable benefit for public health through engaging private sector collaborators to apply their development, manufacturing, and distribution strengths toward innovative technologies that, in the absence of PATH involvement, would not be a private sector priority.

Purpose and Scope

PATH developed these Principles for Private Sector Collaboration to:

- Articulate key institutional policies and positions regarding PATH collaborations with private sector companies.
- Provide PATH staff with guidance in managing private sector collaborations.
- Provide current and potential private sector collaborators with an overview of PATH's perspectives and expectations for collaboration.

PATH's Board of Directors and President fully endorse these principles. The principles convey both the broad direction and the specific actions that they expect of all PATH teams that form collaborations with private sector companies.

These principles primarily address the following types of collaborations:

Transfer of a Technology Developed or Owned by PATH. PATH develops a technology in-house and transfers the intellectual property to a private sector collaborator for further development, manufacturing, and distribution.

Support by PATH for Development of a Collaborator's Product. PATH provides significant resources or expertise (such as funding, management, co-development, and assistance with clinical studies) to a private sector collaborator to support the collaborator's development of a product.

Support by PATH for Introduction of a Collaborator's Product. PATH supports and/or undertakes significant programmatic activities (such as field trials, epidemiological studies, and advocacy programs) that demonstrate and communicate the public health value of a product produced by a private sector collaborator.

Principles for Private Sector Collaboration

To achieve PATH's mission while preserving PATH's integrity and status as a publicly funded, nonprofit, nongovernmental organization, collaborations with private sector companies must be consistent with the following principles.

Clear Link to Mission

PATH's collaborations with private sector companies must lead to positive impact on availability, accessibility, and affordability of important health products for public health programs in developing countries.

When assessing whether a proposed private sector collaboration will have sufficient mission linkage and impact, PATH considers the following key issues:

Availability: Have PATH and the collaborators created a product-development program that is sufficiently rigorous, funded, and prioritized to provide a reasonable opportunity for success?

Accessibility: Have PATH and the collaborators envisioned a manufacturing and distribution plan that can lead to sufficient quantities of the product through appropriate channels to meet clearly defined public sector demand in developing countries?

Affordability: Have PATH and the collaborators openly discussed and agreed upon a product pricing approach that can result in widespread adoption in public sector programs of developing countries over a reasonable time through purchase by local governments or support of international donor agencies?

Because PATH is a nonprofit organization working under U.S. tax law, it is important to document the mission-oriented contributions and commitments of the private sector collaborator. PATH achieves this by developing appropriate commitments by the private sector collaborator to increase the availability, accessibility, and affordability of the technology in developing-country public health programs. Each collaboration will require that PATH and the private sector company explore a variety of approaches, incentives, and mechanisms to reach a balanced relationship aimed at serving both public good and commercial objectives.

Recognition of Private Sector Needs

In collaborating with a private sector company, PATH must recognize the company's need for commercial benefit in order to ensure a sustainable commitment to the collaboration.

PATH's goals for availability, accessibility, and affordability of products for developing-country public health programs will likely be met if PATH's expectations of the private sector collaborator are realistic and structured to take into account many factors, for example:

- The legitimate need of the private sector company to pursue a profit in order to ensure a sustainable supply of the product.
- Recognition of the full range of costs necessary from product development to commercialization.

Clear Definition of Roles, Responsibilities, and Expectations

IN ALL COLLABORATIONS, THE RELATIONSHIP BETWEEN PATH AND THE PRIVATE SECTOR COMPANY MUST BE CLEARLY DEFINED THROUGH AN APPROPRIATE WRITTEN DOCUMENT OR AGREEMENT.

These agreements must cover, at minimum, the following information:

- The objectives of the collaboration, the roles and responsibilities of each partner, and the expected outcomes.
- The accountability and performance milestones that will be used to ensure that the goals of the collaboration are met.
- A clearly defined management and decision-making structure of the collaboration.
- A clearly stated process for monitoring, evaluation, and termination of the collaboration.

Transparent Collaboration

AS A PUBLICLY FUNDED ORGANIZATION, PATH MUST MAINTAIN A LEVEL OF TRANSPARENCY IN ITS COLLABORATIONS WITH THE PRIVATE SECTOR.

At the same time, PATH understands the commercial needs of its private sector collaborators and will meet requirements to maintain confidentiality of proprietary business, project, and product information. For all collaborations with private sector companies, PATH needs, at minimum, to be able to disclose:

- The existence of the collaboration and identity of company.
- The broad purpose of the collaboration.

PATH will work with the collaborator to agree upon the appropriate level of disclosure.

Appropriate Selection of Collaborators

BECAUSE THE SUCCESS OF ANY COLLABORATION DEPENDS ON THE SELECTION OF A GOOD PARTNER, PATH MUST CONDUCT A THOROUGH ASSESSMENT BEFORE ENTERING INTO A FORMAL COLLABORATION WITH A COMPANY.

PATH will:

- Assess the reputation of the company, its corporate behavior, and its economic viability to ensure compatibility with PATH's mission and reputation.
- Review the scientific and technical capabilities of the collaborator to make sure they are appropriate for the collaboration.
- Ensure that the public health outcomes and return on public sector investment will be commensurate with the effort involved in establishing and maintaining the collaboration.

PATH MUST CAREFULLY ASSESS AND MANAGE BOTH THE BROAD INSTITUTIONAL RISKS AS WELL AS THE SPECIFIC PROJECT RISKS WHEN COLLABORATING WITH A PRIVATE SECTOR COMPANY.

Examples of risks that PATH may face include product liability, financial loss, and damage to its reputation. Risks can be appropriately managed by following the principles outlined in this document and ensuring that proper indemnification and enforcement mechanisms are in place in contractual agreements between PATH and private sector collaborators.

Dissemination of Results

AS A PUBLICLY FUNDED ORGANIZATION, PATH HAS A FUNDAMENTAL OBLIGATION TO ENSURE DISSEMINATION OF THE RESULTS OF ITS PRIVATE SECTOR COLLABORATIONS.

PATH also recognizes the importance of linking dissemination of results with appropriate protection of intellectual property, and will work with private sector collaborators to achieve this objective.

Awareness of Potential Conflicts of Interest

IN ALL COLLABORATIONS WITH PRIVATE SECTOR COMPANIES, PATH MUST CAREFULLY ASSESS THE POTENTIAL FOR BOTH PERCEIVED AND REAL CONFLICTS OF INTEREST AT BOTH THE INSTITUTIONAL AND INDIVIDUAL STAFF MEMBER LEVEL.

Proactive disclosure of PATH's relationships with private sector companies is fundamental to the proper management of conflict of interest issues.

Ensuring High Standards of Quality and Ethics

PATH MUST ENSURE THAT ALL COLLABORATIVE RESEARCH, PRODUCT DEVELOPMENT, AND INTRODUCTION ACTIVITIES MEET THE HIGHEST STANDARDS OF SAFETY, QUALITY, AND INTEGRITY.

In particular, PATH places the utmost importance on ensuring the ethical and respectful treatment of human participants in research endeavors. PATH also believes in humane treatment of animals involved in research and production.

PATH expects its private sector collaborators to:

- Meet international standards for good manufacturing, clinical, and laboratory practices.
- Maintain scientific integrity in all collaborative work.
- Ensure that proper reviews and approvals are obtained by Institutional Review Boards.
- Adhere to mutually agreed-upon standards of humane treatment of animals.

path
Program for Appropriate Technology in Health (PATH) is an international, nonprofit, nongovernmental organization. Contact: 1455 NW Leary Way, Seattle, WA 98107 U.S.A. Phone: 206-285-3500 Fax: 206-285-6619 E-mail: info@path.org www.path.org January 2002 Printed on recycled paper

APPENDIX F

FIGURES

Figure 1

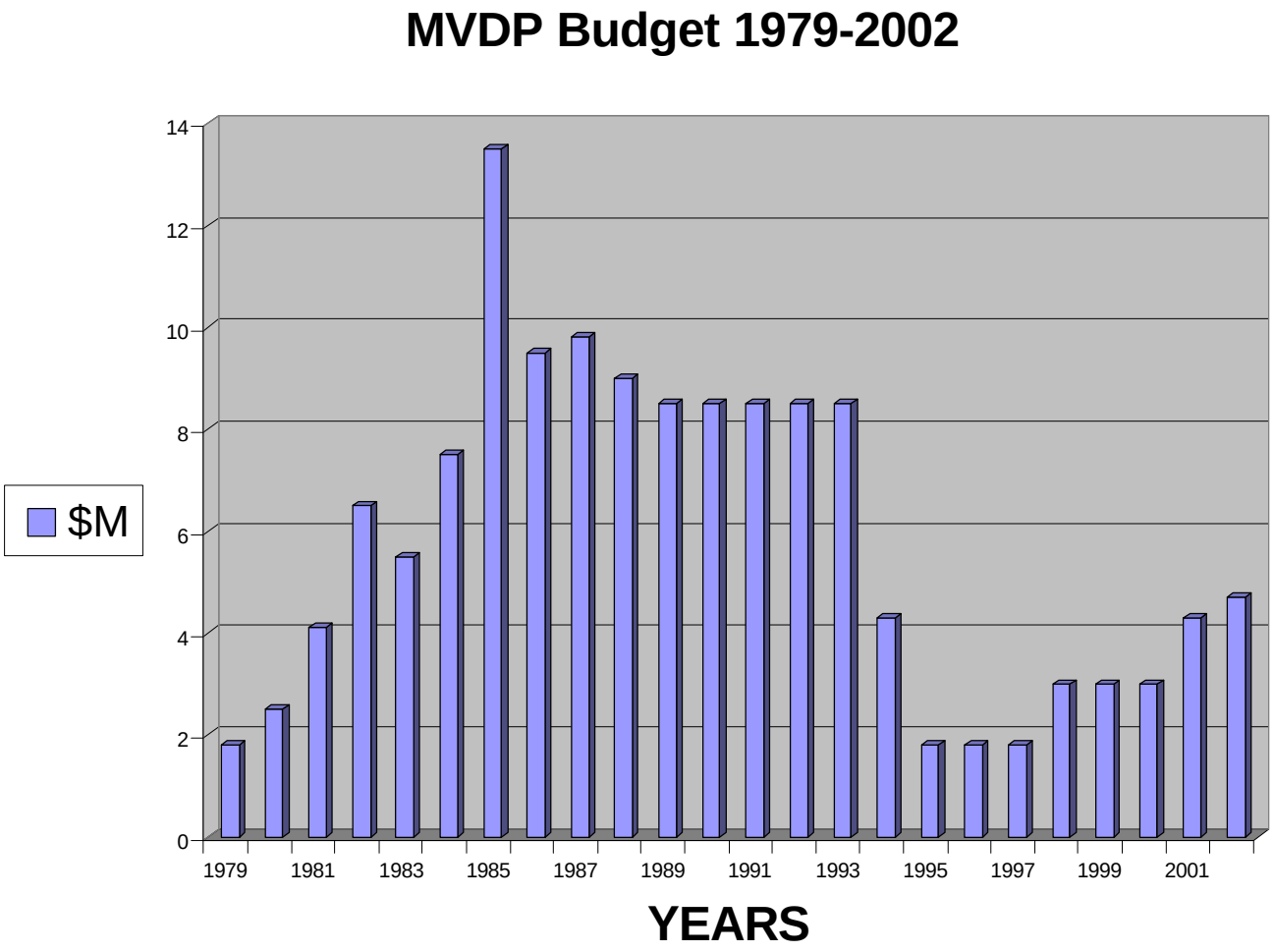

MVDP Budget 1979-2002
$M
14
12
10
8
6
4
2
0
1979
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
YEARS

Figure 2

Malaria Vaccine R&D Expenditures
All Donors Worldwide
(US $M)

	1999	2000	2001	2002
USAID	3.0	3.0	4.3	4.7
U.S. DoD	4.9	5.2	7.5	5.0
TDR/WHO	1.2	1.0	0.9	0.6
NIH	21.3	25.0	28.7	33.2
Malaria Vaccine Initiative (MVI)	0.3	2.5	13.0	13.8
European MVI (EMVI)	0.6	0.9	1.0	2.2
European Commission	4.1	4.1	4.1	4.1
GlaxoSmithKline	Proprietary; probably <$1M direct			
Totals	**36**	**43**	**61**	**65**

Source: MVI

Figure 3

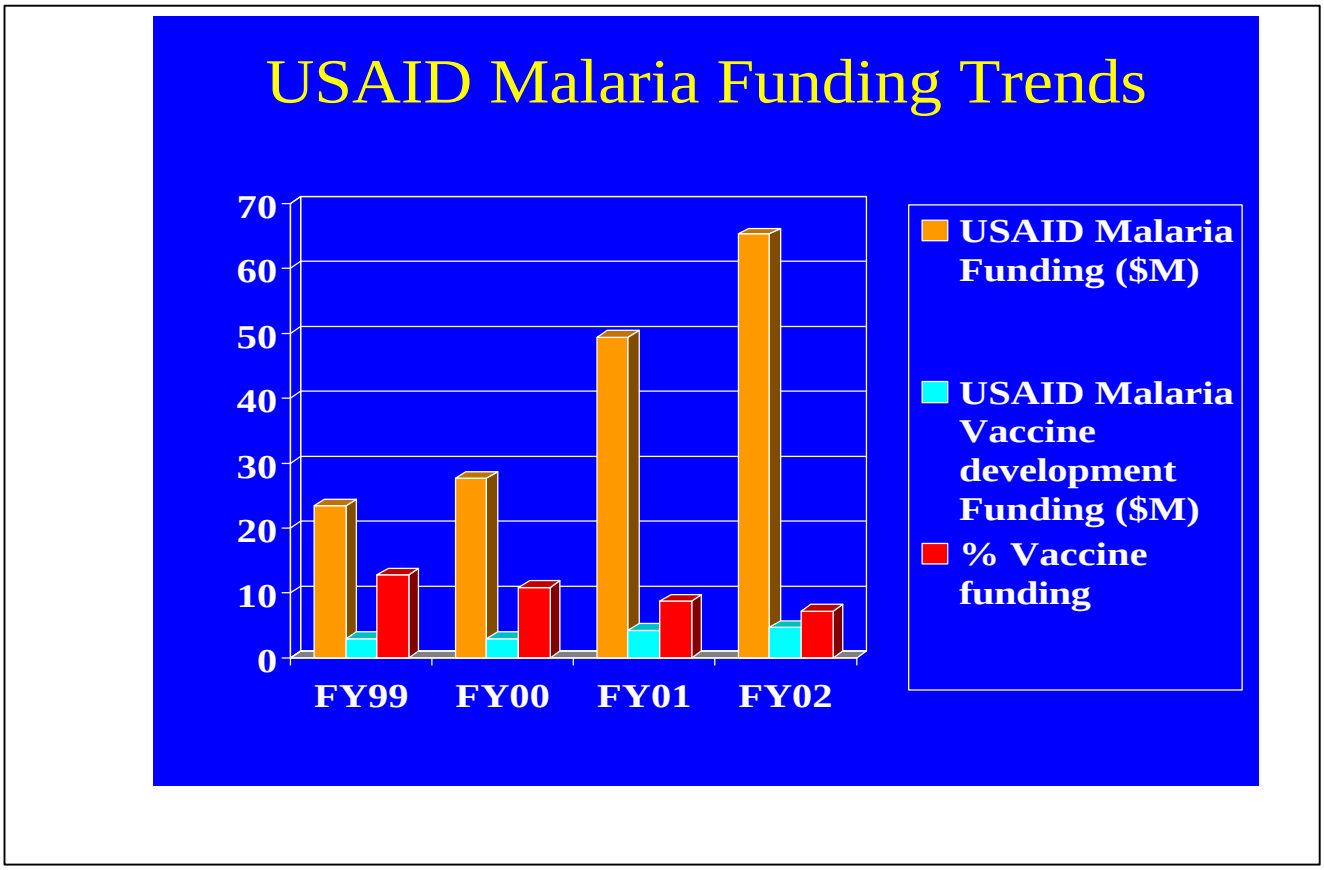

USAID Malaria Funding Trends
70
60
50
40
30
20
10
0
FY99
FY00
FY01
FY02
USAID Malaria Funding ($M)
USAID Malaria Vaccine development Funding ($M)
% Vaccine funding

Figure 4

Institutions involved in Malaria Vaccine Development

AMANET	African Malaria Network Trust
Apovia	Apovia, Inc
Aventis	Aventis Pasteur
Biotech Aus	Biotech Australia
CISM	Centro de Investigaçao em Saude de Manhiça
CRC VT	Cooperative Centre for Vaccine Technology
CSL	Commonwealth Serum Laboratories
CVD	Center for Vaccine Development
EMVI	European Malaria Vaccine Initiative
Gabon	Albert Schweitzer Hospital
GSK	GlaxoSmithKline
ICGRB	International Centre for Genetic Engineering
	& Biotechnology
KeMRI	Kenya Medical Research Institute
La Trobe	La Trobe University
LSH	London School of Hygiene
Mali MRTC	Mali Malaria Research & Training Center
Monash	Monash University
MRC	UK Medical Research Council
MVI	Malaria Vaccine Initiative at PATH
NIAID MVDU	US NIAID Malaria Vaccine Develop Unit
NIH	US National Institutes of Health
Nijmegen	Nijmegan University
NMRC	US Naval Medical Research Center
NYU	New York University
Oxford	Oxford University
Oxxon	Oxxon Pharmaccines
Pasteur	Pasteur Institute
PNG IMR	Papua New Guinea Institute for Medical Research
QIMR	Queensland Institute of Medical Research
SEDAC	Société D'Etudes et de Développment
	des Antigènes Combinatoires
SSI	Staten Serum Institute
Swiss TMI	Swiss Tropical Medicine Institute
TDR	Special Programme for Tropical Disease Research
	and Training
U Lausanne	University of Lausanne
USAID	US Agency for International Development
Vical	Vical, Inc.
WEHI	Walter and Eliza Hall Institute
WRAIR	Walter Reed Army Institute of Research

Figure 5

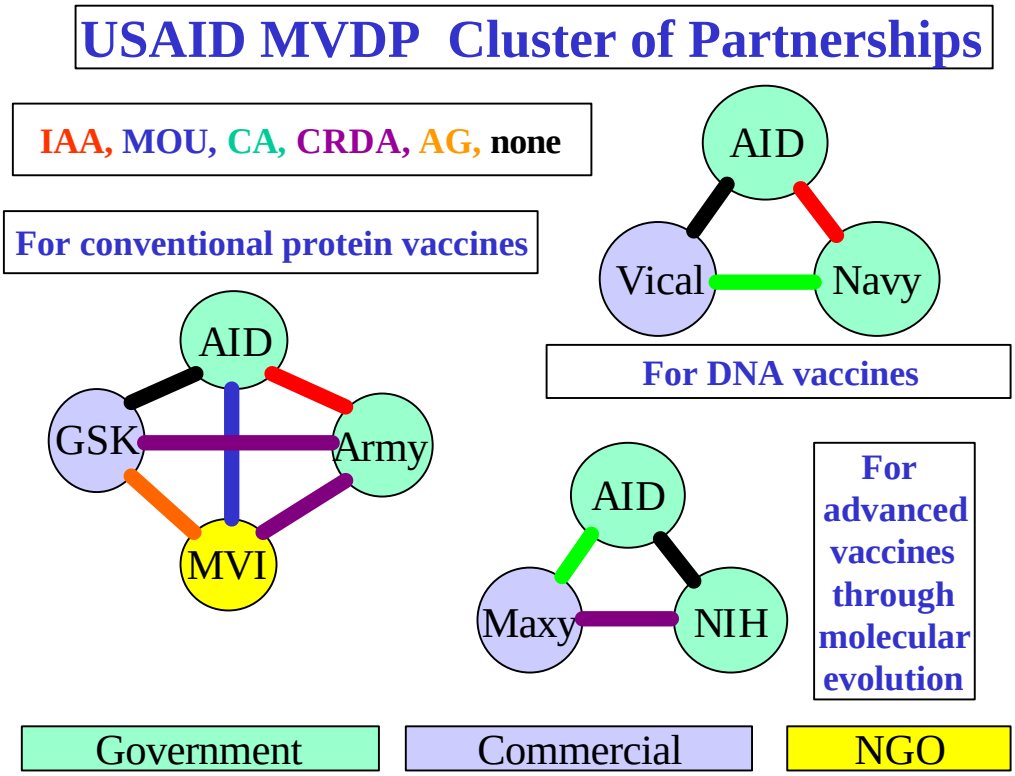
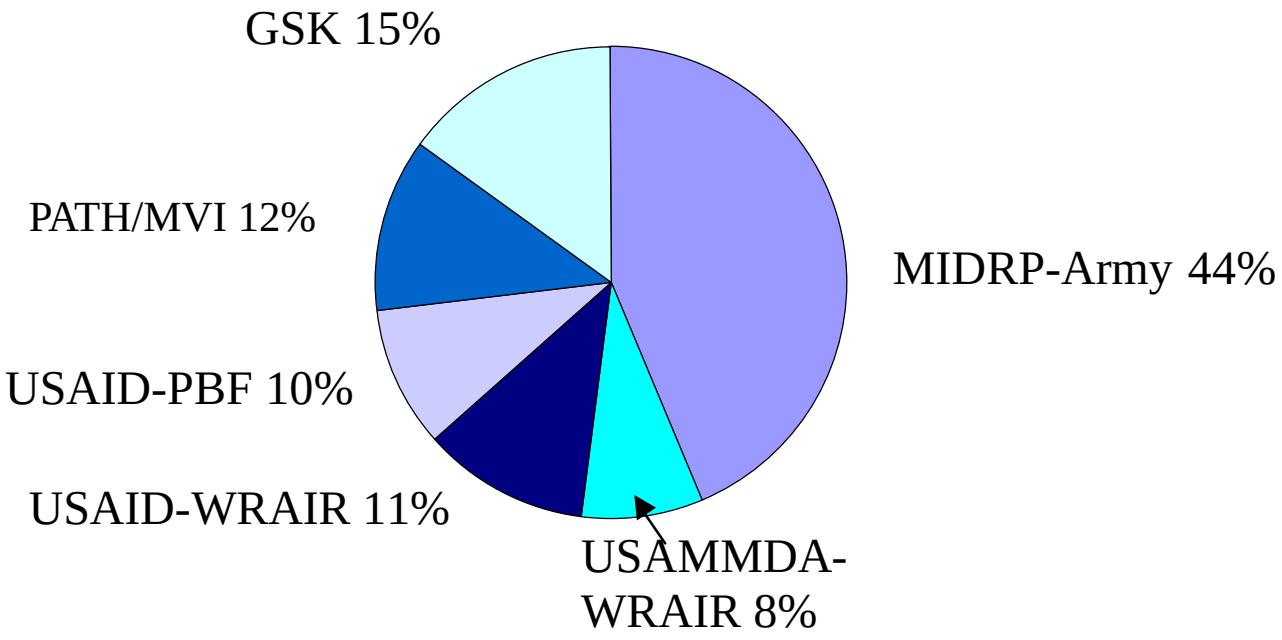

USAID MVDP Cluster of Partnerships
IAA, MOU, CA, CRDA, AG, none
For conventional protein vaccines
AID
GSK
Army
MVI
AID
Vical
Navy
For DNA vaccines
AID
Maxy
NIH
For advanced vaccines through molecular evolution
Government
Commercial
NGO

Figure 6

US Army Malaria Vaccine Budget FY 03



1. Inclusive of funds on hand and expected
2. WRAIR overhead increased 28% this FY
3. LTC Pat Duffy leverages 750K in funding through NIH and the Gates Foundation (not shown)
4. Dr. Urszula Krzych leverages 250K in funding through NIH (not shown)

Figure 7

Naval Medical Research Center Malaria Program FY 03