


Report to Congress

Coordinated Strategy to Accelerate Development of Vaccines for Infectious Diseases

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Acronyms and Abbreviations

AAVP	African AIDS Vaccine Program
ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
AMC	Advance Market Commitments
AVRS	AIDS Vaccine Research Subcommittee
BCG	Bacille Calmette Guerin (childhood vaccine for Tuberculosis)
BMFG	Bill & Melinda Gates Foundation
CHAVI	Center for HIV/AIDS Vaccine Immunology
CDC	Centers for Disease Control and Prevention
DHHS	Department of Health and Human Services
DHP	Defense Health Program
DoD	Department of Defense
DOTS	Directly Observed Treatment, Short Course
EPI	Expanded Program on Immunization
FIC	Fogarty International Center
GAVI	GAVI Alliance (formerly Global Alliance for Vaccines and Immunization)
GSK	GlaxoSmithKline
HepB	Hepatitis B
Hib	Haemophilus influenzae type b
HIV	Human Immunodeficieny Virus
HIVRAD	HIV Research and Design
HVTN	HIV Vaccine Trial Network
IAVI	International AIDS Vaccine Initiative
IDCRP	Infectious Disease Clinical Research Program
IDRI	Infectious Disease Research Institute
IOM	Institute of Medicine
LMIV	Laboratory of Malaria Immunology and Vaccinology
LMVR	Laboratory of Malaria and Vector Research
MIDRP	Military Infectious Disease Research Program
MHRP	U.S. Military HIV Research Program
MMVDP	Military Malaria Vaccine Development Program
MRC	Medical Research Council (of South Africa)
MVDP	Malaria Vaccine Development Program

MVI	Malaria Vaccine Initiative
MVP	Malaria Vaccine Project
NCRR	National Center for Research Resources
NCI	National Cancer Institute
NGO	Nongovernmental Organization
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes for Health
NMRC	Naval Medical Research Center
NTD	Neglected Tropical Diseases
OAR	Office of AIDS Research
PAVE	Partnership for AIDS Vaccine Evaluation
PDP	Product Development Partnership
PEPFAR	President's Emergency Plan for AIDS Relief
PRV	Priority Review Voucher
R&D	Research and Development
SAAVI	South African Vaccine Initiative
SVEU	Simian Vaccine Evaluation Unit
TB	Tuberculosis
UNAIDS	The Joint United Nations Program on HIV/AIDS
USAID	U.S. Agency for International Development
U.S. FDA	U.S. Food and Drug Administration
USG	U.S. Government
VRC	Vaccine Research Center
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

Executive Summary

The purpose of the Tom Lantos and Henry J. Hyde United States Global Leadership against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, Public Law 110-293, is to strengthen and enhance U.S. leadership and the effectiveness of the U.S. response to the HIV/AIDS, tuberculosis, and malaria pandemics and other related and preventable infectious diseases as part of the overall U.S. health and development agenda.

Section 206 of this law states: "the President shall produce a comprehensive report, written by a study group of qualified professionals from relevant Federal agencies and initiatives, nongovernmental organizations, and industry representatives, that sets forth a coordinated strategy to accelerate development of vaccines for infectious diseases, such as HIV/AIDS, malaria, and tuberculosis, which includes:

i. initiatives to create economic incentives for the research, development, and manufacturing of vaccines for HIV/AIDS, tuberculosis, malaria, and other infectious diseases;
ii. an expansion of public-private partnerships and the leveraging of resources from other countries and the private sector; and
iii. efforts to maximize United States capabilities to support clinical trials of vaccines in developing countries and to address the challenges of delivering vaccines in developing countries to minimize delays in access once vaccines are available."

This comprehensive report responds to this request. This report was compiled and edited by the congressionally mandated study group, which was set up for this purpose. The group met face-to-face on August 12, 2009 and worked virtually in the preparation of this report between July 2009 and September 2009. The study group includes professionals from the U.S. Agency for International Development (USAID), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the National Vaccine Program Office of the Department of Health and Human Services, the Department of Defense (DoD), the Department of Treasury, The Program for Applied Technology in Health (PATH), the National AIDS Vaccine Initiative (IAVI), Aeras Global TB Vaccine Foundation, the Center for Global Development, the Bill & Melinda Gates Foundation (BMGF), and Merck & Co.

Coordinated Strategy to Accelerate the Development of Vaccines for Infectious Diseases

The U.S. Government is engaged in coordinated strategies with partners the world over to accelerate development of vaccines for infectious diseases such as HIV/AIDS, malaria, and tuberculosis, and to deliver vaccines to people in developing countries. Each agency's mandate, funding levels, and availability of expertise determine where they engage on the continuum from basic research through delivery and immunization in developing countries.

HIV/AIDS Vaccine Development Summary

The U.S. Government (USG) is committed to the discovery and testing of a vaccine capable of preventing HIV and controlling the AIDS pandemic. The USG efforts to this end are, in large part, through collaborations with other governments, industry partners, foundations like the BMGF, and nongovernmental organizations, and key biotech sub-partners. The Enterprise (a consortium of independent organizations committed to accelerating the development of an HIV vaccine), as a non-prescriptive but neutral and unifying voice for the field, provides the structure to prioritize the scientific agenda, avoid duplication of efforts, and maintain the focus and momentum to design and develop the most promising HIV vaccine candidates. The Partnership for AIDS Vaccine Evaluation (PAVE) is another voluntary consortium of the USG agencies and USG-funded organizations involved in HIV

vaccine research. Members of PAVE include the National Institutes of Allergy and Infectious Diseases (NIAID), Office of AIDS Research (OAR), the NIAID-funded HIV Vaccine Trials Network (HVTN), USAID, the U.S. Military HIV Research Program (MHRP), CDC, and IAVI.

In 2008, total global investment in HIV vaccine research and development (R&D) was US$868 million, a US$93million (10%) decrease from the previous year, as reported by the HIV Vaccines and Microbicides Resource Tracking Working Group.[1] Public-sector funders provided 85% (US$731 million) of those investments, the philanthropic sector 11% (US$104 million), and the commercial sector 4% (US$33 million). The USG is the leading donor, having invested US$620 million in 2008. The philanthropic sector accounted for US$104 million or about 12% of the total funds disbursed for HIV Vaccine R&D in 2008. The BMGF and the Wellcome Trust together accounted for 91% of all philanthropic investments. Total investment by the commercial sector (pharmaceutical and biotechnology companies) in HIV vaccine development in 2008 was estimated at US$33 million (range US$18 million to US$45 million), a decline of 61% from 2007 levels.

The search for products has been challenging. In efficacy studies, two vaccine candidates have not shown they protect against HIV infection or moderate subsequent HIV disease. A third vaccine entered advanced clinical evaluation in June 2009. As announced in September 2009, a fourth vaccine studied for efficacy in Thailand on 16,402 participants has reported efficacy of 31% in an historic first-time result proving a concept that is sure to lead to improved vaccine candidates. The vaccine studied in Thailand was the first evidence of an HIV vaccine providing any level of protection against HIV infection. Statistical analyses presented as part of their initial announcement support the validity of the finding. The trial was a “test of concept” study designed to identify initial signs of promise in a product. The trial sponsors and implementers led by the U.S. Military HIV Research Program and funded by NIAID, included the U.S. Army, the Thai Ministry of Public Health, Sanofi Pasteur, and Global Solutions for Infectious Diseases. The collaborators will be conducting additional studies to further understand these positive results.

The recent findings in Thailand have important implications for the design of future HIV vaccines and how they are tested; however, additional research is needed to better understand how this vaccine regimen reduced the risk of HIV infection. In addition, scientific advances in defining how the human immune system attempts to protect itself against HIV are unfolding. The earliest events in natural infection, particularly in those that show an immune capacity to resist the virus, are beginning to inform new vaccine design; translating these events into a candidate vaccine holds great promise to have an impact on the epidemic with an eventually licensable vaccine.

Tuberculosis Vaccine Development Summary

The USG is the largest bilateral donor supporting the implementation of biomedical TB research and TB control programs in disease-endemic countries. USG-funded research and support have long been one of the only means by which development of vaccine candidates for TB has been facilitated. In 2007, total spending for TB vaccine research was US $410 million, of which US $323 million was USG-funded research. NIH, through NIAID, is the lead agency for biomedical TB research, including vaccine-related research. As of 2008, NIAID was the largest funder of biomedical TB research, with an annual budget of more than US$120 million and the second largest funder for TB vaccine R&D. While NIH/NIAID’s mission is focused on fundamental and translational biomedical research that includes the preclinical and early clinical evaluation of new vaccines, development of new health care interventions requires the stewardship and support of pharmaceutical companies. Other USG organizations will be critical to facilitate introduction of vaccines and evaluate field effectiveness and will play an important role in completing epidemiological studies to enable late-stage and post-licensure trials.

[1] The Resource Tracking Working Group was established in 2004 to generate and disseminate high-quality, detailed and comparable data on global investments in preventive HIV vaccine and microbicide research and development (R&D), policy and advocacy activities.

The Bill & Melinda Gates Foundation recently established several not-for profit organizations to facilitate development and implementation of new drugs, vaccines, and diagnostics that may be developed through academic, for-profit, or other not-for profit organizations. These organizations (the Global Alliance for TB Drug Development, the Aeras Global TB Vaccine Foundation, and the Foundation for Innovative New Diagnostics) have facilitated the transition of many product candidates and tools that were initially developed with USG funding into advanced-stage clinical testing.

There are several strategies being pursued worldwide to develop new vaccine candidates and approaches for TB, including:

1. Recombinant BCG
2. Virally vectored TB vaccines
3. Adjuvanted subunit vaccines
4. DNA vaccines
5. Other approaches – to expand the diversity of vaccine candidates and approaches, scientists are also evaluating the feasibility of attenuating Mycobacterium tuberculosis (Mtb) through multiple gene deletions to serve as safe, immunogenic vaccines or platforms for advanced vaccination strategies

Coordination among the various global vaccine development entities and private partners is implemented through the Stop TB Partnership's Working Group on New Vaccines. Furthermore, coordination among the various partners is accomplished through continual interaction, mutual consultations, workshops, development of milestones, and leveraging of available resources. Since clinical vaccine candidates for TB have only recently emerged, additional collaboration will be needed to facilitate advanced clinical development and field evaluation.

To contribute effectively to TB control programs worldwide, strategies for combining drugs and vaccines to either enhance efficacy or shorten chemotherapy for adult and pediatric patients will likely be considered. To facilitate the development of advanced vaccination strategies, more sophisticated animal model, immune, and natural disease history protocols will need to be established and validated. The introduction of new TB vaccines will also require tight coordination with TB and HIV control programs to assure the most appropriate use of novel adult or adolescent boosting vaccines, as well as to inform strategies for improving neonatal TB vaccination. All current and future USG TB vaccine R&D efforts are and will continue to be leveraged with European and other global vaccine development efforts to avoid duplication and assure maximum use of limited resources.

Malaria Vaccine Development Summary

U.S. Government agencies have been leaders for more than four decades in efforts to develop a malaria vaccine to mitigate the enormous loss of life, illness, and economic burden of malaria in the developing world. Working both internally and with nongovernmental organizations (NGOs), academic institutions, and commercial companies, these efforts have resulted in major advances in the understanding of the biology of malaria and in the clinical development of many vaccines, one of which has entered Phase III evaluation. Both the Military Malaria Vaccine Program (MMVP), consisting of the U.S. Army Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Center (NMRC), and the USAID Malaria Vaccine Development Program (MVDP) have focused on such product development. NIAID also has made major strategic research contributions.

At this writing, GlaxoSmithKline Biologicals (GSK) is fielding a large multicenter trial of a malaria vaccine, funded by the BMGF and managed by the Malaria Vaccine Initiative at PATH (MVI). Although this trial is made possible through the BMGF, the scientific basis and development of the vaccine is directly attributable to USG programs, principally that of WRAIR. This vaccine has the potential to have significant impact on malaria morbidity and mortality if it achieves licensure. However, it may not be

effective enough to prevent malaria entirely in an immunized population. Next-generation vaccines are badly needed, and the USG malaria vaccine development effort is focused on this goal.

Most of the current U.S. Government malaria vaccine development effort is through the following approaches:

1. Development of new vaccines based on the target molecule used in the GSK vaccine
2. Heterologous or “prime boost” immunization
3. Blood stage vaccines
4. Combination vaccines (Sound reasoning suggests that a combination of more than one parasite component will need to be employed in order to develop highly efficacious malaria vaccines, and this is reflected in the USG strategy.)
5. New target discovery

Coordination among the various USG agencies and private partners takes place through liaison on a daily basis. In addition, the Federal Malaria Vaccine Coordinating Committee (FMVCC) meets at irregular intervals for general coordination or consideration of special topics requiring attention. As needed, FMVCC invites nongovernment partners to participate.

The USG malaria vaccine development effort will continue to work collaboratively both inside and outside the USG toward the goal of practical vaccines to control malaria in the developing world. Efforts not managed by the USG will be watched with interest and the USG strategy modified as new information becomes available. Specific new approaches will be selected and added to the portfolio, based on the best scientific information available. Approaches will be accelerated if shown to be promising or discarded if not. The USG program will remain cognizant of the changing epidemiology of malaria and adjust accordingly. The rate of progress will be proportional to resources available.

Other Infectious Diseases

While HIV/AIDS, malaria and tuberculosis are priorities in vaccine research because of their worldwide prevalence and high mortality rates, the USG also aims to identify new vaccine candidates for many other diseases, such as neglected tropical diseases, enteric diseases, and dengue fever. Investigators are working to make these vaccines safer and effective for the targeted populations, including those with compromised immune systems.

Neglected tropical diseases (NTDs) represent the most common infections of the world’s one billion poorest people and include a group of chronic parasitic and bacterial infections such as hookworm infection, ascariasis, schistosomiasis, lymphatic filariasis, onchocerciasis, Chagas disease, leishmaniasis, and trachoma. Robust vaccine research studies directed at many of these serious and pervasive illnesses are ongoing at NIH in its intramural and extramural research programs. Through the DoD’s NMRC and WRAIR, the USG is focusing its efforts to develop preventive vaccines against Shigella, enterotoxigenic E coli (ETEC), and Campylobacter, three leading bacterial causes of traveler’s diarrhea. WRAIR and NMRC also have well coordinated efforts to develop a dengue vaccine. Through DoD in-house efforts as well as co-development relationships with extramural partners, WRAIR and NMRC are participating in the development and assessment of six candidate vaccines, three of which are in human trials and one in advanced development with a major pharmaceutical partner. The DoD is sponsoring the only attempt to develop an FDA-licensed vaccine for hemorrhagic fever with renal syndrome HFRS, a potentially fatal hantavirus. The DoD is also providing limited support to develop a vaccine that will protect troops from scrub typhus.

The USG will continue to collaborate with public-private organizations in efforts to develop vaccines for other infectious diseases, such as neglected tropical diseases, enteric diseases, and dengue fever. The great majority of these efforts are currently in the basic research and preclinical phases, although it is anticipated that some of them will move into the clinical phase in coming years.

Initiatives to Create Economic Incentives for the Research, Development, and Manufacturing of Vaccines for HIV/AIDS, Tuberculosis, Malaria, and Other Infectious Diseases

There are a range of incentives and innovative financing mechanisms such as Advanced Market Commitments (AMC) in early phases of implementation and others that are being explored. These mechanisms have the potential to stimulate accelerated research and development of vaccines. However, before increased commitment by the USG, the various mechanisms require further study to determine which mechanisms are most appropriate and feasible for investment. The USG will continue to consider options specific to U.S.-based R&D and manufacturing, while monitoring the progress of the pilot Advanced Market Commitment and other economic incentives.

An Expansion of Public-Private Partnerships and the Leveraging of Resources from Other Countries and the Private Sector

USG agencies are engaged with a variety of partners from academia, industry, UN agencies, civil society, developing countries, and product development partnerships (PDPs). An expansion of public-private partnerships and the leveraging of resources from other countries and the private sector could accelerate the development of vaccines. The variety and number of current PDPs make it necessary to determine whether additional PDPs are required to accelerate the development of vaccines or whether the need lies in expanding existing PDPs. As such, as part of the USG strategy to accelerate the research, development and manufacturing of vaccines, the U.S. Government will explore the range of vaccine development partnerships to determine the most efficient way for the USG to leverage private-sector expertise with scarce resources and strategically engage in supporting the indirect determinants around market preparation.

Efforts to Maximize U.S. Capabilities to Support Clinical Trials of Vaccines in Developing Countries and to Address the Challenges of Delivering Vaccines in Developing Countries to Minimize Delays in Access Once Vaccines Are Available

USG agencies engaged in vaccine R&D and immunization delivery are well coordinated and work strategically within individual vaccine areas. However, across vaccine areas more information-sharing and joint strategic development need to take place. The USG has actively developed sustainable clinical trial sites in the developing world over many years and works to continue to make those sites more robust, as the more complex clinical trials for vaccines against more complex diseases are required. To accelerate the development of vaccines, the USG will build upon what was accomplished by PAVE for HIV vaccine trial sites and will conduct a mapping exercise of all vaccine clinical sites that are implemented by or funded by the USG. More robust information on the relevant clinical trial sites will lead to more strategically coordinated, streamlined, and aligned government support for advancing the development of new vaccines for infectious diseases. Delivering vaccines in developing countries is complex. Public health impact is not achieved when the vaccine is developed but rather when it reaches the intended population in developing countries. The U.S. Government will continue to program in a strategic and complementary fashion to build immunization program capacity in developing countries.

In order to coordinate the acceleration of the development of vaccines for infectious diseases, USG agencies will continue to convene a study group or groups around the strategy to further engage across disease-specific areas. Each U.S. Government agency engaged in global health research plays a distinct role at different stages of research, and nongovernmental partners provide unique expertise in vaccine development. For this reason, a study group or groups will meet at regular intervals to continue collaboration to accelerate vaccine development, to share information on vaccine development efforts,

and to maximize the synergies that are created from working in a more coordinated manner. The rate of progress in each area of vaccine research, development, and delivery will be proportional to resources available.

I. Introduction

The purpose of the Tom Lantos and Henry J. Hyde United States Global Leadership against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, Public Law 110-293, is to strengthen and enhance U.S. leadership and the effectiveness of the U.S. response to the HIV/AIDS, tuberculosis, and malaria pandemics and other related and preventable infectious diseases as part of the overall U.S. health and development agenda.

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Section II of this report includes background on vaccine development. Section III provides a summary overview of the U.S. strategy for malaria, HIV/AIDS, tuberculosis, and other infectious diseases. Section IV discusses initiatives to create economic incentives for the research and development (R&D) of vaccines. Section V discusses the role of public-private partnerships and the leveraging of resources from other countries. Section VI provides a summary of the role that the United States Government (USG) plays in supporting clinical trials in developing countries and also provides an overview of current efforts to overcome challenges associated with vaccine delivery. And, Section VII provides a summary of the future direction of the USG vaccine development strategy.

II. Background on Vaccine Development and the Role of the U.S. Government

AIDS, tuberculosis, and malaria account for approximately 5 million deaths a year. However, there is no proven vaccine for any of these three diseases, and there is great variation in the stages of R&D among the vaccines currently under development. This is in large part attributed to the highly complex science required to develop vaccines against these infectious diseases.

The cost of bringing new vaccines to market is substantial and includes costs for animal model studies, preclinical studies, clinical trials, licensing, and start-up. Estimates of the total costs associated with vaccine development range from several hundred million dollars for basic vaccines to more than US$1.5 billion[2] for complex vaccines; costs could exceed these expectations for a vaccine against a disease as complicated as HIV. About 70% of R&D costs for a typical drug are incurred after clinical trials begin[3] vaccine trials are often larger and more expensive than those for other products.

The global community must ensure that the needs of both developed and developing countries are taken into account when developing new vaccines. The science that underlies vaccine discovery and development for diseases of the developing world is largely dependent on scientists in academic, government, and private research institutions. Vaccine studies focus on a broad spectrum of R&D challenges ranging from the need for an improved understanding of host/pathogen interaction and protective immune response to determining which formulation will maintain the viability of heat sensitive products for use in areas where refrigeration is scarce.

A significant share of basic scientific research for health conditions that affect affluent countries is also funded by the public sector, while the greater part of product development and clinical trials are typically financed by private sector investments. Public investment is thus complemented by commercial investments where the promise of a market exists; the largest single source of funding for R&D is the commercial sector. There is less funding for R&D of products that address health problems in developing countries than for products for developed countries. Overall, only a small proportion of total R&D for drugs and vaccines address health problems that disproportionately affect developing countries – about US$6 billion of a total of more than US$100 billion annually; of that, less than US$1 billion is devoted to vaccine research.[4] Almost all of these funds are from public and philanthropic sources. Commercial investments by large pharmaceutical companies are rare because the potential market for these products is likely to be insufficient to provide adequate financial returns to cover the costs of development and a return on investment. Commercial development of new vaccines for developing countries is driven by the same incentives and commercial imperatives facing manufacturers in developed countries.

Product development research, including that for vaccines, occurs in four broad phases: (I) fundamental research, or discovery, defined as research geared toward providing a scientific foundation for the understanding of host/pathogen interactions (e.g., malaria pathogenesis and host-immune response to the various disease stages); (II) translational research to identify points of intervention, early-stage product candidates, as well as needed tools and assays for clinical testing, based on the fundamental knowledge acquired in the first phase; (III) product development, which starts with the selection of a clinical candidate, preclinical studies to gain regulatory and ethical approval for safety and efficacy studies in humans, clinical development (Phases I through III), and licensure and marketing; and (IV) post-marketing, which includes clinical and epidemiological research to evaluate the impact of a newly introduced product on the burden of disease.

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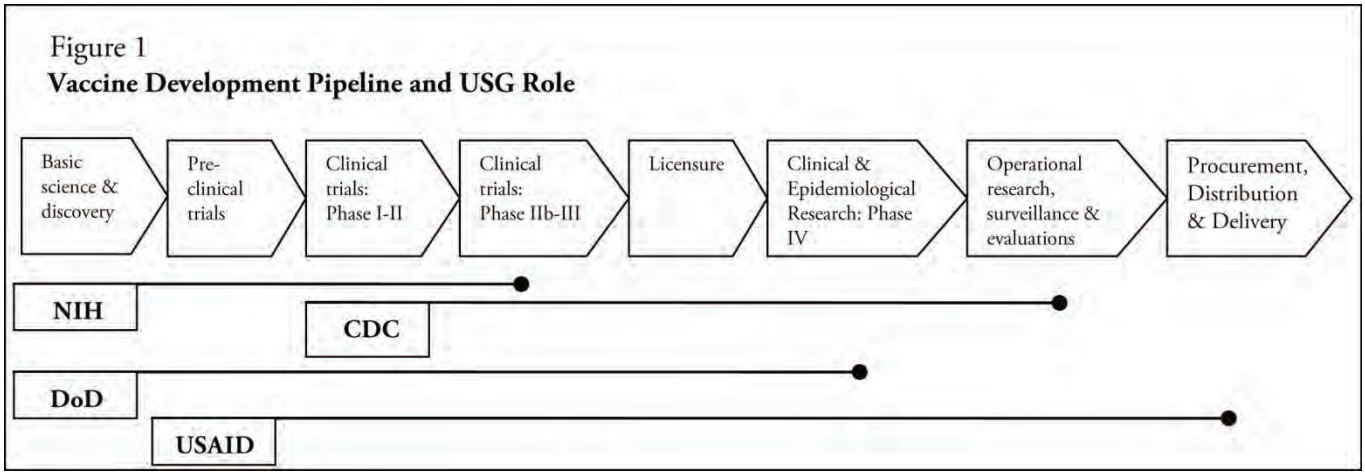
[2] *Making Markets for Vaccines: Ideas to Action*, The report of the Center for Global Development, Advance Market Commitment Working Group, http://www.cgdev.org/doc/books/vaccine/MakingMarkets-complete.pdf, page 12.
[3] *Making Markets for Vaccines: Ideas to Action*, page 18.
[4] Ibid.



Vaccine development is often incorrectly described as a linear process in which a vaccine transitions without interruption from concept through clinical trials to marketing. However, product development, including development of vaccines, usually is an iterative process with a high level of attrition where product candidates often fail to meet criteria for advancement at one of the stages in the development process and are either abandoned or modified and re-tested.

U.S. Government agencies have been and continue to be leaders in efforts to develop vaccines against HIV, malaria, and tuberculosis. The USG vaccine development effort includes NIH, DoD, USAID, and CDC. Each agency has a unique role within the vaccine development pipeline (see Figure 1 above). Within the government, the NIH supports basic research, preclinical testing in animal models, development of candidate vaccine products, and clinical testing of vaccines at intramural and extramural research programs at several institutes and centers. Through the Walter Reed Army Institute of Research (WRAIR), the U.S. Army, and the U.S. Navy, the DoD supports preclinical and clinical research, epidemiological research of vaccines, primarily for military personnel. CDC supports clinical trials, field preparedness, epidemiological research and surveillance, as well as technical assistance to evaluate, monitor, and strengthen the delivery of vaccines in the field. USAID supports preclinical testing in animal models, development of candidate vaccines products, clinical testing of vaccines, operations research, activities to prepare for the introduction of new vaccines, immunization programs, demand forecasting and supply, procurement, and logistics.

AGENCY/INITIATIVE	ROLE IN VACCINE DEVELOPMENT
National Institutes of Health (NIH)	Supports basic research, preclinical testing in animal models, development of candidate vaccine products, and clinical testing of vaccines
Department of Defense (DoD)	Supports basic research, preclinical testing in animal models, development of candidate vaccine products, and clinical testing of vaccines
Centers for Disease Control and Prevention (CDC)	Supports clinical trials, field preparedness, epidemiological research, surveillance; provides data on disease burden to establish baseline, monitor impact, and track specific changes in serotypes as necessary; supports economic studies on cost effectiveness; provides technical support for vaccine procurement, distribution and delivery
U.S. Agency for International Development (USAID)	Supports preclinical testing in animal models, development of candidate vaccine products, clinical testing of vaccines, operations and applied research to strengthen immunization programs and logistics, prepare for the introduction of new vaccines; and provides global expertise in demand forecasting, supply and procurement, and distribution and delivery to developing countries

III. Current Investments and Activities for the Development of Vaccines

HIV/AIDS Vaccine Development Efforts

More than 25 years after the discovery of HIV/AIDS, the pandemic continues to spread, especially in developing countries. HIV infection rates continue to rise in many developing countries; an estimated 2.7 million new infections occur every year, and no cure is available. Infected persons worldwide number nearly 33 million, and in sub-Saharan Africa, almost 60% of infected individuals are women.

No single approach to HIV/AIDS prevention is likely to have a dramatic impact if applied in isolation. Integrated approaches to prevention, detection, and management that are tailored to specific populations yield the best results. Unfortunately, current strategies for preventing HIV infection, including delay of sexual debut, partner reduction, and use of condoms are often not possible for many women in developing countries. Therefore, novel technologies to prevent new HIV infections are needed to complement currently available methods of HIV protection. All existing and developing HIV/AIDS prevention approaches must be tailored to best serve specific at-risk populations.

Adding a globally effective HIV vaccine to a comprehensive prevention strategy is a crucial step to control the HIV/AIDS pandemic. The search for a product has been challenging. In efficacy studies, two vaccine candidates have not shown they protect against HIV infection or moderate subsequent HIV disease. As announced in September 2009, a third vaccine studied for efficacy in Thailand on 16,402 participants has reported efficacy of 31% in an historic, first-time result proving a concept that is sure to lead to improved vaccine candidates. A fourth vaccine entered advanced clinical evaluation in June 2009. Scientific advances in defining how the human immune system attempts to protect itself against HIV are unfolding. The earliest events in natural infection, particularly in those who show an immune capacity to resist the virus, are beginning to inform new vaccine design; translating these events into a candidate vaccine hold great promise to have an impact on the epidemic with an eventually licensable vaccine.

USG HIV Vaccine Development Programs

Department of Health and Human Services, National Institutes of Health

The discovery and development of a safe and efficacious vaccine to prevent HIV/AIDS worldwide is a high priority area of research for the USG. Within the U.S. Government, the NIH, through both intramural and extramural research programs at several institutes and centers, supports basic research, preclinical testing in animal models, development of candidate vaccine products, and clinical testing of HIV/AIDS vaccines. HIV/AIDS research budgeting and planning throughout NIH is coordinated through the Office of AIDS Research, part of the Office of the NIH Director, which annually reviews and establishes NIH-wide scientific priorities and identifies research objectives and strategies to accomplish these goals and priorities through an annual Trans-NIH Plan for HIV-Related Research (http://www.oar.nih.gov/strategicplan/).

Within the NIH, NIAID has the lead on HIV/AIDS vaccine research, and other institutes and centers contribute to this effort by providing access to non-human primates for testing vaccine concepts (National Center for Research Resources mainly through the National Primate Research Centers); conducting intramural research on vaccine designs, model development and therapeutic vaccine concepts (National Cancer Institute); supporting trials in children and adolescents (Eunice Kennedy Shriver National Institute of Child Health and Human Development); and a small, focused extramural effort on mucosal vaccine approaches (National Institute of Dental and Craniofacial Research).

Through its intramural program in the Vaccine Branch, and in the AIDS and Cancer Virus Program, the National Cancer Institute (NCI) supports AIDS vaccine development efforts through research aimed at an

improved understanding of the pathogenesis of HIV infection, especially the early events involved in establishing infection, through the development and evaluation of novel vaccine approaches and candidates, development of improved non-human primate models for AIDS vaccine evaluation, and through providing unique reagents and analytical capabilities to support the AIDS vaccine research community as a whole.

The Vaccine Branch in NCI's Center for Cancer Research has several promising AIDS vaccine strategies under development. In a Cooperative Research and Development Agreement (CRADA) with Sanofi, NCI scientists played a key role in the development of the recombinant ALVAC vaccine that was the first to show clinical efficacy in a phase III trial in Thailand. Based on this discovery, the NCI holds a patent on this technology. Additionally, the NCI has a replication-competent recombinant adenovirus vaccine that has shown dramatic efficacy in non-human primates and is being prepared for clinical trials. NCI scientists have developed optimized DNA vaccines that can protect non-human primates against SIV as a single agent – the first evidence of such efficacy for a DNA vaccine – and that can provide therapeutic benefit to infected animals when given during anti-retroviral therapy.

Furthermore, NCI researchers have developed a mucosal vaccine strategy that induces mucosal T cells that can have an impact on the initial transmission of the virus, and that induces both innate and adaptive protective mucosal immunity against SIV in non-human primates. The NCI has also pioneered work on the use of cytokines such as interleukin-12 and interleukin-15 as vaccine adjuvants to improve the quality as well as the quantity of T lymphocyte response, and has developed ways to block inhibitory effects that restrain the immune response to vaccines. NCI scientists are also developing other novel vaccine vectors and ways to utilize non-neutralizing antibodies in protection. In addition, NCI has formed a consortium with the Institute of Human Virology, University of Maryland, to develop vaccines based on a new recombinant HIV envelope fusion protein that induces broadly neutralizing antibodies coupled with some NCI strategies to induce T cell immunity and to enhance antibody responses. Some of these vaccine strategies are now being developed as combinations for greater efficacy for both prophylactic and therapeutic use.

And finally, in 2009, the NCI issued an RFA initiative for the development of vaccines against HIV-associated malignancies or HIV infection. Progress to date in the understanding of the molecular mechanisms of AIDS and HIV infection and the development and application of treatments such as the widespread use of highly active antiviral therapy (HAART) in the developed world has led to greatly improved patient survival. However, accompanying this increased survival has been an increase in the incidence of HIV-associated cancers among long-term AIDS survivors. Malignancies are becoming the most frequent cause of death in HIV-infected populations. Given both the need for vaccines and the paucity of ongoing research efforts directed at vaccine development targeting HIV-associated malignancies, this initiative is designed to stimulate early exploratory research efforts in either preventative or therapeutic vaccine development for infectious causes of cancer (Kaposi's sarcoma; Epstein Barr Virus, hepatitis C, Merkle Cell Polyomavirus, and human papilloma virus of the types not present in the current vaccine) or HIV to prevent or limit infection in the host. This initiative covers the breadth of vaccine development from basic science studies, through animal model development, to preclinical studies. However, it does not support clinical trials. The outcomes of this new research on vaccine development for HIV-associated malignancies and HIV will help inform NCI's future research efforts in this area.

Because the first efficacy trials did not identify an effective vaccine, the identification of new vaccine concepts and development of potential leads for further evaluation are urgently needed. Basic research in the fields of HIV natural history, pathogenesis, immunology, virology, viral and host genetics, and animal model development can lead to novel discoveries that can form the basis for promising vaccine approaches. Through concerted efforts, basic discovery research can remove fundamental obstacles to achieving this goal by focusing intensively on fostering new cross- and inter-disciplinary collaborations, and sharing of the resulting knowledge may be critical to HIV vaccine discovery.

In March 2008, NIAID sponsored a summit on HIV vaccine research and development. The result of this meeting was a consensus that an increased emphasis on basic vaccine discovery research was needed. Toward this end, NIAID established a new branch within the Division of AIDS' Vaccine Research Program to focus on acceleration of discovery efforts, and new initiatives to support HIV vaccine discovery were developed.

Scientific advances in defining how the human immune system attempts to protect itself against HIV continue to unfold. The earliest events in natural infection, particularly in those that show an immune capacity to resist the virus, are beginning to inform new vaccine design, and the translation of these events into a candidate vaccine holds great promise. The top priority of NIH HIV vaccine research is to accelerate basic research that will lead to new vaccine concepts that induce neutralizing or other broadly protecting antibodies, consistent and high levels of effector and memory cytotoxic T lymphocytes, and/or strong mucosal immune responses. As of spring 2009, NIAID had supported a total of 111 vaccine trials (102 Phase I, Ib, I/IIa or I/II, 4 Phase II, 2 Phase IIa, 2 Phase IIb, 1 Phase III) involving 67 different products and 18 adjuvants.

NIH and other government agencies that conduct and support HIV vaccine research coordinate their efforts in several ways, including with: (1) the Partnership for AIDS Vaccine Evaluation (PAVE), a consortium of USG entities, led by NIAID and other USG-funded organizations involved in development and evaluation of HIV/AIDS preventive vaccines and the conduct of HIV vaccine clinical trials; (2) WHO-UNAIDS Vaccine Advisory Committee; and (3) the Global HIV Vaccine Enterprise, a consortium of independent organizations committed to accelerating the development of an HIV vaccine (see Section V).

In addition, the NIAID-supported HIV Vaccine Trials Network (HVTN) modified its scientific agenda to increase its emphasis on small trials to address fundamental scientific questions. The HVTN, funded by NIAID through a cooperative agreement, conducts the majority of NIH extramural vaccine trials. The mission of the HVTN is to enhance the discovery and drive the development of a safe and globally effective vaccine for the prevention of HIV through well-designed clinical research trials that objectively address the critical questions of the field. The three leadership groups (core/operational, laboratory and statistical) are located in Seattle at the Fred Hutchinson Cancer Research Center, and the sites in the network, also funded by NIAID, are located in the United States and abroad.

NIAID also solicits input from expert vaccine researchers and advocates who comprise the AIDS Vaccine Research Subcommittee (AVRS) of the AIDS Research Advisory Committee. Specifically, the AVRS assists NIAID in developing a comprehensive research program aimed at expediting the discovery and development of an effective HIV/AIDS vaccine. Additional information on NIAID's vaccine research can be found at: www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/ and www.vrc.nih.gov.

PAVE is a voluntary consortium of USG agencies and USG-funded organizations involved in HIV vaccine research. It was formed in 2003 with the recognition that no single entity or institution is likely to succeed alone in the goal to develop a safe and effective HIV vaccine. In addition to NIAID, members of PAVE include OAR, the NIAID-funded HVTN, USAID, MHRP, CDC, and IAVI. NIAID plays a key leadership role in PAVE by providing the chair for the partnership and operational support.

The Global HIV Vaccine Enterprise (Enterprise) was initially proposed in 2003 by prominent HIV/AIDS researchers, public health officials, and advocates, and endorsed by the leaders of the G-8 nations in June 2004. The Enterprise is a "virtual" consortium of independent organizations committed to accelerating the development of a safe and effective preventive vaccine for HIV/AIDS through the creation and implementation of a shared strategic scientific plan, mobilization of resources, and greater coordination and collaboration among HIV vaccine researchers worldwide.

The Vaccine Research Center (VRC) was conceived in response to the growing epidemic of HIV/AIDS. Despite more than 15 years of research, efforts to develop an effective HIV vaccine were unable to

deliver an effective vaccine, and it was proposed that a dedicated research center composed of investigators working on different aspects of this problem would be better able to address this challenge. The primary focus of activities at the VRC is the development of an effective HIV/AIDS vaccine. Using gene-based vaccine platforms, such as DNA plasmids and recombinant adenoviral vectors, VRC investigators have developed and tested numerous vaccine products and have advanced the most promising candidates into clinical testing. In the process of addressing the need for an HIV/AIDS vaccine, innovative technologies (e.g., DNA vaccines, novel viral vectors, structure-designed proteins) have been developed (http://www3.niaid.nih.gov/about/organization/vrc/).

The VRC has engaged the private sector and created multiple collaborative research and development agreements with large and small research and biotechnology organizations. These collaborations have resulted in the development of novel adenoviral vector vaccines against HIV and Ebola. VRC collaborations with the pharmaceutical sector have been implemented to examine the use of adjuvants in reducing vaccine dose requirements and to evaluate different prime-boost regimens for administration of HIV vaccines. In addition to basic research collaborations, partnerships with industrial organizations have expanded in recent years to include the manufacturing and process development activities associated with vaccine development.

Also, Office of AIDS Research annually solicits input for the Trans-NIH Plan for HIV-Related Research from an AIDS Vaccine Coordinating committee, comprised of representatives of NIH institutes and centers, NIH-funded investigators, other USG entities conducting AIDS-related research, pharmaceutical and biotechnology groups, nongovernmental organizations, and community representatives.

Department of Defense

In 1985, the U.S. military recognized the emerging HIV-1 epidemic as a new threat to U.S. and allied forces worldwide. A military directive emerged to develop effective preventive measures to include prevention education, vaccine development, and implementation of novel antiviral therapies and clinical management tools for the DoD. The U.S. Congress mandated the formation of a U.S. Army-led HIV/AIDS research unit in 1986. Initially organized around a reference laboratory at the Division of Retrovirology at the WRAIR in Rockville, MD, the program quickly grew with affiliated research sites in Kenya, Tanzania, Uganda, Nigeria, and Thailand and collaborative efforts with a wide variety of national and international research groups. The collective program is known as the U.S. Military HIV Research Program (MHRP).

The MHRP has since become an important partner in international efforts to combat this devastating disease. From its inception, MHRP has focused on both HIV variants that circulate in the developed (subtype B) and developing (non-subtype B) world given its dual mission to develop a preventive HIV vaccine for U.S. military personnel and for the global community. This global focus and an emphasis on capacity building and sustainable partnerships in Africa and Asia made MHRP unique in the early years of the HIV pandemic.

Funding for the MHRP technical base of the program is provided in approximately equal proportions from the Military Infectious Disease Research Program (MIDRP) via DoD Research and Engineering programs and from external grants from NIAID. The Defense Health Program supports an extensive HIV diagnostics and therapeutic monitoring activity at MHRP inclusive of HIV testing, HIV viral load and resistance genotyping capability, and infectious pathogen confirmatory testing for the Army Blood Program. MHRP is supported by smaller research funding from the BMGF, the Infectious Disease Clinical Research Program at the Uniformed Services University, and other entities. MHRP also executes a large prevention, care, and treatment program in Africa funded by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), Department of State.

MHRP research efforts encompass threat assessment and epidemiology, HIV diagnostics, vaccine development and testing, and therapeutics research. Epidemiologic studies inform vaccine development through the identification of at-risk populations and the enumeration of HIV prevalence, risk factors, and

incidence data that provide the key information to design clinical efficacy trials. Epidemiologic studies also provide the platform for community engagement and preparation for subsequent intervention studies for both vaccine and therapeutic research. Parallel molecular epidemiology studies have identified the precise molecular structure of circulating HIV variants in MHRP focus countries. East African sites are predominately representative of subtypes A, C, D, and intersubtype recombinants thereof. Nigeria is a mixture of CRF02_AG and G infections, while Thailand represents CRF01_AE and B. Together, MHRP research stations are well-positioned to test the concept of global protection of prospective HIV vaccine candidates.

While the MHRP's primary focus is on developing a globally effective preventive HIV-1 vaccine, the program provides effective prevention, care, and treatment programs in each of the communities in which research is conducted in order to provide an ethical, non-coercive environment to conduct clinical research. This aspect of the program is funded by PEPFAR and engages both civilian and military populations in sub-Saharan Africa. The research and PEPFAR programs exist in the same locations. This provides a vibrant synergy among clinical capabilities, enhanced public health infrastructure, and clinical research. The provision of these services makes MHRP a trusted member of the community and develops human capacity for both HIV and non-HIV programs. MHRP PEPFAR programs have developed in-country relationships with CDC, USAID, DoD, Peace Corps, and other stakeholders and has built powerful partnerships with host country civil society, government, academia, and nongovernmental organizations.

Funding of MHRP's technology base is a mixture of intramural Army and extramural NIAID funds. The latter are a blend of a Y01 (interagency agreement; multi-project/core grant) that funds HIV vaccine preclinical and clinical research; clinical research funds from the Division of Clinical Research managed by the Infectious Disease Clinical Research Program supporting therapeutics and Ebola-Marburg vaccine research; funding of a clinical trials unit of the AIDS Clinical Trials Group (ACTG) headquartered in Rockville, MD, with clinical research sites in Kericho and Eldoret, Kenya. Recent direction from the NIAID and ACTG has enabled MHRP to begin to explore HIV-malaria interactive research initiatives in Kenya.

MHRP preclinical research is heavily based on quality humoral and cellular immune assessment laboratories capable of state-of-the-art B and T cell epitope mapping, neutralization assays (PBMC and TZM-bl), ELISPOT, intracellular cytokine staining, chromium release CTL, and multiparameter flow cytometry. Program scientists are engaged in novel antigen discovery, liposomal formulations, and investigation of polyspecific monoclonal antibodies simultaneously binding to lipid and protein epitopes, and dissection of dendritic cell function. A vibrant host genetics group is discovering novel genetic associations with HIV acquisition, disease progression, immune response, and vaccine efficacy using gene-directed and (via collaboration) genome wide association studies. Onsite capabilities in transcriptional profiling and transcriptional control analysis complement the host genetics approach by providing the basis for mechanistic distillation of associative discovery. Extensive capabilities for HIV molecular epidemiology complete the molecular biology discovery group.

The Defense Health Program funds MHRP to maintain key clinical care support to U.S.-based military hospitals and to the Department of the Army. MHRP provides technical oversight of all Army HIV testing (1 million tests/year) and executes 100,000 tests yearly in a College of American Pathologists (CAP) certified laboratory. All HIV viral load and resistance genotyping tests and all confirmatory transfusion transmissible testing for Army Blood Program donations are performed on site. MHRP provides clinical laboratory oversight to CAP certified laboratories in Kenya, Tanzania, Uganda, and Thailand.

MHRP has conducted a Phase III trial of a canarypox prime, gp120 protein subunit boost strategy in 16,402 HIV seronegative, volunteers in Thailand. This study passed interim analysis and futility analysis over the past two summers. The study closed for analysis June 30, 2009. Major trial results announced

worldwide on September 24, 2009, reported that the investigational HIV vaccine regimen was safe and modestly effective in preventing HIV infection. According to final results released by the trial sponsor, the U.S. Army Surgeon General, the prime boost combination of ALVAC HIV and AIDSVAX BE lowered the rate of HIV infection by 31.2% compared with placebo. In the final analysis, 74 placebo recipients became infected with HIV compared to 51 in the vaccine regimen arm. The efficacy result is statistically significant. The vaccine regimen had no effect on the amount of virus in the blood of volunteers who became HIV-infected during the study.

These findings have important implications for the design of future HIV vaccines and how they are tested; however, additional research is needed to better understand how this vaccine regimen reduced the risk of HIV infection. Given the significant threat of HIV infection worldwide, an efficacious vaccine is urgently needed as part of a broader prevention effort to help control the epidemic.

Collaborating partners on this study, referred to as RV144, include the U.S. Army, the Thai Ministry of Public Health, NIAID, NIH, Sanofi Pasteur, and Global Solutions for Infectious Diseases. The collaborators are already working with external experts to determine the need for additional studies on this vaccine regimen and consider the impact of this study's findings on other HIV vaccine candidates.

U.S. Agency for International Development

Since 2001, USAID has funded, through PEPFAR, the International AIDS Vaccine Initiative (IAVI), a U.S.-based, nonprofit organization that acts as a virtual pharmaceutical company to accelerate the development and clinical testing of HIV vaccine candidates. IAVI and its network of partners research and develop vaccine candidates. USAID funding accelerates the development and introduction of new vaccine candidates and technologies and helps link vaccine designers with manufacturers and developing-country sites suitable for testing promising HIV vaccine candidates. Through IAVI, USAID supports biomedical research in all phases of HIV vaccine clinical R&D and other work to pave the way for introducing a vaccine when it becomes available. For IAVI's part, its R&D is focused on developing and evaluating novel vectors and vaccine designs, and testing them in nonhuman and human trials while preparing communities, so they can understand the wide variety of HIV vaccine trial results.

Specifically, USAID support for IAVI encompasses:

- Designing and implementing preclinical and clinical studies of vaccine candidates
- Supporting IAVI's core immunology laboratory and primate facilities
- Building local capacity at trial sites

IAVI's scientists are particularly focused on a few essential areas of viral behavior to inform and accelerate vaccine discovery. Among the most important efforts are the need to develop more reliable animal models that may be more predictive of HIV pathology and resistance in humans; to understand early events in HIV infection; to understand the behavior of HIV and how it does irreversible damage to the host, and how host genetic profiles affect HIV acquisition and disease progression; to discover how protection can be mobilized to the infection site while defining the structures on the HIV envelope that are the targets of broadly neutralizing antibodies; to design a vaccine ultimately capable of inducing antibodies that can be effective against many strains of HIV; and to optimize laboratory techniques capable of more accurately and quickly measuring responses to HIV candidate vaccines – particularly in resource-poor areas.

IAVI invests the bulk of its resources in the research and clinical assessment of candidate vaccines against strains of HIV that are prevalent in the developing world where some 95% of new HIV infections occur. Their scientific team works with more than 40 academic, commercial and government institutions to develop and assess candidate HIV vaccines. Together with their partners, IAVI has evaluated eight vaccines in 26 early-stage clinical trials conducted in 11 countries across four continents. To do this critical work, they, along with local research institutions, have developed a network of sophisticated

laboratories in India and in southern and eastern Africa. Their Human Immunobiology Laboratory in London helps coordinate the work of these laboratories and assures quality across the network.

In the arena of vaccine design, IAVI has brought leading HIV researchers together into three scientific consortia: the Neutralizing Antibody Consortium; the HIV Live-Attenuated Consortium; and the Vectors Consortium, all of which address the key obstacles to the development of an effective HIV vaccine. In developing countries, IAVI works closely with governmental, community, and civic organizations to ensure the transparent and ethical conduct of clinical trials. They support the staffing and training of community advisory boards representative of the communities in which clinical trials are conducted. IAVI assists in educating people about vaccine trials and the need for HIV vaccines, and helps to build both the clinical and scientific capacity required to run a long-term program of vaccine trials. They also analyze, develop, and advocate policies to promote the involvement of the private sector in HIV vaccine research and development, and polices that will ensure that once an HIV vaccine is developed, it will be swiftly produced, distributed, and made affordable worldwide.

Inherent in this public-private partnership, are collaborations among university, government, and private-sector groups to ensure that the appropriate resources are available for each phase of product development. Private sector investment historically brings most vaccines to market, but their contributions are less than 15% of the total investment in HIV/AIDS vaccine (see Figures 2 and 3, below). USAID's partnership with IAVI promotes policies to strengthen the involvement of the private sector in HIV vaccine R&D.

USAID actively collaborates with the NIH, the CDC, and the MHRP through the PAVE, as described above by the NIH.

Figure 2

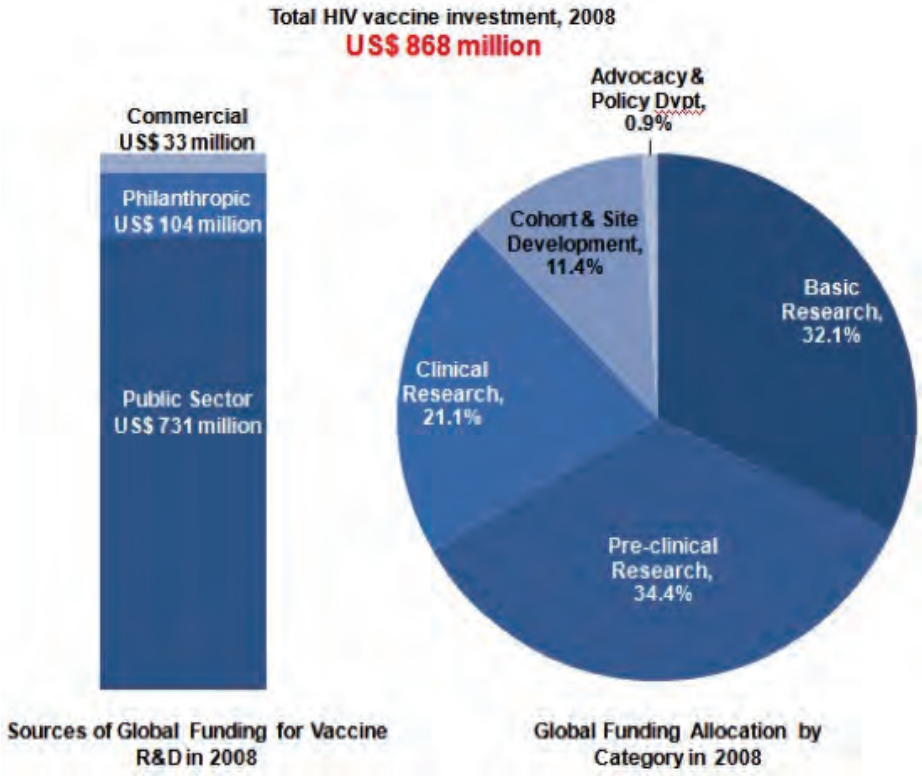
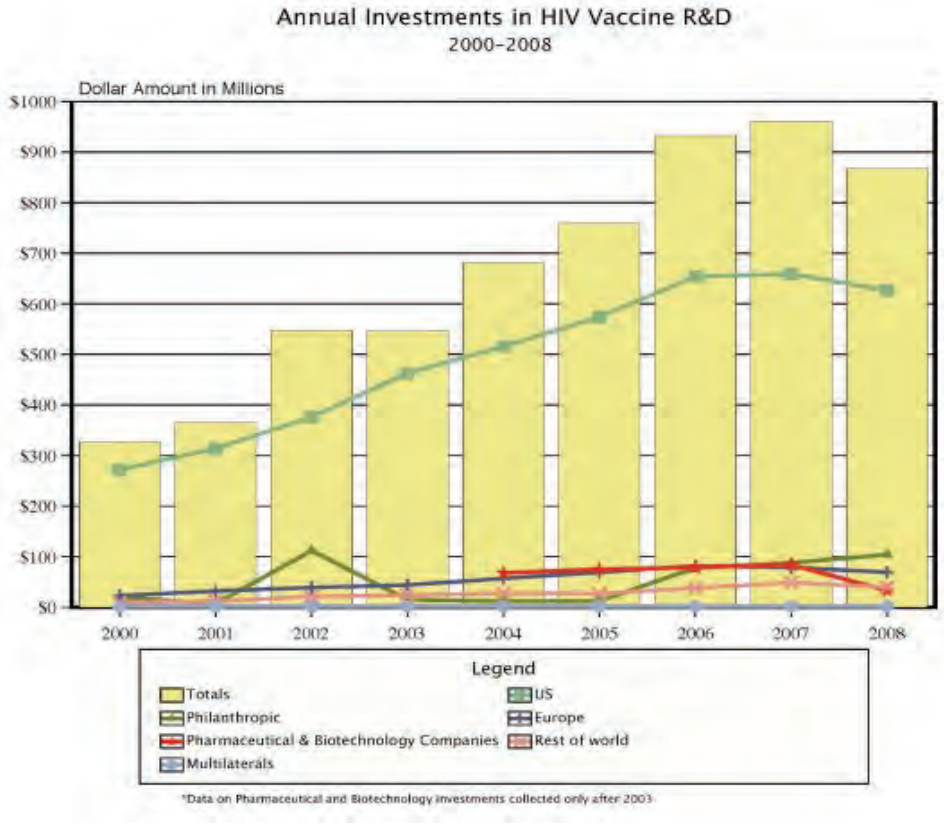


Figure 3



Source: http://www.hivresourcetracking.org/treatments/vaccines

Future Direction of USG HIV Vaccine Development

Department of Health and Human Services/National Institutes of Health

It bears repeating that HIV vaccine clinical research remains a high priority at the NIH and that the NIH will continue to support vaccine research through investigator-initiated grants as well as solicited research programs. The Fogarty International Center will continue supporting extensive training opportunities for international investigators in many prospective vaccine trial sites.

NIAID's active involvement with PAVE and South African AIDS Vaccine Initiative will also continue, increasing its ability to conduct HIV vaccine trials in developing countries and address issues and needs specific to a given region. NIH continues to conduct and/or support clinical trials of vaccine candidates through the HIV Vaccine Trials Network (HVTN) and the NIAID Dale and Betty Bumpers Vaccine Research Center (VRC), as well as through collaborations with the MHRP.

NIAID is supporting a trial (HVTN 505) using the VRC vaccine candidate based on a DNA/rAd5 prime-boost strategy to address specific scientific questions. HVTN 505 will evaluate whether the VRC vaccine can reduce viral load in vaccinated people who subsequently become HIV-1 infected due to sexual exposure. This trial opened to enrollment in June 2009 and is expected to have the first endpoint analysis in 2012; it is being conducted in the United States. The trial design has taken into consideration the findings of the STEP trial, a Phase IIB study of a vaccine developed by Merck. The STEP study efficiently determined that the vaccine candidate was not effective in preventing infection or lowering viral load among those who become infected but has provided important information for further vaccine discovery efforts and trial design. In the wake of the results from the Thai HIV vaccine trial, NIAID will

be actively collaborating with others to garner as much information as possible from the trial data; that information will be used to guide and improve NIAID's future initiatives for HIV vaccine design and development, and support the evaluation of improved HIV candidate vaccines

Department of Defense

MHRP's vaccine development strategy before the termination of the Merck studies was based on the canarypox/gp120 approach and the NIH DNA/Ad5 strategy as a developmental alternative. More novel approaches centered on DNA prime/Modified Vaccinia Ankara (MVA) vectored products were the third developmental line. Post-Merck study results have caused MHRP to redirect its second and third line vaccine development strategies. The NIH DNA prime/Ad5 boost program has been discontinued and the MVA program accelerated. Heterologous vector approaches (MVA/Ad26 with Harvard University and MVA/Ad35 with IAVI) will be pursued. Exploratory alternatives to DNA priming such as BCG are being developed. MHRP has now moved from collaborative integrated non-human primate heterologous SIV challenge studies to clinical development planning. New animal and clinical studies are being pursued using DNA delivered by electroporation and mosaic inserts to raise the magnitude and breadth of the elicited immune response to vaccines.

MHRP has also adjusted to the changing directions of the field by reemphasizing discovery research and establishing strategic partnerships with the NIAID-funded Center for HIV/AIDS Vaccine Immunology (CHAVI), ACTG, DoD Global Emerging Infections Surveillance and Response System, and the Army malaria program. One example of this direction is the development of a novel acute HIV infection study designed to both develop more efficient higher risk HIV cohorts and to identify individuals in the very earliest stages of HIV infection (prior to the humoral immune response) to synergize with CHAVI studies and investigate the earliest host-pathogen interactions with a view to better inform HIV vaccine development. This study (RV 217) is funded by both NIH and intramural Army funding. Taken together, the MHRP represents a broad-based, highly collaborative, and highly integrated research platform with strong epidemiology, preclinical, and clinical research capabilities embedded in a robust prevention, care, and treatment environment operating in six countries on three continents.

The program is well positioned to pursue the development of globally effective HIV vaccines, innovative HIV therapeutics research, informative HIV epidemiology studies, and diagnostic studies. MHRP is diversifying to allow its research platforms to conduct avian influenza/pandemic influenza surveillance and Ebola-Marburg vaccine studies. This provides MHRP a more flexible platform for sustainable clinical research in the current milieu of HIV/AIDS research. MHRP's strategic alignment following the results of the Merck vaccine studies have allowed the program to fully maintain its discovery and clinical research capabilities worldwide and have provided the underpinning of a more novel and value added research approach with its counterpart HIV research partners in the field.

U.S. Agency for International Development

USAID support for IAVI has helped to advance and accelerate HIV vaccine research and development, leading to important discoveries and new directions for the field. Recent HIV vaccine research findings are providing new hope in the search for model antibodies like those of people whose immunity provides effective viral control. These special antibodies known to neutralize, or lock-up the virus will inform scientists on exactly what the structures in a vaccine must look like and how they must function, in order to develop similar structures employing man-made biological techniques. This new body of work is evolving rapidly, and USAID's support of IAVI is key to its progress.

In the coming year, through its cooperative agreement with IAVI, USAID hopes to accelerate the search for safe and effective products that can prevent HIV infection. Among the expectations are IAVI's continued efforts to identify naturally occurring antibodies capable of neutralizing a wide variety of HIV. This promising work relies on activities that USAID supports IAVI to conduct in developing countries. Samples from otherwise healthy, HIV-positive volunteers are collected from IAVI's global vaccine

testing sites and assessed to identify broadly neutralizing antibodies that are already providing invaluable clues in developing a vaccine.

Other USAID priorities include rapidly advancing small-scale efficacy trials, called Screening Test of Concept (STOC) trials, of those HIV vaccine candidates in the current pipeline that will have already exhibited safety in preclinical and Phase I clinical and immunogenicity studies. STOC trials depend on the monitoring of HIV viral load subsequent to infection in the absence of antiretroviral therapy. This trial design may be challenged by the use of antiretroviral therapy in individuals at high risk for acquiring HIV infection if results of current studies show efficacy, as these populations may then be placed on antiretroviral therapy. Next generation candidates that target mucosal immunity and vectors that infect persistently are two other promising new directions that IAVI is pursuing.

This work is supported by ongoing vaccine preparedness activities to ensure that clinical trials proceed ethically and in a manner responsive to the needs of volunteers and their communities. IAVI will conduct gender sensitivity trainings for staff at collaborating research centers and implement recommendations from their ongoing study of gender-related barriers to participation in HIV vaccine clinical trials.

Policy research priorities for the coming year will focus on making the business and investment case for HIV vaccines and promoting policies to encourage greater participation by the public and private sectors in research and development. Additional information can be found at: International AIDS Vaccine Initiative (publicpolicy@iavi.org).

Tuberculosis Vaccine Development Efforts

Tuberculosis (TB) is a global health emergency that kills approximately 1.7 million people each year, the majority of whom are socio-economically disadvantaged or already marginalized in society. In addition to persons with active pulmonary TB, the form of the disease primarily responsible for spreading the TB pathogen, Mycobacterium tuberculosis (Mtb), over one-third of the world's population is thought to carry latent, asymptomatic infection. While TB can be found across the globe, the majority of cases (~80%) are clustered in 22 developing countries. TB was considered "managed" after the advent of chemotherapy in the mid-1900s and widespread vaccination after the introduction of the TB vaccine Bacille Calmette Guerin (BCG) in the 1920s. While it is provided as an almost universal neonatal vaccine in TB-endemic countries through the WHO's Expanded Program on Immunization, BCG is not sufficient to provide protection against pulmonary TB in children or adults; it does provide limited protection against disseminated TB in infants and young children.

The 1980s saw a rapid increase in the number of TB cases, and control programs, guided by the WHO, were established to better track and care for TB patients. In 2007, an estimated 9.27 million new cases occurred, which represents a global average of 139 cases per 100,000 population. Initial gains in TB control were reversed with the appearance of HIV/AIDS, and today, TB is the leading cause of death for people with HIV/AIDS. Of the 1.7 million annual TB deaths, approximately 456,000 are among persons who were HIV positive. HIV-positive persons are 20 times more likely to develop TB than are HIV-negative persons, and HIV infection is the most significant risk factor for a latent Mtb infection to convert to active TB.

In 2000, the global health community launched the Stop TB Partnership, sponsored by the WHO, to coordinate and inspire support for global TB control. The Stop TB Partnership has taken leadership of the global fight against TB, and the USG is a prominent member of the partnership. The first Global Plan 2001–2005 catalyzed governments and donors to address the issue of TB in their countries and

established key global targets for detection and treatment of active TB through Directly Observed Treatment, Short Course (DOTS)[5] programs.

This plan also recognized the need for biomedical research in TB as an integral part of a global strategy with the expectation that further research will modernize health care interventions and create new tools to fight the epidemic. Building on the success of the first Global Plan, the Stop TB Partnership launched the Actions For Life – The Global Plan to Stop TB 2006–2015, which references the Millennium Development Goal of halting and beginning to reverse the incidence of TB by 2015, as well as the more ambitious Stop TB Partnership targets of reducing TB prevalence and deaths by 50% by 2015, relative to the 1990 baseline. The Global Plan 2006–2015 notes that "introduction of new effective TB vaccines will be an essential component of any strategy to eliminate tuberculosis by 2050. New TB vaccines to prevent childhood and adult forms of TB, to reduce TB in people co-infected with HIV, and to shorten drug treatment regimens will fundamentally alter our approach to TB control."

The Current Need for TB Vaccine Development for the Developing World

According to WHO, it is unlikely that the global targets to halve TB prevalence and deaths will be achieved by 2015. This is mainly due to insufficient resources for scale-up of the Stop TB strategy, which remains focused on case detection and treatment of patients with already active disease, and the lack of new health care interventions that would transform care and reverse the trajectory of this epidemic. Despite active coordination around improvement of control practices through diagnosis and chemotherapy, the WHO has only recently recognized that novel vaccines against adult pulmonary TB will be needed to augment and supplement the current TB elimination strategies that are based on identification and treatment of persons with active TB. A mathematical modeling study published in the August 3, 2009, Proceedings of the National Academy of Sciences found that new tools, including vaccines, could significantly reduce TB incidence by 2050. The study concluded that neonatal vaccination with a new vaccine could decrease TB incidence by 39% to 52% by 2050. The same study found that the combination of a new vaccine, drug regimen, and diagnostics would decrease TB incidence by 71%. As such, vaccines would play an integral role in a comprehensive TB prevention and control strategy. (http://www.pnas.org/content/106/33/13980.abstract, accessed August 27, 2009)

The need for an effective vaccine is also underscored by the recognition that inadequate investments in public health infrastructure and human resources, insufficient political commitment and resources for TB control programs to assure timely diagnosis and an uninterrupted, high quality supply of drugs, and insufficient donor funding to sustain the current resource intensive care programs are key factors slowing progress. The growing extent of the HIV/TB co-epidemics, which necessitates use of complicated, poorly tolerated and often non-compatible multi-drug regimens, and the increase of multi-drug and extensively-drug resistant TB, which further complicates treatment regimens, underscores the critical need for vaccines to prevent and control the emergence of all forms of TB. New, effective vaccines would also relieve the burden on already stressed healthcare systems by reducing the need for input-intensive diagnosis and directly observed therapy.

State of the Science and TB Vaccine Development

There are several strategies being pursued worldwide to develop new vaccine candidates and approaches for TB.

1. **Recombinant BCG**

   Neonatal BCG vaccine is accepted as providing good protection against pediatric forms of TB, disseminated TB, and TB meningitis. It does not, however, reduce the burden of adult pulmonary

[5] Directly Observed Treatment, Short Course (DOTS) consists of five components: political commitment with increased and sustained funding; case detection through quality-assured bacteriology; standardized treatment with supervision and patient support; an effective drug supply and management system; and a monitoring and evaluation system, including impact measurement.

TB; BCG vaccine is still the most frequently administered vaccine worldwide. Furthermore, BCG also provides moderate protection against another highly stigmatized mycobacterial disease, leprosy, which is prevalent in many TB-endemic countries.

New recombinant BCG vaccines are intended to either improve neonatal vaccination to produce protection against pulmonary TB later in life, or to improve BCG as a priming vaccine for later boosting with protein, DNA or other types of vaccines. Current approaches to alter BCG include: (1) over-expression of Mtb antigens; (2) introduction of genes modifying the way the BCG interacts with the host; (3) alternation of the BCG genome to attenuate growth of the strain; or (4) combinations of the above in one vaccine. Recombinant BCG vaccine candidates have to date been evaluated in Phase I clinical trials. The most advanced recombinant BCG candidates have been developed by the Max Plack Institute in Germany and have entered Phase I dose-escalation studies.

While recombinant BCG constructs may be an important component of novel vaccination strategy, these vaccines nevertheless will be required to provide tangible benefits over BCG for infants to complete Phase III clinical trials and licensure and to justify replacement of the current vaccine. These facts, combined with limited data on the incidence of pediatric TB, the lack of specific and sensitive tests to diagnose pediatric extrapulmonary TB, and limited data from randomized controlled trials to document the effect of BCG on pediatric TB, make it technically and ethically difficult to conduct placebo-controlled clinical trials for a potential BCG replacement vaccine. On the other hand, recent studies have shown that the risks of administering BCG, a live vaccine, seem to outweigh the benefits of protection for infants born HIV-infected; therefore, safer vaccine candidates will be needed in settings with high co-prevalence of HIV and TB. Recombinant BCG vaccine candidates currently in development are being designed to specifically address this important safety issue.

2. **Virally vectored TB vaccines**

   MVA85, developed by Oxford University, is currently the most advanced virally vectored TB vaccine candidate and has reached Phase IIB trials. This construct is based on the expression of a key Mtb antigen by a viral vector (modified cowpox virus) and has been designed to boost BCG that has been received as part of standard vaccination programs in TB-endemic countries. Other virally vectored candidates include heat-inactivated adenovirus (Ad35) modified to carry mycobacterial DNA to express combinations of selected TB antigens within host cells.

3. **Adjuvanted subunit vaccines**

   These candidates comprise proteins that are made up of fusions of Mtb antigens and are administered in combination with adjuvants to boost neonatal BCG later in life. The most advanced candidate subunit vaccine is GSK M72 (developed by Corixa/GSK with significant funding by NIAID for preclinical development). This vaccine is currently in early-stage Phase II clinical testing.

4. **DNA vaccines**

   Several DNA vaccine candidates have been tested preclinically in animals, but candidates with sufficient activity to warrant advanced preclinical development have not been discovered.

5. **Other approaches**

   To expand the diversity of vaccine candidates and approaches, scientists are also evaluating the feasibility of attenuating Mtb through multiple gene deletions to serve as safe, immunogenic vaccines or platforms for advanced vaccination strategies. Furthermore, a heat inactivated Mycobacterium vaccae preparation, administered as a series of multiple boosting injections, has been studied in a Phase III trial in HIV-infected persons. Observations of reduced incidence of

pulmonary TB in adults have been made in this study and need to be assessed as primary endpoints in repeat prospective, randomized controlled studies.

Irrespective of the type of vaccination strategy proposed for TB, the scientific community faces significant regulatory, practical, ethical and financial hurdles that are becoming increasingly apparent now that new vaccine candidates are entering clinical trials for the first time. Any Phase III clinical trial to seek licensure for prevention of adult pulmonary TB, even as a booster vaccine in adolescents or adults, will have to be conducted in large cohorts in multiple TB-endemic countries and will have to follow volunteers for many years. Phase IV effectiveness studies will have to be conducted in collaboration with existing TB control programs to allow comparison of annual incidence and prevalence rates in the context of WHO case-reporting schemes. At this time, global investment in TB vaccine development is not sufficient to support large-scale, multi-center Phase II and III studies.

USG TB Vaccine Development Programs

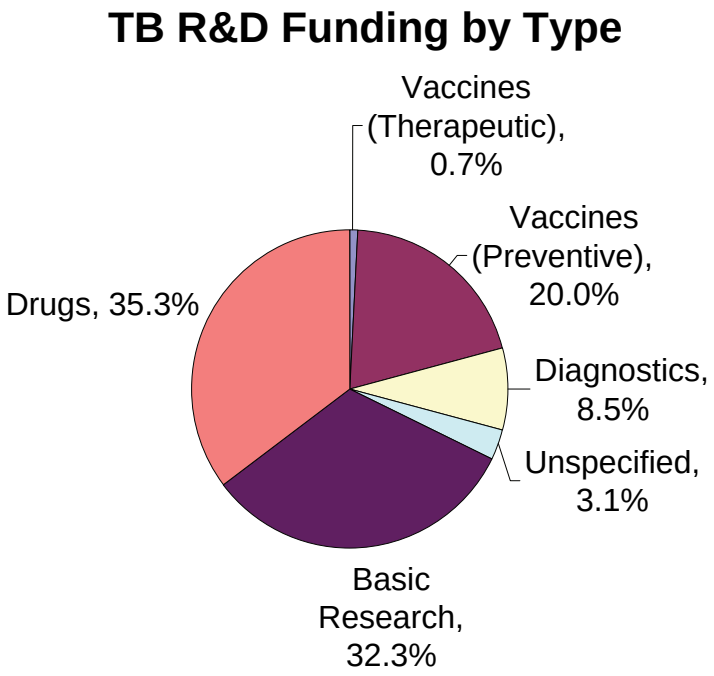
The USG is the largest bilateral donor supporting the implementation of TB control programs in disease-endemic countries and TB-related research. U.S. Government funded research and support has long been one of the only means by which development of vaccine candidates for TB was facilitated. NIH, through NIAID, is the lead agency for TB research, including vaccine-related research. As of 2008, NIAID remains the world's largest funder of TB research overall with an annual budget of over US$120 million and is the second largest funder for TB vaccine R&D.

Figure 4

Top 12 TB Research Funders (2007)

U.S. National Institutes of Health	$121,741,199	29.7%
Bill & Melinda Gates Foundation	$115,864,538	28.2%
European Commission	$21,455,029	5.2%
UK Medical Research Council	$12,710,433	3.1%
Dutch Ministry of Foreign Affairs	$12,187,935	3.0%
U.S. Centers for Disease Control and Prevention	$11,617,000	2.8%
Institut Pasteur	$7,996,742	1.9%
German Federal Ministry of Education and Research	$4,391,435	1.1%
Irish Aid	$4,111,435	1.0%
UK Health Protection Agency	$3,903,521	1.0%
U.S. Agency for International Development	$3,893,436	0.9%
Statens Serum Institute	$3,672,882	0.9%
Subtotal	**$323,545,585**	**78.8%**
Disease Total	**$410,428,697**	

Figure 5



Source: G-FINDER Report 2008 – Neglected Diseases Research and Development: How Much Are We Really Spending, The George Institute for International Health

NIAID funding for TB biomedical research has created a critical mass of qualified scientists to study all aspects of TB, and to contribute to the development of promising new vaccine, drug, and diagnostic candidates. NIAID is the primary USG stakeholder responsible for supporting TB vaccine development. Other USG organizations will be critical for facilitating introduction of vaccines and evaluation of field effectiveness and will play an important role in completing epidemiological studies to enable late-stage and post-licensure trials. Dutch biopharma company Crucell and the Aeras Global TB Vaccine

Foundation have started a Phase I clinical trial in Kenya of the jointly developed tuberculosis vaccine candidate, AERAS-402/Crucell Ad35. This study of the new tuberculosis (TB) vaccine candidate in Kenya will be conducted by the Walter Reed Project-Kenya (WRP) at Kombewa, near Kisumu, western Kenya. The main parameters of the study will be to test the safety of the candidate in healthy adults, all of whom have been previously vaccinated with the Bacille Calmette-Guerin vaccine and a subset of whom have evidence of having been exposed to TB. USG support for TB has been steadily increasing since the mid 1990s initially as a response to outbreaks of drug-resistant TB in HIV/AIDS communities in the United States but since then has paralleled the increasing recognition that TB constitutes a global health emergency that also affects the United States.

While NIH/NIAID's mission is focused on fundamental and translational biomedical research that includes the preclinical and early clinical evaluation of new vaccines, development of new health care interventions requires the stewardship and support of pharmaceutical companies. In recent years, the BMGF established several not-for profit organizations to facilitate development and implementation of new drugs, vaccines, and diagnostics that may be developed through academic, for-profit, or other not-for profit organizations. These organizations (the Global Alliance for TB Drug Development, the Aeras Global TB Vaccine Foundation, and the Foundation for Innovative New Diagnostics) have facilitated the transition of many product candidates and tools that were initially developed with USG funding into advanced-stage clinical testing. Additionally, product candidates are developed through European vaccine development consortia funded through the European Union (TBVac and now TBVI), by small biotechnology companies, and several pharmaceutical firms who also received funding through NIH/NIAID grants and cooperative agreements or for whom NIAID contracts provided contract research support to facilitate vaccine discovery and animal testing.

Coordination among TB Vaccine Development Programs

Coordination among the various global vaccine development agencies and private partners is implemented through the Stop TB Partnership's Working Group on New Vaccines. Coordination among the various partners is also accomplished through continual interaction, mutual consultations, workshops, development of milestones, and leveraging of available resources. Since clinical vaccine candidates for TB have only recently emerged, additional collaboration will be needed to facilitate advanced clinical development and field evaluation.

Future Direction

NIAID plays a critical role in supporting vaccine basic research, early candidate development, and animal testing, while other USG partners will be critical in translating new vaccines into proper use in TB-endemic countries. Research efforts will be expanded to include studies for the development of transmission-blocking vaccination strategies for TB outbreaks that may find application in the United States as well as in TB-endemic countries. To contribute effectively to TB control programs worldwide, strategies for combining drugs and vaccines to either enhance efficacy or shorten chemotherapy for adult and pediatric patients may be considered. Within the USG, TB control programs are currently being led by USAID (lead for international TB control) and CDC (lead for domestic TB control and provides critical technical assistance and operational research support internationally). Inter-agency collaboration is actively nurtured through the Federal TB Task Force and its International TB Working Group.

One of the key gaps in TB vaccine development remains the availability of potent and relevant adjuvants and the development of non-peptide antigens (such as lipids and sugars), which are already known to play a role in host-pathogen interactions. To facilitate the development of advanced vaccination strategies, more sophisticated animal model, immune, and natural disease history protocols will need to be established and validated. The introduction of new TB vaccines will also require tight coordination with TB and HIV control programs to assure the most appropriate use of novel adult or adolescent boosting vaccines, as well as to inform strategies for improving neonatal TB vaccination. All current and future

USG TB vaccine R&D efforts are, and will continue to be, leveraged with European and other global vaccine development efforts to avoid duplication and assure maximum use of limited resources.

Malaria Vaccine Development Efforts

Approximately half the world's population is at risk of malaria, and nearly 1 million people die of malaria each year; most of these deaths occur in young children in sub-Saharan Africa. Malaria is caused by Plasmodium parasites, transmitted by female Anopheles mosquitoes. Although four species of parasites infect humans, two species, *P. falciparum* and *P. vivax*, account for about 90 percent of all human infections; *P. falciparum* is the most deadly.

To mitigate the enormous loss of life, illness, and economic burden of malaria in the developing world, the U.S. Government agencies have led efforts to develop a malaria vaccine for more than four decades. In the mid-1960s, with the emergence and spread both of resistance to DDT among mosquitoes that transmit malaria and anti-malaria drug resistance of malaria parasites, the World Health Assembly terminated the ongoing malaria eradication program as an unsustainable effort. In response to these events, both USAID and the WRAIR initiated efforts to develop U.S. Food and Drug Administration (FDA) licensed malaria vaccines. At the same time, NIAID expanded its commitment to basic and strategic research on the pathogenesis of malaria, yielding new understanding and technology that fueled vaccine development efforts. These programs have made enormous progress, transforming the notion of a malaria vaccine into a working research program coordinated around many investigational vaccines at various stages of development. At this writing, a large multicenter trial of the malaria vaccine, candidate RTS S is being undertaken in Africa by the PATH Malaria Vaccine Initiative (MVI) and GlaxoSmithKline Biologicals (GSK). Although this clinical trial is made possible through the BMGF and GSK, the scientific basis and development of the vaccine is directly attributable to USG programs, notably that of WRAIR. This vaccine has the potential to achieve significant improvements in malaria morbidity and mortality if it can be successfully licensed. Phase II trials have suggested a protective efficacy of 30% to 40% against clinical malaria, and 50% against severe malaria. However, even this candidate is unlikely to be effective enough to prevent malaria entirely in an immunized population. Thus, next generation vaccines are badly needed.

In recent years, there have been increasing calls for efforts to control, eliminate, and eventually eradicate malaria. It is widely recognized that an effective malaria vaccine would substantially accelerate these efforts, but it is also acknowledged that efforts to achieve these goals may require novel types of vaccines that target the malaria parasite in different ways from the vaccine mentioned above (e.g., by blocking parasite stages responsible for malaria transmission) or indeed target other species of malaria parasites (e.g., *Plasmodium vivax*) that are important outside of Africa. In 2008, NIAID published a new Strategic Plan for Malaria Research and the NIAID Research Agenda for Malaria. Together, these documents lay out future directions for research as well as specific topics that will be critical to address for malaria vaccines and to contribute to improved malaria control, elimination and eventual eradication.

The Current Need for Malaria Vaccine Development for the Developing World

The GSK vaccine RTS S/AS01b, currently the most advanced malaria vaccine candidate, has begun pivotal Phase III testing to gather data for submission to regulatory bodies as a part of applications for licensure. This multicenter Phase III evaluation is the largest vaccine trial ever conducted on the African continent. A recently completed Phase II field trial of this vaccine, conducted on 5- to 17-month-old children in endemic malarial areas in East Africa, demonstrated significant efficacy (50%) in children immunized with the vaccine compared to those immunized with a rabies vaccine (8% versus 16% developed malaria respectively) over an approximately eight-month period.[6] If the applications for licensure are successful, it is expected that the vaccine will be available for introduction within the next

[6] http://content.nejm.org/cgi/content/full/NEJMoa0807381v1

four to five years. It remains to be seen whether or not these promising results will translate into a useful modality in malaria control programs.

Thus, although the GSK vaccine is promising, it likely falls short of what is needed to achieve maximum impact on malaria morbidity and mortality. Even with an efficacy of 50%, millions of children would be unprotected. Furthermore, as noted above, the GSK vaccine in its current form is not expected to protect against *P. vivax*. Thus, as the GSK vaccine undergoes final pre-licensure evaluation, the USG strategy remains focused on the development of more effective vaccines for control programs.

USG Malaria Vaccine Development Capacity

Although full advantage is taken of partners in academia and industry and with nongovernmental organizations, much of the "hands on" work of malaria vaccine development is conducted in USG-supported laboratories, clinics, and field operations. Through its various agencies, the USG is fielding robust programs of basic research in malaria pathogenesis and immunology, strategic vaccine research, and vaccine development.

Most of the intramural basic research is done within the Department of Health and Human Services (DHHS), through laboratories at NIAID and within the DoD through to laboratories associated with the Military Malaria Vaccine Development Program (MMVP). Key intramural laboratories include the NIAID Laboratory of Malaria Immunology and Vaccinology and the Laboratory of Malaria and Vector Research, the CDC's Malaria Branch in the Division of Parasitic Diseases, and the WRAIR and Naval Medical Research Center (NMRC), which comprise the DoD MMVP.

Although it has no laboratories or trial facilities, the USAID Malaria Vaccine Development Program (MVDP) is a robust element of the USG effort through its funding of and close coordination with partners. The mission of the MVDP is to develop vaccines for use in control programs in the developing world. The MVDP relies heavily on partners, in particular the Military Malaria Vaccine Development Program, to conduct vaccine development efforts responsive to the missions of both USAID and DoD. This collaboration is managed through interagency agreements between USAID and the Walter Reed Army Institute of Research and between USAID and the Naval Medical Research Center.

The MVDP operates in the context of the worldwide malaria vaccine development effort, which includes the development of vaccines for travelers, including military personnel, as well as vaccines for residents of endemic malarial areas, primarily children and pregnant women. This coordinated approach takes advantage of the innovations made by each program to advance the goals of each individual organization. In addition to its partnership with the MMVP, the USAID MVDP collaborates with the Malaria Vaccine Initiative at PATH (MVI) through congressionally directed funds. Established in 1999 and funded primarily by the BMFG, MVI works to accelerate the development of malaria vaccines and to ensure their availability and accessibility in the developing world. As such, it is a major force multiplier of the USG malaria vaccine development effort.

In addition to the intramural efforts described above, through its extramural research programs, NIAID maintains contracts that support basic tools for malaria vaccine R&D (e.g., genomic sequencing, bioinformatics, research and reference reagents), preclinical services (e.g., process development for vaccine manufacturing, toxicology, formulation), and clinical research and trial capacity both domestically and abroad as well as monitoring and data management for such trials. Through its grants programs, NIAID also supports basic and clinical extramural research on malaria vaccines and other related research. Awardees include academic institutions, research institutes, and small businesses.

CDC has a unique and highly-valued program with a wealth of parasite species and strains available for culture and use in preclinical vaccine testing, an insectary with a wide variety of anopheline species that can be infected with these parasites, and vast experience with non-human primate models to test vaccine candidates.

USG Malaria Vaccine Development Programs

As evidenced above, the U.S. Government has robust programs that utilize both USG capacity and that of other entities. Although formally institutionally based, the programs are in fact intricately networked with each other and with external partners. These vaccine development efforts are usefully divided into two functional categories: those targeting travelers to malaria endemic areas, such as deployed military personnel, and those focusing on affected populations in the developing world, whose victims are largely children and pregnant women. Despite these different objectives, almost all of the advances in one category are relevant to the other. For example, the GSK vaccine mentioned above, which could have an impact on malarial burden in the developing world, grew out of a program at WRAIR intended to develop a vaccine for military personnel.

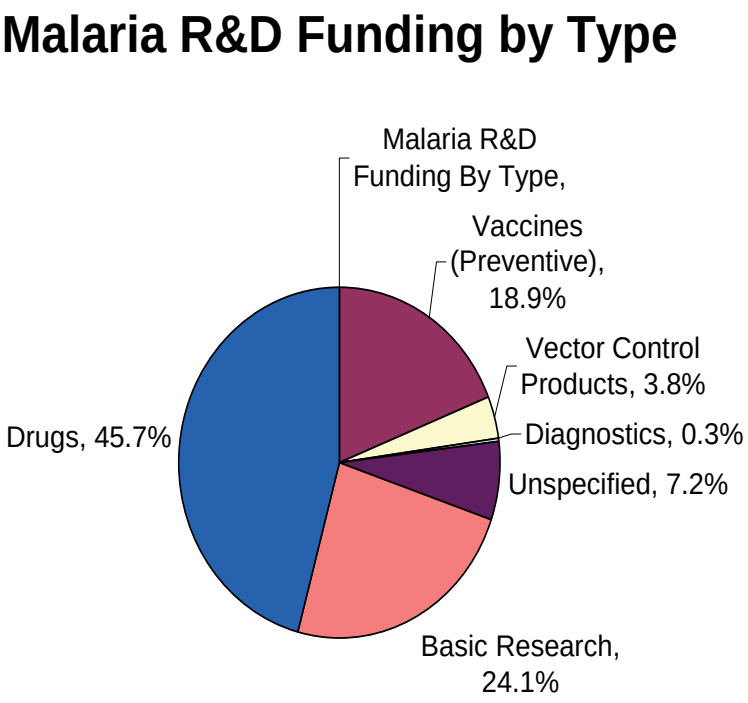
The USG effort toward the development of malaria vaccines for the developing world proceeds through the utilization of the capacities and coordination mechanisms described above. It operates in the context of the worldwide malaria vaccine development effort, which consists of non–U.S. laboratories and trial facilities funded by the European Union and the Wellcome Trust. This coordinated approach takes advantage of advances made by each program to achieve the goals of all organizations.

Figure 6

Top 12 Malaria Research Funders (2007)

Bill & Melinda Gates Foundation	$124,464,185	26.6%
U.S. National Institutes of Health	$84,422,644	18.0%
U.S. Department of Defense	$33,126,578	7.1%
Wellcome Trust	$28,255,207	6.0%
European Commission	$21,673,026	4.6%
UK Medical Research Council	$18,594,597	4.0%
Institut Pasteur	$13,142,888	2.8%
U.S. Agency for International Development	$9,249,900	2.0%
Australian National Health and Medical Research Council	$7,692,288	1.6%
Dutch Ministry of Foreign Affairs	$5,493,975	1.2%
Irish Aid	$5,481,914	1.2%
UK Department for International Development	$4,003,611	0.9%
Subtotal top 12 funders	**$355,600,814**	**75.9%**
Disease Total	**$468,449,438**	

Figure 7



Source: G-FINDER Report 2008 – Neglected Diseases Research and Development: How Much Are We Really Spending, The George Institute for International Health

Many avenues are available for the development of vaccines with improved efficacy; their exploitation is limited only by the availability of human and financial resources. The USG effort is therefore focused on methods that offer the most promise. The following is a summary of these approaches.

1. **Development of new vaccines based on the target molecule used in the GSK vaccine**

   The fact that the GSK vaccine is efficacious, albeit at a lower level than desired provides a signal that the target is a valid one. Thus the development of vaccines based on the same target, but using alternative formulations or "platforms" is judged to be a very promising approach. The USAID MVDP, the MMVP, MVI, and NIAID are all working toward this goal. The effort is greatly facilitated by the Infectious Disease Research Institute (IDRI), a nonprofit organization focused on developing new adjuvants for human vaccines, with financial support from BMGF funding.

2. **Heterologous or "prime boost" immunization**

   The use of platforms such as recombinant proteins based on malaria antigens and incorporated into virus-like particles is an important part of 1, above. Alternatively, recombinant viruses capable of expressing and delivering malaria antigens to the immune system provide an important approach to eliciting immune responses. Both of these approaches, however, run the risk of being inadequate by themselves to elicit robust immune responses to the malaria antigen if the immune

response to the non-malaria aspects of the vaccine accelerates clearance of the vaccine in the human host. Such inadequacy may be averted by the use of two different formulations or platforms, one for the initial immunization (the prime) and another for a subsequent immunization (the boost), so that the immune response is focused on the malaria component.

3. Blood stage vaccines

Malaria disease is caused by parasites in the blood, and naturally acquired immunity is developed against these blood stage parasites. Vaccines that could accelerate development of this naturally acquired immunity could prevent disease onset. A large body of information in experimental systems suggests that such vaccine could be developed, and efforts continue toward this goal.

4. Combination vaccines

Sound reasoning suggests that a combination of more than one parasite component will be needed in order to develop highly efficacious malaria vaccines, and this approach is reflected in the USG strategy. Such vaccines may involve multiple antigens from a given stage of the parasite lifecycle, antigens from multiple stages of the parasite lifecycle, antigens from different parasite strains, and even antigens from different parasite species.

5. New target discovery

Although projected on a longer timeline, new malaria vaccine targets and essential genes identifiable through the knowledge of the malaria parasite genome may ultimately provide the most robust approaches to malaria vaccine development. Identification of novel targets may pave the way for future identification and development of subunit vaccines (including combination vaccines based on multiple subunits) while the technical ability to "knock out" identified essential genes required for parasite growth, development, or virulence may enable the development of attenuated parasite vaccines.

6. Transmission blocking vaccines

Vaccines aimed at blocking development of the parasite in the mosquito could be tremendously powerful tool to decrease malaria transmission and help move toward goals of elimination and ultimately eradication. Several promising candidate antigens have been identified. Malaria parasites have a complex lifecycle, including developmental stages of the parasite that are specialized for transmission to and development within mosquitoes. Thus, a vaccine that targets these stages could prevent malaria transmission from person to person, although it would not prevent disease in an infected individual since that phase is associated with blood-stage parasites. Experimental data have supported the feasibility of blocking transmission with such vaccines, and a number of vaccine candidates have been identified and are undergoing further research, development and evaluation. Linking a transmission blocking candidate antigen with candidate vaccine antigen(s) form other parasite stages (e.g., liver or blood stage) would provide an attractive combination vaccine that could give individual protection and at the same time lead to decreased transmission.

7. *P. vivax* vaccines

P. vivax causes substantial global morbidity, and perhaps more mortality than originally believed. In recognition of the importance of interventions against *P. vivax* malaria to global malaria control, NIAID has actively sought to expand the research base for *P. vivax* vaccines, e.g., through its support for sequencing of the *P. vivax* genome. CDC has also been a leader in *P. vivax* preclinical vaccine development.

8. **Attenuated sporozoite vaccines**

   Two different attenuated whole organism approaches are being tested, one based on a precise dose of radiation administered to normal sporozoites and a second based on targeted disruption (knock-out) of key liver stage genes. These approaches appear particularly promising based on existing models and the overall success of attenuated live organism vaccines.

9. **Novel animal models**

   Malaria vaccine development has been hampered by the absence of animal models that reliably support the human malaria parasites, and this shortfall is being addressed by genetic engineering applied to both the parasite (knocking human malaria genes into rodent malaria parasites) and the host (humanized mouse models).

10. **Novel adjuvant formulations**

    "Subunit vaccines" are composed of malaria proteins produced from other microorganisms. Typically, these types of vaccines are not highly immunogenic and therefore require the addition of strong adjuvants to achieve the desired immune response. These novel adjuvant formulations may induce broad immune responses to enhance immunogenicity of the subunit vaccines currently under development.

Coordination among Malaria Vaccine Development Programs

Coordination among the various USG agencies and private partners is implemented through liaison on a daily basis. In addition, coordination is accomplished through ongoing interaction, annual work plans, development of "go/no-go" criteria for progression, etc. Within the USG, coordination is facilitated through the Federal Malaria Vaccine Coordinating Committee, which meets periodically on an ad hoc basis for general dialogue and consideration of special topics requiring attention. As needed, the committee invites nongovernment partners to participate.

Future Direction

The USG malaria vaccine development programs will continue to collaborate with organizations both inside and outside the U.S. Government toward the goal of discovering and validating practical vaccines to control malaria in the developing world. Efforts not managed by the USG will be reviewed with interest, and the USG strategy will be modified as new research is published. Specific new approaches will be evaluated, often through partnership with biotech companies with specialized expertise in novel technologies, and selected and added to the portfolio based on the best scientific information available. Current approaches will be accelerated if they are determined to be promising, or discarded if ineffective. The USG program will remain cognizant of the changing epidemiology of malaria and adjust accordingly as appropriate. Following a programmatic review commissioned by the U.S. Military Infectious Disease Research Program, the Institute of Medicine recommended substantial expansion of malaria vaccine research by DoD, due to the significant threat posed by this disease to military personnel during deployments to tropical areas. The Institute of Medicine pointed out in 2006 that the current capacity of the MIDRP Malaria Vaccine Program laboratories to carry out *P. falciparum sporozoite* challenge trials is unparalleled in the world. The rate of progress will be proportional to resources available.

Vaccine Development for Other Infectious Diseases

While HIV/AIDS malaria, and tuberculosis are priorities in vaccine research because of their worldwide prevalence and high mortality rates, the USG also aims to identify new vaccine candidates for many other diseases such as neglected tropical diseases, enteric diseases, and dengue fever. Investigators are working to produce effective vaccines that are safe for the targeted populations, including those with compromised immune systems.

Vaccine Development Efforts for Neglected Tropical Diseases

Neglected tropical diseases represent the most common infections of the world's one billion poorest people and include a group of chronic parasitic and bacterial infections such as hookworm infection, ascariasis, schistosomiasis, lymphatic filariasis, onchocerciasis, Chagas disease, leishmaniasis, and trachoma. Robust vaccine research studies directed at many of these serious and pervasive illnesses are ongoing at NIH in its intramural and extramural research programs. The great majority of these efforts are currently in the basic research and preclinical phases, although it is anticipated that some of these studies will transition into a clinical phase in coming years.

Vaccine Development Efforts for the Prevention of Enteric Diseases

Approximately 80% of infectious diarrhea cases among travelers are caused by bacterial agents, with enterotoxigenic E coli (ETEC), Campylobacter sp., and Shigella sp. infections of primary importance due to their frequency and debilitating effects. Viral infections cause an additional 10% of illnesses, with norovirus playing a primary role. While a number of travel-related illnesses have vaccines available for prevention of infectious diseases in deployed troops, there are no vaccines licensed by the FDA for prevention of diseases associated with these bacterial agents. The incidence of diarrheal illness among travelers and the health care savings that could be realized with the reduction in post-diarrheal chronic illness serve to create a viable U.S. market for enteric vaccines.

Through the DoD's Naval Medical Research Center and Walter Reed Army Institute of Research, as well as the National Institute of Allergy and Infectious Disease, the USG is focusing its efforts to develop preventive vaccines against Shigella sp., ETEC and Campylobacter sp. Partnering with other USG departments, academic institutions, industry, and private foundations, vaccines targeting Shigella sp. have reached Phase II testing in the past year. NMRC researchers have developed an ETEC vaccine that has demonstrated proof-of-concept for efficacy in a passive human challenge model and in a diarrheal disease non-human primate model and will likely go into human phase 1 in FY10. A Campylobacter vaccine based on the proven principle of capsule-conjugate vaccine has been developed and under NIH U01 funding is being manufactured for first-in-human testing in FY11. In addition, DoD scientists are working to solidify a collaborative partnership with PATH and other industry partners to develop vaccines targeting ETEC and Shigella. PATH receives funding from the BMGF for the Enteric Vaccine Initiative, a project for advancing the development of safe, affordable, and effective enteric vaccines for developing countries.

Vaccine Development Efforts for the Prevention of Dengue Fever

Dengue is the most important arboviral infection in the world today. The World Health Organization (WHO) estimates more than 500,000 people are hospitalized with severe dengue every year and more than 30,000 people, mostly children, die annually. Dengue's burden is experienced most significantly in resource poor countries of the tropics and subtropics. Dengue also accounts for a significant proportion of the systemic febrile syndromes observed in travelers returning from Southeast Asia and portions of Central and South America. There is currently no vaccine to prevent dengue, no antiviral medication to treat dengue, and vector control measures are resource intensive and are often ineffective. Developing an FDA-approved protective tetravalent dengue vaccine would mitigate effects of dengue in many areas of the world.

Numerous academic, government, military institutions, and the pharmaceutical industry are developing dengue vaccine candidates; more than ten candidates are in preclinical or clinical testing. Six of these candidates are being co-developed by either WRAIR or NMRC investigators including three which have entered into human clinical trials; two are in Phase I testing, one candidate is in Phase II. In addition, WRAIR is exploring providing the pharmaceutical company developing the lead candidate, which will be entering phase III testing in the next two years, access to a mature clinical trial site developed by the U.S. Army in Thailand. Projected timelines for licensure of the world's first dengue vaccine is approximately three to seven years.

Vaccine Development Efforts for Hantavirus vaccine

The DoD is sponsoring the only attempt to develop an FDA-licensed vaccine for hemorrhagic fever with renal syndrome (HFRS). HFRS is a potentially fatal hantavirus infection transmitted to humans by ingestion or inhalation of secreta/excreta originating from infected rodents and has had a serious impact on U.S. military personnel deployed to Korea. Newly emerging hantaviruses that cause highly lethal hantavirus pulmonary syndrome in the Americas are also a concern. Hantavirus research performed by the U.S. military could result in medical countermeasures against both HFRS and hantavirus pulmonary syndrome. Proof-of-concept DNA vaccines against HFRS and hantavirus pulmonary syndrome have been produced and tested successfully in rodents, rabbits, and nonhuman primates. A phase 1 clinical trial of the HFRS DNA vaccine is in progress.

Vaccine Development Efforts for Scrub Typhus Vaccine

The DoD is providing limited support to developing a vaccine that will protect troops from scrub typhus on a global basis. Scrub typhus an infectious disease transmitted to humans through the bite of an infected, immature mite. It is most commonly found in eastern and southeastern Asia, northern Australia, Indonesia, and southwestern Pacific islands. No other organization in the world is trying to develop a globally effective, FDA-approved, preventive scrub typhus vaccine, although scrub typhus is a worsening problem in many parts of the world.

Future Direction

The USG will continue to collaborate with public-private organizations in the efforts to develop vaccines for infectious disease such as the neglected tropical diseases, enteric diseases, and dengue fever. The great majority of these efforts are currently in the basic research and preclinical phases, although it is anticipated that some of these will move into the clinical phase in coming years.

IV. Initiatives to Create Incentives for the Research, Development and Manufacturing of Vaccines

One of the largest challenges in the development of new vaccines designed for the developing world is the financial risk associated with developing products for beneficiaries who may ultimately be unable to afford them. In order to encourage greater private-sector engagement in the research, development, and manufacturing of vaccines, incentives are needed to address specific barriers along the R&D to delivery pathway. The U.S. Government is exploring a range of incentives and innovative financing mechanisms. However, before increasing its commitment to these various mechanisms, further study is required to determine which mechanisms are best designed to share risk at critical junctures, most appropriate for USG investment, and are feasible.

It often takes more than 10 years, and sometimes decades, to develop a vaccine, and many that start out as promising candidates never come to completion for a variety of reasons ranging from scientific barriers, to decisions not to further develop a vaccine based on commercial market failure. Incentives could address specific hurdles identified in the R&D process of a specific vaccine. However, these hurdles and incentives vary by vaccine and the point in the research and development pipeline one is attempting to influence.

Industry operates on a "go/no go" decision framework that is revisited many times along the R&D pathway. They must make multiple strategic decisions about how much longer they will continue to invest time, money, and human resources on a particular vaccine during the development life of a product. Market considerations are taken into account as potential candidates move along the development continuum. Total investment in any product will not exceed a certain percentage of the total estimated market value of the product in development. Decisions around manufacturing capacity for a vaccine are made four-to-five years before a product becomes available on the market, and these decisions are based on complex market analysis. There is continuous reevaluation. Investments in supply capacity are determined against the size of the market for the product and the price the market will bear. If the global community is interested in ensuring developing countries have vaccines available to them, it is critical that by the time industry makes supply capacity decisions, demand forecasting for developing countries is well underway in partnership with industry. There are many points along the decision pathway where incentives could help deliver the positive outcomes for developing country benefit.

There are a range of incentives and innovative financing mechanism that have an impact on the vaccine development. Broadly these mechanisms include:

1. Basic and transnational research incentives
2. Product development incentives
3. Market preparation incentives

Basic and Transnational Research Incentives

Basic research incentives provide investment funds that can be used during the earlier stages of vaccine development. Primarily through NIH, the USG has programs and strategies in place to assist individual investigators to investigate new concepts, small groups to develop vaccine candidates to test in animal models, and larger consortia that can test vaccine-related concepts from basic research through clinical studies.

Examples of such basic research incentive programs can be found in NIH's HIV R&D portfolio. From industry's perspective, the risk-benefit ratio for developing HIV vaccines is heavily skewed toward risk, largely because of the enormous scientific obstacles to developing HIV vaccines. NIH's programs help to mitigate this risk by supporting HIV vaccine-related research aimed at overcoming these scientific

obstacles at several levels. Programs and strategies are in place to assist individual investigators to investigate new concepts, small groups to develop vaccine candidates to test in animal models and larger consortia that can test vaccine-related concepts from basic research through clinical studies.

Although basic and preclinical research is largely conducted in academic institutions, small business innovation research and small business technology transfer programs directly provide economic incentives and the engagement of small businesses in research and development that has the potential for commercialization (http://grants.nih.gov/grants/funding/sbirsttr_programs.htm).

NCI and NIAID intramural investigators have had long-standing material transfer agreements and cooperative research and development agreements with pharmaceutical partners (http://www3.niaid.nih.gov/about/organization/odoffices/omo/otd/When_to_use_MTA_CRADA.htm).

NIAID also encourages industry partnership by directly funding development, manufacturing, and/or testing of vaccines in collaboration with industry, providing opportunities for the private sector to contribute unique capabilities and intellectual property to the effort while minimizing their financial risk. Finally, NIH is the largest USG funder for domestic and international vaccine clinical trials and the supporting infrastructure that test candidate products from both small biotechnology and large pharmaceutical companies.

The status and complexity of HIV/AIDS research require a multi-pronged approach to support discovery and development activities at all levels, from fundamental basic research to clinical research and all phases of clinical trials. NIH has invested significant effort and research dollars on HIV/AIDS vaccines since the mid-1980s and has a number of research programs that target all phases of vaccine research. These include:

Center for HIV/AIDS Vaccine Immunology (CHAVI) – Established by NIAID as its main contribution to the Global HIV/AIDS Vaccine Enterprise, CHAVI is a "virtual" vaccine center comprised of 62 collaborating investigators in 26 institutions in seven countries in North America, Africa and Europe. CHAVI aims to overcome key immunological roadblocks in HIV vaccine development, with the specific goals of:

1. elucidating early viral and immunological events and host genetic factors associated with transmission, establishment of infection, and (partial) containment of virus replication;
2. determining correlates of SIV immune protection in primates;
3. designing, developing, and testing novel immunogens and adjuvants that elicit persistent mucosal and/or systemic immune responses in humans and primates; and
4. evaluating HIV-1 vaccine candidates in early phase clinical trials. CHAVI has developed multiple strategies for addressing these objectives, including the study of early immunological and virological events during infection, characterization of the first seeded viruses and their evolution in response to the host immune response, and the identification of host genetic factors associated with partial containment of virus replication.

Additional information can be found at: http://chavi.org.

Phased Innovation Awards – A grant program that fosters exploratory, high-risk, investigator-initiated HIV vaccine research at the earliest stages of concept genesis and evaluation. These awards are open to competition from investigators at for-profit and not-for profit institutions.

HIV Vaccine Research and Design (HIVRAD) – The goal of this grant program is to use a multidisciplinary approach to answer scientific questions related to HIV vaccine development. The program has been utilized by both academic and industry investigators to support basic vaccine research and design, including concept testing in animal models, mechanism of action studies, and studies of immune correlates.

Integrated Preclinical/Clinical AIDS Vaccine Development – A grant program that targets research at the preclinical-clinical interface of the HIV vaccine research pipeline. This program

supports consortia of experts in animal models, molecular biology, immunology, and early clinical trials to pursue the refinement of specific vaccine concepts. Vaccine clinical lot production and early human clinical studies within the period of the award are expected. This program has enabled several consortia to contract for vaccine development and production with biotechnology or pharmaceutical companies.

HIV Vaccine Design and Development Teams – Public-private partnerships of scientists from industry and/or academia who have identified specific vaccine concepts amenable to accelerated product development. These awards are milestone-driven contracts designed to encourage rapid advancement into clinical studies. Twelve contracts have been awarded since 2000 under this mechanism, involving ten separate companies and multiple academic collaborators.

Funding and technical support as well as selected reagents and evaluation resources are available to both academic and industry partners through the HIVRAD, Integrated Preclinical/Clinical AIDS Vaccine Development, and HIV Vaccine Design and Development Teams programs.

The NIAID initiatives directed at support of HIV vaccine discovery include:

Highly Innovative Tactics to Interrupt Transmission of HIV – A grant program designed to stimulate research on novel, unconventional, "outside the box," high risk, high potential and high impact approaches that might provide long-term protection from HIV acquisition.

Basic HIV Vaccine Discovery Research – A grant program designed to support the generation of new knowledge that will inform new conceptual approaches to HIV vaccine design. The program aims to attract scientists from the basic disciplines of immunology, virology, structural virology, genetics, and cell biology to work on HIV vaccine research and encourages cross-disciplinary research activities.

B Cell Immunology Partnership for Protective HIV-1 Vaccine Discovery – A grant program to foster fundamental research on B cell immunology in conjunction with structure-based immunogen design to derive new understanding and approaches for development of HIV vaccines that induce neutralizing antibodies. The program will foster networking and sharing of knowledge, reagents and protocols to enhance all advancements in the field.

Through multiple contracts, NIAID also provides substantial resources for all phases of preclinical development and evaluation of candidate HIV vaccines, including in vitro laboratory studies and in vivo testing in nonhuman primates. These resources are described below and can be found at www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/resources/.

Reagent Resource Support Program for AIDS Vaccine Development – Produces or purchases reagents needed for HIV vaccine research, carries out quality control, maintains a Web-based reagent database, and ships reagents nationally and internationally to NIAID-supported HIV vaccine grantees, contractors, and others. Industry partners as well as academic investigators have provided reagents to this resource.

HIV Database and Analysis Unit – Compiles and analyzes data in several areas relevant to HIV vaccine research. This unit, based at the Los Alamos National Laboratory in New Mexico consists of three related databases: an HIV Genetic Sequence Database, an HIV Molecular Immunology Database, and a Nonhuman Primate Vaccine Trials Database. These databases are publically available to any investigator conducting HIV-related research.

Simian Vaccine Evaluation Unit (SVEU) – This contract supports the evaluation of the immunogenicity and efficacy of candidate HIV vaccines in the nonhuman primate model with the objective of gaining information that can be applied to the development of HIV vaccines for human use. The SVEUs conduct initial pilot studies for assessment of the immune responses generated in response to the immunization with a candidate vaccine. They also conduct larger studies that allow viral challenge of the immunized non-human primates with SIV or SHIV virus to evaluate the vaccines' ability to generate immune responses that block infection, control virus

replication, or slow/prevent disease progression. Studies designed by individual investigators as well as teams or consortia have utilized this mechanism of support for these expensive, but critical, studies of HIV vaccine concepts. Although pharmaceutical companies may have some resources for these studies, it is rare that a biotechnology company has the ability to conduct nonhuman primate studies without specific support through this mechanism.

Core Immunology and Virology Contracts – These contracts carry out immunological and virological assessment of non-human primates under study through the SVEUs. The objective of the non-human primate core laboratories is to ensure standardization and comparability of the assays conducted for preclinical non-human primate studies and to provide a common basis for assessment of the immunogenicity and efficacy of candidate HIV and SIV vaccines. Several biotechnology groups have worked with NIAID for evaluation of their products on these contracts.

Preclinical Master Contract – This contract provides a complete spectrum of support for investigator-initiated vaccine development including small-scale R&D, cGMP manufacture of investigational prophylactic HIV vaccines, preclinical safety testing, and regulatory documentation support leading to IND submission for Phase I-II clinical testing. It provides a mechanism for rapid movement from vaccine discovery phase to human clinical testing. This contract also allows NIAID to partner with and fund biotechnology and pharmaceutical companies that have the capability of producing test lots of candidate HIV vaccines.

Product Development Incentives

Product development incentives provide investment funds to stimulate the development of new vaccines. Private-public product development partnerships (PDPs) are an example of partnerships that have been created to make incentives available. PDPs are established to provide direct support for basic research and clinical trials in particular disease area. There are several PDPs of varying size and portfolios that have been established that relate to vaccine development and the USG has played a key role in many of them. Examples of PDPs that have been mentioned earlier in this report include the Malaria Vaccine Initiative, Malaria Vaccine Development Program, and the International AIDS Vaccine Initiative. PDPs have proven to be effective in accelerating the development of vaccines for developing countries.

PDPs make strategic investments in vaccine development efforts in academia, biotechnology, and pharmaceutical companies to advance the most promising technologies. In return for those investments, the partner companies agree to pricing or supply terms that will ensure the availability of the product for use by public health systems in low-income countries.

One striking example of a PDP success, where the USG (through FDA, CDC and USAID) has successfully partnered with BMGF, PATH and WHO, is the Meningitis Vaccine Project (MVP). The MVP is a partnership of PATH and the WHO that was created in 2001 as a BMGF-funded partnership with the goal of eliminating epidemic meningitis in sub-Saharan Africa through the development, testing, licensure, and widespread use of affordable conjugate meningococcal vaccines. MVP is in the final stages of evaluation and licensure of a conjugate vaccine that targets group meningococcal meningitis, which causes most epidemics of meningitis in Africa. The group A meningococcal conjugate vaccine (Men A conjugate vaccine) has been shown to be immunogenic and safe in completed Phase I, Phase II, and Phase II/III trials. An infant study is ongoing, and two Phase IV studies are planned to begin in 2009. The regulatory dossier will be reviewed by the Indian licensing authorities and by WHO for pre-qualification by the end of 2009. The FDA's Center for Biologics Evaluation and Research laboratories provided the quality vaccine supplier, Serum Institute of India, a specific required technology and the requisite training. A European company provided the initial supply of one critical material necessary to produce the meningitis vaccine, while Serum Institute developed their own material. USAID provided funding to support the Indian regulatory agency to ensure they will be strong enough to provide oversight for this new vaccine, and for specific African country-level studies to gather the economic data around the

epidemics of meningitis this vaccine is designed to eliminate. CDC assisted with providing the necessary epidemiologic analysis to determine the disease burden, and additional country-level support to strengthen the introduction of the vaccine. Coordination and partnership have been exemplary over the life of this project. USAID is providing funds for an independent evaluation of the business model in light of the promise it holds for potential future projects. This high quality meningitis vaccine will be available for less than 40 cents a dose for the African countries where these epidemics occur. Funding for the vaccine is still not secure, but efforts are underway to find additional funds.

More information about PDPs appears in Section V below, "Expansion of Public-Private Partnerships and Leveraging Resources from Other Countries and Private Sector."

Market Preparation Incentives

Market preparation investment involves the engagement of the USG and partners to lay the ground work for informed, sustainable introduction of vaccines into developing countries. Industry looks to the global community for expertise in immunization programs in developing countries. These markets represent risk for industry. If they invest in the supply capacity to provide vaccines for these populations, will anyone buy the vaccines? For how long? Are they able to safely deliver the vaccine to the intended population? Industry looks to the global community, including USG agencies, to provide the information necessary to ensure robust immunization programs exist to safely reach target populations and to provide the funding necessary to purchase the vaccines. If these risks are not mitigated, industry is not likely to respond to the needs of developing countries.

USAID contributes market preparation expertise in:

Building immunization programs in developing countries
Improving vaccine logistics
Provision of expertise in vaccine demand forecast modeling and estimates
Informing procurement practices
Improvement of regulatory oversight in developing countries
Provision of funds at global, regional and national levels

CDC contributes market preparation expertise in:

Assisting countries with surveillance and laboratory capacity to determine disease burden
Building immunization programs in developing countries

Advance Market Commitment (AMC) is an example of market preparation incentives. AMC is an innovative funding mechanism that provides incentives for private industry to develop vaccines for diseases that primarily affect the developing world. With an AMC, donors commit funding to guarantee the price of a vaccine once it has been developed, thereby creating a predictable market for the vaccine. Developers then make binding commitments to provide vaccines at fixed, lower prices. This benefits long-term planning, as developing countries are then better able to develop sustainable financing plans.

Currently, there is a pilot AMC for the next generation pneumococcal conjugate vaccine that is administered through GAVI and the World Bank. Many of the same donors that contribute to GAVI also donate to this innovative US$1.5 billion AMC. The USG chose not to participate in this pilot AMC due to a variety of concerns around its construct. It is important to note that the AMC financial contribution is only a portion of the total funding necessary to get this vaccine into many of the poorest countries. In addition to the US$1.5 billion AMC fund, the GAVI board has had to commit a matching US$1.5 billion dollars through 2015 to help meet the anticipated demand of the pneumococcal vaccine by GAVI eligible countries. It is estimated that GAVI will have to commit several billion dollars after 2015 to continue the pneumococcal introduction into additional GAVI eligible countries. As an important donor to GAVI, the USG has strong interest in the AMC and its progress. In addition to the multibillion dollar requirement for

vaccine purchases, there are substantial, additional financing requirements for technical assistance to strengthen routine immunization programs expected to deliver the new, high priced vaccines; to train health care workers; for disease surveillance; for cold chain management; and for waste management, among other costs.

Billions of dollars of long-term funding will be required to sustain the introduction of the pneumococcal vaccine; however, it will save a large percent of the approximately 1.8 million children under five years of age who currently die from pneumonia each year. It appears that the AMC pilot may have helped increase the supply of pneumococcal vaccine for developing countries. However, the AMC is only part of the answer as the science was firmly in place, with one vaccine already on the market before the AMC came to pilot.

The AMC launch provides a timely opportunity for the USG to learn from an initiative that seeks to address the challenges of vaccine availability. The USG will continue to monitor the progress of the pilot AMC and other economic incentives, and will engage in the international dialogue on the various incentives, as appropriate. A report outlining advance market commitments has been prepared by the Department of Treasury in response to the Lantos- Hyde legislation.

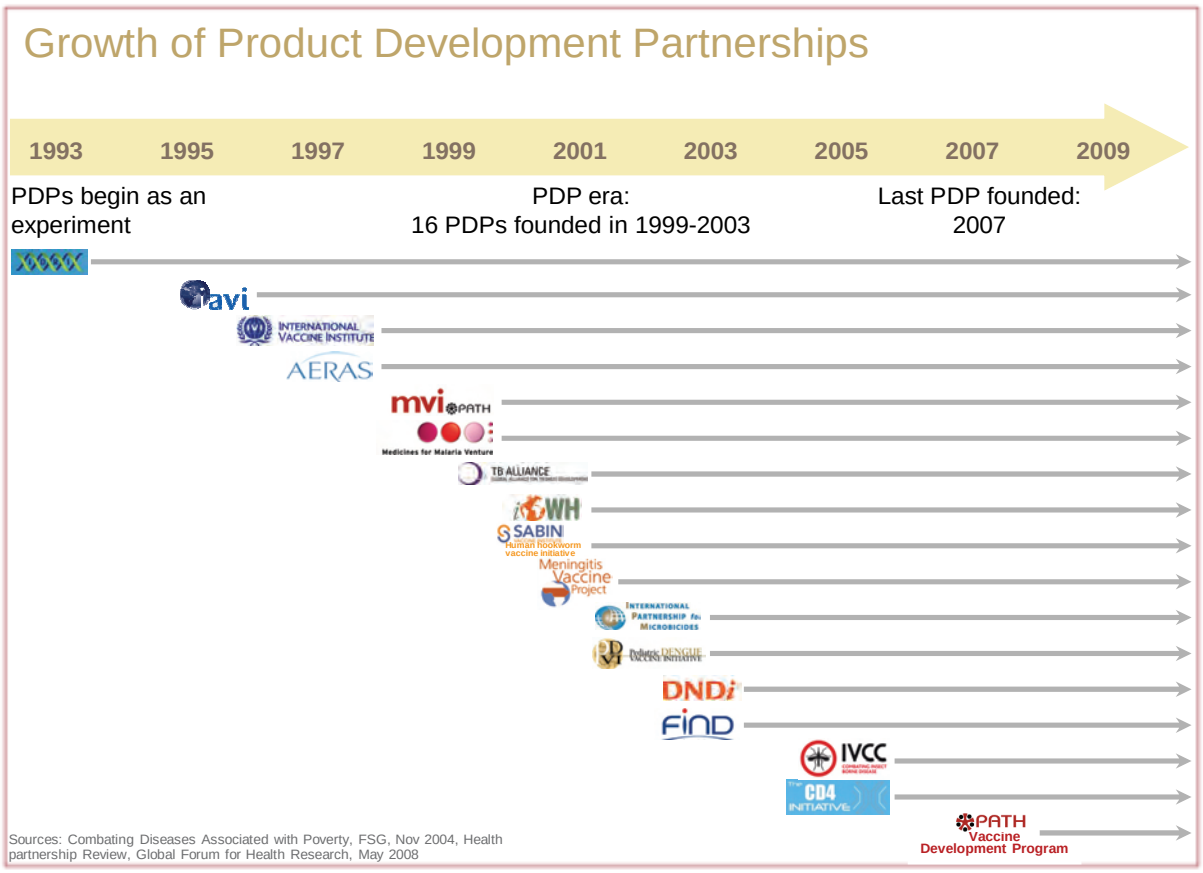
Another market preparation incentive is the priority review voucher (PRV), which is a U.S. specific market preparation tool. A PRV can be granted to any company that gains FDA approval for a new drug or biological product that addresses a neglected tropical disease. The company that holds this PRV is then entitled to receive an expedited FDA review of a future product, which can be transferred – or sold for profit – to another company. This expedited review means that a future product would be ready for licensure several months earlier, which could translate into tens of millions of dollars in additional revenue for the product.

V. Expansion of Public-Private Partnerships and Leveraging Resources from Other Countries and the Private Sector

While the public sector has the expertise and mandate to address the health needs of the underserved, the private sector also brings expertise that is essential to meet that mandate. Key vaccine development experience and know-how that exists within the private sector include the knowledge on how to conduct late-stage product development, the ability to manufacture vaccines to international standards once they are developed, and the capability to navigate regulatory pathways. The public sector possesses critical expertise in designing and delivering products intended for low-resource settings. For this reason, PDPs play an important role by leveraging private-sector expertise and resources alongside public-sector experience in addressing the health needs of developing countries. PDPs are designed to fill the product development gaps in areas where markets are weak and private industry perceives no opportunity to receive a return on their investments in the highly capital intensive R&D process. Moreover, PDPs are an efficient way for the USG to leverage private-sector expertise with scarce resources.

The BMGF has been an integral partner in various PDPs. For the past decade BMGF has invested in global health to develop tools and approaches that will have high impact, as well as developed critical partnerships and financing mechanisms to ensure that these will ultimately be delivered where they are needed most. Partners in their efforts have included bilateral, large and small companies, academia, and PDPs. The foundation currently supports 16 PDPs in infectious diseases (see Figure 8 below).

Figure 8



BMGF research and development programs are being funded from discovery through late-stage development and into introduction. The level of funding depends on the nature of the disease (global versus regional) and demand. The priority list includes:

The "big 3" – HIV, malaria, and TB – Each have a number of candidate products in a managed portfolio that is advancing competitively through the development sequence. The world's most advanced malaria vaccine, termed RTS S, has just entered into Phase III trial in Africa, while the first novel TB vaccine entered into Phase II trial this year. The HIV/AIDS field has refocused on driving early candidates into proof-of-concept. Given the global priority of these diseases, funding of projects and/or PDPs occurs in partnership with other donors (including bilaterals). Each field is aligned around a broad global plan (such as the HIV Vaccine Enterprise, the TB Partnership, and the Roll Back Malaria program).

Vaccines to prevent pneumonia – New vaccines to prevent pneumococcus (particularly common protein vaccine), influenza, and respiratory syncytial virus, would join the global vaccine armamentarium that currently includes measles and Hib. These are urgently needed to prevent the number one cause of death in children under five years of age. Prospective epidemiologic studies in high burden developing countries are ongoing and may identify other priorities for investment. A global market means that there may be opportunities for focusing commitments to trials in developing countries that are required for licensure and introduction. The new AMC provides a unique opportunity to leverage this market combination to incentivize industry to engage in creation of technical solutions for pneumonia.

Vaccines to prevent diarrhea and other enteric infections – rotavirus, cholera, ETEC, and Shigella – Specifically, rotavirus vaccines are now licensed in multiple countries, and GAVI is poised to prioritize the introduction of rotavirus vaccine to prevent the most frequent cause of dehydrating diarrhea of infancy.

Vaccines for select neglected tropical diseases – hookworm, trypanosomiasis, and cysticercosis – These diseases have traditionally received little attention in terms of R&D investments and depend primarily on public and philanthropic sectors – so called push funding – for advancement.

BMGF's program includes grants to support discovery, development, and delivery of new vaccines. Cross-sector partnerships are a key theme of the BMGF program. Partnerships engage the knowledge base in each sector and the resources each brings to the table, and allows these to be combined for impact.

Another example of effective partnerships is specific to HIV through NIAID. NIAID fosters and supports public-private partnerships through several grant or contract mechanisms – the HIV Vaccine Research and Design program, Integrated Preclinical/Clinical AIDS Vaccine Development program, and HIV Vaccine Design and Development Teams. Each of these mechanisms support consortia of researchers from the public and private sectors, but the HIV Vaccine Design and Development Teams, in particular, funds public-private partnerships of scientists from industry and/or academia to help advance promising vaccine concepts.

Examples of Current Partnerships with Private Industry for HIV through NIAID (not inclusive)		
Company	Preclinical Research & Development	Support of Clinical Trial
ABL	X	
AlphaVax	X	*
Althea	X	**
GenVec	X	**
GeoVax	X	X
Merck		X
Novartis	X	*
Profectus	X	*
Sanofi		X
Targeted Genetics	X	*
VGX	X	*
*Clinical trials in planning phase **Products produced under contract in clinical trials		

The NIAID intramural VRC also interacts with industry groups to leverage NIAID research capacity and to foster product development initiatives.

NIAID contributes to the Global HIV Vaccine Enterprise (Enterprise), a "virtual" consortium of independent organizations. The Enterprise is committed to accelerating the development of a safe and effective preventive vaccine for HIV/AIDS through the creation and implementation of a shared strategic scientific plan, mobilization of resources, and greater coordination and collaboration among HIV vaccine researchers worldwide.

The Enterprise seeks to:

Stimulate the development of increased HIV vaccine manufacturing capacity.

Establish standardized preclinical and clinical laboratory assessments for candidate HIV vaccines.

Close the gap between global capacity and future requirements for conducting clinical trials of HIV vaccines.

Promote greater engagement by scientists from developing countries in the HIV vaccine research effort.

NIAID supported the first Enterprise Scientific Strategic Plan through the creation of CHAVI. NIAID also tailors its existing programs to support the priorities identified by the Strategic Plan. As one of the leading stakeholders of the Enterprise, NIAID provides financial support to the Enterprise Secretariat. At present, the Enterprise is developing a 2010 Scientific Strategic Plan, which will include key scientific questions for consideration, a delineation of structural, organizational and capacity-building approaches, recommendations for funding, and milestones to measure success. This plan will be guided by an advisory board and five working groups, each of which will include representatives from the biopharmaceutical industry and leading scientists and advocates inside and outside the field of HIV vaccine research and development.

To ensure global implementation of this plan, NIAID and the Enterprise Secretariat actively foster initiatives that will further HIV vaccine research and development in various geographical regions. These efforts include the African AIDS Vaccine Program (AAVP), whose mission is to promote HIV vaccine development for Africa, through research, advocacy, partnership, and contribution to capacity strengthening and policy development, and the AIDS Vaccine Asian Network (AVAN), which strives to help develop and strengthen a regional platform for clinical trials, including harmonized legal, regulatory, and ethical frameworks.

NIAID also supports the efforts of the South African AIDS Vaccine Initiative (SAAVI), which was formed in 1999 to coordinate the research, development and testing of HIV vaccines in South Africa. SAAVI is based at the Medical Research Council (MRC) of South Africa and is working with key national and international partners to rapidly produce an affordable, effective and locally relevant HIV vaccine. In 2007, SAAVI collaborated with the NIAID and the HIV Vaccine Trials Network for the conduct of a large Phase II vaccine trial in South Africa. Currently, NIAID is supporting the clinical assessment of a vaccine developed by SAAVI, the manufacture of which was supported by NIAID. NIAID works collaboratively with SAAVI in the support of clinical research sites in South Africa.

The Partnership for AIDS Vaccine Evaluation (PAVE) was formed in 2003 with the recognition that no single entity or institution is likely to succeed alone in the goal to develop a sage and effective HIV vaccine. This consortium of USG agencies and USG-funded organizations has a goal of achieving better harmony and increased operational and cost efficiencies in HIV vaccine development and the conduct of HIV vaccine clinical trials, especially Phase III trials. To accomplish this, PAVE serves as a forum and clearinghouse for information sharing and planning. PAVE also aims to eliminate unnecessary duplication of efforts, and pools intellectual resources and experience to achieve the fundamental goals that a number of USG agencies and others share in common. PAVE has coordinated U.S. Government laboratory efforts with a focus on standardization and validation of assays in support of clinical trials internationally, spearheaded efforts to determine critical clinical site needs and to catalogue clinical trial sites both domestically and in the developing world, contributed to novel trial designs, facilitated communication, and harmonized critical path clinical trials. Of note, this partnership led to the successful harmonization of active international trials across several of the partners. Although not implemented, the planning and preparation of PAVE 100, a large Phase IIB trial, marked a major success in scientific and operational coordination and collaboration among all the member organizations, which should be of great significance for future efforts. Additional information can be found at www.hivpave.org.

NIAID is also able to leverage resources in other countries by working closely with the MHRP for the conduct of HIV vaccine trials. The U.S. Military HIV Research Program (MHRP) provides access to a large number of sites overseas and a comprehensive medical infrastructure, particularly in Africa and Thailand.

Given the robust evidence that exists on the impact of safe and efficacious vaccines, forcing a choice between investments in R&D versus introduction of existing vaccines is a false dichotomy. The current economic environment does create challenges, but the first principles for global health should not be forgotten: the concept of equity, the value of prevention, and the known scalability and potential of success of vaccine programs. The case for investment in both R&D and implementation of vaccines has been amply documented as excellent global health “buy.”

The business model for engagement varies by disease and its unique epidemiology. Vaccines for global diseases – such as pneumonia – have a global market, and thus it is possible to enter into agreements that would leverage that market to ensure global access; in this context, industry makes its own investments but it is often critical to provide resources to ensure collection of data to support safety and efficacy under conditions of poverty and other tropical diseases. In contrast, vaccines for orphan diseases, which may be geographically limited (trypanosomiasis; or even a developing country clade of HIV) and often affect those in poverty, are usually doomed to market failure. Development of these vaccines depends largely on government and philanthropic funding for success. It is challenging for large companies to invest in R&D for neglected diseases, but there are well developed public-private partnerships for malaria and neglected diseases that have overcome these constraints. While developing-country manufacturers can often create a viable business model for themselves with large volume and low prices, they have less experience with generating innovation and de novo development, although this is changing.

One of the most pressing problems that this global vaccine enterprise is facing is the challenge of having multiple candidates prepared for advanced trials in endemic countries. This poses two problems: first, the

problem of field trial capacity and second, the financial requirements of such a program. If the NIH is successful in extending engagement of the field trial capacity it has created in HIV endemic areas for evaluation of other global health products, this may ease the capacity constraints. Managing the financial requirements to drive the portfolio of priority global health products will require rigorous prioritization, cross-disease collaborations, as well as additional funds. While the PDPs are prepared to collaborate, aligning the donors, partner countries and academic organizations behind the most effective use of this critical capacity will be a priority for the coming years.

There are investments needed in enabling infrastructure, particularly regulatory systems that need to be prepared to evaluate and approve the new global health products. This has become a priority for the countries themselves. Success would mean fewer delays and thus a cost-savings for the entire system.

The USG commitment to accelerating the development of vaccines for global health is critical for success of this effort. Drawing upon the innovation generated by support from NIH, engaging the specialized experience and knowledge of MHRP, partnering with USAID in the support of PDPs to discover and evaluate candidates in the field – there are a multitude of examples to indicate that USG engagement has a long and without question the most productive history of contributions to vaccine discovery of any country. A few examples: development of conjugate technology by NIH; generation of candidate malaria vaccines by the U.S. Military HIV Research Program (MHRP); and creation of new partnerships for evaluation of rotavirus vaccines by USAID. These are but a few examples that demonstrate the power of the U.S. public and private vaccine development framework. It is upon these successes that overcoming the remaining, even tougher challenges – such as an HIV or an effective malaria or TB vaccine – depend.

PDPs can address various hurdles in the vaccine development pipeline. They have played a key role in vaccine development and will continue to do so in the future. The long-term nature of product development requires long-term, sustainable, and predictable funding to ensure that the most effective vaccine candidates can progress in a timely manner through the full spectrum of clinical development. The variety and number of current PDPs makes it necessary to study whether additional PDPs are required to accelerate the development of vaccines or whether the need lies in expanding already existing PDPs. As such, as part of the USG strategy to accelerate the research, development and manufacturing of vaccine, the USG will explore the range of vaccine development partnerships to determine the most efficient way for the USG to leverage private-sector expertise with scarce resources.

GAVI Alliance

The GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) was launched in 2000 to improve access to immunization for children in impoverished countries. GAVI does not invest in vaccine R&D, but focuses on introducing vaccines into country programs and providing funding for strengthening health systems. As a result, nearly 3.4 million deaths may have been averted since 2000. Governments in developed and developing countries, UNICEF, WHO, the World Bank, the BMGF, nongovernmental organizations, civil society, vaccine manufacturers from developed and developing countries, and public health and research institutions work together as partners in the alliance to support the poorest 72 countries of the world (GNI per capita of less than US$1,000 as of 2003 World Bank data). Since 2001, USAID has provided US$569 million to GAVI; donors such as the Bill & Melinda Gates Foundation, developed and developing country vaccine manufacturers, research and technical institutes, bilateral and multilateral institutions, and civil society organizations have committed roughly US$2.5 billion through 2015.

GAVI supports the introduction of under-utilized vaccines to the poorest countries of the world. Its greatest success to date has been the widespread introduction of Hepatitis B (Hep B) and Haemophilus influenzae type b (Hib) vaccines. These vaccines have been widely available in developed countries for decades but beyond the financial reach of the poorest countries. Since inception, GAVI financing has provided:

Hep B vaccine to 192 million children
Hib vaccine to 42 million children
DTP vaccine to 51 million children

For the past seven years, GAVI focused its resources to reduce the introduction time for two vaccines: pneumococcal conjugate vaccine and rotavirus vaccine. The successful introduction of these vaccines could substantially reduce the 800,000 deaths of children under-five attributed annually to pneumonia and the approximately 250,000 annual deaths of children under-five caused by rotavirus. These two projects focused on elevating the profile of the disease mortality, discovering what country-level decision-makers knew about the diseases, generating missing data on disease burden in developing countries, and analyzing and addressing vaccine supply related issues. Two developing countries have introduced an early version of pneumococcal conjugate vaccine (PCV7); and an additional 11 countries have been approved by GAVI to receive the newer version with additional serotypes in 2010–2011. GAVI has also supported the introduction of rotavirus vaccine in four countries; nine additional countries have been approved for introduction starting in 2010.

GAVI is also having an impact on the vaccine industry by demonstrating to vaccine manufacturers that a profitable developing-country market exists. Armed with substantial, predictable resources and the ability to negotiate longer-term supply commitments with industry, GAVI has generated reliable demand in developing countries for existing vaccines (Hep B, Hib and yellow fever in particular) and is working on improving rapid access for new vaccines. New, complex vaccines are costly, and GAVI will need to attract greater funding to provide for their sustained introduction so that industry will invest in vaccines for developing countries.

Funding will also be needed to build immunization programs and health systems to deliver the new complex, expensive vaccines. GAVI has demonstrated that a combination of funds for the purchase of vaccines for developing countries combined with credible country-level demand forecasting and multi-partner coordination can induce industry to provide a greater supply of newer vaccines at lower prices.

Vaccine purchases alone do not get vaccines into children or their intended population. USAID and CDC continue to invest in routine immunization programs in developing countries to build the capacity of national and local governments and partners to deliver vaccines. Countries need to be prepared at the national and the local level for the introduction of new, expensive vaccines. Without robust immunization programs, investments in vaccine research and development and procurement will fail.

VI. Efforts to Maximize United States Capabilities to Support Clinical Trials of Vaccines in Developing Countries and to Address the Challenges of Delivering Vaccines in the Developing Countries

Clinical Trials of Vaccines in Developing Countries

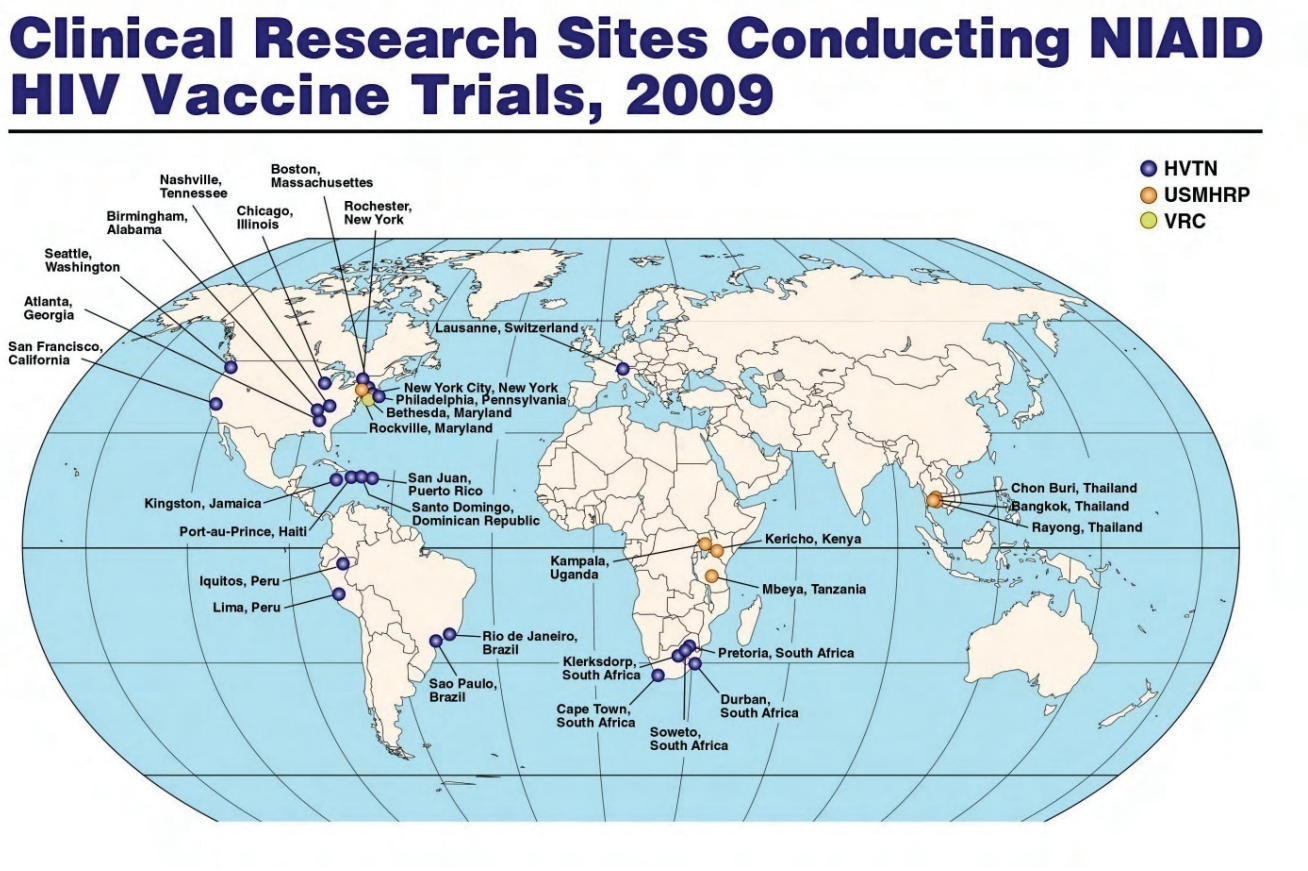
The U.S. Government plays a significant role in supporting vaccine clinical trials and effective delivery of vaccines in the developing world. NIH is a leading agency in supporting clinical trial sites worldwide. An example of their leading efforts can be found in NIH's R&D HIV vaccine portfolio. Specifically, NIH continues to conduct and/or support clinical trials of vaccine candidates through the HIV Vaccine Trial Network (HVTN) and the NIAID Dale and Betty Bumpers Vaccine Research Center (VRC), as well as through collaborations with the Military HIV Research Program (MHRP). The Fogarty International Center supports extensive training opportunities for international investigators in many prospective vaccine trial sites. NIAID's active involvement with the Partnership for AIDS Vaccine Evaluation (PAVE) and the South African AIDS Vaccine Initiative (SAAVI) also increase its ability to conduct HIV vaccine trials in developing countries and address issues and needs specific to a given region. The participation of international sites (see Figure 9 below) and the involvement of diverse populations through partnership with host country researchers, governments, and communities are critical components of NIAID's HIV vaccine effort. They allow for studies that examine differences in HIV diversity, genetic background, nutritional status, effects of other infections, and access to health care, all of which may prove crucial to developing an effective vaccine for use around the world.

NIAID and the HVTN have actively helped to develop sustainable sites in the developing world and continue to support those efforts, exploring avenues to make the activity and support of those sites more robust. The HVTN works closely with community members and programs to educate people about HIV/AIDS, HIV vaccine research, and the importance of clinical trials. Through close collaboration with communities where vaccines will be tested, the HVTN hopes to enroll a diversified population in its clinical trials, ensuring access and representation of populations most affected by HIV. Additional information can be found at www.hvtn.org.

The DoD is also a key USG agency supporting clinical trial sites. Established in 1985 to protect troops entering endemic HIV areas, the MHRP is part of the Walter Reed Army Institute of Research, U.S. Army Medical Research and Materiel Command. It brings together scientists from the U.S. Army, Navy, and Air Force and is closely partnered with the Henry M. Jackson Foundation for the Advancement of Military Medicine. NIAID jointly plans and executes HIV/AIDS research projects and clinical trials with the MHRP through an interagency agreement. This collaboration helps ensure that USG HIV vaccine research is well coordinated, efficient and comprehensive, and allows NIAID access to DoD's presence overseas, particularly in Africa and Thailand, including the extraordinary DoD medical infrastructure and extensive knowledge in establishing and supporting operations in underdeveloped areas. Through this partnership with NIAID, the MHRP, the primary HIV/AIDS research program for DoD, jointly plans HIV/AIDS research that includes the design and construction of vaccine candidates, preclinical research and development, pilot lot production, and Phase I-III human clinical testing of safety, immunogenicity and efficacy of HIV candidate vaccines and vaccine strategies. Additional research is also conducted as required to develop the necessary local capacity to support these vaccine clinical trials and identify effective preventive measures. In September 2009, the first HIV vaccine efficacy trial supported by NIAID, conducted in Thailand in collaboration with the MHRP, reported that the investigational HIV vaccine regimen was safe and modestly effective in preventing HIV infection, proving a concept that is sure to lead to improved vaccine candidates. Additional information can be found at www.hivresearch.org.

Another HIV vaccine efficacy trial started in June 2009 will evaluate the product concept developed at the intramural NIAID VRC. The study (HVTN 505) will be conducted by the NIAID-funded HVTN sites and is expected to have the first endpoint analysis in 2012.

Figure 9



As part of its collaboration with USAID, IAVI is committed to building sustainable capacity in the developing world and is collaborating with scientists in Kenya, Uganda, and South Africa to test vaccine candidates in clinical trials. USAID is working with IAVI to explore how capacity building by IAVI for preparation of clinical trial sites in developing countries can be leveraged to support the roll-out of HIV/AIDS treatment, care, and prevention, especially under PEPFAR. Conversely, new HIV/AIDS treatment programs can be beneficial for large-scale vaccine trials. During the enrollment period of Phase III (efficacy) vaccine trials, it is likely that large numbers of people will be screened who are in immediate need of antiretroviral therapy. Having convenient treatment available and appropriate referral mechanisms in place will help the trials ensure positive relations with the communities where they are conducted.

In addition, USAID collaborates with the NIH, CDC, and MHRP through PAVE, as described above. In 2008, IAVI, with the CDC and MHRP, released landmark work to provide data defining normative laboratory values. Across Africa, drug and vaccine trial participants, for diseases such as HIV/AIDS, TB and malaria have been routinely disqualified from studies due to the standard use of laboratory reference ranges developed for Western populations. Laboratory tests on kidney and liver functions as well as blood counts (e.g., hemoglobin, neutrophils and eosinophils) of healthy African men and women, often fall outside established ranges. Researchers believe that these differences are largely environmental in nature

– people in Africa encounter common parasites and pathogens not typically found in the Western world. The immune cells (CD4) responsible for fighting off infections, which HIV targets and are an important measure of AIDS progression, thus tend to be somewhat lower.

It is of critical importance that clinical trials are conducted among the intended recipients to assure that the vaccine or drug works. Due to the work of IAVI and its partners, reference ranges for healthy African trial volunteers have been established, creating appropriate criteria for the inclusion and exclusion of volunteers in testing for new, preventive health technologies, accurate health monitoring of patients throughout the course of a clinical trial, and, importantly, to guide treatment. This new data is critical in the design and monitoring of clinical trials, particularly trials of potentially life-saving technologies, among African populations.

IAVI's work also builds local capacity at trial sites in human resources, laboratory, clinical, IT, and other sustainable infrastructure. Their work results in reliable incidence and prevalence estimates through extensive cohort studies that define early HIV infection immunologic events and guide decisions on where large-scale efficacy trials may be possible for vaccines and other new prevention technologies. USAID advisors ensure that IAVI establishes referral patterns to interface with existing USG programs for HIV/AIDS treatment, care, and prevention services under PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria while strengthening the capacity to accelerate clinical trials of HIV vaccines in developing countries. These synergies set the stage for eventual product introduction and distribution. To adequately inform public policy, USAID's partnership with IAVI supports analytical models to forecast global demand estimates for HIV vaccines.

The information above provides examples of USG support specific to HIV; however the USG is also involved in clinical trial sites in other diseases including malaria and TB. The USG is committed to building sustainable capacity in the developing world and is already collaborating with scientists in countries such as Kenya, Uganda, and South Africa to test vaccine candidates in clinical trials. To accelerate the development of vaccines for infectious diseases, the USG will strengthen coordination among the various programs that are supporting clinical trials for infectious diseases. Coordination among programs conducting research in the same disease area is already quite strong and will continue to provide a strong base for continued clinical trials. There is opportunity to have more synergies across different disease areas. For example, there may be HIV clinical trial sites that can benefit from collaboration with TB clinical trial sites in the same country or region. This cross fertilization may be already occurring; however, it is necessary to ensure that all opportunities have been maximized. As such, to accelerate the development of vaccines, the U.S. Government will conduct a mapping exercise of all vaccine clinical sites that are implemented by or funded by the USG. More robust information of the relevant clinical trial sites will lead to more strategically coordinated, streamlined and aligned government support for advancing the development of new vaccines for infectious diseases.

Addressing Challenges of Delivering Vaccines in Developing Countries

The delivery of vaccines in developing countries is far more complex than many people imagine. Buying vaccine is only one piece of a complex puzzle. Vaccine delivery preparedness actually often times begins years before the vaccine is actually introduced into a country program. Disease burden needs to be established through surveillance and laboratory capacity. Awareness must be raised if it is a disease that is difficult to understand or detect. Arguments must be made around cost effectiveness. Ministries of Health have to work with Ministries of Planning and Finance to figure out how and when they can afford to bring a vaccine into the program. Regulatory authorities need to be in a position to determine if a vaccine is appropriate for their population, that it is safe and effective. The regulatory authority must be sufficiently strong to know how and when to address an adverse event after immunization. Logisticians must determine if there is sufficient cold chain capacity for storage at national, regional and local levels and

determine how and how often they will have to transport the vaccines safely in a cold chain. Health workers must be trained on a number of issues such as how to administer the vaccine, counsel parents on timing of doses and what to look for if there were a reaction to the immunization. Communities must be informed of new vaccines. Doses must be calculated with wastage rates, orders placed and paid for, all before a dose is ever administered. The above steps are required in order to deliver vaccine, and all take place with the assumption that the immunization program is sufficiently strong to reach the targeted population through careful planning of fixed site immunization or planned periodic intensification. Delivering a vaccine to the target population is only one step of many required in an immunization program. There is a great deal of work that remains to be done across all these areas for immunization programs in developing countries to overcome the challenges of safely delivering vaccines to their target populations.

The quality of immunization programs in developing countries is variable. Some very poor countries have dedicated themselves to building systems that are able to reach a very high percentage, even 95%, of their birth cohort with three or four visits in the first months of life. Other countries are barely able to reach 25% of their children with three visits in the very early months of life. Few countries have immunization programs that extend to reaching children through school-based immunization at strategic ages.

Both USAID and CDC work to build capacity in developing countries to continue to improve immunization programs because without them vaccines simply cannot be delivered. USAID's primary investment in immunization is through GAVI where the focus is largely on the purchase of new and under-utilized vaccines with some additional investments in strengthening health systems. In addition, USAID makes technical assistance available to USAID regional offices and country level USAID missions worldwide to strengthen immunization programs. USAID works closely with national, district and local governments, WHO, UNICEF and civil society in-country to help build programs. USAID also provides short term specific assistance with a component of the immunization program like supportive supervision, planning, training, logistics or assessments and evaluations to prepare for applications to GAVI. USAID also supports programs that strengthen routine immunization systems and provide technical assistance to countries to introduce new and underutilized vaccines.

The expertise of USAID staff is oftentimes tapped at the global and regional level to help inform decision-making at important decision points. USAID makes strategic investments in supporting quality supply globally, providing high-level immunization advisors to strategic countries through WHO, twinning strong regulatory agencies with weak ones in developing countries, and funding specific economic studies on the cost effectiveness of a vaccine compared to the economic devastation of disease. Some USAID missions support immunization programs through provision of immunization advisory staff or disease surveillance or laboratory support while others contribute short-term assistance, financial or technical, in the case of epidemics, outbreaks or campaigns.

CDC supports immunization programs in developing countries by providing their technical expertise to assist with evidence-based decision-making regarding the introduction of new vaccines and to support program implementation and monitoring of the impact of vaccines. CDC deploys its epidemiologists, public health experts, and scientists to WHO, UNICEF, and other international organizations, where they hold leadership positions in global, regional, and country-level immunization programs and help ensure the effective delivery of vaccines to achieve optimal coverage. In addition, CDC helps countries to introduce new and underutilized vaccines into routine immunization systems by assisting with studies that measure disease burden, providing epidemiologic and laboratory expertise to strengthen country capacity, as well as new vaccine safety, effectiveness, and cost-effectiveness analyses; conducting post-introduction studies to show when reductions in disease incidence have occurred and the value of the vaccine relative to the cost of sustaining the vaccine program; and supporting national vaccine advisory committees to enhance data-driven decision-making, including evaluating scientific, programmatic and economic aspects of vaccine introduction.

CDC is also engaged in strengthening routine immunization systems in resource-poor countries. Key activities include providing technical and financial assistance to partners at the global, regional, and national levels as well as directly to Ministries of Public Health to define and implement the most effective immunization strategies (such as the Reaching Every District strategy) for a country's individual circumstances; improving the planning of immunization services; strengthening national capacity building, monitoring, and data collection systems to develop effective program policies. These efforts at strengthening routine immunization systems are supplemented through providing technical assistance to partners and countries to help implement new global, regional and national goals to eradicate, eliminate, or control polio, measles, rubella, hepatitis B, and neonatal tetanus.

Industry has made it clear that delivery of existing vaccines through robust immunization programs is important to them as a consideration for developing additional vaccines for use in developing countries. Developing countries with little commitment to immunization as a priority health intervention, inadequate vaccine policies, weak health systems, weak financial systems, poor disease surveillance systems, inadequate cold chain, and a lack of personnel to deliver vaccines are hurdles industry cannot address. Industry wants the USG and the global vaccine community to continue their work with developing countries to build capacity and improve public health programs.

Through USAID and CDC, the USG is currently providing technical assistance to developing countries to ensure access and availability of lifesaving vaccines once vaccines are available. As described above, USAID's primary investment in immunization is through GAVI, where the focus is largely on the purchase of new and under-utilized vaccines with some additional investments in strengthening health systems. GAVI has been successful in increasing the availability of new and underused vaccine to developing countries. However, this investment alone will not get the vaccines into children. To ensure country preparedness for vaccines, USAID and CDC have continued to invest in supporting routine immunization programs in developing countries; helping to build capacity of national and local governments and partners to deliver vaccines through their programs. More work is needed to continue to build the capacity of developing countries, especially with new and expensive vaccines being made available to developing countries. As such, the U.S. Government will continue its efforts to support routine immunization systems and build the capacity of developing country governments.

VII. Coordinated Strategy

The U.S. Government is engaged in coordinated strategies with partners the world over to accelerate development of vaccines for infectious diseases, such as HIV/AIDS, malaria, and tuberculosis, and to deliver vaccines to people in developing countries. Each USG agency's mandate, funding level, and availability of expertise determines where they are engaged on the continuum from basic research through delivery and immunization in developing countries.

In response to the three specific areas of review that were requested to be included in this report, the study group recognized:

i. **Initiatives to create economic incentives for the research, development, and manufacturing of vaccines for HIV/AIDS, tuberculosis, malaria, and other infectious diseases.** There are a range of incentives and innovative financing mechanisms in early phases of implementation and others that are being explored. These mechanisms have the potential to stimulate accelerated research and development of vaccines. However, before increased commitment by the USG, the various mechanisms require further study to determine which mechanisms are most appropriate and feasible for investment. The USG will continue to consider options specific to U.S.-based R&D and manufacturing, while monitoring the progress of the pilot Advanced Market Commitment and other economic incentives.

ii. **An expansion of public-private partnerships and the leveraging of resources from other countries and the private sector.** USG agencies are engaged with a variety of partners from academia, industry, UN agencies, civil society, developing countries, and product development partnerships (PDPs). An expansion of public-private partnerships and the leveraging of resources from other countries and the private sector could accelerate the development of vaccines. The variety and number of current PDPs make it necessary to determine whether additional PDPs are required to accelerate the development of vaccines or whether the need lies in expanding existing PDPs. As such, as part of the USG strategy to accelerate the research, development and manufacturing of vaccines, the U.S. Government will explore the range of vaccine development partnerships to determine the most efficient way for the USG to leverage private-sector expertise with scarce resources and strategically engage in supporting the indirect determinants around market preparation.

iii. **Efforts to maximize U.S. capabilities to support clinical trials of vaccines in developing countries and to address the challenges of delivering vaccines in developing countries to minimize delays in access once vaccines are available.** USG agencies engaged in vaccine R&D and immunization delivery are well coordinated and work strategically within individual vaccine areas. However, across vaccine areas more information-sharing and joint strategic development need to take place. The USG has actively developed sustainable clinical trial sites in the developing world over many years and works to continue to make those sites more robust, as more complex clinical trials for vaccines against more complex diseases are required. To accelerate the development of vaccines, the USG will build upon what was accomplished by the Partnership for AIDS Vaccine Evaluation (PAVE) for HIV vaccine trial sites and will conduct a mapping exercise of all vaccine clinical sites that are implemented by or funded by the U.S. Government. More robust information on the relevant clinical trial sites will lead to more strategically coordinated, streamlined, and aligned government support for advancing the development of new vaccines for infectious diseases. Delivering vaccines in developing countries is complex. Public health impact is not achieved when the vaccine is developed but rather when it reaches the intended population in developing countries. The U.S. Government will continue to program in a strategic and complementary fashion to build immunization program capacity in developing countries.

In order to coordinate the acceleration of the development of vaccines for infectious diseases, USG agencies will continue to convene a study group or groups around the strategy to further engage across disease specific areas. Each USG agency engaged in global health research plays a distinct role at different stages of research, and nongovernmental partners provide unique expertise in vaccine development. For this reason, a study group or groups will meet at regular intervals to continue collaboration to accelerate vaccine development, to share information on vaccine development efforts, and to maximize the synergies that are created from working in a more coordinated manner. The rate of progress in each area of vaccine research, development, and delivery will be proportional to resources available.

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