USAID
FROM THE AMERICAN PEOPLE

Report to Congress

Health-Related Research and Development Activities at USAID

May | 2006

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Acronyms and Abbreviations

AAV	Adeno-associated virus
ACT	Artemisinin-based combination therapy
AMTSL	Active management of the third stage of labor
ART	Antiretroviral therapy
CA	Cooperating agency
CDC	Centers for Disease Control and Prevention
CHW	Community health worker
CONRAD	Contraceptive Research and Development Program
CTC	Community therapeutic care
DoD	Department of Defense
DOTS	Directly observed therapy, short course
ENC	Essential newborn care
FDA	Food and Drug Administration
FP	Family planning
FY	Fiscal year
GAIN	Global Alliance for Improved Nutrition
GDA	Global Development Alliance
GHAVE	Global HIV/AIDS Vaccine Enterprise
GSK	GlaxoSmithKline
IAVI	International AIDS Vaccine Initiative
IMCI	Integrated Management of Childhood Illness
INACG	International Nutritional Anemia Consultative Group
KMC	Kangaroo mother care
MDR-TB	Multidrug-resistant tuberculosis
MMV	Medicines for Malaria Venture
MOH	Ministry of Health
MVDP	Malaria Vaccine Development Program

MVI	Malaria Vaccine Initiative
NGO	Nongovernmental organization
NHA	National health account
NIAID	National Institute of Allergy and Infectious Diseases
NID	National immunization day
NIH	National Institutes of Health
OR	Operations research
PATH	Program for Appropriate Technology in Health
PAVE	Partnership for AIDS Vaccine Evaluation
PEPFAR	President's Emergency Plan for AIDS Relief
PVO	Private voluntary organization
RH	Reproductive health
RUTF	Ready-to-use therapeutic food
SAM	Severe acute malnutrition
SDM	Standard Days Method
STI	Sexually transmitted infection
TFC	Therapeutic feeding center
UNDP	United Nations Development Program
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USMHRP	United States Military HIV Research Program
VRC	Vaccine Research Center
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

Executive Summary

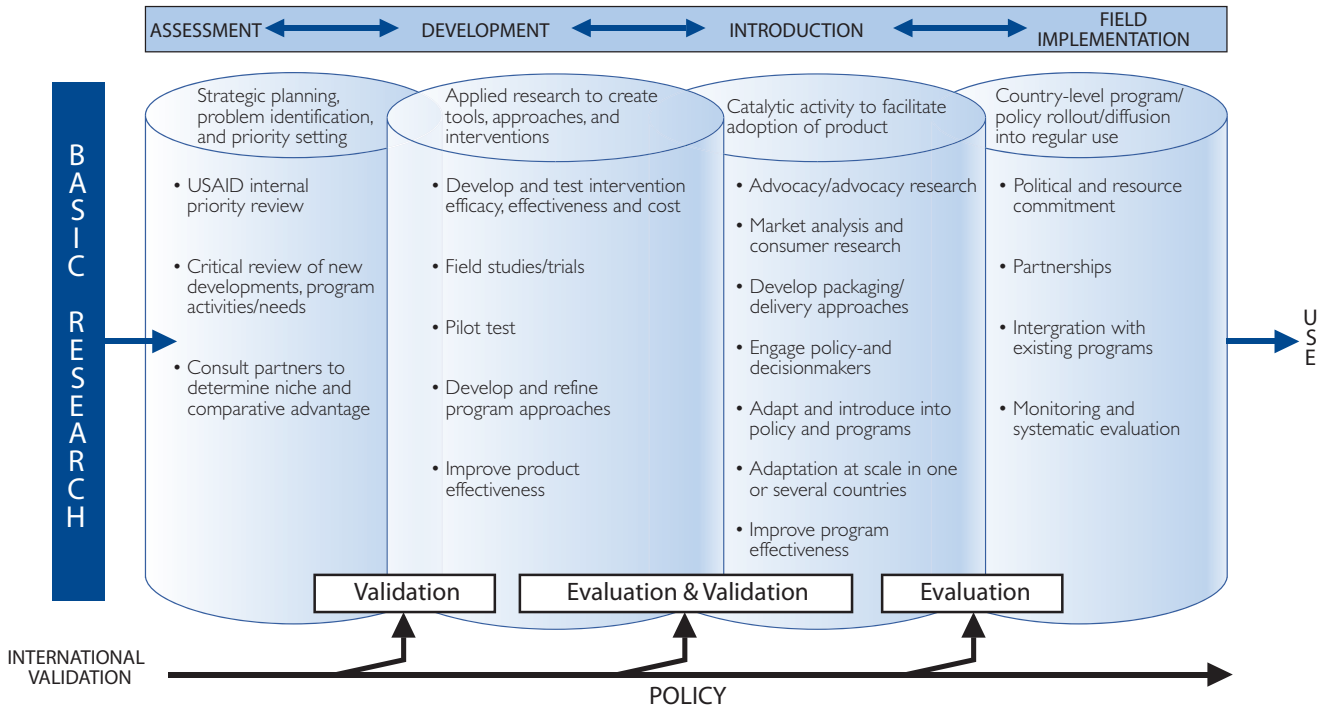
Health research is integral to USAID's ability to achieve its health and development objectives worldwide. Through research, USAID has developed and introduced affordable health products, policies, and practices appropriate for addressing health-related concerns in developing countries. As the U.S. Government's lead foreign assistance agency working in partnership with other public and private sector agencies and nongovernmental organizations (NGOs), USAID applies a cycle of assessment, development, pilot testing, and introduction of products and approaches to tackle the main diseases and health issues of developing countries. This cycle enables USAID to assess needs, solve research and development problems, and improve the effectiveness of health programs that address the main causes of mortality. USAID's research role, aligned with its strengths, is to assess local health conditions, develop and adapt appropriate health products and interventions, and support their field testing and introduction, including strengthening local health systems.

In 2005, USAID submitted a report to Congress on health-related research and development activities that summarized the role, results, and impact of almost 30 years of USAID-supported health research and its coordination with a host of other agencies and partners. Past USAID research investments have led to products that now reach millions, saving lives throughout the developing world – oral rehydration salts, vitamin A, auto-disable syringes, and vaccine vial monitors, to name a few. USAID is also actively applying the results of research supported by others in its operations, such as using the recent evidence of the importance of household water qualtiy and effective hand washing in scaling up USAID's hygiene activities in these areas.

After reviewing the 2005 report, Congress noted the unique and important role of USAID:

> *With its experience in the developing world, USAID does and should play a valuable role in facilitating*

Pathway From Research to Field Implementation and Use



Source: USAID

international clinical trials, consolidating markets, and finding new opportunities to speed the discovery, development, and delivery of products to improve the lives of those in the developing world.

With this report USAID provides a proactive strategy for using research funds and a plan for stimulating the development and introduction of key products to address diseases affecting the developing world and countries in transition. USAID is uniquely positioned to implement this strategy. It has decades of field experience and presence in over 70 countries, combined with in-house technical expertise and recognized strengths in private sector engagement.

Current and future USAID-supported research will help ensure that:

- A vaccine against HIV/AIDS will be developed that is appropriate for use in developing countries
- A new microbicide will be developed that is acceptable to women in Africa
- A vaccine will protect children from the devastation of malaria
- New products will improve the performance and public health impact of country-level tuberculosis programs and mitigate the risks of drug resistance
- New contraceptives will be available, appropriate, and accessible for the more than 123 million women seeking to prevent pregnancy and not currently using family planning
- Simple new interventions will be available to save the lives of mothers, newborns and children in communities throughout the world

This report is organized by the main diseases or health issues affecting the developing world and reviews key products and the plans for speeding their discovery, development, and delivery. It covers approximately 80 percent ($119 million) of the total projected amount USAID will spend on health-related research in 2006. This includes the main areas of research on product development and introduction. The approximate 20 percent ($29 million) not addressed in the report is mainly research funded by USAID field missions that addresses local questions and needs such as formative research on child feeding practices, measurements of local disease burden, or improvements in district health services.

This report highlights seven health issues in the USAID research portfolio:

HIV/AIDS

An estimated 5 million new HIV/AIDS infections occur every year, threatening the prosperity, stability, and development of nations around the world. Under the leadership of the President's Emergency Plan for AIDS Relief (PEPFAR), USAID plays a unique and critical role in shaping the strategic and technical direction of vaccine and microbicide development appropriate for different disease situations and target populations in developing countries.

USAID supports all phases of HIV vaccine development through the International AIDS Vaccine Initiative (IAVI). USAID's new five-year cooperative agreement with IAVI helps build clinical trial capacity in developing countries, advance the development and testing of six vaccine candidates, enrich the pipeline of next-generation HIV vaccine candidates, and analyze policy and implementation issues of concern to the HIV vaccine field. USAID's future strategy includes supporting HIV vaccine activities with partner organizations to prepare for vaccine introduction. These activities would include support to the Global HIV/AIDS Vaccine Enterprise (GHAVE) and links between HIV vaccine clinical trial activities in Africa and HIV/AIDS treatment and care under PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

USAID works collaboratively with National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), other multilateral and bilateral donors, and international and national organizations and foundations that support activities related to microbicide research and development. Microbicides are a new class of health products that could provide an effective chemical barrier to HIV and other sexually transmitted infections (STIs).

Products

- Vaccines
- Microbicides

Malaria

Every year, malaria kills more than 1 million people, primarily children. USAID is committed to reducing

malaria morbidity and mortality worldwide. The Agency focuses on vaccine and drug development, in concert with other global development efforts to accelerate the availability of affordable and appropriate treatments for developing countries. The USAID Malaria Vaccine Development Program (MVDP) focuses on blood-stage vaccines, which may be most appropriate for women and children in developing countries. The most advanced blood-stage vaccine being tested, FMP1/AS02A, was developed on the initiative of USAID at the Walter Reed Army Institute of Research (WRAIR) with GlaxoSmithKline (GSK) and joint support from USAID and the Malaria Vaccine Initiative (MVI) at the Program for Appropriate Technology in Health (PATH).

USAID employs a two-pronged malaria drug development strategy to: (1) fund research leading to the discovery and development of new antimalarial drugs and drug formulations most appropriate for malaria-endemic areas, and (2) undertake concurrent operational and field research that lays the groundwork for the safe and effective use of existing and new antimalarial drugs and drug combinations by national malaria control programs.

Products
- Vaccines
- New Drugs, Formulations, and Approaches

Tuberculosis

Almost 9 million new cases of tuberculosis (TB) occur each year. Nearly 2 million people die annually from this curable disease. HIV/AIDS is fueling the TB epidemic in many parts of the world, most notably Africa, and the emergence of multidrug-resistant TB (MDR-TB) threatens future efforts to control this disease. The global TB community has developed a consensus Global Plan to Stop TB 2006-2015, which aims to halve TB prevalence and mortality by 2015. This strategy relies on the development and introduction of new technologies and approaches. USAID strategy is to invest in products and approaches that will improve the performance and public health impact of country-level TB programs while mitigating the risks of drug resistance by: (1) reducing diagnostic delay, (2) reducing the duration of treatment and improving its efficacy, (3) preventing disease, and (4) increasing access to the "directly observed therapy, short course" (DOTS) strategy. USAID prioritizes research that has the potential to change policy and practice in developing countries within three to five years. USAID is collaborating with U.S. Government partners such as NIH and CDC, numerous technical agencies, and other donors such as the Bill & Melinda Gates Foundation.

Products
- New Drugs
- Improving Performance of and Access to DOTS

Reproductive Health and Family Planning

Approximately 123 million women in less developed countries have an unmet need for family planning. The provision of such services could prevent 20 to 35 percent of maternal deaths. The strategy of USAID's contraceptive research and development program is to improve and expand the use of family planning methods through new and improved contraceptives, including the use of methods that also reduce the transmission of HIV and other STIs. USAID supports the development of new spermicidal microbicides that prevent both pregnancy and HIV transmission. In 2008, six products are slated to be in Phase II/III effectiveness trials for contraception; three of these will also begin testing for STI prevention.

USAID also conducts operations research to improve the coverage, outreach, and quality of family planning and other reproductive health services. The strategy is to assess the needs and gaps in existing national public sector and private sector programs, develop new program and service delivery approaches to address these gaps, develop tools and materials to improve provider performance, and improve the capacity of communications and behavior change programs to increase client awareness and use of existing services, respectively.

Products
- New and Improved Contraceptives
- Improved Use and Service Delivery

Maternal and Newborn Health

Every year, close to 600,000 women die during childbirth. With 50 percent of births in the developing world occurring at home, lifesaving services need to be locally available, accessible, and culturally appropriate. Every year, approximately 4 million newborns die within the first month of life, accounting for over 60 percent of infant mortality and almost 40 percent of deaths among children under 5 years of age. USAID is conducting research and improving programs to reduce the risks of maternal and newborn morbidity and mortality. These efforts include both specific and combined maternal health and neonatal interventions. USAID has also

initiated research on the impact on birth outcomes, neonatal mortality, and maternal morbidities of healthy timing and spacing of pregnancies.

USAID's maternal health research strategy focuses on three specific areas: (1) global data and analysis to guide programming, (2) new intervention development and moving efficacious interventions to the field, and (3) documenting effectiveness and cost-effectiveness of selected strategies to deliver proven interventions. Uniject™ Oxytocin and active management of the third stage of labor (AMTSL) are new interventions under development with USAID support.

USAID's newborn health research strategy focuses on simple, low-cost approaches with the greatest potential to substantially prevent death and treat severe illness in low-resource settings with limited access to quality facility-based care. USAID is playing a leadership role in catalyzing the development of an evidence base and integrating this new knowledge into field programs.

Products

- Healthy Pregnancy and Birth Outcomes
- Assessment of Birth Care Outcomes
- Maternal Mortality Measurement Tools
- New Pregnancy and Birth Interventions and Introduction
- Neonatal Research and Newborn Care Practices

Micronutrient Deficiencies in Women and Children and Management of Severe Malnutrition

Each year, micronutrient deficiencies compromise the health, development, and survival of hundreds of millions of women and children in the developing world. USAID collaborates with partners to identify and prevent nutrient deficiencies, especially those of vitamin A, zinc, iron, folate, and iodine, in mothers and children. A significant focus over the next five years will be on the coordination of micronutrient delivery in the broader context of existing micronutrient dosing among maternal, infant and childhood supplementation, along with other nutritional strategies. Research on vitamin A by USAID and its partners includes confirmatory effectiveness and safety research to determine maternal and neonatal dosing of vitamin A to reduce mortality and morbidity, as well as food fortification delivery strategies. Operational research efforts related to zinc include increasing the availability and use of a quality supply of zinc in the public and private sectors and facilitating the development of guidelines and support to high-need countries for the integration of zinc into regular public health programs. USAID will seek to test safe and effective iron supplementation in deficient populations and will develop best practices for the increased coverage and implementation of reproductive health packages that include anemia control and prevention.

With severe malnutrition continuing to be a significant problem in emergency situations, over the next five years USAID will work with the World Health Organization (WHO), UNICEF, private voluntary organizations (PVOs), host countries, and others to complete the necessary research to advance community therapeutic care (CTC) and related home-based care approaches.

Products

- Vitamin A – Deficiency Prevention and Control
- Zinc – Diarrhea Therapy and Prevention
- Iron – Anemia Prevention and Treatment Packages
- Community Therapeutic Care – Emergencies

Acute Respiratory Infections

Pneumonia in children under 5 years old is responsible for an estimated 1.9 million annual deaths. The research strategy of USAID and its global partners is to promote the training and support of community health workers (CHWs) in order to provide early and appropriate care through operational studies. For severe pneumonia, research is underway to determine the effectiveness of oral therapy administered at home. In malaria-endemic areas, the clinical manifestations of pneumonia and malaria can be difficult to distinguish. USAID supports applied research combining the treatment of both diseases by CHWs to provide greater coverage of care and potentially reduced morbidity and mortality.

The impact of small particles from indoor air pollution on the incidence and severity of pneumonia has emerged as a primary area of concern for child health. Information is limited regarding the health benefits of interventions to reduce indoor air pollution. Key research issues to be addressed include understanding whether known interventions (e.g., improved stoves) will reduce disease burden and determining the most effective implementation strategies for efficacious interventions. USAID is collaborating with WHO on applying forthcoming results froma randomized controlled trial supported by the National Institutes of Environmental Health Sciences to measure the change in incidence of acute lower respiratory infection in young children after the introduction of improved stoves. USAID also contributes to a collaborative effort engaging both health and energy sector experience to

develop practical intervention strategies for use in host countries.

Products

- Community-Based Treatment of Childhood Pneumonia
- Reducing Exposure to Indoor Air Pollution

Health Systems

Health systems research identifies problems and finds and tests solutions to improve the delivery and accessibility of products and approaches to tackle the main diseases and health issues facing developing countries. Some of this research is carried out within specific programs such as in maternal and neonatal health and nutrition programs. In addition, USAID has a more system-wide program of research that addresses overarching problems such as resource and budget tracking, health insurance and other coverage approaches, drug and pharmaceutical management, and quality of services. Over the next five years, USAID plans research activities to develop and apply a few high-priority tools to strengthen health systems and remove key barriers to access to care.

Products

- Performance Assessment and Financing
- Pharmaceutical Management
- Quality Assurance

HIV/AIDS

HIV	Product	Projected FY 2006 Funding
HIV/AIDS	Vaccines	$29,000,000
	Microbicides	$39,600,000

Vaccine Development

Fast Facts

- USAID funding supports all phases of HIV vaccine applied research and development, as well as policy analysis.
- Funding increased from $6 million in 2001 to $29 million in 2006.
- USAID proposes new support for the Global HIV/AIDS Vaccine Enterprise (GHAVE) and greater coordination in developing countries between clinical trial activities and HIV/AIDS prevention, care, and treatment programs.

Issues and Rationale

Twenty-five years after the discovery of HIV/AIDS, the pandemic continues to spread, especially in developing countries. An estimated 5 million new infections occur every year, and no means of cure is available or anticipated. The HIV pandemic can only be stopped through effective prevention. No single approach is likely to be the "magic bullet"; HIV/AIDS prevention approaches must be tailored for different disease situations and target populations. The more options available for HIV prevention, the easier it will be to mitigate and eventually reverse the course of the pandemic. An effective HIV vaccine would be a significant advance as part of a comprehensive prevention strategy, especially since it would only need to be administered once or a few times. The promise of a vaccine, however, is counterbalanced by the challenge of developing and introducing an HIV vaccine. The only way to know if an HIV vaccine works is to test it in humans at high risk for HIV infection. It has proven difficult to stimulate a protective antibody response against HIV, and the high rate of genetic variability of HIV could mean vaccines will be ineffective against some or most variants of the virus. It is possible that the first generation HIV vaccines will only be partially effective or will mitigate disease without eliminating transmission.

Despite real technical challenges, scientists are making advances in defining the correlates of protection and inducing antibody responses. In the next few years, at least two promising vaccine candidates that induce cell-mediated immunity could be ready for human efficacy trials. Even if these studies document partial efficacy, the results will provide valuable information about the correlates of protection and guide the design of new vaccine candidates.

Current USAID Activities

Since 2001, responding to Congressional directives, USAID has funded IAVI, a nonprofit organization that acts as a virtual pharmaceutical company to accelerate the development and clinical testing of HIV vaccine candidates. USAID's support for IAVI is currently a part of PEPFAR. IAVI facilitates collaborations among university, government, and private sector groups to ensure that the appropriate resources are available for each phase of product development. IAVI also provides analyses of important issues affecting the HIV vaccine field such as new strategies to engage biopharmaceutical companies in HIV vaccine development, regulatory and licensing issues, and preparations for the manufacture and distribution of vaccines once they are proven effective. Through IAVI, USAID supports all phases of HIV vaccine research and development, as well as other activities important for the field, including:

- A partnership with Crucell, a biotechnology company, to develop low-seroprevalent adenovirus vectors for next-generation HIV vaccine candidates
- Development of adeno-associated virus (AAV) vector-based HIV vaccine candidates
- Applied research on how to stimulate neutralizing antibody responses to HIV
- Collaborative applied research with European and developing country scientists to support HIV vaccine development and prepare for clinical trials

- IAVI's core immunology laboratory and primate facilities
- Building local capacity at trial sites
- Estimates of demand and impact of HIV vaccines to inform public policy

USAID collaborates with NIH and CDC of the Department of Health and Human Services and with the U.S. Military HIV Research Program (USMHRP) through the Partnership for AIDS Vaccine Evaluation (PAVE). PAVE is a voluntary consortium of U.S. Government agencies and key U.S. Government-funded organizations involved in the development and evaluation of HIV/AIDS preventive vaccines and the conduct of HIV vaccine clinical trials. USAID is represented on the PAVE Executive Steering Group as well as on the working groups for clinical trial site development and community involvement.

USAID's Role and Strategy

USAID brings valuable expertise and resources to the table to facilitate the development of an HIV vaccine appropriate for use in developing countries. In addition to the Agency's 45 years of experience in international development and its field presence in over 70 countries, USAID has in-house expertise in immunology, virology, product development, clinical trial design, pharmaceutical regulatory affairs, ethics, community involvement, and gender issues. As large-scale human trials get under way in developing countries, USAID's international perspective is essential to the success of HIV vaccine development.

USAID also has a particular vocation and expertise in engaging with the private sector and recently won the Lewis & Clark Award for Innovation in Collaborative Governance from Harvard University's Kennedy School of Government for its Global Development Alliance (GDA) business model. The specialized expertise of the private sector is essential for HIV vaccine development. USAID supports IAVI's vaccine development partnerships with biopharmaceutical companies and policy research on incentives such as advance purchase commitments for private sector engagement.

In October 2005, IAVI submitted a proposal to USAID for a new five-year $29 million per year cooperative agreement. A panel including representatives from the National Institute of Allergy and Infectious Diseases (NIAID) and USMHRP vaccine programs reviewed the proposal to ensure interagency coordination. USAID's new cooperative agreement will support IAVI to:

- Develop clinical trial capacity in developing countries
- Advance the development and testing of six vaccine candidates
  - AAV
  - Cytomegalovirus
  - Sendai virus
  - Low-seroprevalent adenovirus in collaboration with Crucell
  - C6/C7 adenovirus in collaboration with GSK
  - NIAID Vaccine Research Center adenovirus in collaboration with PAVE
- Enrich the pipeline of next-generation HIV vaccine candidates
- Analyze policy and implementation issues of concern to the HIV vaccine field

A five-year implementation plan with timelines and milestones for each product and activity will be developed in 2006 along with a monitoring and evaluation plan.

Coordination and Engagement in Other Vaccine Research Efforts

If approved by Congress, USAID plans to use up to 5 percent of its HIV vaccine funds to support coordination with others engaging in HIV vaccine research and development and related activities. For example:

- Vaccine development will be accelerated by GHAVE. In 2004, President Bush led the G-8 in endorsing the establishment of GHAVE, a growing new global initiative to coordinate resources, share reagents and data, and foster greater collaboration within the HIV vaccine field through the implementation of a shared scientific strategic plan. The GHAVE concept is analogous to the successful alliance and strategic plan characterizing the Human Genome Project.

  GHAVE is not a funding mechanism, but it will require resources for its coordination functions. A permanent secretariat will be established in 2006 with a notional annual budget of $3 million that will be supported by a number of funding sources. USAID would like to collaborate with NIAID in helping to support the secretariat during the first year

while it gets up and running, with the hope that less U.S. Government support will be needed in future years as other countries see the value in this effort. A successful GHAVE secretariat would ensure that USAID's work through IAVI is well coordinated not only with other U.S. agencies but also with the Bill & Melinda Gates Foundation and other stakeholders worldwide.

USAID also will participate in GHAVE's working groups, contributing its developing-country expertise toward the GHAVE objectives of coordinating clinical trials and clinical trial site capacity.

- USAID will work to facilitate better linkages between HIV vaccine clinical trial activities in Africa and Asia and HIV/AIDS treatment, care, and prevention services under PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Clinical trial activities such as epidemiological studies, counseling and testing, training of personnel, community outreach, and laboratory infrastructure development can be leveraged to support PEPFAR activities. Also, during the enrollment period of efficacy trials, large numbers of people will be screened for HIV and many will be found to need immediate care and antiretroviral therapy (ART). Having convenient care and treatment available and appropriate referral mechanisms in place will help the trials to ensure positive relations in the communities where they are conducted.

- USAID could work collaboratively with NIH to develop a training program to orient U.S. vaccine researchers to issues specific to working in developing countries, similar to the ethics and patient privacy training already required for NIH-funded scientists.

Future Activities

As promising vaccine candidates are identified, USAID plans to:

- Conduct research on how a vaccine might affect people's risk behaviors and how to counter these effects

- Plan for (and eventually execute) introduction of HIV vaccines in developing-country settings, including engaging host country governments to register the new products, managing supply chain and logistics of vaccine delivery, developing protocols, and training health care workers

Microbicides

Fast Facts

- Current strategies for preventing HIV infection are not available for many women in developing countries.
- USAID support of microbicide research has led to the development of three potential products (Carraguard, Ushercell, and Savvy) that are in the final stages of international clinical trials to evaluate safety, effectiveness, and acceptability in preventing or decreasing HIV transmission.
- USAID supports targeted activities to ensure that after testing is completed, the introduction and distribution of these microbicides is expedited in the developing country populations where the need is greatest.
- Total funds provided by USAID for FY 2001 to FY 2005: $96.5 million

Issues and Rationale

In 2005, the number of HIV-infected persons worldwide exceeded 40 million. In sub-Saharan Africa almost 60 percent of infected persons are women. Current strategies for preventing HIV infection, including delay of sexual debut, partner reduction and use of condoms, are not negotiable for many women in developing countries.

Microbicides are a new class of health products that would provide women an effective chemical barrier to sexually transmitted HIV. For more than a decade, USAID has supported the biomedical and behavioral research needed for the successful development of safe, effective, and acceptable microbicides with low cost and appropriated product characteristics for use in HIV prevention in developing countries and public sector programs. The development of an effective microbicide would help fill the enormous need for a new prevention option for women and would complement existing or new prevention approaches, including a future HIV vaccine.

As a key implementer of PEPFAR, USAID plays a critical role in shaping the strategic and technical direction of microbicide development to meet developing-country needs. In order to measure the protective effect of microbicides, for example, testing of candidates must be done in developing-country populations with very high rates of HIV incidence. USAID has extensive field pres-

Microbicides Research Strategy 2006-2010

Public Health Problem	FY 2006 Funding	Product
HIV/AIDS	$39,600,000	Microbicides
2006 Development	Continue Phase III large-scale clinical effectiveness trials initiated FY 2004 and FY 2005 New clinical trial sites for Ushercell and Savvy to begin in Africa and India Continue next-generation microbicide research/capacity building for future trials	
2007 Development	Continue Phase III trials: Carraguard, Ushercell, and Savvy Address policy and logistical issues for successful introduction into countries Pursue transfer of manufacturing capacity to developing-country sites	
2008 Introduction	Final results of Carraguard trial available Continue Phase III trials: Ushercell and Savvy Continue to address policy and logistical issues for introduction Continue to transfer manufacturing capacity	
2009 Introduction	Final results of Ushercell and Savvy trials available Continue to address policy and logistical issues for introduction Continue to transfer manufacturing capacity	
2010 Implementation	Continue to address policy and logistics for introduction: Procurement and financing, distribution networks within public and private sector, health delivery system, information needs, licensing safety Potential need for additional trials to be determined	

ence and experience in collaboration and research in countries with these characteristics. USAID also is uniquely positioned to leverage and coordinate the intellectual, proprietary, and financial capital of a host of contributors, including other public sector agencies, private foundations, and commercial partners.

Once the testing of a safe, effective, acceptable, and affordable microbicide is completed, it must be introduced and quickly made available in developing countries. USAID's experience in pre-introductory studies, distribution, logistics management, service delivery, provider training, and social marketing will position the Agency to introduce microbicides and support their appropriate and effective use.

USAID's Role and Strategy

USAID's strategy to promote the development of microbicides focuses on the advanced testing of the most promising candidates available. Clinical trials demonstrating the effectiveness of these products must be completed for their approval by the appropriate regulatory agencies. Proof of concept (demonstration of effectiveness at reducing the risk of HIV acquisition) will speed up the availability of the best product, stimulate the future development of alternative or better products, permit the determination of the most appropriate preclinical models for evaluation of candidate products, and attract additional resources, investigators, and donors.

The history of pharmaceutical development shows it is usually necessary to evaluate clinically a number of product leads because some will be eliminated, even at advanced stages of testing. To date, USAID has moved three promising candidates – Carragard, Ushercell (cellulose sulfate), and Savvy (C31G) – into the final stages of clinical testing in international trials for their safety, effectiveness, and acceptability in reducing the risk of HIV transmission.

USAID collaborates in microbicide research and development with NIH, CDC, and FDA to implement the jointly developed the U.S. Government Strategic Plan

for Microbicides. USAID contributes to the following objectives of the Strategic Plan:

- *Preclinical development and evaluation of potential microbicide candidates* to support the discovery, characterization, and early-stage development of potential new active agents for use as microbicides
- *Formulation and delivery of potential microbicides* to develop and assess safe, effective, and acceptable formulations and modes of delivery for microbicides, applying knowledge from the chemical, pharmaceutical, physical, bioengineering, and social sciences
- *Clinical testing of microbicides* to assess the human safety, effectiveness, and acceptability of potential microbicides in reducing the transmission of HIV and other STIs, and in preventing pregnancy for products that are also contraceptive, in developing countries and the United States
- *Behavioral and social science research* to enhance microbicide development and testing and to better understand factors that will affect future microbicide use and acceptability in developing countries
- *Provision of training and infrastructure* to establish, maintain, and strengthen the appropriate training and infrastructure needed to conduct microbicide research internationally and to accelerate future access to microbicides in diverse populations and settings

USAID's role in microbicide development is coordinated through extensive representation and collaboration with the efforts of other U.S. Government agencies. This includes serving on the Microbicide Research Planning Committee of NIH's Office of AIDS Research, together with FDA, CDC, and other collaborators. USAID is a member of the International Working Group on Microbicides, originally established by the Joint United Nations Programme on HIV/AIDS, which includes U.S. Government agencies, multilateral and other donors, and international and national organizations that support or conduct activities related to microbicide research and development. Other U.S. Government agencies and nongovernmental partners participate in the technical advisory committee meetings of the USAID cooperating agencies (CAs) in this field. Finally, USAID sits on the Microbicide Coordinating Board, which was established with support from the Bill & Melinda Gates Foundation as a donors-only forum for strategic thinking and program planning. This collaborative approach among USAID CAs and all agencies and partners has been successful in coordinating algorithms for preclinical testing, prioritizing promising microbicide candidates, designing clinical testing protocols, building local research capacity, preparing communities for clinical trials, and encouraging reciprocal learning.

Financial support for microbicide research and development through USAID increased significantly in fiscal year 2001, when Congress allocated $12 million for this purpose. The level of support for microbicides reached nearly $40 million in FY 2006. USAID implements its program through nine cooperative agreements that use subawards as needed to accomplish their research objectives (see table 1).

Strategy for the Next Year

In FY 2006, USAID will continue to support the large-scale multiyear clinical effectiveness trials for USAID-sponsored microbicide candidates that were initiated in FY 2004 and FY 2005. These Phase III trials are evaluating the Carraguard, Ushercell, and Savvy brand microbicides in thousands of volunteers in international Phase III studies (see table 2). These large clinical studies are required by the FDA, along with the European and South African regulatory agencies, to determine if these products can meaningfully reduce or prevent the sexual transmission of HIV. They are among the first trials in humans to evaluate the effectiveness of this prevention technology and will have a critical role in the effort to demonstrate that a microbicide can be effective and make a significant contribution to reducing the risk of HIV infection. The initiation and progress of these landmark trials confirm the success of the USAID strategy in this research effort and are conducted in collaboration with other agencies and donors to the greatest extent possible to share costs and to maximize the speed and efficiency of this work. New clinical trial sites for Ushercell and Savvy are planned to begin this year in Africa and India. The Phase III clinical trials of these two products, as well as the ongoing trial for Carraguard, will continue beyond 2007.

USAID also has contributed to research and development of product leads that will undergo advanced testing with other sources of primary funding. Buffergel, For example, the HIV Prevention Trials Network, funded by NIH, has just begun Phase III testing of Buffergel, which was produced with USAID funding. The safety of each product has been tested extensively in Phase I and II clinical trials.

Table 1 USAID Cooperative Agreements for Microbicide Research and Development

USAID Cooperating Agency	FY 2001 Obligations	FY 2002 Obligations	FY 2003 Obligations	FY 2004 Obligations	FY 2005 Obligations	FY 2006 Obligations (In Progress)
Population Council	3,300 ($ thousands)	4,013 ($ thousands)	7,722 ($ thousands)	6,990 ($ thousands)	8,300 ($ thousands)	
CONRAD Program	4,850	7,136	3,279	4,904	9,424	
Family Health International	1,900	1,444	5,191	8,439	8,210	
WHO	1,000	835	1,000	400	700	
Global Campaign for Microbicides	0	947	529	221	430	
Int'l Partnership for Microbicides	0	0	0	0	1,884	
CDC	450	250	0	698	583	
PATH	0	375	170	81	129	
EngenderHealth	500	0	0	0	0	
Synergy Project	0	0	0	137	100	
TOTAL	**12,000**	**15,000**	**17,891**	**21,870**	**29,760**	**39,600**

Until one or more microbicides that are safe, effective, and acceptable are available for regulatory approval and introduction in developing countries, it is necessary to continue supporting research and development of the most promising next-generation microbicide leads. The present leads in the pipeline incorporate multiple agents that will prevent viral infection and inactivate the virus and/or prevent key replication steps. Careful targeting of funds to the essential early-stage research is required to allow these leads to advance to clinical testing.

In the next year, as in recent years, the largest part of the USAID microbicide research and development budget (about 75 percent of the total) supports the Phase III clinical studies for the three most promising product leads. The remaining funds will be used to advance research on selected next-generation microbicide leads and develop capacity at sites for future clinical studies. This will entail targeted studies of local HIV incidence among risk groups and assessment and/or development of research capacity and community awareness in preparation for clinical trials of new microbicides. Some funds will be used to prepare for the policy and regulatory requirements that need to be addressed for the approval and introduction of these new products. Funding in excess of the FY 2006 level ($39.6 million) will be needed to support these activities in FY 2007.

Strategy for the Next Three Years

In FY 2007, FY 2008, and FY 2009, the Phase III trials for Carraguard, Ushercell, and Savvy will continue and be completed. The final results of the Carraguard trial should be available in FY 2008 and of the other two trials in FY 2009.

Simultaneously, USAID will address critical policy and logistical issues to successfully introduce microbicides in developing countries. The multiple social, cultural, economic, and political factors that will influence acceptance and use of microbicides at the individual and community levels will be studied. USAID will support behavioral and social science research on the contextually specific factors that could inhibit or encourage microbicide acceptance and use in order to guide message development, product imaging, and behavior change for communities and users. Other studies will identify the necessary adjustments in the service delivery context, assess future marketing potential, and plan for programmatic impact.

USAID funding will be used to pursue transfer of manufacturing capacity to developing-country sites to ensure the lowest possible cost for products and support transfer of technology to sites where it is most needed for both public health and economic reasons.

Table 2 Phase III Microbicide Studies Supported by USAID

	Carraguard	Savvy (Includes 2 studies)	Ushercell	Ushercell
# of Sites and Locations	Three in South Africa	Two in Ghana Two in Nigeria One in South Africa	Two in Nigeria	Benin, Burkina Faso, Uganda, South Africa, two in India
Start of Screening and Enrollment	March 2004	March 2004	November 2004	June 2005
# of Volunteers to Be Screened	Approx. 12,540	Approx. 10,000	Approx. 6,500	Approx. 5,000
# Expected to Be HIV-Positive When Screened	Approx. 5,016 (40%)	Approx. 1,200 (12%)	Approx. 975 (15%)	Approx. 2,000 (40%)
# of Volunteers to Be Enrolled	6,300	4,284	2,160	2,574
Expected HIV Incidence Rate	3.5%	5%	5%	4%
# of HIV Seroconversions Expected During Study	194	132	66	66
Final Report Expected	Early FY 2008	Early FY 2009	Early FY 2009	Early FY 2009
USAID Partner Conducting Trial	Population Council	Family Health International	Family Health International	CONRAD Program

During the next three years, the cost of the large, ongoing, and possible new multisite clinical trials will increase, especially in view of the need to ensure that HIV incidence rates are evaluated before studies begin in communities where the trials will be conducted. In addition, an increased investment in product introduction activities will be needed. Since it is very likely that continued clinical testing of the next-generation product leads will be warranted, further increases in the total level of funding are needed to maximize success in microbicide development and introduction.

Strategy for the Next Five Years

Over the next five years (through 2010), USAID will continue to work with partners to prepare for microbicide manufacturing and introduction in developing countries. Activities will focus on policies, procurement and financing, and logistics and distribution networks within public and private sectors. Countries will need assistance to plan for the relevant information needs of diverse audiences, including policymakers, providers, community members, and consumers. USAID funding will aid in developing regulatory review procedures that will minimize the hurdles to licensing safe and effective microbicide products at national and global levels.

By 2010, it is very likely that the need for costly clinical trials to test effectiveness will continue, as the development of the next generation of products with promise of greater effectiveness will be ongoing; these large trials will require even greater funding than presently required. With the approval of the first effective microbicide, greater resources will be needed for product introduction activities and, eventually, for supporting the HIV prevention programs that provide these products to the people who need them. The cost of introducing effective new microbicides into service delivery programs and into other delivery approaches outside the health system, and of promoting their use among the recipients of those services, although substantial, will be essential to the success of this prevention option. In addition, it is likely that some regulatory authorities will require postmarketing surveillance studies (Phase IV trials) to

monitor side effects that might only be seen after thousands of women are using these products; these studies would require additional funding. Long-term studies on the impact of microbicides on reducing HIV incidence and prevalence also will be needed.

Key HIV/AIDS Research and Introduction Partners are:

Bill & Melinda Gates Foundation
Centers for Disease Control and Prevention
CONRAD Program
Crucell
Department of Health and Human Services
EngenderHealth
Family Health International
Food and Drug Administration
Global Campaign for Microbicides
Global Fund to Fight AIDS, Tuberculosis and Malaria
Global HIV/AIDS Vaccine Enterprise
International AIDS Vaccine Initiative
International Partnership for Microbicides
International Working Group on Microbicides
National Institutes of Health
PATH
Population Council
President's Emergency Plan for AIDS Relief
Synergy Project
U.S. Military HIV Research Program
World Health Organization

Malaria

Health Issue	Product	Projected FY 2006 Funding
Malaria	Vaccines	$6,200,000
	New Drugs, Formulations, and Approaches	$3,800,000

Fast Facts

- Each year malaria is estimated to cause between 300 million and 500 million illnesses and kill more than 1 million people, primarily children.
- While highly effective prevention and treatment modalities exist, major reductions in overall incidence of malaria morbidity and mortality have not occurred.
- USAID's malaria research agenda addresses the development of new interventions through the Malaria Vaccine Development Program (MVDP) and support of new drug development.

Issues and Rationale

More than 90 percent of malaria illnesses and death occur in sub-Saharan Africa, where one African child dies of malaria every 30 seconds. Malaria is both a disease of poverty and a disease that causes poverty. It has been estimated that malaria retards economic growth in Africa by one-third when compared with nonmalarious areas – a total of $12 billion per year lost for the continent.

USAID is committed to reducing malaria morbidity and mortality worldwide through strategies and investments that help the global community achieve the international targets and goals of the Abuja Summit, the Millennium Declaration, and the President's Malaria Initiative.

Under suitable conditions, insecticide-treated nets, indoor residual spraying, intermittent preventive treatment, prompt use of effective treatment, and environmental control measures can have an impact on the prevention of malaria morbidity and mortality. New treatment modalities such as artemisinin-based combination therapy (ACT) are highly effective. Major reductions in the overall incidence of malaria morbidity and mortality, however, have not occurred, largely because these effective tools are only now beginning to be available to those most vulnerable to malaria. Immunization has repeatedly proven to be the most effective intervention against diseases for which vaccines are available, and a malaria vaccine has the same potential.

Vaccines

USAID's MVDP operates in the context of the worldwide malaria vaccine development effort, which focuses on vaccines for travelers, including military personnel, and vaccines for residents of endemic areas, primarily children and pregnant women.

A vaccine that completely prevented infection, even for a relatively short time, would be very satisfactory for travelers. Unless the protection was lifelong, however, it would not be satisfactory for children in endemic areas. These children are exposed weekly or more often to infected mosquitoes. A vaccine that does not entirely prevent infection but protects against disease could be optimal in endemic areas because it would allow immunity to develop through the repeated episodes of infection and would protect from severe disease and death. Such a vaccine would not be suitable for travelers, however, because of the potential for at least mild disease coincident with infection.

Travelers' malaria vaccines most likely will be achieved through an approach targeting the forms of the parasite in the liver, prior to their entry into the blood stream. Since symptoms occur due to bloodstream infection, this approach could prevent disease entirely. Since naturally acquired immunity is primarily against bloodstream forms, vaccines targeting these forms would be most appropriate in modulating, but not preventing, blood-stage infection, thus allowing natural immunity to be acquired. Because of these theoretical considerations, efforts to develop travelers' vaccines have focused on liver-stage targets while efforts to develop children's vaccines have focused on blood-stage targets.

The vaccine that is currently most advanced is a liver-stage vaccine that has a significant effect in moderating clinical disease. The vaccine was developed by WRAIR and GSK and recently has been evaluated by MVI at

PATH in collaboration with WRAIR, GSK, the Maniça Health Research Center in Mozambique, and the University of Barcelona. The vaccine consists of two parts: (1) an antigen, termed RTS,S, which is related to a portion of the parasite, and (2) an adjuvant, AS02A, which enhances the effect of the antigen. AS02A is a proprietary product of GSK. RTS,S/AS02A protects against both infection and disease; efficacy is about 30 percent against uncomplicated malaria and about 60 percent against severe malaria. Based on evidence that these effects are sustained over an 18-month observation period, the Bill & Melinda Gates Foundation has provided $107 million for advanced development and licensure of the vaccine.

The most advanced blood-stage vaccine, FMP1/AS02A, was developed on the initiative of USAID at WRAIR with GSK and is being tested with joint support from MVI and USAID. The current efficacy trial is the culmination of work begun in 1995 to implement a strategy targeting children. The trial is blinded, with unblinding scheduled for 2006. The outcome of this trial will have a major effect on USAID's subsequent MVDP strategy.

These two major efforts have been made possible by the pooling of resources by partners. Major operating expenses until 2000 were borne by WRAIR (for RTS,S/AS02A) and USAID (for FMP1/AS02A). Since its inception in 1999, MVI has been a major supporter of both programs.

Vaccine Strategy

The outcome to the efficacy trial of FMP1/AS02A is pivotal for USAID MVDP strategy. Several scenarios are under consideration:

1) If no efficacy is shown, USAID will continue the strategy it has used for more than a decade: the development of a robust pipeline of primarily blood-stage investigational vaccines that are evaluated in field trails for efficacy. It is normal to experience failures during the development process, so it is necessary to have this pipeline. USAID would continue this strategy because although RTS,S/AS02A could be an adjunct to current control measures, it is not optimal. It does give encouragement that more advanced vaccines will be more efficacious.

   In order to continue this strategy, additional partners likely will be sought. Several other groups, including NIAID, have developed vaccines similar to FMP1/AS02A that provide opportunities for continued development. In 2006, USAID is supporting NIAID through a Cooperative Agreement with MVI, and discussions with NIAID are ongoing to broaden this support.

2) If the FMP1/AS02A trial demonstrates efficacy comparable to RTS,S/AS02A, the option is to combine the two vaccines in a new formulation. This combined vaccine might provide synergistic efficacy greater than that of either vaccine alone. This is an option that would likely be attractive to GSK and might provide the basis for a second-generation vaccine that would be licensed after RTS,S/AS02A. In this case, additional funding, perhaps from the Gates Foundation, may be forthcoming for advanced development.

3) Demonstration of FMP1/AS02A efficacy that is clearly superior to RTS,S/AS02A would raise the possibility of its development as a stand-alone vaccine. Such a vaccine might be more cost-effective than a combination vaccine. USAID would evaluate opportunities to develop such a vaccine with partners.

The Role of USAID in Relation to Other U.S. Government Partners

Among U.S. Government Agencies, USAID has the specific charge of improving control of infectious diseases in the developing world. USAID has pursued malaria vaccine development for more than 40 years and has made many of the advances leading to the current state of the art. Although in recent years NIAID has initiated a strong malaria vaccine development program, it is hampered by constraints on its available acquisition and assistance mechanisms. In general, USAID's more flexible mechanisms allow for greater continuity of effort and product focus. In FY2005, for example, USAID financially supplemented a collaborative USAID/NIAID vaccine trial that was underfunded due to an artificial NIAID ceiling on the mechanism used for NIAID funding.

To date, the Department of Defense (DoD) has been the strongest scientific collaborator with USAID, but its target products (travelers' vaccines) have different profiles than USAIDs target products (children's vaccines). Thus, although DoD's efforts have contributed to the overall vaccine effort in a major way, it will not support the final development of children's vaccines unless they also conform to the profile required for malaria prevention in military personnel.

USAID's mission is most closely aligned with that of MVI at PATH, which is to accelerate the development of malaria vaccines for the developing world.

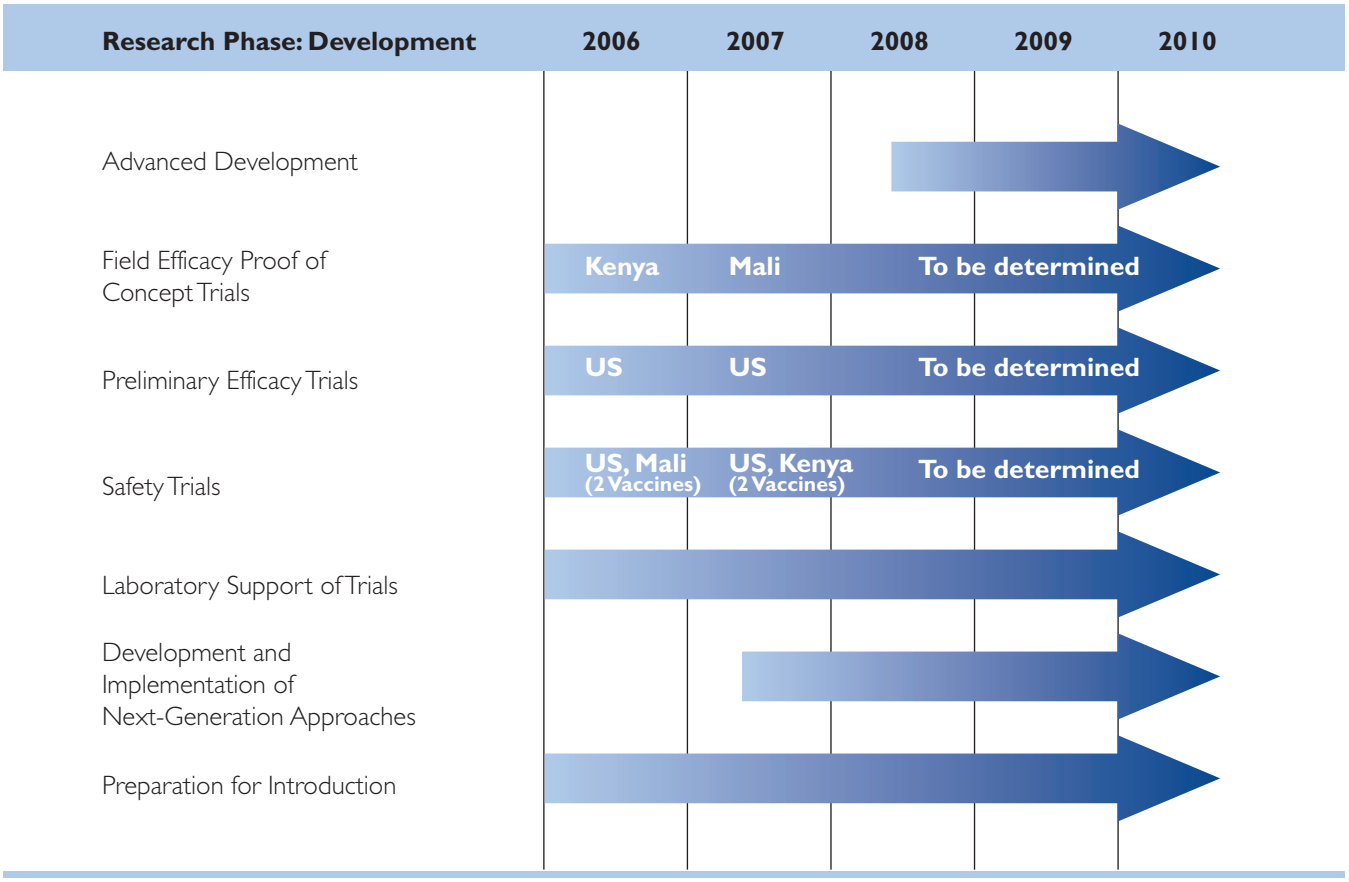
Figure 1 outlines USAID's currrent and planned malaria vaccine development activities, assuming continued support for efforts for further development of vaccines shown to be efficacious.

Antimalarial Drugs and Drug Formulation Strategy

With the spread of antimalarial drug resistance, the choice of first- and second-line drugs for malarial treatment has become much more difficult. Only a limited number of alternative drugs are currently available, as historically the private sector has had little economic incentive for new drug discovery and development, given its high cost and the fact that malaria predominantly affects the world's poorest nations. To reduce the risk of resistance developing to new antimalarial drugs, it is now recommended that these drugs always be used in combination, as is done with the treatment of tuberculosis and HIV/AIDS. The most rapidly acting and effective antimalarial combination drugs are ACTs, which are based on the natural product artemisinin.

USAID has a two-pronged malaria drug development strategy: (1) to fund research leading to the discovery and development of new antimalarial drugs and drug formulations, especially those that will be affordable to populations living in malaria-endemic areas, and (2) to support operational and field research that lays the groundwork for the safe and effective use of existing and new antimalarial drugs and drug combinations by national malaria control programs.

Figure 1 USAID Malaria Vaccine Development Program Activities



Since 2004, USAID has provided $1.5 million per year to the Medicines for Malaria Venture (MMV), a non-profit, public-private partnership created to replenish and then sustain the global pipeline of antimalarial drugs. MMV's goal is to register at least one new antimalarial drug every five years with an emphasis on drugs that are effective against drug-resistant strains of *Plasmodium falciparum* and can be used safely in young

children and pregnant women. The research and development activities are carried out at a broad variety of institutions, comprising 42 academic and pharmaceutical organizations located in 10 different countries, including the United States. MMV currently has a portfolio of 22 different pharmaceuticals at various stages of development from initial laboratory studies to Phase III field testing and registration. Several of these products are of particular interest to USAID:

1) A pediatric formulation of lumefantrine-artemether (Coartem), which is expected to be registered in 2008

2) Dihydroartemisinin-piperaquine, a new ACT, which should be registered in 2008 or 2009

3) A new synthetic peroxide, which is a close relative of the artemisinin drugs and appears from initial clinical testing to be safe, highly efficacious, and much less expensive to produce – this drug should be ready for registration in 2010

To complement this funding, USAID also supports the UNICEF/United Nations Development Program (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, which has focused on operational and field research related to ACT and artemisinin drugs. Efforts are under way to develop a rectal formulation of artesunate, a semi-synthetic derivative of artemisinin that could be used as a substitute for injectable therapy for patients in malaria-endemic areas who do not have immediate access to injectable antimalarial treatment and cannot take drugs by mouth due to the severity of their illnesses. This formulation is now being reviewed for registration in several countries.

Key Malaria Research and Development Partners are:

Center for Vaccine Development
GenVec, Inc.
GlaxoSmithKline, PLC
Host countries
Johns Hopkins University
Kenya Medical Research Institute
Malaria Research and Training Center
Medicine for Malaria Venture
National Institute of Allergy and Infectious Disease
PATH's Malaria Vaccine Initiative
UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
U.S. Naval Medical Research Center
USAID country missions
Walter Reed Army Institute of Research

Tuberculosis

Health Issue	Product	Projected FY 2006 Funding
Tuberculosis	New Drugs	$2,300,000
	Improving Performance of and Access to DOTS	$1,400,000

Fast Facts

- An estimated 9 million new cases of TB occur each year. Nearly 2 million people die annually from this curable disease.
- The newest TB drug is 40 years old; the standard diagnostic technology used in developing countries is 100 years old, and the BCG vaccine, with almost no protective effect in adults, was introduced in 1921.
- With USAID support, three new drugs (gatifloxacin, moxifloxacin, and PA-824) are in clinical trials, and faster, more sensitive diagnostic technologies (MGIT, MODS, and TK medium) are being tested in the field.

Issues and Rationale

The ancient scourge of tuberculosis remains a public health threat, with almost 9 million new cases each year. TB is a disease of poverty that disproportionately affects poor countries and marginalized populations. The internationally recommended DOTS strategy for managing TB cases has been accepted nearly worldwide, and its use has increased considerably in the last five years. Yet, only 53 percent of estimated TB cases are detected and benefit from this therapeutic intervention.

The DOTS strategy is the best proven line of defense against tuberculosis. However, it relies on a 100-year-old diagnostic technology, a drug regimen whose newest addition came 40 years ago, and labor-intensive case management of the six- to eight-month treatment. The only vaccine available for TB, BCG, was introduced in 1921 and offers protection against severe forms of disease in children under age 5 but offers minimal protection to adults.

For decades, TB was a neglected disease that saw little investment in research for new tools. The TB community has forged ahead with these antiquated tools and has succeeded in slowing the epidemic in most regions of the world by successfully treating 82 percent of the patients managed under DOTS. Yet almost half of TB cases remain undetected, largely due to barriers to access to appropriate diagnosis and care. Fortunately, increasing attention to TB is stimulating research to address these constraints.

In Africa high rates of HIV have ignited a resurgence of TB with some countries experiencing increases in TB incidence of up to 300 percent during the last decade. In many settings up to 50 percent of TB patients are estimated to be HIV-positive, and TB is the primary single infectious cause of death among those living with HIV/AIDS. HIV is making it more difficult to diagnose the disease as current diagnostic technologies are not highly sensitive in HIV-infected individuals. The complexities of treating TB and HIV/AIDS simultaneously are not yet resolved. Preventing the emergence of TB in those infected with HIV/AIDS is possible through chemoprophylaxis, but the evidence base is insufficient to guide practice.

Another powerful threat to the control of TB is the emergence of multidrug-resistant TB (MDR-TB). A recently completed survey of 74 countries and geographical regions found MDR-TB in an average of 1.7 percent of TB cases. Eleven countries/settings reported rates higher than 10 percent. Cases of MDR-TB must be treated with second-line drugs that can cost 10 to100 times more than first-line drugs. Death rates for MDR-TB are high and as experienced in New York City in the early 1990s, outbreaks of MDR-TB can wreak havoc on TB control efforts.

Even with promising new drugs on the horizon, the protection of the limited number of second-line drugs is an urgent priority. The emergence of drug resistance is associated with poorly performing routine TB control services. Inappropriate use of second-line drugs to treat resistant disease could result in untreatable strains of TB. Research is still needed to improve the detection of drug resistance in resource/infrastructure-poor settings, and to manage drug-resistant TB in HIV-infected patients who are simultaneously receiving ART. Further additional efforts are needed to develop new, safer, and more effective drugs against MDR-TB and ensure that they reach the market.

The global TB community recently developed a consensus "Global Plan to Stop TB 2006-2015," which aims to halve TB prevalence and mortality by 2015 from the 1990 baseline. The achievement of this plan will result in the treatment of 50 million TB patients, and 14 million lives will be saved. The plan emphasizes the need for new drugs, new diagnostics, a new vaccine, and other innovations to improve program performance and patient access to DOTS. The critical role of research in meeting these aims is evident.

USAID's Role in TB Research

The "Global Plan to Stop TB 2006-1015" and the new Stop TB Strategy proposed by WHO mainstream innovations in service delivery such as DOTS-Plus for drug-resistant disease, algorithmic approaches to screening for TB, public-private partnerships for implementing TB control, coordinated management of TB-HIV, and revised treatment regimens that only five years ago were topics of research. USAID was a key donor for the research behind many of these advances.

USAID brings its field presence to bear on the TB research agenda, both informing the research community about the field-based needs and priorities, enabling field-based trials of new technologies, and moving the results of research into policy and practice in the field. USAID's significant comparative advantage is in its ability to contribute to research where it has direct implications for country-level TB programs, i.e. clinical trials at Stage IIb and beyond, field demonstrations of new technologies and implementation approaches, and operations research to improve program performance.

USAID collaborates with other U.S. Government partners to ensure seamless and non-duplicative support to the continuum of research, drawing on the comparative advantages of each agency (figure 2). USAID participates in several cross-agency partnerships to nurture this collaboration, including the TB International Workgroup, hosted by NIH; the Federal TB Task Force, coordinated by CDC; and the TB-HIV Working Group, convened by the Office of the U.S. Global AIDS Coordinator. Once promising developments are ready to be tested in the field and moved into policy, USAID has a clear role to fund and coordinate their introduction.

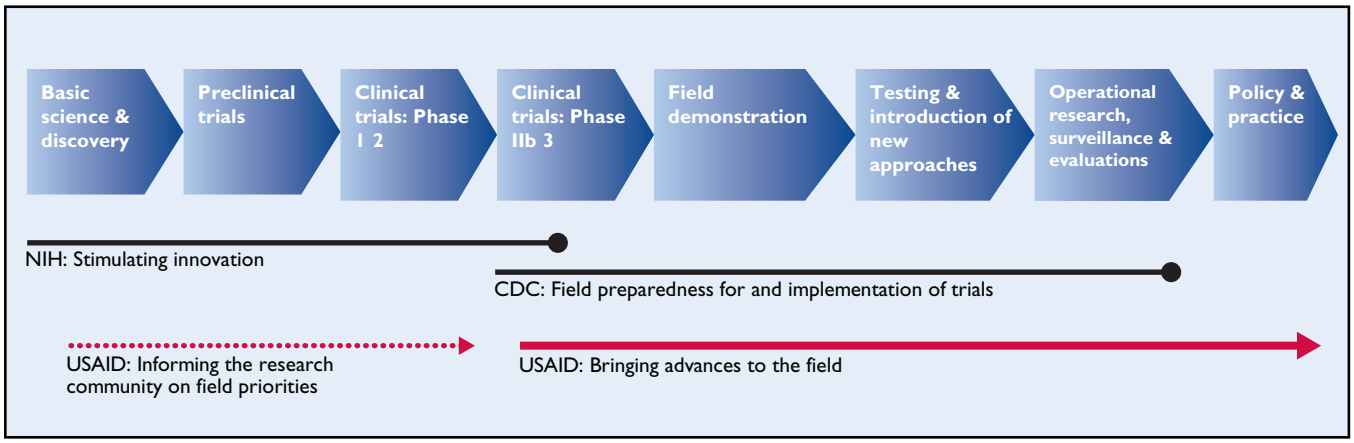
Strategy

USAID's strategy is to invest in research that will improve the performance and public health impact of country-level TB programs while mitigating the risks of drug resistance by: (1) reducing diagnostic delay, (2) reducing the duration and improving the efficacy of treatment, (3) preventing disease, and (4) increasing access to DOTS.

USAID will invest in new tools and approaches that are less labor intensive, more cost-effective, and can be delivered close to patients to minimize the health workforce burden and improve patient access, thereby improving case detection and treatment success rates. USAID will prioritize research that has the potential to change policy and practice in developing countries within three to five years.

These strategic investments mean that USAID will *not* invest in several other possible lines of research. For example, USAID will not support research related to TB

Figure 2 New Technologies and Approaches Continuum: The Role for USAID and U.S. Government Partners



in animals nor will it engage in research for which the resulting technologies or approaches would not be cost-effective or feasible for use in developing countries. USAID will not invest in basic science or Phase I or II clinical trials, as this work can be better supported through NIH. USAID will not invest in research related to pediatric TB, with the exception of research to better cotreat TB and HIV in children, as there is less of a public health burden resulting from pediatric cases.

During the first year of the implementation of this strategic plan, USAID will support research to optimize the effectiveness of existing technologies while continuing its support for late-stage clinical trials of new drugs and diagnostics. It will also ramp up efforts to prepare the field for the introduction of new technologies and to address barriers to access to services. By 2009, USAID will be responding to a robust pipeline of potential new diagnostics and drugs by supporting field trials and test-

Tuberculosis Research Strategy 2006-2010

Strategy Themes	Areas of Research and Introduction
New Drugs/ Improved Regimens	Identify and introduce new, shorter treatment regimens, new second-line drugs for resistant disease, and drugs compatible with antiretroviral drugs (ARVs) for HIV; supporting trials of drugs at Phase IIb and beyond
	Evaluate different formulations and combinations of drugs (existing and new) for effectiveness and impact on resistance
New Diagnostics	Increase the sensitivity and specificity of existing diagnostic technologies in individuals with and without HIV infection
	Develop new diagnostic technologies that more easily detect TB in individuals with and without HIV infection, enable rapid detection of drug resistance, and detect latent TB infection; supporting trials of diagnostics at Phase IIb and beyond
New Vaccines*	Test a vaccine that prevents infection with TB; supporting trials of vaccines at Phase IIb and beyond
	Develop an effective vaccine to protect TB-infected individuals from developing TB disease; supporting trials of vaccines at Phase IIb and beyond
Improve Care of Persons Infected with TB and HIV	Improve diagnosis of TB among HIV-infected individuals
	Improve detection of latent TB in HIV-infected individuals
	Evaluate efficacy and safety of TB drug regimens used in combination with ARVs for children and adults
	Test approaches to increase HIV testing among TB patients as an entry point to care
	Determine effective initiation, duration, and programmatic impact of preventive therapy regimens in consideration of ART use
Improve Performance of and Accessibility to DOTS Programs	Monitor patterns of drug resistance, TB-HIV, and TB prevalence**
	Enhance laboratory and program readiness for the adoption of new tools
	Evaluate innovations in service delivery to improve case finding, increase access to treatment, and improve program performance
	Build and utilize capacity for clinical trials in priority countries
	Identify and address epidemiological risk factors for TB, such as tobacco and diabetes

* It is not anticipated that this work will begin until 2008.

** As much of this work is considered routine surveillance, costs are not included in the total research budget.

ing novel approaches to deliver these new tools at the country level. USAID will leverage country-level resources, such as those from the Global Fund, to support mainstreaming of new technologies into standard practice and to guide investments in infrastructure and human resources for future adoption of technologies and approaches. It is anticipated that by 2011, a new vaccine that will prevent disease among adolescents and adults may be ready for demonstration trials in the field, warranting targeted support from USAID. Meanwhile, USAID will continue to move successes from research into practice and policy.

Key Partners in TB Research and Development are:

Aeras
Centers for Disease Control and Prevention
Foundation for Innovative New Diagnostics
Global Alliance for TB Drug Development
International Union Against TB and Lung Disease
Johns Hopkins University
Office of the Global AIDS Coordinator
PATH
Stop TB Partnership Working Groups
UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
University of Alabama
World Health Organization

Reproductive Health and Family Planning

Health Issue	Product	Projected FY 2006 Funding
Reproductive Health	Contraceptive Technologies	$10,500,000
	Improved Use and Service Delivery	$14,000,000

Fast Facts

- Satisfying the unmet need for contraceptives in developing countries would avert 52 million unintended pregnancies, save 1.5 million lives, and prevent more than half a million children from losing their mothers.
- USAID invests more in contraceptive research and development than any other foreign assistance donor.
- USAID's investments have contributed to the development of 12 new contraceptive products over the last 20 years.
- USAID has demonstrated the feasibility of integrating family planning into alternative health points and settings such as maternal care services in both public and private sector settings.
- USAID research has shown that the provision of family planning services to prevent mother-to-child transmission of HIV is more effective and less costly than the provision of antiretroviral medications.
- Findings from USAID-funded research inform and influence the WHO's Medical Eligibility Criteria for Contraceptive Use, the leading directive used for standards of practice worldwide.

Contraceptive Research and Development Program

Issues and Rationale

The range and availability of contraceptive methods around the world has expanded significantly in the past 40 years due to the work of USAID. Nevertheless, there is still an urgent need to further expand the range of methods and ensure access to women and men who wish to use contraception. Nearly 123 million women in less developed regions have an unmet need for family planning, and the demand for expanded access to safe, effective, acceptable, and affordable contraceptives will continue to grow as millions more young women and men reach reproductive age. Two consequences of the unmet need for contraception and unintended pregnancy are abortion and maternal death – 19 million unsafe abortions occur each year in less developed countries, contributing to approximately 15 percent of maternal mortality (or 68,000 deaths),[1] while an estimated 20 to 35 percent of all maternal deaths could be prevented through the use of contraception.[2] Family planning reduces unintended pregnancy and consequently reduces abortion, improves birth spacing, and enables couples to achieve their desired family size. Thus, a wide range of contraceptive choices ultimately promotes maternal health and child survival.

In addition to the unmet need for contraceptives, nearly every developing country needs substantial improvements in coverage and quality of family planning services and effective ways to reach out to youth, men, and the hard-to-reach rural poor. Access to services that can provide a minimal range of contraceptive options, for example, is not available in 75 percent of sub-Saharan African countries.

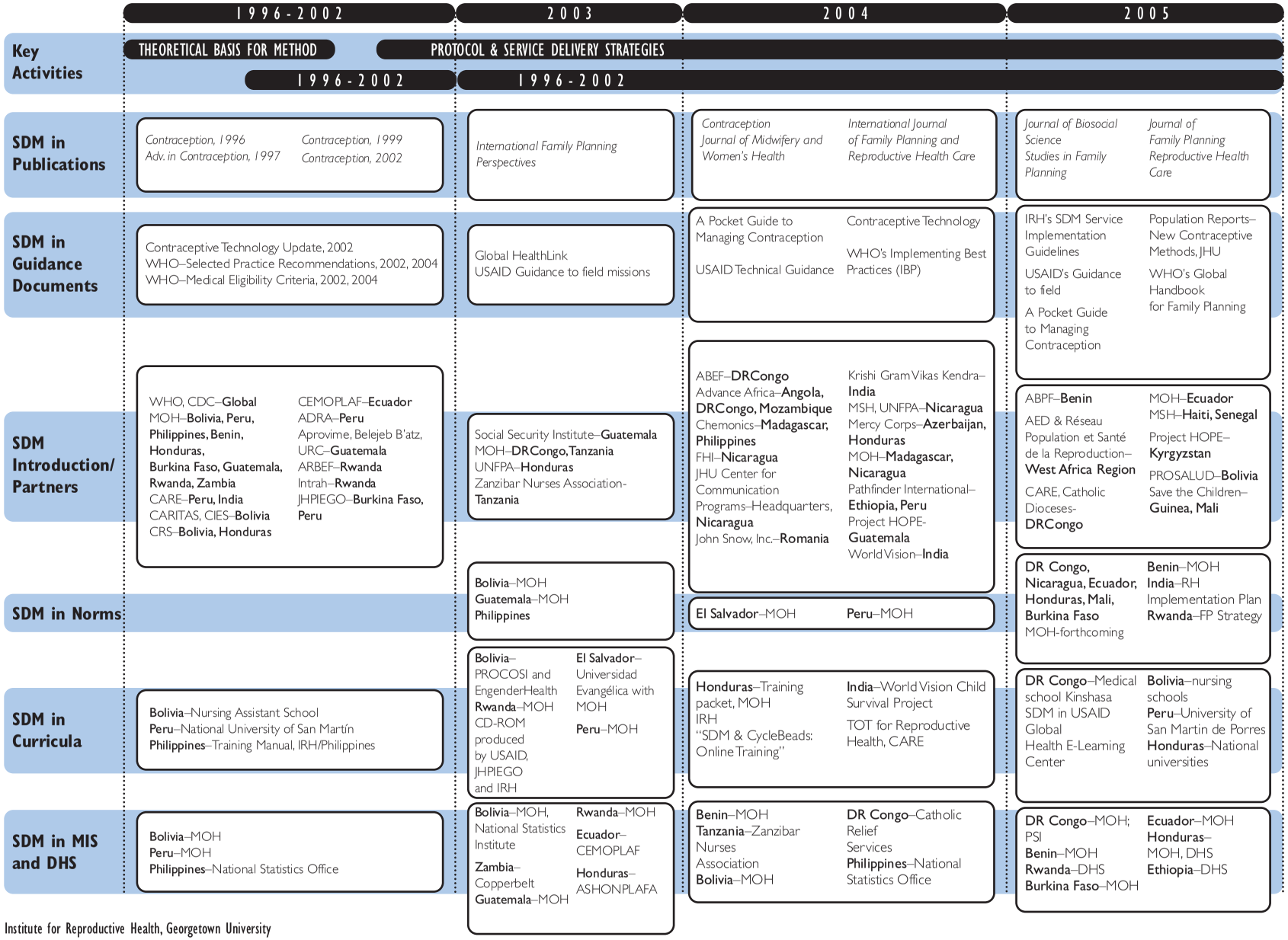
USAID's Role

USAID plays a crucial role in bringing new contraceptive products to market, especially for public sector use in developing countries. Over the past 15 years, support for USAID's contraceptive research program has been relatively steady, although declines have been seen during the past two years. The program enables USAID to support research to develop improved and new methods, gain better understanding of current methods, and increase the overall use of family planning. Figure 3 on the Standard Days Method illustrates this work. USAID is the only major donor agency, bilateral or multilateral, actively contributing to the field of contraceptive

[1] Ross, J., Stover, J., Adelaja, D., Profiles for Family Planning and Reproductive Health Programs: 116 countries, 2nd Edition, The Futures Group, 2005

[2] Singh, S., et al 2003. Adding it up: The Benefits of Investing in Sexual and Reproductive Health Care. Washington DC and New York: The Alan Guttmacher Institute and UNFPA.

Figure 3 Research to Practice: The Standard Days Method®



Institute for Reproductive Health, Georgetown University
Supported by the United States Agency for International Development under Cooperative Agreement HRN-A-00-97-00011-00 • April 2006

research and development; other donors look to USAID for leadership in this field. With few exceptions, private sector drug companies are not prepared to pursue contraceptive development, particularly of methods appropriate for use in low-resource settings, due to issues of product liability and limited profit potential.

USAID coordinates its contraceptive research program with other federal agencies, intergovernmental agencies and multilateral donors, private foundations, NGOs, and pharmaceutical companies. The high level of coordination has eliminated unnecessary duplication of effort and has facilitated cost-sharing with other donors. USAID's leadership has helped to focus the international agenda on maximizing the use of effective and affordable technologies and approaches.

Strategy for Research and Development of Contraceptive Technologies

The objective of USAID's contraceptive research program is to improve and expand family planning use through provision of new and improved contraceptive methods, including methods that also reduce the transmission of HIV and other STIs. Activities in support of this objective include:

- Development and implementation of preclinical, clinical, and acceptability studies on a wide range of methods with a focus on new and improved barrier methods for both contraception and STI prevention
- Epidemiological studies to assess the effectiveness, safety, and long-term risks and benefits of current and new contraceptive methods

Contraceptive and Family Planning Research Strategy 2006-2010

Strategy Themes	Areas of Research and Introduction
Contraceptive Research	PATH Woman's Condom – Complete contraceptive effectiveness trials and seek FDA approval for contraception
	Depo-Provera Sub-Q in Uniject – Purchase by USAID and introduce into programs
	Nesterone-EE Vaginal Ring – Introduce method into USAID programs
	SILCS Diaphragm – Introduce method into programs as a contraceptive
	TU+NET EN Male Hormonal Injection – Coformulate two products and begin bridging studies
Improving and Expanding the Use of Contraceptive Methods and Services	Develop service delivery tools and best practices to improve counseling and reduce barriers to contraceptive use
	Answer questions about the long-term effects of currently available contraceptive methods
	Expand the availability of the Standard Days Method of natural family planning in family planning/reproductive health programs
	Introduce and expand the availability of the Two-Day Method of natural family planning in pilot family planning/reproductive health programs
Improving Integration of Family Planning and Other Health Care Services	Understand the costs and outcomes of integrating family planning and other health services
	Increase access, improve quality, and expand use of contraceptives among people at risk of HIV and those already HIV-positive
Improving Approaches to Address Unmet Need for Family Planning Services of Underserved	Determine effective and appropriate programs to improve the reproductive health of youth
	Identify effective models to provide family planning safely through rural community networks, especially in Africa

The contraceptive research and development program is integrated within USAID's comprehensive family planning program and is thus driven by the need for culturally acceptable, easy-to-use, and affordable methods for family planning providers and their clients. This integration is the key to USAID's success as the primary donor agency concerned with developing and evaluating methods appropriate for use in developing-country settings.

Ongoing and Planned Activities to Advance Product Research and Introduction

Over the next five years, USAID's contraceptive research strategy will focus primarily on the development of several new hormonal and barrier methods and on improvements to existing methods. The portfolio includes support for the development of new spermicidal microbicides that prevent both pregnancy and HIV transmission. Six products are slated to enter Phase II/III effectiveness trials for contraception, and three will also begin testing for STI prevention. USAID and its partners will seek FDA approval for new methods, identify private sector and new manufacturing partners, and introduce new methods into existing USAID family planning programs. The following are the main product "leads" that will move through the product development cycle over the next five years.

Improvements of Existing Technologies

- *PATH Woman's Condom.* USAID will support a comparative trial of this new and novel female condom design (which may overcome some of the user issues with the current female condom) along with two other female condom products, with the aim of identifying the most acceptable female condom to move forward into contraceptive effectiveness trials by 2007.

- *Depo-Provera in Uniject.* In a move to expand the use of the injectable contraceptive Depo-Provera while also increasing injection safety and safe medical waste disposal, USAID has developed a public-private partnership with three entities: the Pfizer pharmaceutical company (Depo-Povera's manufacturer); the USAID-supported PATH project, which developed the Uniject injection device (a proprietary, prefilled device designed to prevent reuse); and Becton, Dickinson and Company, the world's largest syringe manufacturer and licensee of Uniject. With USAID's leadership, the parties have come to agreement, and Depo in Uniject should be ready for roll-out by 2008.

Development of New Technologies

- *Nesterone 12-Month Contraceptive Ring.* Developed by the Population Council, this vaginal ring releases Nesterone (150 micrograms per day) and ethynylestradiol (15 micrograms per day), and would be used on a three-weeks-in /one-week-out schedule for up to 12 months. A Phase III contraceptive effectiveness trial was initiated in 2005.

- *PATH SILCS Diaphragm.* This one-size-fits-most diaphragm-like device has proven very successful in safety and acceptability studies and is slated to move into a Phase III contraceptive effectiveness trial (required for FDA approval) in late 2006. If proven to be effective, the PATH-SILCS Diaphragm would benefit women by being available without prescription, entirely under the user's control, and reuseable (and thus inexpensive). Ultimately, this device could also be used with a microbicide for dual protection against HIV and other STIs as well as pregnancy.

- *TU+NET EN Male Hormonal.* Male hormonal methods have been under development for many years. Only recently has an effective, safe and possibly practical combination of androgen plus progestagen been identified. CONRAD, WHO, and USAID have negotiated with Schering AG on a male hormonal method that combines a long-acting injectable testosterone formulation, T undecanoate (TU) with a long-acting injectable progestagen, norethisterone enanthate (NET-EN). This combination injectable will enter Phase II contraceptive effectiveness and safety trials in late 2006.

Family Planning Operations Research

The objective of USAID's operations research (OR) program is to improve the availability and effectiveness of family planning and integrated reproductive health care in developing countries. This objective is achieved through assessing the needs and gaps in existing programs, developing new program and service delivery approaches to address these gaps, developing tools and materials to improve provider performance, and improving the capacity of communications and behavior change programs to increase client awareness and use of existing services.

The OR process begins with identifying problems and developing potential solutions to service delivery problems that fall under the control of program managers. It then continues with testing these solutions through experimental and quasi-experimental designs and dis-

seminating findings to local, regional, and international policymakers and program managers. Finally, the OR provides technical assistance to replicate or scale up successful interventions on a broad scale.

The success of USAID's OR program is largely a result of the integration of research activities within service delivery programs. USAID's OR program addresses issues of global importance as well as issues relevant to specific local contexts. Assessment and identification of problems and solutions are conducted in collaboration with ministries of health, NGOs, and other local stakeholders. Testing solutions within existing service delivery programs maximizes the utilization of findings. USAID disseminates OR findings to other donors and international organizations so they can incorporate new approaches into their programs.

Ongoing and Planned Activities in Operations Research to Improve Contraceptive Use and Service Delivery

- *Improving and Expanding the Use of Contraceptive Methods and Services.* USAID will address questions concerning the effects of long-term use of currently available contraceptive methods. Studies will address such service delivery challenges as reducing high discontinuation rates for some methods and improving the cost-effectiveness of long-term methods used for only short periods of time. USAID also will promote dissemination of accurate evidence-based information on the safety of using hormonal methods even in high-prevalence HIV/STI environments.

- *Improving Integration of Family Planning and Other Health Care Services.* USAID will study the costs and outcomes of effectively integrating family planning information and services with other health care services. Other studies will develop models to increase access, improve quality, and expand the use of contraceptives for people at risk of HIV, those already HIV-positive, and for postpartum women.

- *Improving Approaches to Address the Unmet Need for Family Planning Services in Underserved Groups.* USAID will develop effective, evidence-based programs to improve the reproductive health of youth, men, and other underserved groups. USAID will identify effective models to provide family planning safely through rural community networks, especially in Africa, where delivering family planning services to the hard-to-reach rural poor can be difficult.

Key Partners in Contraceptive and Family Planning Research are:

Becton, Dickinson and Company
CONRAD
Extending Service Delivery
Family Health International
Georgetown Institute for Reproductive Health
PATH
Pfizer
Population Council
Schering AG
World Health Organization

Maternal and Newborn Health

Health Issue	Product	Projected FY 2006 Funding	
Maternal and Newborn Health	Healthy Pregnancy and Assessment of Birth Care Outcomes	$1,985,000	$7,310,000
	Maternal Mortality Measurement Tools	$0*	
	New Pregnancy and Birth Interventions and Introduction	$3,725,000	
	Neonatal Research and Newborn Care Practices	$1,600,000	

* FY 2006 activities are based on prior-year investments. Future activities have been proposed for FY 2007 funding and beyond.

Every year, close to 600,000 women die during childbirth. With 50 percent of births occurring at home in the developing world, lifesaving services need to be locally available, accessible, and culturally appropriate. Every year, approximately 4 million newborns die within the first month of life, accounting for over 60 percent of infant mortality and almost 40 percent of deaths among children under 5 years of age. USAID is conducting research and improving programs to reduce the risks of maternal and newborn morbidity and mortality. These efforts include both specific and combined maternal health and neonatal interventions.

Healthy Timing and Spacing of Pregnancies

Fast Facts

- USAID analysis estimates that in 2003, if all women in developing countries (excluding China) had spaced births 36 months apart, approximately 3 million deaths among children under the age of 5 could have been averted, accounting for at least 30 percent of all deaths to children in this age group.
- In 2005, USAID brought the new evidence to ministries of health, donors, technical agencies, policymakers, program managers, community leaders, and NGOs advocating the need for education and services for the healthy timing and spacing of pregnancies as part of maternal and newborn health programs.
- Operational research is needed to determine the best way to integrate healthy timing and spacing of pregnancies into existing maternal and neonatal care programs.

Issues and Rationale

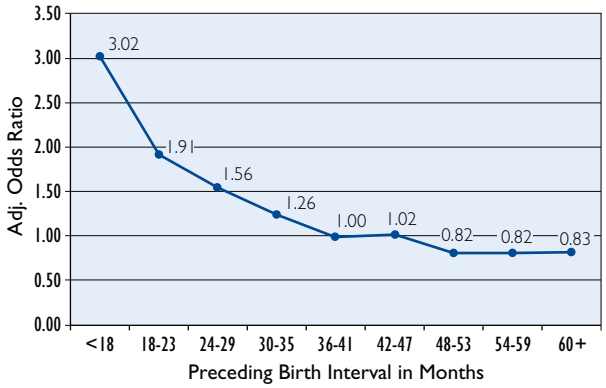
For the past several years, USAID has sponsored a series of analyses to determine the birth-to-pregnancy intervals associated with the lowest mortality and morbidity risks for newborns, infants, children, and women.

USAID sponsored analyses, completed in 2005, found that:

- Short birth-to-pregnancy intervals (less than two years) are associated with significant increased risk of neonatal, infant, child, and under-5 mortality; low birthweight and preterm births; infant/child malnutrition in some populations; stillbirths; miscarriages; and maternal morbidity.
- Intervals between abortions (spontaneous or induced) and the next pregnancy that are shorter than six months are associated with significant increased risk of adverse maternal and perinatal outcomes in the next pregnancy (low birthweight, preterm births, small for gestational age, premature rupture of membranes, and anemia).

- Earlier analyses have found significant perinatal risks associated with pregnancies occurring to women less than 20 years of age, and significant maternal and perinatal risks associated with pregnancies occurring to women less than 16 years of age.

Figure 4 Under-5 Mortality by Birth Interval

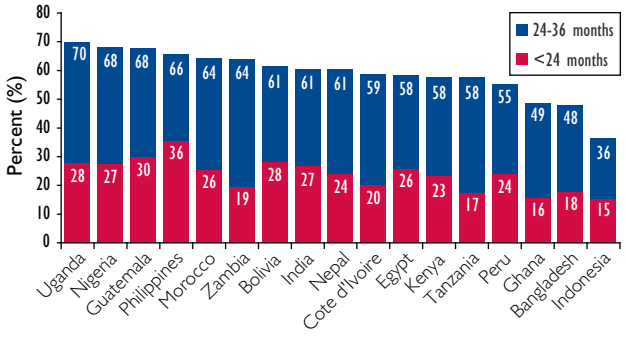


USAID-supported studies have helped establish healthy pregnancy timing and spacing as an important intervention to improve infant, child, and maternal health.

Healthy timing and spacing of pregnancies is defined as delaying the first pregnancy until the mother is at least 18 years of age, and spacing pregnancies at least 24 months apart (or 36 month birth-to-birth intervals). Pregnancy timing and spacing is the outcome of a complex set of behaviors, perceptions, and motivations at the individual, family, community, and sociocultural levels, and is influenced by socioenvironmental factors (e.g., access to health services). Interventions to achieve healthy timing and birth spacing of pregnancies include use of modern contraceptive methods (including the Standard Days Method and the Lactational Amenorrhea Method), delayed marriage, and education of families on the benefits of healthy timing and spacing of pregnancies. In developing countries, substantial percentages of births occur after birth-to-birth intervals less than 36 months apart (see figure 5).

While birth spacing was a common theme of family planning programs in the past, a 2004 USAID review identified substantial programmatic gaps. To date, many programs have effectively improved knowledge of contraceptive methods, but education on the healthy timing and spacing of pregnancies is often lacking. In many countries, such guidance is not included in mortality reduction strategies.

Figure 5 Percent of Birth Intervals That Are Short: Select Developing Countries



USAID Role and Strategy

The research strategy for healthy timing and spacing of pregnancy is to:

- Determine the health impact of this intervention; and
- Develop and support the implementation of effective communication, education, and service delivery activities

In 2004 and 2005, USAID developed a global healthy timing and spacing of pregnancies strategy encompassing:

- *Technical Consultations on the Evidence.* With USAID support, WHO sponsored a review of the evidence in June 2005 that included 30 international experts. USAID will continue to disseminate the evidence to other donors and international organizations for program development.
- *Advocacy, Policy Change, and Training.* For 2006 and 2007, USAID partners have been requested to review and strengthen policies and training needs in Haiti, Yemen, Rwanda, Cambodia, and Sudan.
- *Integration into Child Survival Programs.* USAID implementing partners will adapt existing pregnancy spacing materials for inclusion within Integrated Management of Childhood Ilness (IMCI) and pediatric AIDS programs, as well as community-based child health services in the countries listed above.
- *Integration into Maternal and Newborn Care Programs.* Guidance will be integrated into global curriculum materials, as well as essential packages for postpartum and newborn care. Focus countries for 2006 and

2007 will include Nigeria, Haiti, Kenya, Bangladesh, and Nepal.

- *Partnerships with Pharmaceutical Corporations*. USAID's implementing partners are collaborating with pharmaceutical corporations (Wyeth and Schering-Plough) to support dissemination of the evidence.

- *Service Delivery and Community Education and Outreach and Research Activities*. To strengthen service delivery counseling and education that reflects the evidence, a training guide and a pocket guide for CHWs were developed and implemented.

Research Strategy

USAID programs are increasing communities' knowledge about the healthy timing and spacing of pregnancies. The most effective approaches to bring about behavior change and improved health outcomes have not yet been identified. USAID is supporting research to show the health impact of healthy timing and birth spacing on maternal and newborn health. USAID will support the operational research necessary for scale-up of the implementation of feasible, cost-effective approaches.

- *Research.* A 2002 Institute of Medicine report, *Improving Birth Outcomes,* concluded that no large-scale programmatic interventions have been identified to prevent low birthweight, a condition that affects 18 million newborns annually and accounts for a large proportion of newborn deaths. USAID's observational studies suggest that healthy pregnancy spacing may be a new programmatic intervention to help prevent low birthweight. To test this hypothesis, USAID has initiated a five-year clinical trial, to be undertaken by Johns Hopkins University, to assess the health impact of adding a pregnancy spacing and timing component to a neonatal care activity at three sites in Bangladesh. The study examines the impact on neonatal mortality, low birthweight, preterm birth, fetal death, and small size for gestational age, as well as maternal morbidities. Formative research findings will be available in September 2006.

Research in Egypt (2005-07) will identify the most effective approaches to reach women with birth spacing education and counseling. The study will examine education and guidance approaches in antenatal and postpartum care, including home visits by the CHW, to determine the combination of counseling sessions that is most effective in helping families to make informed decisions related to the timing and spacing of pregnancies.

Other research, to be undertaken in Kenya and Haiti, will examine the most effective approaches to reach HIV-positive women, whose infants are at higher risk of low birthweight, with pregnancy spacing information and guidance.

Maternal Mortality

Fast Facts

- Every year, 500,000 maternal deaths occur worlwide, with an associated 4 million newborn deaths and 3.2 million stillbirths.
- Some countries have a measurable decline in maternal mortality; other have stagnated, while significant increases have occurred in some countries in sub-Saharan Africa.
- The burden of maternal illness and its economic and social consequences have not been measured.
- Significant differences exist in the burden of disease by region of the world and by subnational areas within countries.
- Approximately 50 percent of births occur at home in the developing world. Women and their families have been reluctant to use skilled birth attendants for birth or even life-threatening emergencies. Cultural preferences, discrimination, geography, transport and fees are common barriers to connecting women with lifesaving services.

Issues and Rationale

Maternal conditions due to complications of pregnancy and child birth are the second largest contributor to the burden of disease for women of reproductive age. The subsequent maternal death and disability significantly affect the health of families and communities and the productivity of nations. As documented in the Institute of Medicine report *Improving Birth Outcomes*, most maternal deaths can be prevented with current technologies available in health facilities. A replication study is currently evaluating evidence on selected technical interventions (e.g. medications, procedures) for prevention or effective treatment of obstetric complications, as well as

Figure 6 Geographic Variation in Distribution of Causes of Maternal Mortality

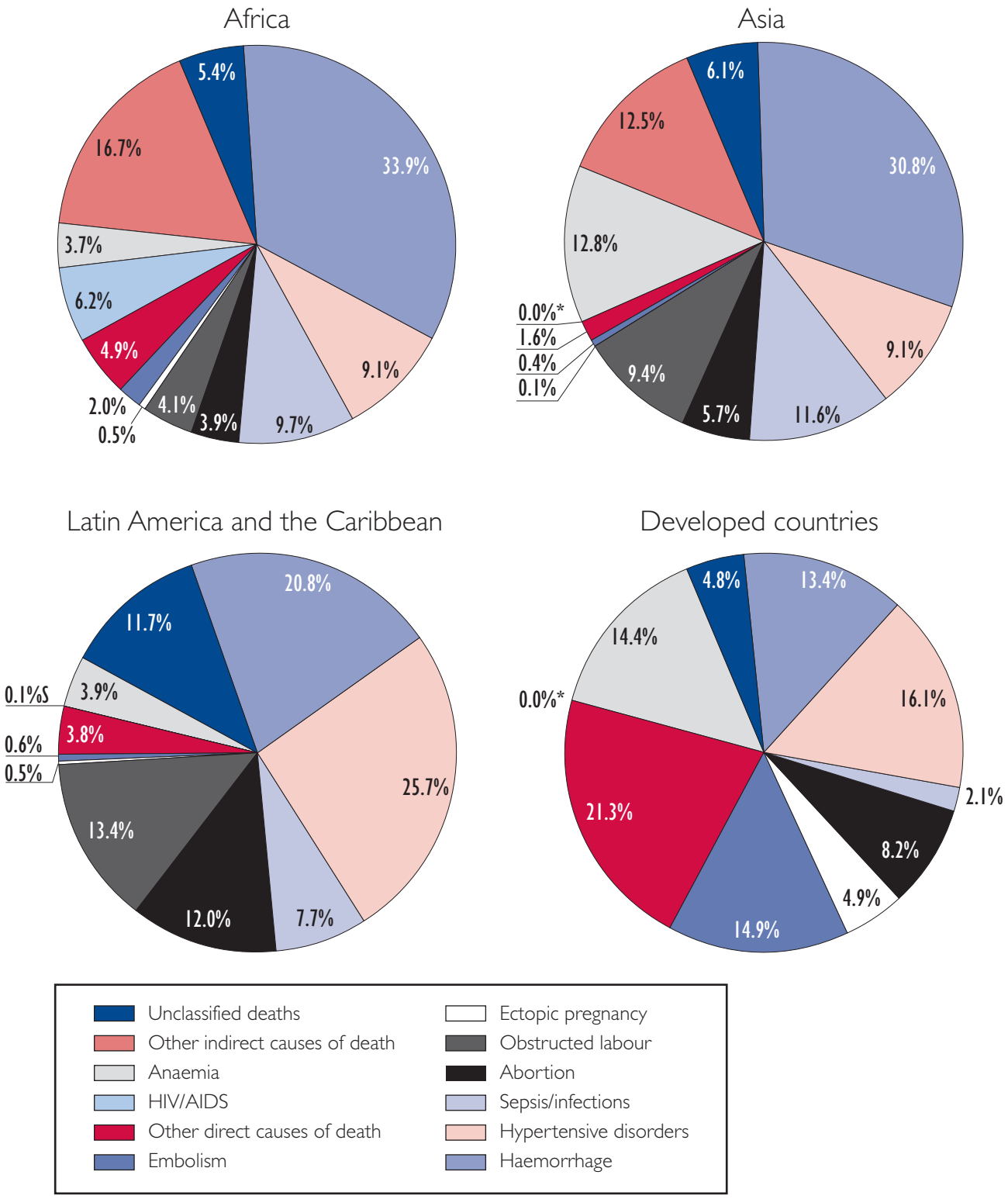


Figure 3: Geographical variation in distribution of causes of maternal deaths
*Represents HIV/AIDS. Represents embolism. Represents ectopic pregnancy. Represents anaemia.

From: *The Lancet*, Early Online Publication, 28 March 2006. DOI:10.1016/S0140-6736(06)68397-9.

emerging evidence of the effect of low-dose vitamin A in pregnancy.

However, with 50 percent of births in USAID presence countries still occurring at home, delivery of the effective interventions at the community level to reduce hemorrhage, infection, and obstructed labor, and thereby decrease mortality, is a key challenge. There is a need to build upon the evidence of the effectiveness of discrete interventions and undertake research on the effectiveness and cost-effectiveness of programmatic approaches on how to deliver the interventions (e.g., education of communities, effective facility management, community-based financing) in low-resource settings.

An additional issue in the maternal health field is the measurement of illness and death. Lengthy, costly population-based surveys have been the gold standard for measuring progress in reducing maternal mortality from decade to decade but have been inadequate for measuring program progress. USAID, with other donors, is supporting tool development for measuring pregnancy outcomes. In addition, USAID is expanding the limited body of evidence on the causes of birth complications and their impact on individuals and the community.

Research Strategy for Priority Activities

USAID is helping to fill the evidence gap to inform how effective programming of limited resources by governments, donors, and NGOs can prevent maternal death and disability. The Agency focuses its maternal health research strategy in four specific areas:

1) Global data and analysis to guide programming

2) New tools to measure progress

3) Testing new interventions and moving efficacious interventions to the field

4) Documenting effectiveness and cost-effectiveness of selected strategies to deliver proven interventions

- *Global Data and Analysis to Guide Programming.* USAID works primarily with WHO and ORC/MACRO to link the needs of the field for data and analysis to inform programming. USAID works through its field missions to assess the need to implement appropriate Demographic and Health Survey modules/questions and with WHO and MACRO to analyze data and work collaboratively on appropriate strategies to bring information to the field. USAID is supporting a Bangladesh site of a multicountry study of the effects of maternal mortality and disability and its long-term consequences. USAID is supporting WHO's systematic review of the causes of maternal death (see figure 6) and the health outcomes of operative delivery so that program design is not dependent on developed country work that is not applicable in low-resource environments where home birth is the norm.

- *New Tools.* In partnership with the Gates Foundation, the U.K. Department for International Development, and the European Commission, USAID is supporting the University of Aberdeen to develop a set of tools to evaluate safe motherhood interventions. The Sampling at Service Site tool currently under development is an innovative and affordable method to capture maternal deaths that avoids more expensive and lengthy population-based surveys. The Rapid Ascertainment Process for Maternal Death improves capture of pregnancy-related deaths in hospitals, which can be used to identify reporting gaps that are exceedingly important in monitoring quality of care and birth outcomes. A new tool (interval-M), under development, is a time-efficient model for determining cause of death in order to focus programming on the most frequent direct causes of death. These tools will be validated in USAID program countries and then introduced for widespread use.

- *Testing Interventions and Moving Efficacious Interventions to the Field.* The strategy is tailored to investigation and introduction of individual biomedical interventions. A surprising result from a USAID-supported study in Nepal showing a huge effect of low-dose vitamin A on maternal mortality led USAID to make a substantial investment through Johns Hopkins University to replicate the work in order to determine if sufficient evidence exists for instituting widespread supplementation. USAID is also working with WHO, the International Federation of Obstetricians and Gynecologists, and the International Confederation of Midwives to develop policy guidelines for standards of care related to postpartum hemorrhage. Oxytocin as part of active management of the third stage of labor (AMTSL) has been documented to reduce postpartum hemorrhage, and AMTSL with oxytocin in a traditional syringe is ready for widespread implementation with births in health facilities. Research is now needed on community delivery and demand. This will also require stability studies of oxytocin in the Uniject syringe in cooperation with PATH. In addition, important pre- and

postoperative care practices related to fistula repair need scientific evidence.

- *Documenting Effectiveness and Cost-Effectiveness of Selected Strategies to Deliver Proven Interventions.* USAID selects some of the most promising approaches that address barriers to use of care and health systems issues to deliver proven biomedical interventions and tests them in various contexts. The strategy varies based upon context and opportunity, such as the advantages of linking nonskilled with skilled birth attendants to improve birth outcomes in Burkina Faso, the effect of elimination of user fee for maternity care in Ghana, the cost-effectiveness of the village midwife strategy in Indonesia, and the comparative advantages of community-based financing vs intensive community education in use of services in Mali. Additional studies are being conducted to validate results or test interventions in different contexts, in collaboration with the University of Aberdeen, Abt Associates, University Research Corporation, and The Futures Group. When possible, USAID compares strategies to determine "best buys" for governments with limited resources.

Newborn Health

Fast Facts

- Most newborn births in developing countries occur at home, often without the assistance of a skilled birth attendant.
- Newborn deaths account for the largest share of child mortality.
- The leading direct causes of newborn deaths are infections, asphyxia, and complications from prematurity.
- Half of newborn infection-related deaths occur during the first week of life.
- Emerging evidence from ongoing research studies is documenting the feasibility and impact of a simple household care approach.

Issues and Rationale

Every year, approximately 4 million newborns die within the first month of life, accounting for over 60 percent of infant mortality and almost 40 percent of deaths among children under 5 years of age. Most neonatal deaths are caused directly by infections (36 percent), complications of prematurity (27 percent), and birth asphyxia and injuries (23 percent). Low birthweight is the most important indirect cause of death with 60 to 80 percent of neonatal deaths occurring among low-weight newborns. Other indirect causes of perinatal and neonatal death are poor maternal health and nutrition, malaria, and maternal infections. Newborn health is a new technical focus area for USAID and one where the agency is playing a leadership role in catalyzing the development of an evidence base and integrating this new knowledge into field programs.

Strategy

Until fairly recently, the scientific community felt that absent access to high-tech neonatal care wards, little could be done for ill neonates. Based on some promising research findings, the USAID neonatal research agenda will test simple low-cost approaches with the greatest potential to substantially prevent death and treat severe illness in low-resource settings with limited access to quality facility-based care. USAID's research agenda is focused on the following intervention areas:

- Newborn home care practices or essential newborn care (ENC)

Maternal and Newborn Health Research Strategy 2006-2010

Strategy Themes	Areas of Research and Introduction
Healthy Pregnancy and Birth Outcomes	Determine the health impact of healthy timing and spacing of pregnancies *Develop and support the implementation of effective communication, education, and service delivery activities for healthy timing and spacing of pregnancies*
Assessment of Birth Care and Outcomes	Impact of cesarean section on birth outcome *Global systematic review of direct causes of maternal mortality* Review of physical, psychological, and economic consequences *Impact of family planning in different settings on maternal mortality* Evaluation of effectiveness and cost-effectiveness of approaches
Maternal Mortality Measurement Tools	"Sampling at Service Site" to measure population-based maternal mortality *Rapid Assessment Process for Maternal Death to measure maternal mortality in facilities* Refine and validate "Verbal Autopsy" tool and apply in two to three countries
New Pregnancy and Birth Interventions and Introduction	Complete study on effect of low-dose vitamin A supplementation on pregnancy outcome and disseminate findings globally *Uniject Oxytocin: conduct stability studies, scale up production, launch in multiple countries* AMTSL: Apply at scale and measure coverage in five countries *Efficacy and outcomes of practices for fistula repair*
Neonatal Research and Newborn Care Practices	ENC: Complete effectiveness and cost-effectiveness studies and implement and evaluate minimal package of essential care *Treatment and prevention of infections: Effectiveness and cost-effectiveness studies, alternative formulations, and delivery strategies* Strategies for care of low-birthweight infants: Evaluate and implement coordinated "kangaroo care" in facility- and community-level care *Resuscitation device availability: Work with manufacturers to produce and distribute low-cost devices*

- Treatment and prevention of infections
- Simple strategies for care of low-birthweight infants
- Increasing availability of resuscitation devices

Home Care of the Newborn or Essential Newborn Care (ENC)

A major focus of USAID's current neonatal research strategy is to test the effectiveness and cost-effectiveness of the impact of increased knowledge and sustained appropriate household newborn care and treatment practices. The research strategy draws upon the results of two small groundbreaking studies in Nepal and India that documented significant mortality reductions related to community-level health promotion and treatment. Current USAID studies in south Asian countries – Bangladesh, India, Nepal, and Pakistan – are testing simple community-based care packages delivered through community education and home visits by CHWs. These packages include promotion of clean delivery and cord care, simple resuscitation, warmth, early and exclusive breathing, limited community treatment, and early recognition and referral to health facilities for serious infections. Even before the research

is completed, the evidence was sufficiently compelling in Bangladesh for the USAID Mission to introduce this approach in its program outside of a research setting.

USAID is supporting effectiveness research to adapt the ENC approach to African settings with high-HIV prevalence. Both HIV-positive and -negative newborns could benefit from an ENC approach.

Treatment and Prevention of Infections

Because of the large burden of mortality due to infection, USAID is studying preventive and curative strategies that could be employed in health facility and community settings. Currently, many severely ill newborns are not treated in health facilities or reach health facilities too late. Whereas mild infections and pneumonia can be treated with oral antibiotics, more severe illness or sepsis requires injectable antibiotic treatment. USAID has commissioned a review of current evidence on management of the sick newborn to help guide facility and community care. This review will serve as the basis for the development of guidelines for improved care and help identify additional research efforts.

USAID supports field trials in Bangladesh, Pakistan, Nepal, and Zambia to determine the effectiveness and feasibility of different approaches for CHWs to diagnose and treat infections with oral and injectable antibiotics.

USAID also is supporting the development of an antibiotic formulation to be pre-filled in a Uniject device. Uniject was previously developed with funds from USAID and is instrumental for safe injection practices, allowing for individual dose delivery of the product. This device can be transported easily and administered in the home by trained CHWs. Starting in June 2006, the antibiotic prefilled Uniject device will be tested to assess feasibility, efficacy, and cost-effectiveness as part of a multicountry infection treatment study in Africa and Asia.

While tetanus toxoid immunization and clean delivery are excellent preventive measures against infection, USAID is supporting a small study of additional prevention approaches, including antiseptics that could be included in birthing kits. Ongoing research is testing the use of chlorhexidine to reduce cord infection. Additional research efforts may examine other antiseptic uses.

Simple Strategies for Care of Low-Birthweight Infants

Reducing the proportion of babies born with low birthweight (< 2,500gms) is challenging because of the link with the mother's long-term health and nutritional status prior to pregnancy. Death of moderately pre-term and at-term low-birthweight newborns can be prevented with extra attention to warmth, feeding, and prevention or early treatment of infections. Ongoing research in India and planned research in Africa is testing whether Kangaroo mother care (KMC), a warming technique of extended skin-to-skin contact used in hospitals, would be safe, acceptable, and effective in the home setting. USAID will support one or two studies in Africa to demonstrate the feasibility of reducing death due to hypothermia using community-based KMC.

Increasing Availability of Resuscitation Devices

Although asphyxia remains a major cause of newborn death, the supply of low-cost, easy-to-use resuscitation devices is limited in Africa and Asia. To address this problem, USAID is supporting a study of optimal device designs and available products on the market and will provide technical assistance to facilitate the production and distribution of neonatal resuscitation devices.

Key Partners in Maternal and Newborn Health Research and Introduction are:

Abt Associates
ACCESS
BASICS
Boston University
European Commission
ICDDR,B (Bangladesh)
International Confederation of Midwives
Int'l Federation of Obstetricians and Gynecologists
Johns Hopkins University
Melinda & Bill Gates Foundation
Multiple host government ministries of health
National Institutes of Health
ORC/Macro
PATH
Saving Newborn Lives/Save the Children
Schering-Plough
The Futures Group
U.K. Department for International Development
University of Aberdeen (Scotland)
University Research Corporation
Wellcome Trust
World Health Organization
Wyeth

Micronutrient Deficiencies in Women and Children and Management of Severe Malnutrition

Health Issue	Product	Projected FY 2006 Funding
Micronutrient Deficiencies	Vitamin A – Deficiency Prevention and Control	$700,000
	Zinc – Diarrhea Therapy and Prevention	$884,000
	Iron – Anemia Prevention/Rx Packages	$1,100,000
	Community Therapeutic Care – Emergencies	$1,100,000

Each year micronutrient deficiencies compromise the health, development, and survival of hundreds of millions of women and children in the developing world. USAID collaborates with partners to identify and prevent nutrient deficiencies, especially those of vitamin A, zinc, iron, folate, and iodine in mothers and children.

In its 2005 research report to Congress, USAID summarized its research and programmatic approach to address vitamin A deficiencies through public health research, policy development and program implementation. This proactive, evidence-based strategy has established the standard of care to control vitamin A deficiencies that is widely implemented by host countries, development agencies, and the international public health community. USAID is currently applying the same research and programmatic approach to the use of zinc to treat diarrhea. Looking to the future, USAID-supported research efforts will have a greater focus on operational questions on delivery strategies of proven interventions as well as understanding the interface of micronutrients and infection on maternal and child health.

USAID stays abreast of technical advances in nutrition and micronutrient research and periodically adjusts its research priorities to reflect advances that have the most promise to impact the effectiveness of Agency programs. Contributing to this strategic approach, USAID organized a meeting with WHO and UNICEF on micronutrients and health in April 2005. Through a consultative process, scientists, donors, and policy makers identified emerging issues related to the safety and effectiveness of single and multiple micronutrient supplementation that impact health and nutrition policies. This process has set a global agenda for clinical research and programmatic research for service delivery of micronutrient programs.

USAID focuses the major portion of its micronutrient research efforts on program operations and delivery. The Agency's continued support of national food fortification programs to prevent micronutrient deficiency in Central America, Southeast Asia, and some African countries is reflective of this strategic research approach and the emphasis on translation of scientific findings into high-impact program implementation.

Also in line with the micronutrient research and development strategy, USAID-supported the merger of the International Nutritional Anemia Consultative Group (INACG) and the International Vitamin A Consultative Group into a new "Micronutrient Forum" with a broader "nutrient mandate" to ensure evidence of effectiveness and safety in all micronutrient interventions both singly and in combination. USAID has served as a global proponent of evidence-based programs for the prevention of iron deficiency and anemia for the past 25 years through its support of INACG. In consultation with USAID, INACG has convened expert panels, workshops and international meetings to promote applied research to interpret scientific evidence and guide policy to prevent iron deficiency through diet, fortification, supplementation, and disease control measures.

Vitamin A Deficiency

Fast Facts

- Vitamin A supplementation can reduce child mortality by 23-34 percent and virtually eliminate Vitamin A deficiency related blindness.
- In women, vitamin A deficiency causes night blindness during pregnancy. About 10 percent of pregnant women in rural developing-country settings develop night blindness.
- Vitamin A is most effective in reducing risk of child death from measles, diarrhea, and malaria.
- With recent increases in coverage, vitamin A programs prevent an estimated 1 million child deaths each year.

Issues and Rationale

Major reductions in child mortality and blindness are being achieved through an ongoing global public health campaign to provide periodic or biannual vitamin A supplementation to young children. While this successful public health effort has evolved directly from USAID-led research, the use of additional vitamin A may be able to address approximately 20 to 24 percent of child mortality from measles, diarrhea, and malaria and 20 percent of all-cause maternal mortality that can still be attributed to this preventable condition.[3] While periodic supplementation for children 6 months to 5 years old is paramount for childhood vitamin A deficiency, newborn and maternal vitamin A supplementation may offer new opportunities to reduce mortality or improve health during these high-risk stages of life.

In the early 1990s, at a time when USAID-supported research trials found that vitamin A could reduce child morbidity by 34 percent, WHO estimated that 250 million children in the developing world were vitamin A-deficient. In response, USAID helped dozens of countries to reinvigorate vitamin A supplementation through semi-annual campaigns, often with national immunization days (NIDs), which vastly increased coverage. With the planned phaseout of NIDs, many countries continue their momentum to deliver vitamin A by transferring it to national child health days held every six months. These and other intervention successes have reduced the estimated numbers of preschool child deaths from vitamin A deficiency from approximately 1.7 million in 1990 to approximately 700,000 million at present and halved the number of deficient children to roughly 130 million. Vitamin A supplementation continues to be a core element of child survival programs supported by USAID. UNICEF presently distributes 400 million to 800 million vitamin A supplements with funding from the Canadian International Development Agency to more than 80 countries each year.

Even with these successes, vitamin A deficiency is responsible for nearly 10 percent of all early childhood deaths due to severe infection. USAID is working to develop and implement feasible approaches that at a minimum will increase coverage to reach more children and work toward the elimination of vitamin A deficiency.

Strategy

A significant focus over the next five years will be on the coordination of delivery in the broader context of existing micronutrient dosing among maternal, infant, and childhood supplementation, along with other nutritional strategies. Research to further these goals will include:

- Confirmatory effectiveness and safety research to determine maternal and neonatal dosing of vitamin A to reduce mortality/morbidity
- Operational research and analytical strategies to guide efforts to expanded sustainable vitamin A coverage through supplementation and food fortification delivery strategies

Effectiveness and Safety Research to Determine Maternal and Neonatal Dosing

Ongoing research studies in Bangladesh and Ghana (which received preliminary USAID funding) are exploring the potential benefits of vitamin A supplementation for pregnant women. A previous trial in Nepal reported a 40 percent decrease in pregnancy related mortality. A companion study is seeking to replicate research previously conducted in Indonesia and India and confirm if newborn vitamin A dosing could reduce mortality by 20 percent.

[3] Rice, Amy et al. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors", vol 1. ed M Ezzati, AD Lopez, A Rodgers and CJL Murray. Geneva:WHO, 2004: pp 211-256 (chapter 4).

Operational Research and Analytical Strategies to Expand Vitamin A Coverage

Through the Micronutrient Forum and in collaboration with other USAID partners, the Agency will develop evidence-based policy and programmatic approaches that guide enhanced global and country-level strategies to increase coverage of vitamin A supplementation.

Illustrative of this approach will be the Agency's use of the results of the ongoing trials in Bangladesh and Ghana. If the research studies have a positive outcome, USAID could advocate and work with UN agencies, donors, host governments, and manufacturers to prepare for the standardization of supplemental dosing of vitamin A for improved maternal or infant health and survival. Analysis suggests that if the Bangladesh trial validates positive results seen in the India and Indonesia neonatal dosing trials, a scaled-up vitamin A neonatal supplementation strategy could avert an additional half-million infant deaths annually in South Asia alone. However, before working on the introduction of a vitamin A effort, the Agency and its partners will carefully review the research results and assess feasible alternative delivery strategies, including supplementation and fortification; costs; benefits; and sustainability. In addition, the Agency will develop a business/rollout plan to guide a scale-up strategy and engage partners such as other U.S. Government agencies, United Nations agencies, host governments, other donors, manufacturers, and other private sector partners in this process.

USAID also continues to address key operational questions and issues needed to introduce or expand food fortification efforts. Working with the Global Alliance for Improved Nutrition (GAIN) and other partners, USAID support is helping developing countries to develop national food fortification programs, select commonly consumed staple foods, and increase the consumption of fortified foods and condiments. Illustrative of this approach is an ongoing effort in Zambia to eliminate iron deficiency anemia and vitamin A deficiency. In February 2006, the Zambian Ministry of Health partnered with the Millers Association of Zambia and GAIN to fortify all commercially milled maize meal with vitamins and minerals. Within three years' time, government officials project over half of the maize meal sold will be fortified. Zambian officials estimate that one in every two children under age 5 has iron deficiency anemia and is vitamin A-deficient.

Zinc

Fast Facts

- Ten to 14 days of zinc given as adjunct treatment during a diarrhea episode reduces the severity and duration of the episode by 25 percent in young children.
- A USAID-supported meta-analysis documented a 34 percent decrease in the prevalence of future diarrhea episodes after short-term zinc treatment during a diarrhea episode.
- Zinc has been added to the Interagency Emergency Health Kit and has already been used in complex emergencies/disasters
- A recent USAID-supported study demonstrated that daily ongoing zinc supplementation in HIV-positive children is an effective way to reduce diarrhea and does not negatively impact viral load.

Issues and Rationale

The importance of zinc as an essential micronutrient for immune function, growth, and development is well documented. Clinical and field studies since the 1980s have consistently shown an association between zinc deficiency and high rates of infectious diseases, including diarrhea and respiratory infections, and growth retardation. Zinc deficiency is widespread among young children in developing countries, who typically do not consume adequate zinc in the diet and have high rates of diarrhea, increasing zinc loss. An estimated 1.5 million children die annually from diarrhea-related causes.

Using childhood stunting rates as a proxy for zinc deficiency, it is estimated that 33 percent of young children are living at risk of zinc deficiency. In addition, diarrhea and pneumonia remain the leading causes of death among children under age 5. USAID has been a critical partner in generating the wide body of evidence supporting the use of zinc for diarrhea treatment and continues to support the effort to promote the inclusion of zinc in diarrhea treatment programs. This evidence was the basis of a joint WHO and UNICEF global recommendation for the use of zinc in conjunction with oral rehydration therapy in the treatment of diarrhea. USAID is supporting ongoing community effectiveness trials in Tanzania and Nepal to determine the potential benefits of regular zinc supplementation in children to prevent pneumonia and diarrhea.

Strategy

Building upon the evidence base of the effectiveness of zinc in treating diarrhea, in the coming years USAID's primary focus will be on accelerating the introduction of this new treatment into regular use in programs. Major approaches will include:

- Efforts to increase the availability and use of a quality supply of zinc in the public and private sectors to meet anticipated demand
- Facilitating the development of guidelines and support to high-need countries to integrate zinc into regular public health programs and program learning to make zinc available most efficiently and effectively to those most in need.

Increasing Supply and Demand for Zinc Treatment of Diarrhea

USAID is collaborating with United Nations procurement agencies to identify qualified suppliers of zinc products formulated for diarrhea treatment in children. The Agency is working with manufacturers interested in investing in zinc production to meet international pharmaceutical goods manufacturing practices, thereby ensuring quality and properly taste-masked products are available around the world. It is expected that by the end of 2006 more than one supplier will be prequalified by UNICEF to supply zinc to countries around the world.

In addition to working with public sector partners such as ministries of health, United Nations agencies, and NGOs to make zinc available, USAID is supporting initiatives to expand access to and demand for zinc treatment through private sector mechanisms. The Agency is supporting models of private sector engagement that are being tested and evaluated. These include:

- The classic approach to social marketing, with zinc being delivered in a subsidized form as part of a package with oral rehydration salts
- A commercial model, in which producers and suppliers engage their workforces in marketing mechanisms to reach underserved populations

Table 3 Zinc Use in the Treatment of Diarrhea

Activity	FY 2005	FY 2006 Target
Availability of quality zinc products	Bangladesh Nepal	India Nepal Ethiopia Bangladesh Tanzania Kenya Democratic Republic of Congo
Adoption of zinc policy	Bangladesh Nepal	Madagascar Tanzania Democratic Republic of Congo Cambodia India
Service delivery of zinc established	Cambodia	Nepal Ethiopia Madagascar Tanzania Democratic Republic of Congo
Increase consumer awareness and demand		Nepal

Source: USAID.

Development of Guidelines, Adaptation, and Documentation of Program Introduction Experiences at Country Level

USAID is working with host governments, international organizations, NGOs, and other partners to ensure that zinc is adopted and integrated into host-country policies. In selected early adopter countries and high-need countries, the Agency will provide expertise to ensure sound implementation and roll-out into regular programs. This will involve ensuring that policy is translated into standard treatment guidelines and training materials for health workers, and that drug management and distribution to public and private health facilities and drug retailers is effective. Many of the early data and lessons learned about zinc introduction are results from USAID-funded pilot studies in Mali, India, and Pakistan, which focused on the analysis of barriers for adoption and implementation. Within the next few years, USAID will have even greater program experience of zinc use

in actual practice to document successful approaches to targeting zinc to high-need populations.

Regular Supplementation of Zinc in Preventing Childhood Illness

As a secondary investment area, USAID is supporting research studies in Tanzania and Nepal to test the effectiveness of regular zinc supplementation in preventing childhood illnesses and mortality due to diarrhea and pneumonia. Once these studies are completed, USAID in consultation with other partners will assess the effectiveness, programmatic feasibility, and cost/benefit of this approach prior to committing to additional studies of potential programmatic use.

Iron: Anemia Prevention and Treatment Packages

Fast Facts

- Iron deficiency affects approximately 2 billion people, making it the most common nutritional deficiency in the world.
- Over 40 percent of preschool-age children in the developing world are anemic, believed to be mostly a consequence of iron deficiency.

Issues and Rationale

Iron deficiency affects approximately one third of the world's women and children, impairing cognitive development in 40 to 60 percent of infants, compromising the health and productivity of 500 million women, and leading to more than 60,000 perinatal deaths per year. Iron deficiency may also stunt child growth and has been viewed as a possible cause of early childhood mortality. However, giving supplemental iron has also been associated with increased infection, especially *falciparum* malaria, and may not benefit children with normal iron status. The need to generate evidence on childhood consumption of iron motivated USAID to join WHO, the Bill & Melinda Gates Foundation, the United Nations Foundation, and NIH in funding two large preschool-child supplementation trials to evaluate iron plus folic acid and/or zinc, one in nonmalarial South Asia (Nepal) and one in a malaria-endemic region of Africa (Zanzibar). The aim was to inform and guide policy on the efficacy and safety of these nutrients to improve child survival, health and development.

Anemia has many causes, including iron deficiency, hookworm, acute infections, and chronic inflammatory diseases. It is critical to prevent anemia by addressing these causes. For example, where hookworm or malaria is endemic, anthelmintic or antimalarial interventions can help to treat and prevent anemia. Multiple causes may require multiple preventive approaches. Future implementation of childhood iron supplementation programs hinges on determining if and how it can be done safely and feasibly, especially across regions of diverse nutritional and disease risks. Where iron deficiency is widespread and the dominant cause of anemia, as is the case in Nepal, iron supplementation prophylaxis had no impact on child survival but could improve child development. In contrast, where *falciparum* malaria is endemic, universal childhood iron prophylaxis may harm iron-replete children in the absence of effective malaria control measures. Where hookworm is widespread, deworming may substantially reduce anemia.

Strategy

In the coming year, USAID will support a WHO/UNICEF consultation on safe delivery of iron to deficient children in order to provide programmatic guidance to countries and to identify research priorities. Based upon the recommendation of the WHO meeting, and in consultation with other external experts, USAID anticipates commissioning targeted research on safe approaches for iron supplementation in deficient child populations.

Women of reproductive age continue to be an important target population for anemia prevention interventions. Operations research is under way to develop best practices for the increased coverage and implementation of reproductive health packages that include anemia control and prevention. Over the next five years, USAID will support research into the identification of constraints to anemia control and programmatic options to overcome them.

Community Therapeutic Care: Management of Severe Acute Malnutrition

Fast Facts

- Severe acute malnutrition (SAM) affects approximately 10 million children under age 5 and contributes to almost 2 million preventable child deaths each year.
- Community- and home-based approaches are a significant advance in treating SAM.
- Between 2001 and 2005, USAID was associated with successful treatment of over 20,000 severely malnourished children in 21 community therapeutic care (CTC) programs in Ethiopia, Malawi, and Sudan.
- During the 2005 emergency in Niger, Médecin Sans Frontières/France treated more than 60,000 children using a modified CTC approach and achieving a very low case fatality rate of just 5 percent.
- CTC represents an entry point for HIV/AIDS care and support for malnourished children and adults. It is often free of stigma because it targets the malnourished rather than the HIV-positive.

Issues and Rationale

In the past, the management of severe acute malnutrition (SAM) – severe wasting and/or presence of edema of children – in emergency situations was exclusively managed through setting up therapeutic feeding centers (TFCs) in health centers and hospitals. These facility-based nutritional rehabilitation approaches are difficult to establish and sustain, expensive to operate, and provide limited treatment coverage, often to less than 10 percent of the affected population; in addition, the TFCs are sources of cross-infection. The case fatality rate for facility-based treatment of SAM is 20 to 30 percent. Facility-based approaches do not support or build on the capacity of communities and caregivers. At times, they undermine traditional coping strategies, as caregivers may be required to remain with their malnourished child in TFC for three weeks or longer, with high opportunity costs and disruption of family life.

CTC and related home-based care approaches are an innovative new approach to managing acute malnutrition in emergencies. The CTC approach involves treating the majority of the severely malnourished at home. Central to this home-based care is the provision of safe, appropriate, ready-to-use therapeutic foods containing the right concentrated mix of nutrients that will assist in treatment and rapid rehabilitation.

Ready-to-use therapeutic foods (RUTFs) have been specifically designed, marketed, and locally produced for this purpose. One common RUTF is the peanut butter-based Plumpy'Nut®, developed by Nutriset France. Plumpy'Nut is nutritionally equivalent to the F-100 therapeutic milk used in TFCs for many years in the rehabilitation phase. Unlike F-100, RUTFs require no preparation, and the products are oil-based with low water activity. As such, RUTFs can be easily transported and stored at home with little risk of microbiological contamination.

USAID's Role and Strategy

Severe malnutrition remains a significant problem around the globe, and USAID will continue to take the lead and be actively engaged in the adoption of this innovative approach to managing it. Over the next five years, USAID will work with WHO, UNICEF, PVOs, host-country governments, and others to complete the necessary research and introduction activities to:

- Develop and establish global guidelines and introduce CTC at the national level in five countries.
- Facilitate local production of RUTF in developing countries and pilot test alternative RUTF formulations
- *CTC Guideline Development and Implementation.* Based on USAID-supported research since 2003, there is now sufficient evidence to establish global guidelines on the management of severe malnutrition at the community level. In November 2005, USAID, WHO, UNICEF, and the United Nations Standing Committee on Nutrition joined together to identify the main areas of consensus in CTC that can be translated into evidence-based global guidelines. Over the next five years, USAID will work with international partners toward the issuance of such guidelines and will help five country governments adopt and implement CTC programs.
- *RUTF Production Capacity in Less Developed Countries and Development of Locally Appropriate RUTF Formulations.* Local production of RUTFs has been accelerated by the partnership of Nutriset with USAID's Global Development Alliance. Niger and Malawi have begun local production of Plumpy'Nut and in Malawi, the government has expanded CTC to include RUTF for malnourished patients receiving ART. Similar alliances are being developed in the Democratic Republic of Congo, Ethiopia,

Micronutrients/Management of Severe Malnutrition Research Strategy 2006-2010

Strategy Themes	Areas of Research and Introduction
Vitamin A – Deficiency Prevention and Control	Establish effectiveness of newborn dosing in Asia to reduce infant mortality and delivery approaches in an effective and cost-effective manner
	Establish effectiveness of maternal vitamin A supplementation in reducing maternal mortality
Zinc – Diarrhea Therapy and Prevention	Assess impact of inclusion of zinc into diarrhea treatment programs to reduce child morbidity and mortality
	Develop and support the implementation of effective use of zinc in diarrhea treatment programs
Iron – Anemia Prevention and Treatment Packages	WHO/UNICEF consultation on safe delivery of iron to deficient children in order to provide programmatic guidance to countries and to identify and undertake priority research as appropriate
	Establish best practices for the increased coverage and implementation of reproductive health packages which include anemia control and prevention
	Determine the constraints to anemia control and develop programmatic options to overcome them
Community Therapeutic Care	Implementation of developed and accepted WHO guidelines for community therapeutic care and home-based care in five countries
	Assess and identify suitable locations and institutions for local production of ready-to-use therapeutic foods (RUTFs)
	Test alternative formulations of RUTFs for cost and local effectiveness

Mozambique, and Sudan. USAID will work through the GDA with host governments of selected countries to identify suitable locations and institutions for local production of RUTF. Over the next five years, alternative formulations of RUFT will be tested for cost and effectiveness.

Key Partners in Micronutrient Research and Introduction are:

A2Z Project/Academy for Educational Development
Bill & Melinda Gates Foundation
FANTA/Academy for Educational Development
Host government ministries of health
ICDDR, B (Bangladesh)
Int'l Food Policy Research Institute/Harvest Plus
Johns Hopkins University/Global Research Activity
National Institutes of Health
POUZN/Academy for Educational Development and Abt Associates
Rational Pharmaceutical Management Plus/Management Sciences for Health
U.S. Pharmacopeia Drug Quality and Information
United Nations Foundation
United Nations Children's Fund
World Health Organization

Acute Respiratory Infections

Health Issue	Product	Projected FY 2006 Funding
Acute Respiratory Infections	Community-Based Treatment of Pneumonia	$550,000
	Reducing Exposure to Indoor Air Pollution	$100,000

Community-Based Treatment

Fast Facts

- Pneumonia is among the leading causes of childhood mortality in developing countries.
- There are 150 million cases of childhood pneumonia every year.
- Most cases of pneumonia can be treated with inexpensive, low-cost antibiotics.
- While an estimated 11 million to 20 million pneumonia cases (7 to 13 percent) are severe enough to require hospitalization, there is emerging evidence that severe pneumonia could be treated at the community level.
- As early symptoms are similar between malaria and pneumonia but drug treatments vary, research is needed on new strategies for diagnosis and treatment for both illnesses by CHWs.

Issues and Rationale

Pneumonia in children under 5 years of age is among the leading cause of childhood mortality, and is responsible for an estimated 1.9 million annual deaths in this age group. Fortunately, most childhood cases of pneumonia are caused by bacterial infections – mostly *Streptococcus pneumoniae* and *Haemophilus influenzae* – that can be treated with effective and inexpensive oral antibiotics. If pneumonia is not treated at an early stage, it can progress to more severe disease and death, particularly in malnourished or undernourished children.

The standard of care for pneumonia in developing countries is to provide diagnostic and curative services through health centers operated by ministries of health and NGOs. Owing to lack of transport to these facilities, inadequate supplies or equipment, or limited health care personnel, children in resource-poor areas often do not receive timely or adequate care from health facilities. These factors may result in significant delays in care for childhood pneumonia and contribute to preventable deaths. In addition, parents may seek care from poorly trained or untrained members of their community. When prescribed by such individuals, antibiotics may be of unknown quality or incorrect dose or duration, thus increasing the risk of treatment failure and the development of antibiotic resistance to existing effective low-cost drugs.

To address these shortcomings in facility-based or informal sector care of childhood pneumonia, USAID, in conjunction with WHO, UNICEF, select host governments, and others, has promoted the enhanced training and support of CHWs to provide early and appropriate care for children with pneumonia. A recent meta-analysis of research assessing the use of CHWs to treat nonsevere pneumonia in Bangladesh, India, Nepal, Pakistan, the Philippines, and Tanzania has concluded that this is an effective approach. Across these varied country contexts, the use of CHWs resulted in a 26 percent reduction in child mortality and a 37 percent reduction in pneumonia-specific mortality.[4] These studies demonstrate that CHWs can be trained to reliably diagnose and treat childhood pneumonia with antibiotics in the community and can appropriately refer children with severe pneumonia where referral is possible. Most of these studies were in settings, such as in Nepal, with very poor access to effective and reliable care at first-level health facilities. Building on evidence from initial studies, the USAID-funded Nepal program was able to demonstrate that community-based treatment in the program setting was both feasible and effective. This has provided the evidence to support a substantial scale-up of community-based management of pneumonia in a number of countries, including Nepal and Pakistan.

In addition to nonsevere pneumonia, an estimated 11 to 20 million (7 to 13 percent) pneumonia cases currently

[4] Sazawal S, Black RE; Pneumonia Case Management Trials Group. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infect Dis. 2003;3:547-56

require hospitalization.[5] Where access to quality health care facilities is lacking, there is currently no globally endorsed approach to treat children with severe pneumonia. Results from a USAID-supported multicountry research study suggests that the main rationale for facility-based treatment of children with severe pneumonia – i.e., the use of injectable antibiotics – may not be necessary, and that oral medication is equally as effective. This suggests that a larger and substantially sicker proportion of children with pneumonia could also be treated in the community by community-based health workers.

In malaria-endemic areas the clinical manifestations of pneumonia and malaria may be difficult to distinguish. The signs and symptoms of childhood malaria may overlap the pneumonia case definition (cough or difficulty breathing, and fast breathing or chest indrawing), and almost all children meeting a pneumonia case definition will have the cardinal sign of malaria or fever. Specific antimalarial treatment alone in an incorrectly diagnosed case of malaria may result in death from pneumonia. Conversely, antibacterial medication (ineffective against malaria) given for a presumptive case of pneumonia will not affect the course of malaria and may, likewise, result in death.

Strategy

While USAID endorses a three-tiered UNICEF/WHO strategy to expand access to quality care (namely, improving quality of care at community health centers, improving quality of care in the private sector, and increasing access to care through community-based care), the focus of USAID's research investment is on expanding community-based care strategies in developing countries that will reach poor children living beyond good access to care. Strategic approaches include:

- Studies to demonstrate the feasibility of community treatment of nonsevere and severe pneumonia
- Studies to improve joint treatment of malaria and pneumonia in light of the planned introduction by many countries of a new generation of antimalarial drugs (ACTs), which will require the development of new delivery strategies

Demonstration Studies for Nonsevere Pneumonia

USAID is providing assistance to host governments where commitment, permissive policies, and specific program supports are favorable for the introduction of community-based treatment models, and where the needs, in terms of low access to appropriate care and high mortality burden due to pneumonia, are greatest. These operational studies are undertaken at the request of host governments when such a study would be needed to facilitate a change in national policy by demonstrating the feasibility of this strategy prior to the host government implementing the strategy at scale.

Community Treatment of Severe Pneumonia

If proven effective, the potential benefits of oral therapy for severe pneumonia administered at home would be to:

- Reduce mortality by limiting the progression to very severe pneumonia/disease
- Reduce the risk of needle-associated complications such as needle-borne infections
- Minimize the need for referral or hospitalization
- Reduce the pressures on inpatient services
- Decrease the cost of delivering treatment
- Reduce transport, food, and lost income costs for the family

The ongoing research in this area supported by USAID will provide the evidence necessary for policymakers to change the global recommendation to community-based management of severe pneumonia. Building upon previous USAID-supported research that suggests combined antibiotic and zinc treatment of severe pneumonia would reduce the severity and duration of illness, the Agency is also supporting a small replication study to confirm the adjuvant use of zinc.

Joint Treatment of Malaria and Pneumonia

In areas where malaria and pneumonia are major causes of childhood mortality and cannot be easily distinguished, the combined treatment of both diseases and the use of community-based health workers to expand access to care may provide far greater coverage of these two most lethal childhood diseases. The persistently high child mortality rate for malaria and pneumonia make these USAID-supported applied research projects a high

[5] Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H. Global estimate of the incidence of clinical pneumonia among children under 5 years of age. Bull WHO 2004: 82: 891-970.

priority for improving child survival. Results of this research are needed to inform decisions by host governments, which need to determine how a new generation of antimalarial drugs could be best deployed in conjunction with antibiotics to treat malaria and pneumonia at the community level.

Reducing Exposure to Indoor Air Pollution

Fast Fact

- The impact of small particles from indoor air pollution on child health has emerged as a primary area of concern, with risks of pneumonia two to three times as high for exposed vs unexposed children.

Issues and Rationale

More than 3 billion people worldwide depend on solid fuels, including biomass fuels (wood, animal dung, agricultural residues) and coal, for their household energy needs. Cooking and heating with solid fuels on open fires or traditional stoves results in high levels of indoor air pollution, which contains a number of health-damaging pollutants, resulting in exposures that far exceed WHO guidelines.

According to the *World Health Report 2002*, indoor air pollution is responsible for 2.7 percent of the global burden of disease, including an estimated 1.6 million premature deaths annually, primarily among women and children. One estimate suggests that in India alone indoor air pollution is responsible for as many as 500,000 premature deaths each year. For child health, the impact of small particles from indoor air pollution on the incidence and severity of pneumonia has emerged as a primary area of concern, with risks of pneumonia two to three times as high for exposed vs unexposed children. Nevertheless, the evidence for the health benefits of specific interventions to reduce indoor air pollution, such as improved stoves, is limited.

Key research issues to be addressed in developing programmatic, scaleable approaches to reducing the impact of indoor air pollution on health include:

- Understanding whether known interventions (e.g., improved stoves) will reduce disease burden
- Determining the most effective implementation strategies for interventions that are efficacious

Strategy

USAID is collaborating with several partners to address three areas related to the reduction of indoor air pollution:

- Determining what factors lead to the most effective adoption of appropriate improved stoves and other technologies
- Determining what approaches motivate improved behaviors to reduce exposure to indoor air pollution
- Determining the reduction in air pollution exposure and associated health impacts resulting from the adoption of improved technologies and behaviors

USAID supports WHO in providing technical assistance to an intervention study in the rural highlands of western Guatemala, led by a team from the University del Valle (Guatemala City), University of California at Berkeley, and University of Liverpool (U.K.) and funded by the National Institutes of Environmental Health Sciences. This randomized controlled trial directly measures the change in the incidence of acute lower respiratory infections in young children after the introduction of improved stoves. USAID is also supporting WHO in compiling the evidence on the association of indoor air pollution with low birthweight, increasing vulnerability to disease and infant and child mortality.

To develop practical intervention strategies at the field level, USAID contributes to a collaborative effort engaging both health and energy sector experience, with trials under way in three countries. In Kenya, USAID is supporting social marketing approaches for the adoption of smoke-reducing devices produced by two women's cooperatives. In Peru, a USAID-supported intervention is designed to reduce indoor air pollution in a typical high-Andean district, Inkawasi, in the department of Lambayeque, through access to improved technologies and information on healthy practices. The activity focuses on working with rural microentrepreneurs, including stove builders and ceramic artisans, to commercialize household energy technologies. In Bangladesh, USAID is working with two NGOs that have experience with behavior change communication in health and participatory implementation of improved cookstove programs, respectively.

Ultimately, program success will be measured by sustained changes in behavior, including adoption of improved stove technologies, use of higher quality fuels, improved household ventilation, and other approaches

Acute Respiratory Infections Research Strategy 2006-2010

Strategy Themes	Areas of Research and Introduction
Community Treatment of Nonsevere Pneumonia →	Conduct demonstration studies in selected countries
Community Treatment of Severe Pneumonia →	Effectiveness studies of outpatient and CHW treatment of severe pneumonia
Joint Treatment of Malaria and Pneumonia →	Effectiveness studies of antibiotics and ACT
Reduction of Indoor Air Pollution →	Determine what factors lead to the most effective adoption of appropriate improved stoves and other technologies Determine what approaches motivate improved behaviors to reduce exposure Determine the reduction in exposure and associated health impacts resulting from the adoption of improved technologies and behaviors

to reduce exposure. This approach explicitly recognizes the need for cross-sectoral collaboration to improve household energy-related health impacts. Various factors, such as access to clean energy technologies, household socioeconomic status, existing health threats and services, cultural practices and biases, and subsidies and market forces, all play a role in influencing indoor air quality and, consequently, health. With USAID support, WHO is providing organizations implementing household energy projects and programs with the tools to evaluate multiple impacts of interventions, including not only health but other outcomes, such as time savings. A cost-benefit analysis of different interventions is nearing completion; a review of different technologies and programmatic approaches is expected to become available by the end of 2007.

USAID expects the results from the Kenya, Peru, and Bangladesh programs to be available by the end of calendar year 2006 or early in 2007, and data analysis from the completed field activities in the Guatemala field trial is under way. It is anticipated that within one to two years, this current area of inquiry should be well positioned for scale-up of proven interventions.

Key Partners in Acute Respiratory Infections Research are:

Boston University
Johns Hopkins University
National Institutes of Environmental Health Sciences
Nongovernmental organizations
Select host governments
United Nations Children's Fund
University del Valle (Guatemala City)
University of California at Berkeley
University of Liverpool (U.K.)
World Health Organization

Health Systems

Health Issue	Product	Projected FY 2006 Funding
Health Systems	Performance Assessment and Financing	$380,000
	Pharmaceutical Management	$125,000
	Quality Assurance	$325,000

Issues and Rationale

Health systems research identifies problems and finds and tests solutions to improve the delivery and accessibility of products and approaches to tackling the main diseases and health issues facing developing countries. Some of this research is carried out within specific programs such as in maternal and neonatal health and nutrition programs. In addition, USAID has a more system-wide program of research that addresses overarching problems such as resource and budget tracking, health insurance and other coverage approaches, drug and pharmaceutical management, and quality of services.

Strategy

USAID's global research agenda studies how to better finance services, manage pharmaceutical quality and availability, and apply quality assurance methods. Over the next five years, USAID plans research activities to develop and apply a few high-priority tools to strengthen health systems and remove key barriers to access.

Performance Assessment and Financing

In partnership with WHO and the World Bank, USAID has developed and introduced a low-cost country-led approach to producing health expenditure data in a country, including both the public and private sectors. This approach, known as national health accounts (NHAs), has been applied in more than 65 developing countries. It creates accurate and comprehensive health funding data to guide host country and donor investments in the health sector. The current research challenge is to improve estimates of household expenditures, to track HIV-specific expenditures, and assess the potential use of NHAs in benchmarking health system performance. USAID is developing a standard methodological tool to assess host-country health system capacity. This tool will help host countries identify priority health interventions to enhance health system performance,

Disadvantaged and marginalized populations often face barriers to obtaining quality health care because they cannot afford user fees and associated out-of-pocket costs of obtaining services. Ongoing research studies are testing different financing options for these populations including: community-based health insurance, social insurance, *caisses maternelles*, targeted government subsidies, and tax-financed free services. These options must have the potential to be sustainable and ensure that people are not prevented from essential treatment and care.

Pharmaceutical Management

USAID has been a global leader in studying and setting up effective pharmaceutical management approaches, including the following:

Drug and Therapeutic Committees are considered a key intervention in the WHO global strategy to ensure drug quality and contain antimicrobial resistance in health care settings. The presence of these committees in a health program provides a valuable platform to establish cost-effective drug selection and address medication use problems, in particular those that contribute to the development of antimicrobial drug resistance.

The Pharmaceutical Monitoring-Training-Planning approach offers a training and implementation modality that places tools and responsibility for pharmaceutical management in the hands of local staff. Monitoring, traning, and planning sessions are conducted within the trainee's place of work or local environment.

Standard Operating Procedures are necessary to ensure continuity of practices in public sector facilities in the face of organizational changes, high turnover of the most qualified personnel who are often siphoned off to work for the private sector, and generally poor staff preparation and training. USAID is developing and implementing standards procedures as part of a national effort to strengthen pharmaceutical services and laboratory management in selected provincial general hospitals and other high-volume sites in Kenya, South Africa,

Table 4 USAID-Supported Quality Assurance Improvement Collaboratives Active During 2005

Country	Topic	Scale
Benin	Essential obstetric care	28 facilities in two of 34 health districts (100%)
Ecuador	Essential obstetric care	42% of 168 health districts
Eritrea	Essential obstetric care	17 health facilities in one of 6 health zones (50%)
Eritrea	Pediatric hospital care	20 hospitals (100%)
Honduras	Essential obstetric care	52 facilities in five of 20 districts (100%)
Malawi	Pediatric hospital care	26% of health districts
Nicaragua	Essential obstetric care	80% of health districts
Nicaragua	Pediatric hospital care	13 hospitals (62%)
Niger	Pediatric hospital care	11 national/regional (85%); 21 district hospitals (64%)
Russia	HIV/AIDS care/support	70 facilities serving 1.8 million in four *oblasts*
Rwanda	Prevention of mother-to-child HIV transmission	36 facilities in all 12 provinces
Rwanda	Malaria treatment	23 facilities in four of 39 districts
Rwanda	ART for HIV/AIDS	30 facilities in all 12 provinces, including 100% of ART facilities in 2004
South Africa	AIDS counseling, treatment, and support	154 facilities in four provinces
Tanzania	Family planning	15 facilities in one of 25 regions (100%)
Tanzania	Pediatric HIV/AIDS hospital care	8 hospitals in four of 25 regions (100%)
Uganda	ART for HIV/AIDS	56 facilities in all 56 districts

Ethiopia, Zambia, and Namibia, as well as to support procurements under the Global Fund to Fights AIDS, Tuberculosis and Malaria.

Quality Assurance

USAID is adapting and testing quality improvement approaches in developing country settings. The experience of the U.S. health system has shown that quality improvement approaches improve the cost-effectiveness and client use of health services. Evaluations of USAID host country health systems consistently show deficiencies in the way providers deliver services, such as not following evidence-based clinical guidelines, failure to meet the needs of the patient as a person, and organization of care that wastes resources.

USAID's improvement collaborative organizes providers from a number of facilities to work together to improve a specific area of health care. USAID is the leading donor in adapting this approach to the needs of developing countries, with 17 collaboratives in 12 countries in 2005 (see table 4). USAID has the only research program designed to support the adaptation process. This program documents how collaboratives work, evaluates performance, and tests design modifications. The program addresses the major objective of collaboratives – producing measurable improvements in health services – and the spread of those improvements through the health system. USAID-supported research also explores the effectiveness of other quality enhancement approaches such as job aids.

For the past three years, USAID has adapted this quality improvement methodology for use in low- and medium-income countries. Collaboratives have produced measurable improvements in a growing range of health issues. The methodology's focus on spreading best practices through a peer-to-peer network also provides a new, low-cost strategy for scaling up.

Key Partners in Health Systems Research and Implementation are:

Canadian International Development Agency
Department of Health and Human Services
Global Alliance for Vaccines and Immunizations
Global Fund to Fight AIDS, Tuberculosis and Malaria
President's Emergency Plan for AIDS Relief
Swedish International Development Cooperation Agency
United Nations Children's Fund
U.K. Department for International Development
World Bank
World Health Organization

Addendum 1 FY 2006 Projected Core Funding for Targeted Health Issue Strategies

Health Issue	Product	Projected FY 2006 Funding	
HIV/AIDS	Vaccines	$29,000,000	$68,600,000
	Microbicides	$39,600,000	
Malaria	Vaccines	$6,200,000	$10,000,000
	New Drugs, Formulations, and Approaches	$3,800,000	
Tuberculosis	New Drugs	$2,300,000	$3,700,000
	Improving Performance of and Access to DOTS	$1,400,000	
Reproductive Health	Contraceptive Technologies	$10,500,000	$24,500,000
	Improved Use and Service Delivery	$14,000,000	
Maternal and Newborn Health	Healthy Pregnancy and Birth Care Outcomes	$1,985,000	$7,310,000
	Maternal Mortality Measurement Tools	$0**	
	New Pregnancy and Birth Interventions and Introduction	$3,725,000	
	Neonatal Research and Newborn Care Practices	$1,600,000	
Micronutrient Deficiencies	Vitamin A Deficiency Prevention and Control	$700,000	$3,784,000
	Zinc – Diarrhea Therapy and Prevention	$884,000	
	Iron – Anemia Prevention/Rx Packages	$1,100,000	
	Community Therapeutic Care – Emergencies	$1,100,000	
Acute Respiratory Infections	Community-Based Pneumonia Treatment	$550,000	$650,000
	Reducing Exposure to Indoor Air Pollution	$100,000	
Health Systems	Performance Assessment and Financing	$380,000	$830,000
	Pharmaceutical Management	$125,000	
	Quality Assurance	$325,000	
	FY 2006 FUNDING*		$119,374,000

* This report highlights approximately 80 percent of the total health-related research at USAID in FY 2006.

** FY 2006 activities are based on prior-year investments. Future activities have been proposed for FY 2007 funding and beyond.

Source: USAID

Addendum 2 Key USAID Global Health Research and Introduction Partners

A2Z Project/Academy for Educational Development
Abt Associates
ACCESS
Aeras
BASICS
Becton, Dickinson and Company
Bill & Melinda Gates Foundation
Boston University
Centers for Disease Control and Prevention
CONRAD
Crucell
U.S. Military HIV Research Program
Department of Health and Human Services
EngenderHealth
European Commission
Extending Service Delivery
Family Health International
FANTA/Academy for Educational Development
Food and Drug Administration
Foundation for Innovative New Diagnostics
Georgetown Institute for Reproductive Health
Global Alliance for TB Drug Development
Gobal Alliance for Improved Nutrition
Global Campaign for Microbicides
Global Fund to Fight AIDS, Tuberculosis and Malaria
Global HIV/AIDS Vaccine Enterprise
Host governments/Ministries of health
ICDDR,B (Bangladesh)
International AIDS Vaccine Initiative
International Confederation of Midwives
International Federation of Obstetricians and Gynecologists
International Food Policy Research Institute/Harvest Plus
International Partnership for Microbicides
International Union Against TB and Lung Disease
International Working Group on Microbicides
Johns Hopkins University
National Institutes of Health
Office of the U.S. Global AIDS Coordinator
ORC/Macro
PATH
Pfizer
Population Council
POUZN/Academy for Educational Development and Abt Associates
President's Emergency Plan for AIDS Relief
Rational Pharmaceutical Management Plus/ Management Sciences for Health
Saving Newborn Lives/Save the Children
Schering-Plough
Stop TB Partnership Working Groups
Synergy Project
The Futures Group
U.K. Department for International Development
UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
United Nations Children's Fund
United Nations Foundation
University del Valle (Guatemala City)
University of Aberdeen (Scotland)
University of Alabama
University of California at Berkeley
University of Liverpool (U.K.)
University Research Corporation
U.S. Pharmacopeia Drug Quality and Information
Wellcome Trust
World Health Organization
Wyeth

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