NIAID GLOBAL HEALTH RESEARCH PLAN FOR HIV/AIDS, MALARIA, AND TUBERCULOSIS

May 7, 2001

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
NATIONAL INSTITUTES OF HEALTH
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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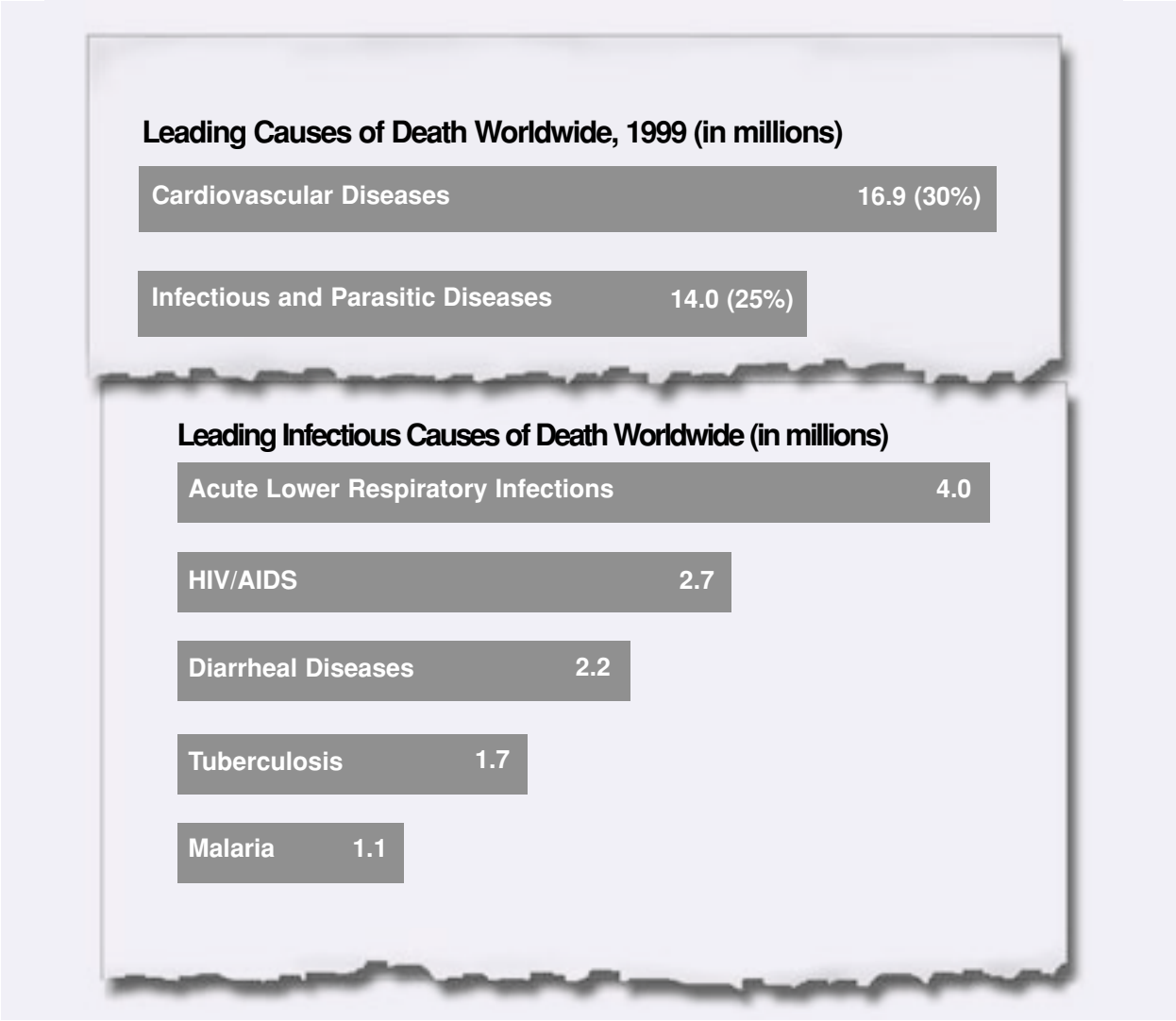
The World Health Organization (WHO) estimates that 1,500 people die each hour from an infectious disease. Half of these deaths occur in children under 5 years of age, and most of the remaining deaths are in working adults who frequently are breadwinners and parents. Every year, newly identified infectious diseases are added to the burden of known infectious conditions.

To an unprecedented extent, issues related to infectious diseases in the context of global health are now on the agendas of national leaders, health policymakers, and philanthropic organizations. This new attention to the globalization of health problems and their relevance to the United States was underscored in the eyes of the American public as a result of the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic.

Research advances, funded through extraordinary investment in biomedical research at the National Institutes of Health (NIH), have resulted in effective treatments and a striking decrease in the AIDS-related death rate in the United States. However, the toll in suffering and death in developing nations remains enormous and dwarfs the epidemic in the United States. HIV/AIDS has evolved into a global health catastrophe. Every day, 14,500 people become infected. In some African countries, between 25 and 35 percent of the adult population is infected. The life expectancy in several African countries has decreased dramatically and has negated gains made during the past few decades.

In drawing attention to global health, HIV/AIDS has also brought greater attention to the impact that diseases such as malaria and tuberculosis (TB) have had in developing countries for decades. Among infectious diseases causing death worldwide, HIV/AIDS, malaria, and TB account for more than 5 million deaths each year (World Health Report 2000).* In some countries in sub-Saharan Africa, HIV/AIDS, malaria, and TB account for more than half of all deaths. The AIDS pandemic and the resurgence of malaria and TB are impeding the health, economic development, and political stability of many of the world's poorest and most vulnerable countries.



* The World Health Organization. *The World Health Report 2000—Health Systems: Improving Performance.* Geneva, 2000.

In the past year, global health problems have been recognized as important destabilizing threats to the world. In January 2000, the Security Council of the United Nations designated HIV/AIDS a threat to national security and peace in Africa—the first time that body, normally concerned with issues of war and peace, had devoted an entire session to a health issue. In July 2000, the Group of Eight Nations (G8) pledged to work toward improving health worldwide and focused on the need to reduce the burden of disease for HIV/AIDS, malaria, and TB.

Interest in global health has also led to increasing levels of financial investment in biomedical research and health care delivery. In the past year, philanthropic organizations have begun investing billions of dollars to assist developing countries in improving health. Together with technical advances, such as the sequencing of human and microbial genomes and advances in functional genomics, these investments will provide extraordinary opportunities for infectious disease research in the 21st century.

To capitalize on these opportunities, the National Institute of Allergy and Infectious Diseases (NIAID) has created a Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis, which outlines the Institute's goals and plans for fighting infectious diseases by building sustained research capability domestically and internationally and enhancing international partnerships. This plan will augment NIAID's longstanding commitment in global health research and will help to ensure that NIAID-supported activities are conducted within the broadest research framework.

The plan provides a long-term strategy for supporting research that will lead to prevention and treatment strategies that are effective, feasible, and realistic for individual countries struggling with the burden of numerous infectious diseases.

The plan also outlines NIAID's short-term, intermediate, and long-term goals for addressing the challenges put forth by the G8 nations in July 2000 and for strengthening the Institute's role in collaborative international research. In addition, the plan is directed toward coordinating research activities and resources among HIV, malaria, and TB so that feasible measures for fighting all three infectious diseases can be implemented within individual countries.

The AIDS pandemic and the resurgence of malaria and tuberculosis are impeding the health, economic development, and political stability of many of the world's poorest and most vulnerable countries.

By working with partners in endemic countries, NIAID broadens the input of local communities in the design, implementation, and conduct of clinical research so that in-country research capability and capacity are enhanced. Such partnerships ensure that the research will lead to findings that are ultimately feasible and meaningful for impacted communities.

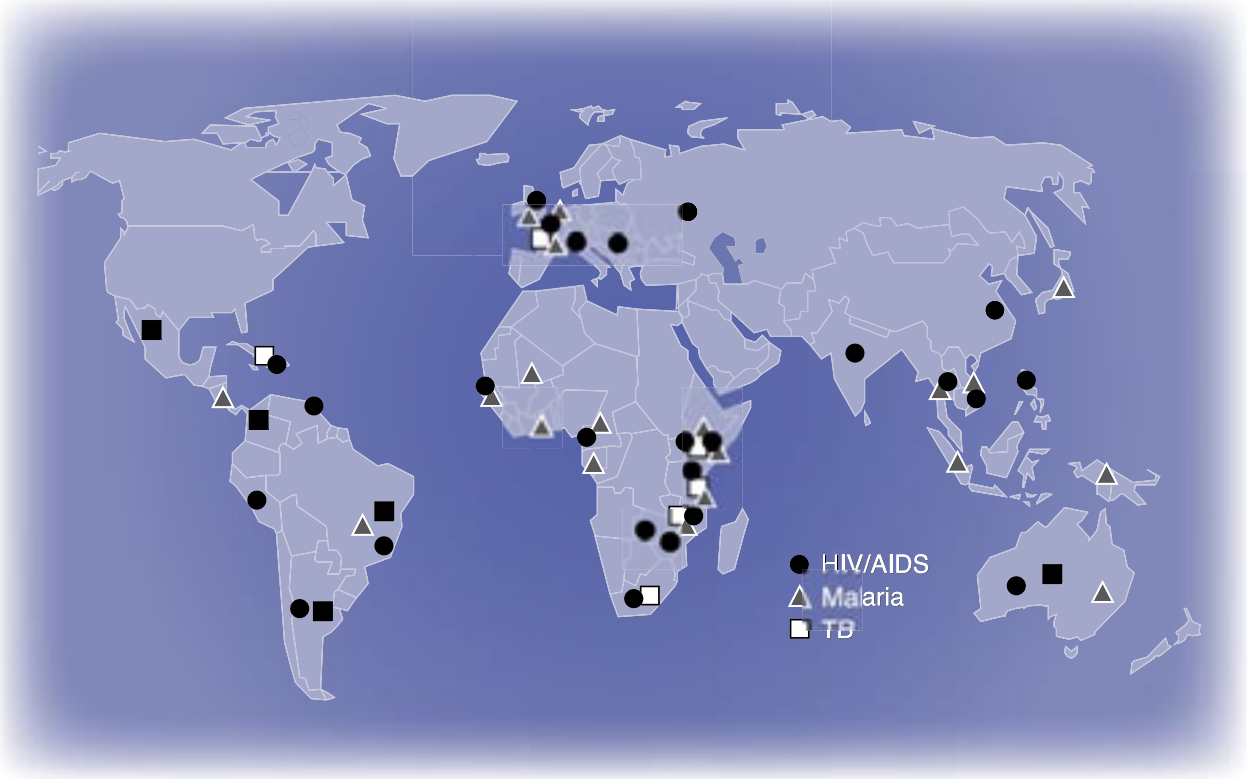
Guiding Principles for NIAID Global Health Research

- Target research efforts to develop prevention and therapeutic strategies adapted for the unique needs of developing countries;
- Develop multidisciplinary research programs on AIDS, malaria, and TB in developing countries;
- Build and sustain research capacity in-country;
- Stimulate scientific collaboration and global, multisector partnerships; and
- Work with in-country scientists to develop training, and communication and outreach programs.

G8 Goals

- Reduce the number of HIV/AIDS-infected young people by 25 percent by 2010 (U.N. Secretary-General Report to the General Assembly on March 27, 2000).
- Reduce the burden of disease associated with malaria by 50 percent by 2010 (WHO Roll Back Malaria).
- Reduce TB deaths and prevalence of the disease by 50 percent by 2010 (WHO Stop TB Initiative).

NIAID International Projects in HIV/AIDS, Malaria, and Tuberculosis



For more than 50 years, NIAID has maintained a longstanding commitment to conduct and support research on infectious diseases with the goal of improving global health. NIAID-supported research on malaria in Mali, pneumococcal disease in the Gambia, tropical diseases in NIAID-sponsored International Centers for Tropical Disease Research (ICTDR), and HIV prevention through the NIAID HIV Vaccine and Prevention Trials Network has demonstrated that effective international research involves coordinated partnerships with local governments and other agencies and organizations. Moreover, these research networks have shown that scientists in developing countries can be effective collaborators within a global network.

Technical advances, such as the sequencing of human and microbial genomes and advances in functional genomics, will provide extraordinary opportunities for infectious disease research in the 21st century.

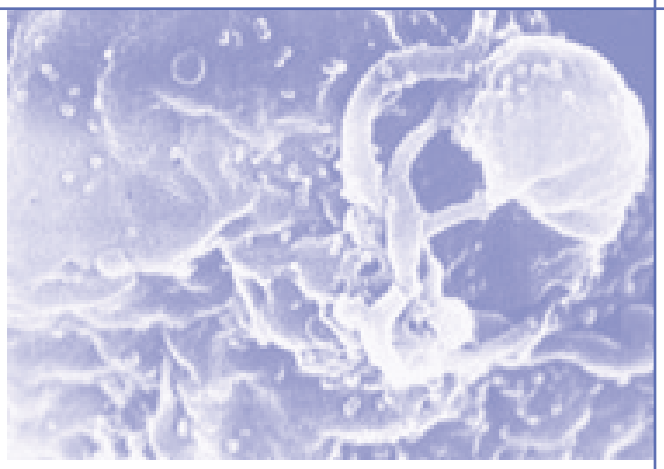
The Disease

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). Infection with the virus leads to destruction of a person's immune system, making the victim highly susceptible to multiple infections and certain cancers. AIDS is a fatal disorder, and a vaccine is not available.

Worldwide Incidence

- As of the end of 2000, 36.1 million people were living with HIV/AIDS, including 1.4 million children younger than 15 years.
- About 5 young people aged 15 to 24 become infected with HIV every minute.
- More than 21 million people have died from AIDS, including 4.3 million children.
- Ninety-five percent of worldwide AIDS cases occur in developing countries, with nearly 70 percent of all cases occurring in sub-Saharan Africa.
- Over 80 percent of global HIV infections result from heterosexual intercourse.
- Mother-to-child (vertical) transmission has accounted for more than 90 percent of all HIV infections worldwide in infants and children.

NIAID Global Health Plan for HIV/AIDS



Since HIV was first identified in 1983, enormous progress has been made in understanding how the virus attacks the immune system to cause disease and how to intervene therapeutically. NIAID-supported scientists have led much of this progress. New techniques have enabled researchers to detect HIV in blood and tissue, and new therapies have achieved excellent results in suppressing the virus and delaying disease progression and death. NIAID-funded researchers have also made great strides in reducing mother-to-infant transmission of HIV. In the area of prevention research, a variety of vaccines have been evaluated, and efforts are under way to increase the number of new vaccine and microbicide candidates that can be tested.

Despite this progress, AIDS continues to expand rapidly in developing nations, home to more than 95 percent of all HIV-infected people. AIDS is the leading cause of death in Africa and the fourth leading cause of death in the world. In some countries, the prevalence of HIV infection among adults has grown as high as 35 percent, with life expectancy decreasing by 20 years. Current estimates indicate that 600,000 children were newly infected in the year 2000.

The International AIDS Conference in Durban, South Africa (July 2000), highlighted the disparities in HIV treatment and care worldwide and marked a significant change in attitude by researchers and world leaders regarding access to treatment and prevention. Most recently, the G8 leaders pledged to work together to combat HIV disease, uniting behind the goal to reduce, by 25 percent, the number of HIV/AIDS-infected young people by the year 2010.

NIAID has developed a global HIV/AIDS research agenda with the goal of helping the foundation and providing the knowledge and resource base for the development of effective treatment and prevention strategies in developing countries. The NIAID global health plan will build upon the Institute's longstanding commitment to international infectious disease research, to expand basic and clinical research capacity; enhance partnerships for public health; and foster the training, outreach, and education efforts needed to establish and maintain in-country research capability to address scientific and public health questions facing countries hit hardest by the HIV/AIDS epidemic.

HIV Vaccine Research

The discovery and development of a vaccine that protects against HIV infection is one of the highest priorities of the NIAID HIV/AIDS research program. A great challenge of vaccine research is the need for contributions from a variety of scientific disciplines (e.g., basic science, empirical animal testing, epidemiology, human

trials) to develop efficacious vaccines. NIAID's comprehensive vaccine research program has led to a number of significant scientific advances. NIAID-supported researchers have made substantial contributions in elucidating the structure of HIV, understanding the role of the immune system in controlling HIV, improving vaccine antigenicity, and developing new and better animal models for testing candidate vaccines. To accelerate identification of effective vaccine candidates, future studies will need to address the significance of latently infected cells, immune responses induced by current vaccine candidates, and the impact of HIV and human leukocyte antigen (HLA) diversity.

Because the vast majority of new HIV infections are occurring in the developing world, it is imperative that HIV vaccine research address the unique aspects of HIV natural history and pathogenesis (e.g., incidence, modes of transmission, host and virus diversity) in endemic regions and populations. A key component of NIAID's global health plan is to support prevention and therapeutic research of relevance to host countries, while strengthening the foundation of clinical and laboratory knowledge, resources, and capability, to enable participation in international vaccine and prevention efficacy trials and to help identify practical diagnostic and therapeutic interventions that can be widely utilized in local settings.

NIAID Goals

Short-term

- Determine optimal vaccine design and strategies.
- Establish comprehensive capacity to conduct international vaccine trials.

Mid-term

- Evaluate the safety, immunogenicity, and clinical efficacy of HIV vaccines in endemic regions.
- Identify effective vaccines by determining which vaccine-induced immune responses predict effectiveness.

Long-term

- Determine how effective vaccines can be delivered in high-risk endemic populations.
- Maintain capacity to sustain a comprehensive, long-term HIV vaccine research program that can respond to changes in the epidemic and address vaccine research questions of relevance to patients in endemic regions.

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Non-Vaccine HIV Prevention Research

The AIDS epidemic continues to take its toll worldwide, despite major advances in understanding the pathogenesis and treatment of HIV infection. Even in the presence of an effective vaccine, control of the epidemic will probably require a combination of prevention strategies to protect against HIV infection. Methods to interrupt mother-to-child transmission (MTCT) of HIV, topical microbicides, antiretroviral therapy (ART) to reduce the infectiousness of "carriers," treatment of sexually transmitted diseases (STDs), and behavioral interventions to reduce high-risk behaviors will need to be evaluated in the context of the varied host, gender, extrinsic, and viral factors that affect HIV transmission.

MTCT of HIV, either at birth or through breastfeeding, accounts for more than 90 percent of all HIV infections in infants and children worldwide. Research is needed to develop and implement biomedical strategies to interrupt MTCT of HIV in developing countries, and in breastfeeding and non-breastfeeding populations, using interventions that are widely affordable, accessible, and practical in those populations.

Research is also needed to develop acceptable strategies to inhibit transmission of HIV through exposure to HIV-containing blood, tissue, and other fluids. There is an urgent need for female-controlled methods, such as topical microbicides that would offer protection against HIV infection and other STDs. If proved to be effective vaginally, these products could also be applied rectally and could be used by HIV-positive and -negative persons. ART can lower the concentration of HIV in blood and genital secretions, but it is unknown whether ART can prevent transmission of HIV and, if so, whether ART represents an acceptable and practical means of HIV prevention in many endemic regions.

Finally, it is essential to develop and evaluate effective social and behavioral interventions to prevent HIV transmission by reducing risk behaviors and increasing protective behaviors. It is crucial that research addresses the risks in specific social and cultural contexts and evaluates strategies to prevent or minimize the negative physical, cognitive, and social consequences of HIV/AIDS, including stigmatization of persons with or at risk for HIV infection.

NIAID Goals

Short-term

- Establish capacity to conduct a broad range of international HIV prevention trials.
- Develop new biomedical and behavioral prevention strategies for clinical testing.

- Determine the feasibility of implementing successful strategies for preventing MTCT of HIV.
- Establish proof-of-concept for HIV topical microbicides.

Mid-term

- Evaluate the clinical efficacy of prevention approaches (e.g., treatment of STDs, ART, behavioral risk reduction).

Long-term

- Determine how best to implement successful HIV prevention measures in hardest-hit countries.
- Maintain capacity to sustain a comprehensive, long-term HIV prevention research program that can respond to changes in the epidemic and address prevention research questions of relevance to patients in endemic regions.

HIV Therapeutics Research

Since the recognition of AIDS in 1981, considerable progress has been made in understanding how HIV attacks the immune system to cause disease and how to intervene therapeutically. Researchers have developed new methods to detect and measure HIV in blood and tissue and to test for antiretroviral drug resistance. Therapeutic regimens using combinations of drugs (highly active antiretroviral therapy or HAART) have extended and improved the quality of life for many HIV-infected people in developed nations and have led to dramatic declines in AIDS-related deaths. However, AIDS has devastated parts of the developing world, and HAART is not available to most HIV-infected individuals in developing nations. These countries have neither the financial resources to provide the medications, nor the health care delivery infrastructure to ensure that treated patients are adequately monitored for toxicity, metabolic effects, and antiretroviral drug resistance. Research is needed to determine how best to deliver and monitor ART and to clinically manage the treatment of adults and children in resource-poor nations where HIV/AIDS hits hardest.

Prophylaxis and treatment for opportunistic infections is an important part of effective therapy and can dramatically reduce morbidity and mortality. Even these interventions are not available in many areas of the world. Furthermore, research is needed to determine the spectrum of opportunistic and co-infections in threatened populations and their impact on HIV infection and disease progression.

Worldwide, TB is now the leading cause of death in HIV-infected persons. HIV infection accelerates the course of TB, and in people with

...AIDS is decimating parts of the developing world, and HAART is not available to most HIV-infected individuals in developing nations.

HIV infection, TB infection hastens progression to AIDS. Research is needed to determine the incidence of TB infection and co-infection, improve diagnostic capability, and develop and deliver affordable and effective therapies to adults and children in developing countries.

NIAID Goals

Short-term

- Characterize the epidemic in developing countries to guide the design of therapeutic trials.
- Determine the feasibility of delivering sustainable antiretroviral and antimicrobial therapies to adults and children in developing countries.
- Establish comprehensive capacity to conduct international therapeutic efficacy trials.

Mid-term

- Evaluate the clinical efficacy of antiretroviral therapeutic interventions deemed feasible for sustained use in developing countries.
- Evaluate the clinical efficacy of prophylactic and therapeutic interventions for prevalent co-infections (e.g., TB, malaria, opportunistic infections).
- Enhance clinical, diagnostic, and research laboratory capacity to support the expanded delivery of antiretroviral and antimicrobial therapies in developing countries.

Long-term

- Maintain capacity to sustain a comprehensive, long-term therapeutics research program that can respond to changes in the epidemic and address therapeutics research questions of relevance to patients in developing countries.

Capacity Building, Training, Communications, and Outreach

Within the next few years, NIAID plans to sponsor several large, international prevention and vaccine efficacy trials. To ensure the success of these trials, baseline clinical research is needed to characterize the epidemic in participating regions and populations. The unique aspects of HIV natural history and pathogenesis may impact on the design and evaluation of preventive interventions and their translation into cost-effective public health measures. In addition, the implementation of effective therapeutic strategies will require partnerships coordinated with vaccine and prevention researchers.

The lack of affordable HIV therapy in many regions of the world may become an impediment to research on prevention efforts. Many countries are reluctant to embark on vaccine or other prevention research, when no treatments are available for those who are already or become infected.

NIAID will establish multidisciplinary research programs and infrastructure that will lay the foundation for the development of practical methods for prevention and treatment of HIV/AIDS in endemic countries. The goal of the Comprehensive International Program of Research on AIDS (CIPRA) is to provide long-term support for fundamental epidemiological, laboratory, and clinical studies on HIV/AIDS and concomitant infections and enhance in-country capability to conduct relevant and ethically sound public health research in local populations. The program will encourage partnerships among other agencies and foundations, industry, and government to help build and sustain research infrastructure in resource-constrained countries and to translate and implement research findings as public health practices.

NIAID Goals

Short-term

- Launch the Comprehensive International Program of Research on AIDS (CIPRA).
- Develop, in conjunction with the Fogarty International Center, training programs and research opportunities for scientists in endemic regions.
- Establish community advisory boards at sites identified for future infrastructure investment and research projects.

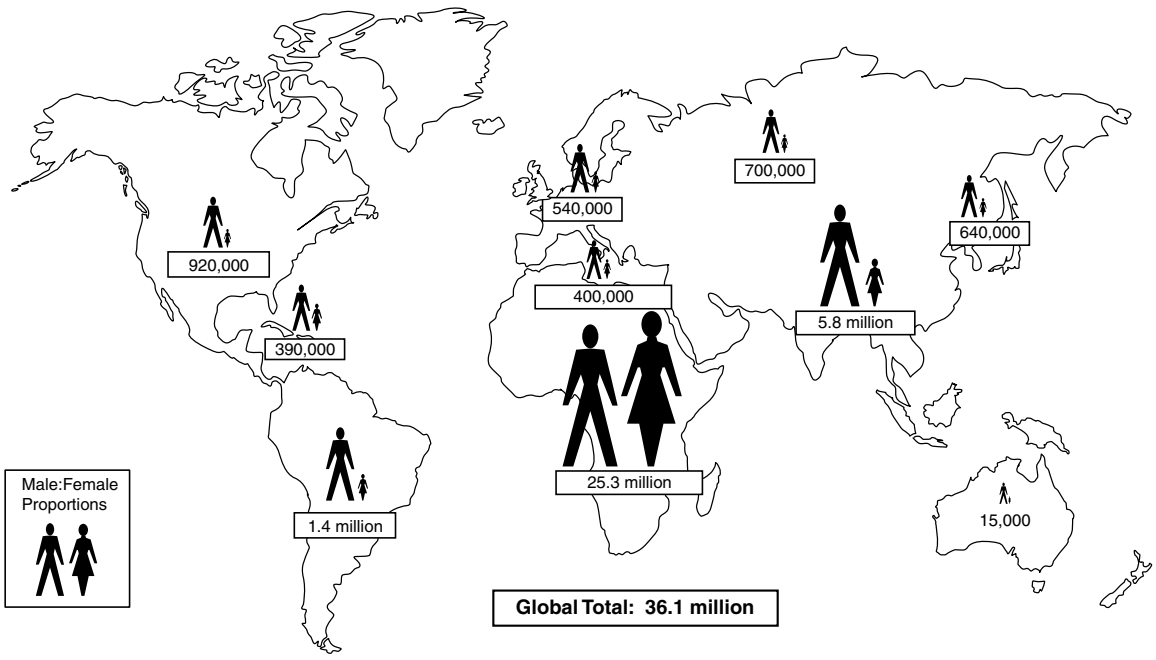
Mid-term

- Develop in-country scientific research capability and capacity to address a comprehensive HIV/AIDS research agenda through expansion of CIPRA.
- Educate communities and create supportive environments for the conduct of clinical trials.

Long-term

- Maintain partnerships and avenues of communication with in-country health care providers and public health officials to translate research findings into public health education.
- Maintain a strong and stable in-country scientific research community that can respond to changes in the epidemic and address research questions of relevance.

Estimated Number of Persons Living with HIV/AIDS, December, 2000



Source: UNAIDS, 12/2000

NIAID Implementation Plan for Global Research on HIV/AIDS

Research Focus	Initiative
Vaccine Research	
Basic Research and Development	HIV vaccine design research
	HIV preclinical vaccine development and production
	HIV Vaccine Trials Network—developing-country expansion (sites, infrastructure, trials), expanded delivery
Clinical Trials	Correlates of immune protection study linked to efficacy trials
	Additional clinical research
Non-Vaccine Prevention Research	
	HIV microbicide design research
	HIV microbicide development and production
	HIV Prevention Trials Network expansion (sites, infrastructure, trials)
Therapeutics Research	
Basic Research and Development	Expansion of preclinical drug development resources
	Feasibility studies for antiretrovirals and antimicrobials
Clinical Trials and Diagnostics	Efficacy trials for antiretrovirals and antimicrobials and expanded delivery
	Laboratory support for diagnostics, clinical trials, and expanded therapeutics delivery
Capacity Building, Training, Communications, and Outreach	
Capacity Building and Training	Comprehensive International Program of Research on AIDS (CIPRA); training programs
Communications and Outreach	Education and outreach related to all aspects of clinical trials support; international community advisory boards
	International Centers for Excellence in Research

The Disease

Malaria is caused by a single-celled parasite of the genus *Plasmodium* that is spread to humans by mosquitoes. Four different species cause the disease; however, *P. falciparum* is the most deadly. *Plasmodium* parasites infect the liver and red blood cells and can cause anemia and disorders of the liver, lungs, kidneys, and nervous system. The organism has a complex life cycle and passes through several stages as it travels through mosquitoes and its human host. No vaccine is available, and treatment is hampered by development of drug-resistant parasites and insecticide-resistant mosquitoes.

Worldwide Incidence

- 500 million cases and 1.5 to 3 million deaths are estimated to occur annually.
- Kills one child every 30 seconds; 3,000 children per day under age 5.
- Forty percent of the world's population is at risk of becoming infected.
- Global warming and other climatic events, such as El Niño, play a role in increasing spread of disease.
- "Airport malaria," or the importing of malaria by international travelers, is becoming more common; more than 12,000 cases of malaria were reported among European travelers in 2000.

NIAID Global Research Plan for Malaria

Malaria, a mosquito-borne disease caused by *Plasmodium* parasites, is a major global health concern. More than 40 percent of the world's population live in areas where they are at risk for malaria, and approximately 300 to 500 million people are infected annually. Malaria represents a threat to survival for millions of women and children; every 30 seconds a child dies from malaria. In addition, malaria is often cited as a substantial impediment to economic and social development in endemic regions. The threat posed by malaria is increasing as a result of the spread of drug-resistant parasite strains and insecticide-resistant mosquitoes, changing epidemiological and ecological patterns that alter the distribution of the disease and requirements for control, and limitations of the medical and public health infrastructure in many endemic areas.

In recognition of the urgency of this problem, WHO, the United Nations Development Program, United Nations Children's Education Fund, and the World Bank recently created the Roll Back Malaria (RBM) initiative, with the goal of reducing the global malaria burden 50 percent by 2010. While emphasizing the need for better implementation of currently available control tools (for example, improved access to treatment, wider use of available prevention methods), RBM acknowledges that new products are essential to this goal. RBM has thus called for a focused research effort to develop better tools for malaria control.

In 1997, an alliance of international research donors and scientists, collectively known as the Multilateral Initiative on Malaria (MIM), held a meeting in Dakar, Senegal, to discuss the scientific questions impeding development of better methods for combating malaria. NIAID was a founding member of the MIM and responded to the needs expressed at Dakar with increased funding for malaria research.

NIAID has developed a global malaria research agenda that will expand efforts on vaccine development while also augmenting support for the other cornerstones of malaria control—antimalarial drugs, diagnostics, and mosquito control methods. This plan aims to attract and retain new interest and expertise from industry as well as academia by providing sustained targeted funding in these key research areas. This research plan builds on opportunities presented by recent scientific and technologic advances, such as those in genomics research, to assure a robust pipeline of new ideas and approaches. In the spirit of Dakar, the plan is grounded in collaborative international research, with a strong emphasis on field-based programs and capability strengthening in endemic areas as the surest path to achieving appropriate and sustainable malaria control.

Malaria Vaccine Development

Despite widespread belief that vaccines could provide the most effective tools for malaria prevention and control, no licensed vaccine for malaria currently exists. Vaccines would be valuable not only for people living in endemic areas but also for travelers to such regions. In 1997, NIAID introduced its research agenda for malaria vaccine development, which aimed to support discovery and characterization of new vaccine candidates, production of pilot lots, and clinical evaluation of promising candidate vaccines.

Other organizations have also expanded efforts in vaccine development. Nonetheless, the global capability to address malaria remains woefully inadequate, and private sector interest is limited. Moreover, most existing efforts are directed toward vaccines for *P. falciparum,* the most deadly form of malaria, while research on *P. vivax*, the most widespread form that affects humans, has been de-emphasized because of lack of resources. In addition, more research on malaria immunology and pathogenesis is needed for the design of safe and effective vaccines.

NIAID Goals

Short-term

- Expand clinical research on the pathogenesis and pathophysiology of severe malaria (malarial anemia, cerebral malaria, and the effects of malaria in pregnancy), including exploration of the role of both human and parasite genetic factors.
- Expand partnerships with industry, particularly the biotechnology sector, and academic scientists to foster innovative approaches for discovery and design of malaria vaccines. These would include partnerships to use information coming from the *P. falciparum* genome-sequencing project.
- Augment capability for production and preclinical testing of pilot lots of malaria vaccines.
- Supplement capability for early phase clinical testing of vaccine candidates.
- Develop additional clinical research centers in Africa, Latin America, and Asia for future field-testing of new vaccines.

Mid-term

- Develop a robust and self-sustaining pipeline of promising vaccine candidates against *P. falciparum* and *P. vivax*.
- Support several candidate vaccines in Phase 1 or Phase 2 clinical development programs, including combination vaccines aimed at more than one parasite stage or species.

Roll Back Malaria has set a goal of reducing the global malaria burden 50 percent by 2010.

- Establish a network of clinical research sites in regions endemic for *P. falciparum* and/or *P. vivax* with capability to carry out Phase 1 and 2 clinical evaluation.

Long-term

- Understand the immunologic basis of malaria pathogenesis and apply this information to the design of candidate vaccines, immunotherapeutics, and the identification of clinical endpoints for evaluation of vaccine safety and efficacy.
- Evaluate several candidate vaccines in clinical development programs, and identify potential commercial partners for promising candidates.
- Conduct large-scale field trials of the most promising malaria vaccine candidates in collaboration with partner institutions and agencies.

Malaria Drug Development

Antimalarial drugs are the foundation of malaria control in most of the world today. People living in malaria endemic areas use antimalarial drugs to prevent mortality and decrease morbidity from infection. Antimalarial drugs are also used prophylactically to protect travelers to those regions. Unfortunately, resistance of parasites to common antimalarial drugs is increasingly reported in Southeast Asia, Africa, and Latin America and is cited as the major factor contributing to the growing problem of malaria around the world. Improved monitoring of drug resistance, in order for endemic countries to design effective malaria control policies, and new drugs for minimizing the development of resistance by the parasite are needed. Advances in genetics and genomic research, synthetic chemistry, and computational biology will provide important and novel opportunities for understanding the genetic basis of resistance.

NIAID Goals

Short-term

- Develop an international network to evaluate the emergence and spread of drug resistance by
  - — establishing monitoring sites in endemic areas for analysis of molecular markers that correlate with parasite resistance to antimalarials;
  - — developing and implementing standardized protocols for clinical assessment of treatment failure; and
  - — developing bioinformatics tools and databases to link information from monitoring sites and facilitate analysis.
- Capitalize on information from recent sequencing of the *P. falciparum* genome for drug development by
  - — providing genomics resources for malaria parasites, including analysis of gene and protein expression in different

developmental stages of the parasite as well as changes in gene expression that correlate with drug resistance;

— developing facile methods for *Plasmodium* genetic engineering to identify essential genes as potential targets for inhibitory drugs; and

— providing computational resources to collect and analyze genetic and genomic data on malaria parasites.

- Sequence the genomes of *P. vivax* and relevant animal malaria parasites to facilitate identification of genes critical to parasite metabolism and virulence that might serve as drug targets.
- Establish a resource for the acquisition, screening, and preclinical development of new antimalarial agents, including identification of active compounds from herbal medicines and natural products.
- Strengthen additional clinical research sites in endemic regions for future field-testing of therapeutics, including networking of sites in areas with differing malaria transmission patterns.

Mid-term

- Establish an interactive network of research sites in malaria endemic regions that are trained and equipped for ongoing monitoring of drug resistance patterns and have the capability to carry out clinical evaluation of new drugs in conjunction with local public health authorities.
- Identify and validate new parasite targets for future antimalarials.
- Provide additional resources for the design, development, and preclinical testing of inhibitory compounds by the malaria research community.
- Conduct studies of several drug candidates in Phase 1, 2, and 3 clinical development programs, including trials for new indications, combinations of drugs, and/or adjuvant therapies for severe malaria.

Long-term

- Establish sustainable drug monitoring and clinical evaluation sites in endemic areas using relevant state-of-the-art diagnostic technologies and standardized protocols for clinical assessment.
- Identify commercial partners for new drugs and evaluate additional drug candidates in Phase 1, 2, and 3 clinical development programs.
- Transition drugs with demonstrated efficacy into implementation within national control programs, in partnership with local authorities, international development programs, and other relevant entities.

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Malaria Diagnostics

Improved diagnostic tools are essential in making early diagnosis and providing rapid treatment. Moreover, access to rapid, sensitive, inexpensive, and field-deployable diagnostics is essential for both drug and vaccine development.

Currently, malaria diagnosis is most commonly done by microscopic analysis of blood smears, a cumbersome and subjective method under the best of conditions and logistically difficult for extensive field studies. This method offers no insights into whether the parasite is drug resistant. In addition, because *P. falciparum* malaria parasites often sequester in the spleen or other organs, blood-based methods cannot be used to quantitate the level of infection within clinical trials.

While advances have been made in development of more rapid immunodiagnostics that are based on detection of parasite proteins, these are currently unable to distinguish various parasite species, drug sensitivity, or level of infection. Diagnostic development is yet another research area that can profit enormously from recent advances in genomics and related technologies. For example, molecular markers correlating with resistance to common antimalarials have been reported. Prospects for rapid, field-applicable, low-cost diagnostics based on detection of parasite nucleic acids or proteins are promising; however, discovery, development, and commercialization are limited by expectations of a low profit margin.

NIAID Goals

Short-term

- Expand partnerships with industry, particularly the biotechnology sector, and academia to develop rapid, field-applicable, diagnostic tests that can distinguish between different species of *Plasmodium* and provide quantitative information correlating with total infection level for use in clinical trials of vaccines and therapies.
- Facilitate development of innovative genomics-based technology for identification of molecular markers of drug resistance.
- Encourage the development of field-adaptable technologies for determining genetic polymorphisms in malaria parasites that can be used to detect parasite strain differences for tracking of vaccine or drug efficacy and reinfection rates in clinical trials.

Mid-term

- Field-test new diagnostics for malaria detection in endemic regions in preparation for licensure.
- Adapt assays for detection of molecular markers of parasite drug resistance and strain differences to a field-deployable format.

Long-term

- In partnership with local authorities and other interested partners, introduce state-of-the-art diagnostic tests into standard practice for case management and monitoring of drug resistance in malaria-endemic areas.
- Develop state-of-the-art diagnostic technologies to measure total infection level as well as differences in parasite strain distribution for use in large-scale field trials of vaccines and drugs.

Malaria Vector Control

Elimination of the mosquitoes that carry malaria and/or limitations of their contact with humans have been a central focus of malaria control programs throughout the 20th century. The insecticide DDT was a powerful tool in global efforts to eradicate malaria until problems such as environmental concerns, the development of DDT-resistant mosquitoes, and the financial drain imposed by long-term vector control campaigns in resource-poor countries limited its effectiveness. Current efforts, such as those spearheaded by RBM, to reduce malaria transmission by mosquitoes emphasize the use of bednets treated with a second-generation insecticide (synthetic pyrethroids).

Such controlled use of insecticides could be expected to pose negligible environmental hazards or risk of inducing pesticide resistance. However, agricultural use of the same insecticide has already been reported to have selected for resistant mosquitoes in certain malaria-endemic areas. As is the case with every aspect of malaria control, development of environmentally friendly pesticides for public health use has stimulated little commercial interest, although it is clear that insecticide resistance by mosquitoes poses the same type of ongoing challenge to malaria control as does drug resistance by the parasites. Improved understanding of the basic biology and ecology of mosquitoes may lead to innovative ideas for vector control. Advances in genomics hold the potential to contribute greatly to the ability to understand and monitor insecticide resistance, to develop new insecticides, and possibly even to render mosquitoes incapable of transmitting malaria.

NIAID Goals

Short-term

- Expand research on the biology of mosquitoes that transmit malaria and continue to examine the interactions between malaria parasites and mosquitoes. In 2001, sequence the genome of *Anopheles gambiae,* the most important mosquito vector of malaria in Africa.
- Use information from ongoing genome-sequencing efforts to identify new targets for insecticide action as well as mechanisms and markers for insecticide resistance.
- Expand research on the ecology and population dynamics of the different vector species.

Improved understanding of the basic biology and ecology of mosquitoes may lead to innovative ideas for vector control.

Mid-term

- Take advantage of new information on mechanisms and markers of insecticide resistance to develop rapid, field-appropriate detection methods for insecticide resistance traits.
- Use basic information on mosquito ecology to design and develop methods of vector control, such as attractant-baited traps or methods to inhibit larval breeding.
- Identify partner organizations to develop and commercialize new vector control methods.
- Establish field sites for pilot testing of new insecticides or other vector control methods and study their environmental effects.

Long-term

- Investigate promising new vector control methods through field trials in collaboration with local scientists and public health authorities and other partners.

Strengthening of Malaria Infrastructure and Research Capability

Strengthening the research capability of scientists in their own countries is an important focus of NIAID efforts. The Institute was a founding member of MIM and has been a major contributor to the MIM/WHO Special Program for Research and Training in Tropical Diseases Task Force for Malaria Research Capability Strengthening in Africa. Enhancing research capability within endemic countries is also an important component of programs within NIAID's longstanding ICTDR network.

NIAID will expand the development of field sites in endemic countries. These projects will support the strengthening of research capacity at host sites through direct scientific exchange with U.S. institutions, formal coursework in the United States, and in-country instruction through on-site and Internet-based workshops and coursework. One focus of this program will be to stimulate formation of action-oriented networks of scientists working in malaria-endemic countries, organized around issues of relevance to development of vaccines, drugs and vector control methods, and surveillance of drug and insecticide resistance.

In an extension of ongoing collaborations with the U.S. National Library of Medicine and others, a major provision of the program will be the establishment of Internet connectivity at malaria research sites. This capacity greatly increases collaborative potential by enhancing ability to communicate with colleagues, access to scientific literature, and technology transfer. This also encourages the development of independent and self-sustaining research centers in malaria-

endemic regions that will make an ongoing contribution to local control of malaria and other infectious diseases.

At the same time, there is a need to strengthen the tropical disease research infrastructure within the United States. The challenge of attracting physicians to research has been difficult. Even more challenging is a research career that demands the extensive overseas time commitment associated with tropical medicine. Centers for international clinical research would provide a supportive environment for developing a new cadre of U.S. physician-scientists, epidemiologists, and others capable of conducting field-based research on malaria and other emerging diseases.

NIAID Goals

Short-term

- Designate additional overseas sites for clinical research and establish mechanisms for ongoing technology transfer and educational activities on issues relevant to development of research centers, such as good clinical practice, clinical research methodology, biosafety, bioethics, international regulatory policies, clinical and research laboratory management, administrative and financial management, and collection of biological specimens.
- Begin to establish Internet connectivity at these sites and instruct local personnel for on-site maintenance of these facilities.
- Support a partnership between U.S. and African institutions for formation of an Endemic Area Data Management Center to facilitate transfer of technical expertise in biostatistics, clinical trial methodology, collection and management of clinical data, and management of complex data management systems.
- Stimulate collaborations between researchers, clinicians, and public health officials for the establishment of consensus guidelines for care of patients with severe malaria, with the goal of reducing morbidity and mortality through better application of currently available tools.
- Stimulate collaborations between researchers, clinicians, and public health officials for the assessment of local burden of disease from malaria (including morbidity and mortality measures).

Mid-term

- Expand the number of field sites capable of conducting clinical trials according to internationally accepted guidelines and continue ongoing technology transfer and educational activities in the context of field testing of diagnostics, vaccines, and therapeutics.
- Designate sites for field testing of new vector control methods and establish mechanisms for ongoing technology transfer and education on

Strengthening the research capability of in-country scientists is an important focus of NIAID efforts.

relevant issues; expand efforts to include these sites in Internet connectivity.

- Initiate formation of clinical research networks; link with other partners to develop methods for coordination and standardization of the collection and maintenance of data across all sites, to provide software that will allow transfer of files between the sites, and to establish and maintain newsgroups/list servers for all those with common interests (technical and research).
- Supplement the Endemic Area Data Management Center to include familiarization with advanced concepts such as molecular and genomic epidemiology.
- Establish several Centers for International Clinical Research at university-affiliated medical centers or similar institutions within the United States that can provide an opportunity for specialized training in tropical medicine and clinical/public health research, including overseas malaria research experience.

Long-term

- Support clinical and field-based research centers in malaria-endemic regions, with access to state-of-the-art technology and capable of remaining self-sustaining through competition for independent funding.
- Collaborate on and be actively engaged in coordinated, large-scale field trials of new vaccines, therapies, and vector control methods.
- Establish consortia of scientists, local public health authorities, and funders to support the integration of new malaria surveillance and control tools into national control programs.

NIAID Implementation Plan for Global Research on Malaria

Research Focus	Initiative
Vaccine Development	
	Expand clinical research on malaria pathogenesis
	Expand partnerships with industry
	Augment capability for pilot lot production
	Supplement capability for clinical testing
	Additional clinical research
Drug Development	
	Drug resistance network
	Drug development
	Genome sequencing
	Screening for active compounds
	Additional clinical research centers
	Clinical testing
	Development of lead compounds
Diagnostics	
	Expand partnership with industry
	Identify markers of drug resistance
	Determine genetic polymorphisms
Vector Control	
	Expand research on vector biology and genome sequencing
	Identify targets of insecticide action and mechanisms of resistance
	Expand research on vector ecology and develop new control methods
	Develop detection methods for resistance
	Establish field sites
	Field-test new control methods
Infrastructure/Research Capability Strengthening	
	Technology transfer/education
	Internet connectivity
	Endemic Area Data Management Center
	Centers for International Clinical Research

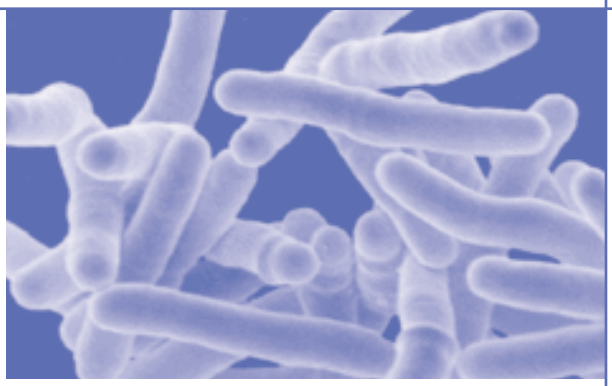
The Disease

WHO estimates that between the years 2000 and 2020, nearly 1 billion additional people will become infected by *Mycobacterium tuberculosis*, 200 million will develop active disease, and 35 million people will die from tuberculosis (TB), if current tools for treatment and prevention are not improved. Human TB is caused by the bacterium *Mycobacterium tuberculosis* or, to a much lesser extent, *M. bovis.* It generally affects the lungs but can lead to disease in virtually every organ system in the body. Current Bacille Calmette-Guerin (BCG) vaccines are relatively ineffective against adult pulmonary TB. Treatment is increasingly difficult because over 50 million people worldwide are currently infected with multi-drug-resistant strains of *M. tuberculosis.*

Worldwide Incidence

- Almost 2 billion people are infected. One person is infected every second.
- Two million people died in 2000.
- Leading infectious killer of women of reproductive age.
- During the next decade, 300 million more people will become infected, 90 million people will develop active disease, and at least 30 million people will die.
- One-third of the world's population is currently infected with TB.

NIAID Global Health Research Plan for Tuberculosis



Tuberculosis is the second leading infectious cause of death in the world, behind only HIV/AIDS, killing approximately 1.7 million people per year. Twenty percent of AIDS patients also die of TB, bringing the total deaths each year from this disease to almost 2.5 million people. Eight million new cases of active TB occur every year, and one-third of the world's population is already subclinically infected, creating an enormous reservoir of potential future cases of disease. More than 1.5 million new cases of TB occur every year in sub-Saharan Africa, nearly 3 million in Southeast Asia, and over a quarter million in Eastern Europe. These numbers are rapidly rising, due in large part to the impact of the HIV/AIDS epidemic.

Bacille Calmette-Guerin (BCG) vaccine, the only currently available vaccine for TB, is the most widely delivered vaccine globally, given to infants under the Expanded Program on Immunization (EPI). In many parts of the world, it is effective in preventing TB in young children. However, the major burden of morbidity and mortality from this disease is adult pulmonary TB. BCG has shown highly variable efficacy in clinical trials against this most common form of TB and clearly has not been effective in controlling the epidemic in most countries of the Southern Hemisphere, where the burden is greatest. EPI has estimated that BCG is actually preventing only 5 percent of potentially vaccine-preventable deaths from TB. Improved vaccines for TB are imperative for the ultimate elimination of TB as a public health problem in both developed and developing countries.

In April 1993, WHO declared TB a global health emergency, the first time such a declaration has been made about an infectious disease. Since then, the incidence and prevalence have increased worldwide and drug-resistant strains have continued to develop and spread. In July 2000, the G8, meeting in Japan, announced its goal of reducing TB deaths and prevalence of disease 50 percent by the year 2010.

NIAID has developed a global TB research agenda, which will involve collaboration and coordination of activities with sister agencies of the Federal Government and other organizations with similar goals, such as the Global Alliance for TB Drug Development and the Stop TB Initiative. The success of this research agenda will depend primarily on establishing and maintaining true partnerships with endemic country scientists, governments, public health officials, and national TB control programs.

Tuberculosis Vaccine Development

In March 1998, NIAID, the Department of Health and Human Services (DHHS) Advisory Committee for Elimination of Tuberculosis (ACET), and the U.S. National Vaccine Program Office convened a workshop to develop a *Blueprint for TB Vaccine Development*. The Blueprint report outlines the specific steps needed to develop new, improved anti-TB vaccines. NIAID's TB Vaccine Development Plan closely follows the Blueprint recommendations.

Other organizations have also recognized the need for effective TB vaccines—the Bill and Melinda Gates Foundation is supporting TB vaccine development efforts with a $25 million (total, over 5 years) grant to the Sequella Foundation, and the European Union has recently established a TB Vaccine Cluster. There is, however, limited industrial activity in this area in part because of the numerous unresolved scientific questions.

Major questions remain about the mechanisms of TB pathogenesis and the human immune response to this pathogen. The key stages of persistent or latent infection and reactivation of disease are poorly understood. Virulence factors and protective antigens are just beginning to be identified, animal challenge models have not yet been demonstrated to be predictive of protection in humans, and there are no validated correlates of protection for use in vaccine trials. Efficacy trials will be challenging to design and will raise difficult ethical questions in areas where BCG is already in use and HIV infection rates are high. On the positive side are advances in genomic technologies, immunology, cell biology, and the ability to manipulate the *M. tuberculosis* genome. In addition, more than 100 potential TB vaccine candidates have been developed and screened for protective efficacy in small animal models with some promising results. These developments all bode well for progress, if a concerted global effort and adequate resources are devoted to TB vaccine development.

NIAID Goals

Short-term

- Expand research on the pathogenesis of human TB and elucidation of the human protective immune response, using new technologies including genomic, proteomic, and high-throughput structural biology approaches. Emphasize elucidation of the mechanisms underlying latency (persistent infection) and reactivation of disease, and demonstration of the predictive value of animal models for assessing protection in humans.
- Develop and expand partnerships with both large pharmaceutical and small biotechnology

...the G8...announced its goal of reducing TB deaths and prevalence of disease 50 percent by the year 2010.

companies to increase their involvement in TB vaccine development, encourage novel approaches to vaccine and adjuvant delivery, and decrease the projected timeline for successful vaccine development.
- Increase capacity for animal model screening, preclinical testing, and good manufacturing practices pilot-lot production of promising vaccine candidates.
- Expand the network of clinical trial sites capable of conducting high-quality early human testing.
- Develop additional clinical research centers in endemic countries with effective national TB control programs. (See the section on Research Capability Strengthening.)

Mid-term

- Establish useful models of TB latency and reactivation and develop innovative methods for studying human TB.
- Establish a network of clinical trial sites and associated research centers in high-burden countries capable of conducting Phase 1, 2, and 3 trials according to international standards.
- Study one to three vaccine candidates in Phase 1 and 2 clinical trials.
- Support one or more efficacy (Phase 3) trials.
- Develop one or more candidate markers of protective immunity for validation in clinical trials.

Long-term

- Understand TB pathogenesis, the human protective immune response to *M. tuberculosis* infection, and mechanisms underlying TB latency and reactivation.
- Validate at least one marker of human protective immunity to *M. tuberculosis* useful in a clinical trial setting.
- Support several vaccine candidates in Phase 1, 2, and 3 clinical testing, with appropriate partner organizations.
- Identify industrial partners to undertake further development, manufacturing, and distribution of successful candidates.

Tuberculosis Drug Development

Although regimens exist for treating tuberculosis, they are far from ideal. Treatment usually involves a combination of drugs—isoniazid (INH) and rifampin, which are given for at least 6 months, and pyrazinamide and ethambutol (or streptomycin), which are used only in the first 2 months of treatment. Because this regimen is extremely difficult to adhere to, WHO recommends a program of directly observed treatment, short-course (DOTS), which involves health care workers routinely watching patients take their medicine. Only 21 percent of the world's TB patients were treated under DOTS in

1998. Inconsistent or partial treatment leads to the development and spread of drug-resistant strains. These strains have a much lower cure rate and can be up to 100-fold more expensive to treat.

There is thus an urgent need for shorter, simpler therapeutic and prophylactic regimens to increase adherence. In addition, new drugs are needed to combat the increasing number of multi-drug-resistant strains (MDR-TB). Treatment for MDR-TB often requires the use of a second line of TB drugs, all of which can produce serious side effects. Therapy for 18 months to 2 years may be necessary, and patients should receive at least three drugs to which the bacteria are susceptible.

A better understanding of TB latency and development of predictive screening assays are key to identification of novel bactericidal compounds that could significantly shorten therapy and thereby improve compliance. Validated surrogate markers are needed to simplify clinical trial designs and speed regulatory approval processes.

NIAID Goals

Short-term

- Capitalize on the availability of the *M. tuberculosis* genome sequence and new genetic tools by providing resources for investigators to
  - — identify novel drug targets;
  - — develop approaches to high-throughput structural genomics and use these to determine target structures and identify active sites;
  - — identify specific inhibitors of these targets; and
  - — develop high-throughput screens for identifying "hits" for further development.
- Develop potential surrogate markers of therapeutic efficacy and begin to validate them in clinical trials.
- Encourage development of novel approaches to studying human TB, including use of human tissues.
- Develop and validate animal models of persistent infection and reactivation of disease.
- Begin to establish a network of trial sites in high-burden countries suitable for conducting efficacy trials on novel therapeutic regimens and agents.

Inconsistent or partial treatment [of TB] leads to the development and spread of drug-resistant strains.

Mid-term

- Develop validated surrogate markers of TB disease for cured and/or persistent infection.
- Support several promising candidates in late preclinical and clinical testing (Phases 1, 2, and 3).
- Establish a clinical trial site network capable of conducting efficacy trials of new TB drugs and therapeutic regimens.
- Create and/or contribute to a seamless pipeline for TB drug development involving public and private partners, as appropriate.

Long-term

- Support studies that lead to licensure of one or more safe and efficacious compounds that shorten and simplify the duration of TB therapy, and/or develop a significantly more effective therapeutic regimen.
- Support studies that lead to licensure of one or more compounds efficacious against MDR-TB (in combination with other agents).
- Work—in partnership with local authorities, international development programs, and other appropriate partners—to help move these newly licensed compounds and/or improved therapeutic regimens into national TB control programs in high-burden countries.

Tuberculosis Diagnostics

The current gold standard for TB diagnosis is the microscopic analysis of sputum smears for acid fast-stained organisms. This method is labor intensive and not sensitive, requiring approximately 10,000 mycobacteria per milliliter of sputum for a positive diagnosis. The acid-fast smear test also is not specific; the test is unable to distinguish among mycobacterial species. Therefore, the top priority for TB diagnostics development, worldwide, is a low-cost, rapid, sensitive, and specific test that could replace the acid-fast smear examination. In addition, only half of all cases of active TB worldwide are smear-positive. Most smear-negative TB cases are ignored and remain undiagnosed. Therefore, improved diagnostic methods for smear-negative TB are also needed.

Drug-resistant TB develops as the result of inappropriate therapy. In settings with high prevalence of drug resistance, diagnostics are needed so that clinicians can rapidly determine drug susceptibilities of patient isolates. This is important because treatment with ineffective drugs quickly leads to the development of resistance and the spread of drug-resistant strains.

NIAID Goals

Short-term

- Support research to identify *M. tuberculosis*-unique components that may serve as the basis for development of more specific diagnostic tools, including genomic and bioinformatic-based approaches.

- Expand partnerships with industry and academia to develop more sensitive and specific diagnostic tools and rapid drug susceptibility testing (DST) methods, suitable for use in high-burden countries.
- Conduct two or more field tests in high-burden settings to evaluate novel diagnostic methods—one for improved, low-cost diagnosis of smear-positive TB and one for rapid DST.
- Convene a workshop (in collaboration with other interested agencies) to examine difficult TB diagnosis-related issues, including diagnosis of pediatric TB and TB in HIV-infected individuals (often smear-negative).

Mid-term

- Support development of multiple diagnostic and DST assays, suitable for use in high-burden countries. In addition, work to ensure a seamless transition from the bench through preclinical development to field trials, in coordination with interested partners (WHO, Centers for Disease Control and Prevention [CDC], Gates Foundation, industry).
- Establish and support, in conjunction with WHO and other interested partners, a repository of well-characterized human samples from smear-positive and -negative TB patients (HIV-positive and HIV-negative) and appropriate controls, available for testing and validation of novel diagnostic tools suitable for use in high-burden countries.

Long-term

- Develop effective, robust diagnostic tools suitable for use in high-burden countries. These new tools would allow clinicians to replace sputum smear microscopy, perform rapid DST, diagnose smear-negative TB (including pediatric TB and TB in HIV-positive individuals), and distinguish TB infection from vaccination and exposure to environmental mycobacteria in the setting of vaccine efficacy trials and TB screening programs.
- Work with appropriate partners to integrate these improved diagnostic tools into TB control programs in high-burden countries.

Tuberculosis Infrastructure and Research Capability Strengthening

NIAID is conducting TB research in collaboration with high-burden country partners at a number of sites throughout the world. NIAID partners with governments and national TB control programs, as well as with other interested organizations (including WHO, CDC, U.S. Agency for International Development, Medical Research Council, Fogarty International Center, and International Union Against Tuberculosis and Lung Disease [IUATLD]), to increase research capability in high-burden countries. Important elements of capability strengthening from NIAID's perspective include

A low-cost, rapid, sensitive, and specific diagnostic is needed to replace the acid-fast smear test.

core research infrastructure building, training (of scientists, policymakers, public health personnel, administrators, and health care workers), and research sustainability.

NIAID Goals

Short-term

- Establish partnerships, set initial priorities, and initiate research capability-strengthening activities in two or more high-burden countries.
- Establish an international network of sites ultimately suitable for conducting TB drug and vaccine efficacy trials in collaboration with the involved countries and research organizations.
- Increase training opportunities for candidates from high-burden countries, in research, research and clinical administration and management, and ethical and regulatory oversight, to increase in-country capability.

Mid-term

- Establish core infrastructures or centers in several high-burden countries, devoted to high-quality immunology, microbiology, biostatistics, epidemiology, clinical research, and ethical and regulatory oversight. These centers will be established in partnership with host countries and, where appropriate, with other interested organizations.
- Conduct research collaborations, including but not limited to field trials of novel TB diagnostic tests and early clinical trials of TB drug and vaccine candidates.
- Develop, in collaboration with endemic country partners, a long-term career track (in home countries) for highly trained and qualified individuals.
- Initiate at least one efficacy trial of a novel TB drug or vaccine within an international network of clinical trials sites in endemic countries.

Long-term

- Establish a sustainable research and clinical trial infrastructure that includes training for endemic country scientists, public health and health care personnel, bioethicists, regulators, administrators, and managers.
- Conduct two or more successful efficacy trials of novel TB vaccine and drug candidates, in high-burden countries, with local leadership and in partnership with other interested organizations, as appropriate.

NIAID Implementation Plan for Global Research on Tuberculosis

Research Focus	Initiative
Vaccine Development	
	Expand pathogenesis and human immune response research; animal models development; human TB
	Expand partnerships with pharmaceutical/biotechnology companies
	Increase preclinical testing and pilot-lot production capacity
	Expand network of clinical trial sites for Phase 1, 2, and 3 testing; conduct trials
	Establish research centers and strengthen research capability in high-burden countries
Drug Development	
	Identify new targets and inhibitors; develop high-throughput screens and structural genomics approaches
	Develop surrogate markers of drug efficacy
	Develop and validate animal models of latency and reactivation for drug testing
	Expand capacity for preclinical development
	Expand network of sites for drug testing, including Phase 1, 2, and 3 trials in high-burden countries
Diagnostics	
	Expand use of genomic and bioinformatics approaches to identify *M. tuberculosis*-unique targets
	Establish repository of human tissues
	Expand partnership with industry to develop and validate new diagnostics
	Establish field-testing sites and strengthen research capability in high-burden countries; conduct field tests
Infrastructure/Research Capability Strengthening	
	See above
	Training and technology transfer in high-burden countries
	Internet connectivity
	Expand partnerships with other organizations involved in global health