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Promoting Effective Tuberculosis Control and Vaccine Development

The Princeton Project 55 Tuberculosis Initiative
Washington, DC, USA

Mission:
To increase public awareness about tuberculosis, encourage U.S. leadership in tuberculosis prevention and control, and foster tuberculosis vaccine development by enlisting government, foundation, and industry support.

Case for Support

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OVERVIEW

This report describes the impact of the global tuberculosis (TB) epidemic and formulates a strategy for redressing this threat to global health. Because this deadly disease is transmitted through the air, no person, community, country, or region in the world is protected from TB. Effective control programs must be established in countries where TB is endemic to stop the spread of disease and save the lives of those already ill from TB. However, the best hope for ultimately eliminating TB is the development and widespread use of an effective vaccine. TB treatment programs and vaccine development must occur in tandem to contain and fight the epidemic.

The Princeton Project 55 Tuberculosis Initiative (TBI) is an independent, non-profit, non-partisan organization dedicated to increasing public awareness about tuberculosis, encouraging U.S. leadership in tuberculosis prevention and control, and fostering tuberculosis vaccine development by enlisting government, foundation, and industry support.

THE GLOBAL TB EPIDEMIC

Tuberculosis is the second leading infectious cause of death worldwide behind only HIV/AIDS and has already infected one-third of the world's population. In 1997, more people died from TB than in any other year in history. Approximately 2-3 million people around the world die annually from the disease, and each year an additional 8 million people become ill from tuberculosis. This communicable bacterial disease is spread from an active patient to another person through the air by mere coughing, sneezing, or even talking.

Currently, only about 16% of TB patients worldwide receive adequate treatment. Poor treatment programs which lack adequate drugs or trained staff promote multi drug-resistant strains of TB (MDR-TB) that are even more difficult to treat and cure. Already, an estimated 50 million people globally are infected with MDR-TB, a virtual death sentence for those in the developing world.

Because TB is airborne, an outbreak abroad can spread to the U.S. within a single plane flight. With the added danger of the growing prevalence of drug-resistance, tuberculosis threatens to again become an incurable plague. **According to the World Health Organization, if nothing new is done in TB control, the death toll could rise to 4 million per year as soon as 2004.**

THE IMPACT OF TUBERCULOSIS

The economic impact of TB is immense. Because TB takes its toll primarily on people in their most economically productive years of life, TB carries not only a direct cost to health service systems, patients, and families, but also an indirect cost to general society and local communities. The World Bank estimates that for every dollar invested in TB control and prevention, a developing country will see a $50 return in the future through restored economic productivity and savings from avoidable TB cases. TB often strikes down adults in their prime working years, devastating local and regional economic capabilities.

Besides being unable to support themselves and their families due to sickness, people suffering from TB carry the personal burden of rejection, shame, and discrimination from their own communities. Many women delay getting treatment due to the social stigma attached to having TB. This delayed action allows an infected patient to spread TB to 10-15 others each year that individual is not properly treated. Delayed action also diminishes chances of survival. Consequently, TB kills more women worldwide than all causes of maternal mortality combined. Without family income and parental care, many children are left destitute, orphaned, and often infected with the disease by their dying parents.

THE GROWING THREAT OF TB

In many of the hardest-hit countries, inappropriate treatment regimens, inferior drugs, and erratic drug supplies all provide TB bacilli the opportunity to become drug-resistant over time, making the disease more difficult and expensive to cure. As a result, MDR-TB is becoming increasingly prevalent worldwide. In the U.S., treatment of MDR-TB costs about $250,000 – more than 100 times the cost of treating a susceptible case of TB – and nearly half of all MDR-TB patients die, even with state of the art care. In the developing world, a case of MDR-TB is usually equivalent to a death sentence since most countries simply cannot afford to treat MDR-TB patients. Even if no new drug resistance is formed, the WHO estimates 50 million cases of MDR-TB already exist worldwide. Their imminent spread to others will encompass a major public health crisis for decades to come.

The rise of TB has been accelerated, both in the U.S. and the developing world, by the deadly partnership between TB and HIV/AIDS. Each disease accelerates the devastation caused by the other. Already, TB is the leading cause of death among HIV-positive people and accounts for one-third of AIDS deaths worldwide. Someone who is HIV-positive and infected with TB is 30 times more likely to become sick with TB than someone infected with TB who is HIV-negative. Considering that nearly 31 million people were HIV-positive in 1997 worldwide and almost one-half are believed to be infected with TB, the case for TB control is staggering. By the year 2000, experts estimate that HIV infection will result in nearly 1.5 million cases of TB annually that otherwise would not have occurred. Places like Botswana, which have a good TB control program but an exploding caseload of TB/HIV co-infection, are seeing increasing rates of TB in spite of successful control efforts.

The combination of MDR-TB and the explosion of TB/HIV co-infection, if allowed to proceed unchecked, means that the cost of treating and curing the world's TB infected population will grow to astronomical proportions.

A COST-EFFECTIVE ANTIBIOTIC TREATMENT

The World Health Organization (WHO) has endorsed an antibiotic treatment regimen called the Directly Observed Treatment Short-course (DOTS) strategy which is highly effective in controlling and preventing TB throughout the world. It is a five-pronged strategy which incorporates resource allocation toward diagnosing cases, direct observation of patients taking their medications, continual monitoring of patients during treatment, assurance of correct and quality drug regimens, and the building of political will and support for TB policies. The success

of the strategy has been proven under the most challenging conditions, including economically devastated and war-torn areas. Areas as diverse as New York City, Bangladesh, Tanzania, Peru, China, and South Africa have used the DOTS strategy, yielding cure rates of 85% and higher.

The strategy can be easily integrated within existing general health service systems and reach a widespread population by using trained health workers, civic leaders, and community volunteers to administer anti-TB treatment. When applied correctly, the DOTS strategy can cure patients, inhibit transmission, and help prevent the emergence of drug resistance by ensuring completion of treatment. Furthermore, the WHO reports that DOTS costs as little as $3-5 per healthy year of life it preserves, making it one of the most cost-effective health interventions available today.

Yet many factors have caused antibiotic treatment programs to be less effective in some regions than in others. The widespread disparity in treatment length and combination of prescribed drugs result in ineffective treatment regimens that fail to cure patients. Few regulations exist worldwide that require pharmaceutical companies in developing countries to ensure the quality of the drugs they produce and put to market. The result is the proliferation of sub-standard and counterfeit TB drugs being used in developing countries. The diagnosis of latent disease in most countries is impossible, as most nations where TB is endemic use the BCG vaccine, which ruins the predictive value of tuberculin skin tests. Countries such as India often rely on x-rays or physical symptoms to test for the disease, leading to a large number of missed or incorrect diagnoses. Even the proper diagnostic tools that are available to nations have their drawbacks. Sputum smear microscopy at best only diagnoses 70% of TB patients, and though culture is a sensitive test, it takes three weeks to confirm a case.

Even with quality diagnostics and drugs, erratic drug supplies often cause patients to be cut off from their treatment too early. Such incorrect drug use has resulted in the emergence of MDR-TB, an entirely man-made phenomenon. Once multi drug-resistance develops, TB bacilli become virtually impossible to kill. Furthermore, even if no new drug resistance occurs, the number of drug resistant strains already in existence and their imminent spread to other victims makes MDR-TB a major public health crisis that will have to be dealt with for decades to come.

In the foreseeable future, the DOTS regimen remains the best available treatment, and should be implemented as widely as possible. However, its shortcomings require that research continue to improve the drugs, diagnostics, and regimens used.

THE NEED FOR NEW TB TOOLS AND STRATEGIES

TB cannot be completely controlled, cured, prevented, or eliminated without the development and widespread use of new tools and strategies. Even with DOTS, current regimens for treating patients with tuberculosis still require many months to be effective, and sustaining adherence to therapy remains a challenge. With TB/HIV co-infection and the regular outbreaks of drug-resistant strains, more and more experts believe that real control of tuberculosis, particularly on a worldwide basis, will not occur until better diagnostics, drugs, and an effective vaccine become available.

An inexpensive, rapid, accurate, and easily applied test is needed for diagnosing TB infection and disease. The current sputum smear microscopy tool, standard in DOTS programs, is at best only 70% sensitive and thus can only detect 70% of TB patients. Numerous patients can be infected with TB but show a negative sputum sample, causing them to be falsely

overlooked and misdiagnosed as healthy individuals. Culture is an extremely sensitive test, but takes up to three weeks to identify a case, which is often too long to be practical. Even less useful in developing countries is the tuberculin skin test, which is read after an incubation period of several days and indicates exposure to TB at some time in the patient's life. The skin test's efficacy is marred by the widespread use of the BCG vaccine in the developing world. BCG is effective in preventing forms of TB associated with meningitis sometimes encountered in infants. However, the vaccine is ineffective in adolescents and adults and renders the tuberculin skin test useless as a positive result will be indicated whether or not the patient has been infected.

Currently, the BCG vaccine is the world's most widely used vaccine, covering 80% of the world's child population. Nevertheless, 8 million new cases demonstrate that it is not effective in adults. A new vaccine would be a form of primary prevention that can significantly decrease TB incidence, rather than the secondary prevention of the DOTS strategy applied after infection. **Thus, the greatest research need by far is for a new, effective, and safe vaccine that can prevent infection as well as block reactivation of disease in those who have already been infected.**

TB/HIV co-infection is and will continue to cause an explosion in the number of TB cases for decades to come. The growing number of cases will be a challenge for current TB control programs to handle. Moreover, the increasing number of multi-drug resistant strains are requiring health care workers to further specialize individual TB treatments to combat these more difficult and expensive strains of the disease. Consequently, without a major breakthrough in the form of a preventive vaccine, the incidence of TB worldwide will probably not decline significantly and elimination in low-incidence nations such as the United States will not become a reality.

Many researchers believe that it is more likely that a TB vaccine can be developed before a new TB drug can be developed which cures a patient in significantly shorter time than is needed now. Yet the development of new drugs that reduce treatment times and produce fewer side effects are also crucial. In recent history, it should be noted that no significant new TB drug has been developed in the last twenty-five years. Like smallpox and polio, TB will most likely be eliminated only with the help of new drug therapies and, most importantly, an effective vaccine.

EXPANDING TB RESEARCH

For most of the last half century, funding for TB research has been virtually non-existent because of the mistaken, general belief that the discovery of antibiotics had solved the problem of TB. Evidenced by the increasing morbidity and mortality rates, this simply is not the case.

Of the approximately $90 million spent annually on TB research worldwide, the National Institutes of Health (NIH) accounts for about $65 million. This figure has increased since 1991, when NIH contributed only $5 million to what they believed to be a disease of the past. Yet a significant increase in funding is necessary if the development of better drugs and a vaccine is to become a reality. Other than this premiere research facility, few international partners have been able to complement NIH's research activities.

Most countries directly affected by the TB epidemic are in no way prepared financially or academically to create a long-term research infrastructure. Proper education, training, facilities, and long-term resources are years away. While extensive international training and education

campaigns can and must be waged, the current resources for much of the biomedical research regarding TB are located in the western nations.

Private industry has shown relatively little interest in development of new drugs, vaccines, and diagnostic tools. Most international pharmaceutical companies choose not to conduct basic research and development for a TB vaccine given the lack of financial incentive. Because 95% of TB patients reside in resource poor, developing countries, major pharmaceutical companies believe that TB-related innovations will not be profitable. Indeed, if a new TB drug or vaccine were developed, pharmaceutical companies would be forced to price it cheaply or risk being denounced for immorally condemning millions in developing countries to their deaths. Thus, pharmaceutical companies are unlikely to recover the costs of TB drug or vaccine development, at least in the short-term.

The figure of $65 million for TB research here in the U.S. is a very meager number compared to the funding allocated for research on similarly destructive diseases like HIV/AIDS and cancer. Currently, the NIH spends $1.7 billion on HIV/AIDS research and $2.3 billion on cancer research annually. This seems incongruous given the fact that TB is the leading infectious disease killer behind AIDS and is the number one killer of HIV-positive patients. Funding for TB research has lagged because most believed that, with the advent of antibiotics, TB was no longer a threat. Others argue that not enough TB researchers exist to handle a large influx of money. Yet if the story of AIDS is used as an example, no HIV/AIDS researchers existed before funds were available. Today more than enough scientists are able to use the available funds. It is clear that TB deserves to be given the level of priority and funding that has been granted diseases like cancer and AIDS.

Since we are now at a crossroads in understanding tuberculosis, new funding can have a great impact. Researchers have recently deciphered the entire genetic code of the TB organism, providing entirely new opportunities for the creation of sophisticated drugs and vaccines. Furthermore, the NIH has already drafted a comprehensive blueprint for the development of a TB vaccine. Several new vaccine candidates are currently being developed and tested in animal models, and will be available for human testing in a few years. What is needed now is funding for the implementation of this strategy. The recent scientific accomplishments suggest that the time is ripe for a significant push forward in tuberculosis research.

NEXT STEPS TO AN EFFECTIVE TB VACCINE

In order for TB research to be successful, a significant long-term investment must be made. Experts estimate that an investment of $800 million over 20 years will lead to the development of an effective vaccine. Given that the U.S. government already spends an estimated $700 million on TB control and treatment every single year, this is an investment we cannot afford to ignore, as a vaccine will save the millions spent on control and treatment in the long run.

Many scientific tasks need to be accomplished in the development of a vaccine. Basic research on the nature of TB infection in humans must be continued. Researchers must determine which factors may protect people from TB infection, the predictive value of animal models, and the nature of latent TB infection. Moreover, there must be consensus on the characteristics of an ideal vaccine, and the minimum acceptable characteristics for a vaccine product. But before such work can take place, private industry will have to become involved.

However, pharmaceutical companies will not commit themselves to developing a vaccine until it can be demonstrated that there is sufficient demand and a market for TB vaccines.

Politically, there must be a real commitment to vaccine development among government agencies, researchers, and the pharmaceutical companies. In order for this to occur, a serious dialogue is needed among these constituencies. Ultimately, there must be a very high degree of collaboration and coordination between the research communities and various public health agencies (domestic and international), together with representatives of countries where TB is endemic, in order to implement an effective vaccine manufacturing and distribution program. This is essential, as past experience with vaccines such as the hepatitis B vaccine have shown the severe lag time in the worldwide distribution of vaccines.

Given the persistent, pervasive nature of TB and long lead-time required to develop and deploy a vaccine, unless a commitment to its development is made now, we will undoubtedly face a far more serious TB epidemic in the future.

TB PREVENTION AND CONTROL

The United States government must continue to encourage foreign governments in which TB is most endemic to support strong TB control efforts. Governments will have to work together to guarantee funding assistance for target countries, assure an ongoing supply of quality drugs, proper laboratory and health worker training, and provide increased support and guidance.

A global strategic plan has been adopted to redress the growing TB epidemic. Funding priorities have been identified, but long-term, large sums of money are required for further progress. The WHO estimates that over $1 billion is currently needed to address the global TB emergency with DOTS annually. The current U.S. contribution of $12 million per year through the United States Agency for International Development (USAID) will make a small impact in TB control in a few locations around the world. Most of these funds have gone towards education, training, and laboratory equipment in order to create the basic infrastructure for solid TB control programs, but little money has gone to actual patient treatment. If any positive outcome is to be realized from initial investments, these new USAID programs must be augmented and must be guaranteed long-term funding support.

The U.S. Centers for Disease Control and Prevention (CDC) must also be allocated new resources to expand not only their domestic activities, but also their international activities. The level funding in the face of inflation for CDC's TB program over the last four years has limited the Division of TB Elimination's extent of involvement in international activities. The CDC will need to continue and expand its consultant services to international health workers, as its expertise is required for regional surveillance programs, drug quality studies, and TB training programs for indigenous specialists.

The United States has a vital interest in having federal agencies invest in control globally. Due to frequent importation of TB across international borders, 40% of our TB cases are among foreign-born patients. We cannot continue to make headway against TB in this country until we improve both treatment and prevention efforts in the most severely affected countries. After all, the better TB is controlled abroad, the fewer cases will appear in the U.S.

Consequently, there is little hope for the elimination of TB in the United States, until the federal government makes an honest commitment to the control of TB in the countries where TB is most prevalent throughout the world while increasing research funds at home.

WHAT YOU CAN DO

As a Congressman or Senator, you can work to influence and direct the FY2000 funding for "Combating Infectious Diseases." A total of about $12 million went towards international TB control in FY98 and FY99. The WHO estimates that $1 billion is needed to combat TB worldwide. According to TB experts, Congress should allocate $60 million in new money to for the development of TB control programs in the 22 most affected countries, via the USAID. Please write Foreign Operations Appropriations Subcommittee Chairs Senator Mitch McConnell and Representative Sonny Callahan or Ranking Members Senator Patrick Leahy and Representative Nancy Pelosi in support of this issue.

In terms of research funding for TB, you can encourage the Labor/HHS Appropriations Subcommittee to increase NIH funding and direct some of these new resources towards TB drug and vaccine development. Funding for TB vaccine research will be especially important in the coming year, as the *Blueprint for TB Vaccine Development* is finalized and approved by the cooperating agencies. TB research funds must be brought up to the level of other equally devastating diseases.

As a pharmaceutical company representative, you can pursue cooperative investments with the U.S. government for the development of new medications and diagnostics to meet the new challenges of drug resistance and patient management. There has been no significant breakthrough in TB drugs or diagnostics in decades. Pharmaceutical companies should form a collaborative foundation or fund for TB research or a "TB drug bank" that would guarantee a source of safe, affordable anti-TB drugs.

As a representative of a philanthropic foundation, you can encourage your board to make TB control a major priority under your international health guidelines. Currently, most foundations involved in international health have overlooked tuberculosis. Thus far, the Soros and Damien Foundations are exceptions and have contributed to the development of national TB control programs in countries where TB is endemic, but there is a great need for additional, direct financial support to address the growing TB epidemic. Foundations can also contribute indirectly through grants for biomedical research, public awareness drives, and TB control advocacy.

As a state or local health official, you can encourage your local government and federal representatives to support directly observed treatment programs in your area. It is our goal to unite local, state, federal, and international TB control organizations to establish United States leadership of an effective program for TB control worldwide.

As a physician, you can refer all suspected cases of active TB to appropriate treatment centers to receive DOTS. You can encourage your local health agencies to bolster their TB control facilities. You can also contribute to Princeton Project 55's efforts by writing your Congressmen and educating your patients about the threat of TB.

Princeton University alumni, physicians, health officials, government officials, pharmaceutical and foundation representatives are encouraged to join the Princeton Project 55 TBI's national network to spread public awareness about TB and encourage U.S. leadership in global TB control and prevention.

THE PRINCETON PROJECT 55 TUBERCULOSIS INITIATIVE – TBI

Princeton Project 55, Inc. is an independent, non-profit, public interest organization established by Princeton University's Class of 1955 to encourage more effective involvement in combating social problems that face our nation. Princeton Project 55's engagement in the fight against TB began at the urging of founding board member Ralph Nader and several recognized TB experts in 1996.

In February 1997, with the support of the primary international TB control agencies, PP55 hosted a conference entitled "Tuberculosis: A Global Emergency," attended by a group of international TB experts from twenty-five health organizations and a general audience of 200. In subsequent discussions, the twenty-five participating organizations encouraged Princeton Project 55, Inc. to become an advocate for tuberculosis control and research by stimulating collaboration, facilitating innovation, and providing a vocal appeal for greater efforts in TB control and research.

In June 1997, the Princeton Project 55 Tuberculosis Initiative was created with a start-up grant from the Robert Wood Johnson Foundation and contributions from Princeton University's Class of 1955.

> *The Princeton Project 55 TBI is an independent, non-profit, non-partisan organization dedicated to increasing public awareness about tuberculosis, encouraging U.S. leadership in tuberculosis prevention and control, and fostering tuberculosis vaccine development by enlisting government, foundation, and industry support.*

The Princeton Project 55 TBI seeks to increase awareness about the TB epidemic by keeping decision makers informed about regional trends, methods of control, and the roles that various organizations can play; through media advocacy to increase attention paid to the epidemic, and expand the media's understanding of the complexities of this threat; by enhancing the coalition-building effort that was launched at the initial conference; and by encouraging public and private support for the research and development of an effective TB vaccine.

We are dedicated to ensuring that one of the world's leading infectious causes of death is treated with the urgency and gravity it deserves.

SUPPORTERS OF PRINCETON PROJECT 55 TBI

TBI was launched in 1997 with a one-time start-up grant from the Robert Wood Johnson Foundation and contributions from the Princeton University Class of 1955. Its ongoing funding is provided by the Safety Systems Foundation, members of Princeton University's Class of 1955, and private donations.

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BLUEPRINT FOR TUBERCULOSIS VACCINE DEVELOPMENT

Report of a Workshop held

March 5-6, 1998, Rockville, MD

Chair: Barry Bloom, Ph.D.

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BLUEPRINT FOR TUBERCULOSIS VACCINE DEVELOPMENT

On March 5-6, 1998 the US Dept. of Health and Human Services Advisory Council for Elimination of Tuberculosis, the US National Vaccine Program Office and the National Institute of Allergy and Infectious Diseases of the US National Institutes for Health convened a workshop to develop a national strategy for development of effective tuberculosis vaccines. The report from that Workshop follows:

RECOMMENDATIONS AND CONCLUSIONS

Tuberculosis remains the largest cause of death in the world from any single infectious disease. It is a major killer of adults, and the major attributable cause of death of people with HIV/AIDS. In addition to its immense human burden, it is a major economic burden in the US and globally. Antituberculous drugs are expensive, treatment requires many months, compliance with treatment is difficult to maintain, and drug resistance is increasing globally. The failure to develop measures to prevent tuberculosis everywhere threatens our ability to control the disease anywhere, including in the US. Despite limited resources for research on tuberculosis, new scientific advances encourage the view that development of an effective vaccine to prevent tuberculosis is scientifically feasible, and worthy of a significant national and international effort.

The conclusions and recommendations of this report are that:

- A long-term commitment to develop an effective vaccine against tuberculosis is required, with the recognition that it will be a major and difficult scientific challenge.

    - Despite the difficulty of this task, the proposed vaccine research is sure to have significant ancillary benefits. It will serve to increase knowledge of how the tubercle bacillus is transmitted and causes disease and of the nature of protective human immune responses to bacterial pathogens, and it will lead to improved approaches to diagnostic tool development and complex clinical vaccine trial design.

- Such an undertaking will require a long-term investment, at least 20 years, until the candidate vaccines that are most likely to be safe and protective will be implemented globally.

- A high degree of collaboration and coordination will be required for a successful effort to develop vaccines against tuberculosis. Development of a working partnership will be necessary that links the expertise of the NIH in biomedical research, CDC in epidemiology, FDA in regulatory affairs and interactions with industry, USAID in international health, WHO and the International Union Against Tuberculosis and Lung Disease in global tuberculosis control, academic and industrial researchers, and scientists and health workers in countries that have both the need and the infrastructure to evaluate vaccines against tuberculosis.

- Development of an effective vaccine will first require a significant commitment to basic scientific research to identify the immune mechanisms and antigens necessary or sufficient to elicit protection against tuberculosis.

  > The scientific advances of the past few years, including the sequencing of the entire genome of the tubercle bacillus, represent a promising beginning to understanding the nature of this pathogen and immune responses in animals to it. In a very short time, 50-100 candidate vaccines have been developed to the stage of evaluation in animal models. Greater understanding of human immune responses to the tubercle bacillus is required in order to learn which responses best correlate with resistance in the natural course of infection, and in individuals given the currently existing vaccine, BCG.

- Expanded facilities and training must be made available for the development and use of animal models, including both small animals and primates, to learn which of many vaccine candidates are safe and most likely to confer protection, and to select the most worthy for human clinical trials.

- There is a critical need for facilities to produce vaccine candidates arising from basic research under Good Laboratory Practice (GLP) or Good Manufacturing Practice (GMP), required to assure that products used in human vaccine trials are as safe and effective as possible.

- The ability to conduct vaccine trials will require establishing sites in the US that have the immunological and microbiological expertise to develop useful endpoints or surrogate markers of protection and where early human trials (Phase I and II trials) can evaluate safety and immunogenicity.

- To evaluate the protective efficacy of vaccine candidates, areas of the world with high tuberculosis rates of infection and disease will have to be identified that can provide the statistical power necessary for obtaining definitive results and can assure value-for-money in conducting human trials.

- Long-term international scientific collaborations need to be encouraged and initiated, with training and infrastructure development, to enable study of tuberculosis epidemiology, and development of sites where large scale, long term field trials can best be carried out.

- There will be a continuing need for epidemiologic surveillance in vaccine trials, repositories for specimens, centralized data management and clinical monitoring of trials.

- In both human and economic terms, prevention of tuberculosis is preferable to treatment of the disease. An effective vaccine strategy is justified in the US by projected reductions in risks for disease from global travelers, treatment costs, patient care costs and program costs. An investment of $800 million over 20 years to develop an effective vaccine would approximate the cost of control and treatment of tuberculosis in the US for a single year, currently estimated to be $700 million (Batelle study, 1995, Arch Int Med, 155:1595-600). The return in health benefits of a vaccine that is 80% effective in preventing tuberculosis over the next 50 years would be to prevent 135 million cases of tuberculosis and 40 million deaths from tuberculosis.

One of the historic ironies of tuberculosis research is that it has always been assumed that the current interventions would eliminate this disease as a major public health problem. BCG, an attenuated bovine tuberculosis strain was discovered in 1908, and was thought to be the vaccine for tuberculosis. Streptomycin in the1940's was hailed as the wonder drug for tuberculosis. Yet even with better antibiotics, tuberculosis remains a major global health problem. Concomitant with these historically shortsighted miscalculations were reductions in support for research on new tools and strategies, based on the assumption that with existing interventions the disease would disappear. It has not. We recommend a concerted national effort to develop a vaccine or vaccines that would have a significant impact on tuberculosis in the US and globally.

THE GLOBAL BURDEN OF TUBERCULOSIS

Infectious diseases remain the largest cause of death in the world, and among infectious diseases tuberculosis is responsible for the greatest number of deaths. Each year, 54 million people are infected with the tubercle bacillus *(Mycobacterium tuberculosis)*, 6.8 million develop clinical disease and 2.4 million people die of tuberculosis. Tuberculosis is responsible for 5% of all deaths worldwide, and 9.6% of adult deaths in the 15-59 age group. Tuberculosis kills more women worldwide than all causes of maternal mortality. The case fatality rate of tuberculosis is high; approximately 50% of untreated cases die of the disease.

Tuberculosis is transmitted by the respiratory route, and the principal risk factor for acquiring infection is breathing. Most infected individuals develop a latent or persistent infection that can reactivate at any time during the individual's lifetime; on average, 10% of infected individuals will develop active disease over their lifetime. It is estimated that there are currently 10-15 million people in the US and 2.1 billion people worldwide who are infected with the tubercle bacillus and whose infection could reactivate. Thus, the major current strategy of treating only patients with active disease limits our ability to control tuberculosis and will require decades to reduce the incidence of disease significantly.

Until the mid-1980s, tuberculosis in the United States had been declining, a trend which probably began over 70 years previously due in large part to improved living conditions and public health measures. Then starting in 1986 there was a dramatic rise in the number of new cases (to 27,000 in 1992). This increase has been attributed to a number of factors, including deterioration in the public health infrastructure, rising numbers of homeless individuals and the growing AIDS epidemic. In recent years explosive outbreaks of tuberculosis have devastated hospitals, prisons and schools, and new strains have emerged with increased transmissibility. Since 1992, there has been once again an annual decline in tuberculosis case rates in the US, but the economic costs of this tuberculosis control have been and continue to be enormous. New York alone expended $750 million between 1993-1996 to protect hospitals and jails, assure compliance with treatment and reduce multidrug resistant tuberculosis. The increase in cases above the expected number in the US during the 1980's and early 1990's (excess cases) was 68,000, which on average cost $25,000/case. The cost of multidrug resistant cases was found to be as high as $250,000 per case (D. Snider, TB Eradication, CDC, MMWR 39:369-371,1990). The current cost of tuberculosis control in the US is estimated to be approximately $700 million to $1 billion per year (Brown RE et al, Arch Intern Med, 155:1595-1600, 1995).

While the US has controlled tuberculosis more successfully in recent years, a

number of factors point toward future increased tuberculosis risk even in the US. Over the course of this century, there has been a steady rise in population density in the US (3.4-fold since 1900), and tuberculosis rates are highest in urban areas. While environmental control strategies have successfully reduced the spread of tuberculosis infection in hospitals, it is difficult to effectively adapt these measures to individual households or community group settings. In addition, the ominous emergence of multidrug resistant tuberculosis is a concern both in the US and abroad. In the US, multidrug resistant strains were detected in 43 states and the District of Columbia between 1993-1997 compared to only 13 states in 1991. In countries such as S. Korea and China, resistance to isoniazid, the major drug, is 10-15%, and in parts of Russia and Eastern Europe, resistance to isoniazid is virtually 100%.

Compounding the impact of tuberculosis is the co-epidemic of HIV/AIDS. Susceptibility to tuberculosis is one of the earliest manifestations of immunosuppression in HIV infection, and tuberculosis has been shown to be the attributable cause of death in a third of AIDS patients in Africa. While the lifetime risk of developing tuberculosis for immunocompetent individuals in the US is approximately 10%, for HIV infected individuals the risk is markedly increased to 4-8% annually.

With the globalization of the economy has come a globalization of health risks. There are 500 million international travelers, 5000 airports supporting international travel, and 49 million international travelers who enter the US each year. While the majority of tuberculosis patients here are US born, an increasing percentage of cases in the US (now approximately 39%) is observed among the foreign-born. The failure to develop measures to prevent and treat tuberculosis everywhere threatens our ability to control the disease anywhere, including in the US.

The tools (drugs and, in low endemic areas, skin testing) used to treat and prevent tuberculosis were developed in the first half of this century and are inadequate for today's epidemic. The most effective tuberculosis treatment strategy, Directly Observed Treatment, Short-course (DOTS), has been adopted as the World Health Organization strategy for the global control of tuberculosis. DOTS requires that drug therapy be supervised to assure compliance. Unfortunately, this requirement and other significant barriers limit DOTS implementation; it is currently available to only 12% of patients with active disease worldwide. In addition, chemotherapy is expensive, has significant side effects and a cure requires 6-9 months of directly observed therapy. As a consequence, patient compliance is difficult to maintain even in countries with strong tuberculosis control programs. Moreover, current DOTS drugs are largely ineffective against MDR-TB, a growing concern. Preventive chemotherapy to block the conversion of infection to active disease may be a

useful tool, but limitations include difficulties in identifying the best population for treatment and in assuring compliance, and the hazards of exposing this group to potential drug toxicities.

BCG is the only currently available vaccine against tuberculosis and is the most widely administered of all vaccines in the WHO Expanded Programme for Immunization. It demonstrably confers protection from disseminated and meningeal tuberculosis in children, which are associated with high mortality rates, and it has recently been shown to protect against leprosy, but its efficacy in preventing pulmonary tuberculosis in adults has varied dramatically in careful studies in different parts of the world (from 77% in the UK to 0% in India). As a result, its effect on the epidemiology of tuberculosis has been negligible. BCG vaccine is not recommended for general use in the US because the vaccine has low efficacy and interferes with skin test screening. In 1989, the US Advisory Council for Elimination of Tuberculosis (ACET) published a strategic plan for tuberculosis elimination in the US by the year 2010. Tuberculosis incidence in the US is now 74-fold higher than it should be to accomplish this elimination goal. ACET therefore recently declared that "Without a breakthrough in intervention strategy (i.e., a new TB vaccine), the global toll of TB will not be reduced substantially, nor will the disease be eliminated in the United States and other low-incidence countries...." (Centers for Disease Control and Prevention. ACET. MMWR 1998;47 (No. RR-13):3). Current models (Murray C and Salomon J, PNAS 1998,95:13881-13886; Blower SM, Small PM, and Hopewell PC. Science 1996;273:497-500) demonstrate the beneficial effect that would result from combining effective vaccination with antituberculous treatment.

OPPORTUNITIES IN TUBERCULOSIS RESEARCH

With the rise of tuberculosis in the US and Europe in the 1980's and 1990's, and the emergence of drug resistance as a major problem, support for tuberculosis research at NIH and for disease control at CDC increased in recent years. Despite the difficulties of working with the tubercle bacillus, its slow growth and biohazard safety considerations, a number of new opportunities and potential vaccine concepts and strategies have already emerged. The sequencing of the genomes of two strains of *Mycobacterium tuberculosis* are making available the DNA sequences of all 4000 genes of the pathogen to scientists all over the world. This information will be used in part to help identify antigens that confer protection against tuberculosis. In only a few years, over 100 vaccine candidates have emerged that deserve screening in small animal models and this number is likely to increase. Since the necessary and sufficient immunologic mechanisms of resistance to tuberculosis remain unclear, it will be necessary to pursue many candidates to identify those most promising to be brought forward for human trials. Vaccine

concepts currently being investigated in experimental animals include:

1. **Live attenuated vaccines:** either genetically modified BCG vaccines expressing protective antigens of *M. tuberculosis*, or genetically engineered mutants of *M. tuberculosis* that are attenuated, and have lost both the ability to produce disease and revert to virulence. Other live attenuated vaccines would utilize protective antigens of *M. tuberculosis* expressed in live attenuated vectors, such as vaccinia or avipox viruses, or engineered bacteria such as salmonella and listeria. Advantages of these vaccines are their potential ability to engender immunological memory that persists for long periods of time, induce immune responses at mucosal surfaces, and be relatively inexpensive to manufacture. A disadvantage is the risk of adverse effects engendered by any live attenuated vaccine, particularly in immunodeficient hosts.

2. **Subunit vaccines:** consisting of proteins or peptides, and possibly lipids and carbohydrate antigens. Several subunit vaccine candidates have been shown to contribute to protection in animal models, when given in adjuvant formulations that enhance their ability to generate immune responses and perhaps increase the duration of protection. Given that *M. tuberculosis* has 4000 genes each encoding a different protein, there will be many antigens to screen and a great need to simplify the logistics of prioritizing candidates to identify the most promising proteins. The advantage of subunit vaccines is that they consist of defined molecular components, which in general elicit fewer adverse reactions and are easier to manufacture reproducibly than whole cell vaccines. A limitation of this approach is that the purification of subunit material is relatively expensive and duration of immunity relatively short lived. Booster shots and complex adjuvants or delivery systems are likely to be required.

3. **Naked DNA vaccines:** consisting of DNA encoding protective antigens, which can be produced and purified relatively inexpensively in *E. coli*. The DNA is injected into the muscle or the skin, and the protective protein antigens are expressed by the host's own cells. This represents an exciting new approach to immunization. It is noteworthy that responses in small animals have included both cytotoxic T cells and antibodies, and in a significant proportion of cases, have persisted for long periods of time. Although long-term efficacy and safety of naked DNA vaccines have not yet been established in humans, advantages of these vaccines include simplicity and the possibility of introducing multiple antigens at low cost.

How to choose the most promising candidate vaccines for entry into clinical trials

remains a complex but critical question. The best approach currently available is to screen the vaccine candidates in animal models, but there are limitations to the existing animal models. Mice are intrinsically resistant to tuberculosis and not very discriminating of efficacy above a particular threshold; guinea pigs are more susceptible, but more expensive to study. Both can be challenged by an aerosol route resembling the route of human infection. Neither model readily lends itself, at present, to screening for protection against induction of latent or persistent infections, and a major priority for research should be to develop better models for studying how to prevent and cure persistent infection. Expanded small animal screening capacity for testing vaccine candidates will be required to accelerate vaccine development. Because of limitations in each of the existing small animal models of tuberculosis, the possibility of establishing a primate challenge model that more closely resembles human disease must also be given consideration.

Optimized animal models are also critically needed for the development of easily measured immunological correlates and surrogate endpoints for protection. The development of correlates of protection and, ultimately, surrogate endpoints will require basic research to define the immunologic mechanisms required for engendering protection in animal models, and simple tests measuring those mechanisms that can be applied to each of the vaccine candidates in animals and in human trials. Current knowledge is inadequate concerning the roles of specific T cell subsets, lymphokines, cytokines, and antibodies to the tubercle bacillus in mediating protection or in serving as correlates of mechanisms critical for immunity.

STRATEGIES FOR DEVELOPING TUBERCULOSIS VACCINES

The basic epidemiologic pattern of tuberculosis indicates that, of people infected with *M. tuberculosis,* only 10% develop disease in a lifetime. This suggests there is a natural protective immune response in most individuals. This suggestion is corroborated by the tragic finding that individuals whose immune response is compromised by HIV infection have a vastly heightened risk of developing tuberculosis. Thus one of the goals of vaccination against tuberculosis is to strengthen the natural immune responses developed against the tubercle bacillus in most people, in order to increase the percentage of infected individuals who remain disease free. Another goal is to improve on natural immune responses, in order to guarantee that higher and more lasting levels of protection are induced by vaccines than by natural infection. The scientific challenge is to raise the level of protection without creating significant tissue damage or adverse effects.

Characteristics of an <u>ideal</u> vaccine: An ideal vaccine against tuberculosis should: i) be safe; ii) have demonstrated protection in animal models; iii) protect against disease, and also against infection; iv) be protective after a single or, if necessary,

small number of doses, preferably not requiring administration by injection; v) be long-lasting and able to engender immunological memory; vi) not compromise the tuberculin skin test for diagnosis; vii) be inexpensive to manufacture; viii) be heat stable and have a long shelf life; and ix) not interfere with protection engendered by other vaccines, and x) be capable of being integrated into existing immunization schedules. However, a candidate that falls short of one or more of these ideal characteristics could still prove extremely useful. A dialog within the tuberculosis research and public health communities to determine characteristics of a minimally acceptable vaccine would also be valuable.

What kind of immune responses are to be sought, and what level of protection can be accepted? Most vaccines in use today against infectious diseases, such as MMR and DPT, protect against disease, not infection. Similarly, no vaccine to date has protected animals from infection with the tubercle bacillus ---- rather they protect against development of clinical disease. The question is whether 'sterilizing immunity' is possible by immunization against tuberculosis, or whether vaccines that render infections subclinical and prevent reactivation are adequate for this disease as they have been for so many others. At present it is not known how to prevent infection with the tubercle bacillus, or even how to prevent reactivation of old infections. These are questions that need to be addressed in animal models.

There are clearly defined steps required for evaluating vaccine candidates in humans. Phase I safety trials, with as few as 10-60 volunteers, are designed to establish safety from adverse effects and establish maximal tolerated doses of vaccine formulation. If this milestone is achieved, Phase II expanded safety trials are undertaken, usually with 200-300 subjects, to screen for lower frequency adverse effects, to characterize responses to different doses and schedules, and importantly to establish what immunological responses are elicited by the vaccine. For example, this might include T cell proliferative responses to antigen, induction of lymphokines such as interferon-gamma and tumor necrosis factor, cytotoxic T cells, and antibodies to specific antigens of the pathogen. Phase II trials represent the first opportunity in humans to examine easily measured immunological parameters that may be correlates of protection, and may ultimately be used as surrogate endpoints in subsequent clinical trials. When a vaccine candidate emerges that produces the immune responses thought to be necessary for protection without significant adverse effects, then large scale Phase III trials (in the case of tuberculosis, likely to require 7,000 - 300,000 subjects) to determine vaccine efficacy and search for even lower frequency adverse effects can be undertaken.

At least three different Phase III trial designs for tuberculosis vaccine candidates have been suggested:

1. **Pre-infection vaccine trial.** The test of a pre-infection vaccine would be immunization of skin test negative individuals, children or young adults, not previously infected with the tubercle bacillus. Here the goal would be to prevent primary infection, or at least progression to disease, and to prevent the establishment of a latent or persistent infection. Questions that need to be addressed are whether optimal cell-mediated immune responses by the appropriate T cell subsets can localize whatever infection occurs and either kill the invading organisms or totally prevent their spread, and whether antibodies and mucosal immune responses to the tubercle bacillus can prevent infection. The advantages of this strategy are that one can generate an immune response in an individual before infection that may be sufficient to provide full protection in most subjects. A disadvantage of this strategy is that, since most adult cases of tuberculosis occur following the age of 15y, it could require 20-30 years to evaluate protective efficacy fully.

2. **Post-infection vaccine trial.** This trial strategy targets the population at highest risk to develop active tuberculosis, those apparently healthy individuals already infected with the tubercle bacillus. The annual rate of progression of infected individuals to active disease in some parts of the world can be as high as 3-5% per year; thus with this strategy, one could evaluate vaccine efficacy in 5-10 years. It is unclear, however, whether once the tubercle bacillus establishes infection, immune responses induced by vaccines will be able to stop progression to disease or to kill existing latent or persisting bacilli. There are few precedents in BCG studies in animals or humans that indicate whether BCG is effective in already infected individuals.

3. **Total population vaccine trial.** One strategy taking advantage of the best of both of the other strategies would be to carry out vaccine trials for efficacy in total populations in regions of the world with a high risk for infection. If the recipients were first skin tested to identify those previously infected, it would be possible to get information on the effectiveness of vaccines in previously infected individuals within the first 5-10 years and on previously uninfected individuals during a longer follow-up period.

Immunologic correlates and surrogates of protection: Since efficacy trials of tuberculosis vaccines inevitably will be complex, requiring large numbers of recipients followed for long periods of time, it will be critical to provide generally accepted clinical and laboratory definitions of infection and disease and to define meaningful endpoints of protection. Phase II trials provide the critical opportunity to identify immunological correlates of protection that can be measured simply and

quickly. These correlates will then be tested in efficacy trials to learn whether they represent valid surrogate endpoints that predict protection. It will be of particular importance to note whether changes in potential surrogate markers induced by vaccination, e.g. bacilli in sputum or cytotoxic T cells, correspond to changes in levels of protection. There is likely to be a need for highly coordinated studies, in which standardized assays can be developed and used to assess correlates and endpoints, and standardized databases are developed for dose, dose schedules, adjuvants, and responses to immunization with other vaccines, particularly childhood vaccines. There must be the capability of introducing new vaccine candidates over time into the general protocol. For both Phase II and III trials, carefully organized repositories of human samples will need to be established so that maximum knowledge can be gained. Such studies enhance basic knowledge of the candidates and provide the best analysis of candidates most likely to be worthy of large-scale efficacy trials. Since efficacy trials will of necessity be large and long, the critical scientific information on the most likely candidates to be advanced to efficacy trials will have to be obtained largely from complex coordinated Phase II trials.

Size and duration required for efficacy trials: A fundamental relationship exists between vaccine efficacy, degree of certainty desired, number of subjects and duration required in a trial. For example, the power to distinguish definitively between two levels of vaccine efficacy is determined by the number of endpoints (cases of active tuberculosis, for example) expected to be observed in the control group. Trials designed to observe about 60-100 endpoints in the control arm will have 90% power to distinguish vaccine efficacy of 30% (null hypothesis) from 70% (alternative hypothesis), or efficacy of 50% from 83%. For post infection vaccines, assuming annual rates of progression to disease of 0.05-0.2%, a trial with 6,000 to 24,000 total participants followed for 10 years would provide the power required. For preinfection vaccines, populations with infection rates of 1-2%/year, and a 20 year trial would be required, involving 20,000 to 130,000 individuals. In addition, the likely dropout rates must be taken into account in long-term trials, and more subjects entered into the study to assure the power of the final results. The history of BCG trials offers precedent that these numbers are feasible. Nevertheless it must be recognized that trials of this size and duration are technically very demanding.

The need for international collaborations: tuberculosis efficacy trials will require large populations at risk for tuberculosis that can be studied and followed carefully for many years. Although the rates of tuberculosis in the US and Western Europe are sufficiently low that Phase III efficacy trials, if at all feasible, would have to be very long and expensive in these countries, Phase I and II trials could effectively be carried out there for a limited number of vaccine candidates. The large scale trials

required for evaluating vaccine efficacy are likely to require large cohorts at relatively high risks for infection or progression to reactivated disease. This almost certainly will require collaborations with scientists and study of populations in high endemic countries in Asia and Africa. Any such trials will require the involvement and support of the governments and local populations. To carry out effective trials, there will be a crucial need for detailed epidemiologic knowledge of the tuberculosis problem in the sites selected for trials, and competent laboratory facilities for diagnosis, immunologic studies and evaluating surrogate endpoints. Independent of the protective efficacy of any particular vaccine candidate, such large-scale trials provide an extraordinary opportunity to develop new techniques for analyzing and measuring immunological correlates of protection and the natural course of tuberculosis within populations. Such complex international trials will require long-term investments in training, and infrastructure development in epidemiology, immunology, and data management, which will remain as a permanent scientific legacy to the developing country collaborators.

The need for national collaborations: Development of a working partnership that links the expertise of the NIH in basic science, CDC in epidemiology, FDA in regulatory affairs and interactions with industry, USAID in international health, and academic and industrial researchers will be critical, in addition to close links with WHO and the International Union Against Tuberculosis and Lung Disease for their global experience in tuberculosis control, and with scientists and health workers in countries that have both the need and the infrastructure to evaluate vaccines against tuberculosis.

Logistics: For obtaining definitive results, there must be consensus regarding case definitions, defined endpoints, standardized protocols and safety studies, good communications between centers, competent laboratory infrastructure with verified quality assurance and quality control of reagents, methods and data, supply and resupply of necessary reagents in overseas sites, patient-friendly study clinics to ensure that patients return for follow-up, and appropriate drugs and personnel for adequate treatment of any cases of tuberculosis occurring within the trial cohorts.

RISKS, UNCERTAINTIES AND CONCERNS IN DEVELOPING TUBERCULOSIS VACCINES

Uncertainties exist at all levels in the development of a cost-effective new vaccine against tuberculosis. At the population level, we cannot yet anticipate the number of vaccine candidates to be tested in clinical trials, the number and duration of trials required to establish safety and efficacy, the maximal degree of efficacy that can be achieved, or the demand for, or cost-effectiveness of, such vaccines. At the scientific level, we do not know the precise immunological mechanisms necessary

and sufficient for protection, the best antigens to elicit protective responses, the optimal way to deliver a vaccine, the predictive value of existing animal models, potential adverse effects, or surrogate endpoints for protection. The best populations for evaluating vaccines, i.e. those with high incidence and well-developed infrastructures, remain to be defined. These issues form the basis of the scientific agenda required. Uncertainties exist within the vaccine industry as to the markets for tuberculosis vaccines, and the willingness of public and private sectors to pay for such vaccines, and possibilities for economic returns. Finally, the extraordinary effectiveness and low cost of childhood vaccines against polio, measles, etc, may lead to a number of unrealistic expectations, for example, about the degree of efficacy that can be achieved against a formidable pathogen such as tuberculosis, the time required to reduce the transmission and burden of disease, the cost involved in developing such a vaccine, and the economic returns possible from a vaccine for a disease primarily afflicting populations of developing countries.

Political considerations: For collaborative research in developing countries, it is essential that the trial design meet the needs of the host country, and that there is full participation of investigators of the host country from the beginning. Beyond the formalities, and involvement of the study populations and investigators involved, there needs to be engagement of the medical community and public at large. A public awareness of what is being done needs to be created, so that the risks and benefits likely to affect the individuals and communities involved in the trials are understood and accepted.

Ethical concerns: Informed consent must be obtained before any subjects are vaccinated. To assure this, protocols must be reviewed by local IRB's, collaborating institution IRB's, and social scientists should be involved in verifying that consent is freely given and truly informed. Individual, community and family rights must be considered from the beginning, and the risks and benefits accruing to the trial subjects and communities must be fully discussed. Adequate medical care must be provided for those who contract tuberculosis in the trial cohort. Assurance of the "reasonable availability" of the vaccine product if it is found to be effective in the trial must be provided to the subjects and the public.

Ideally, in vaccine efficacy trials, subjects should be randomized, and the investigator and subjects blinded to the nature of the vaccine being given. This may require a placebo with similarities to the vaccine to be tested, and hopefully of some benefit to the recipients, to be tested in a control group, or the careful and gradual substitution of the new vaccine to be compared with BCG, if BCG is the currently used vaccine.

Despite these difficulties and the long term commitment required, we must commit

TUBERCULOSIS VACCINE ACTION PLAN

The above report has outlined the urgent global need for an effective tuberculosis vaccine (see also Centers for Disease Control and Prevention. Development of new vaccine for tuberculosis: recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET). MMWR 1998;47 (No. RR-13):1-6), the scientific opportunities and risks involved in a concerted effort to develop such a vaccine, and general recommendations for accomplishing this critical task. This final section lays out specific strategic steps needed to make an effective tuberculosis vaccine a reality. These include additional targeted basic (or laboratory) research, manufacturing needs, and requirements for testing in human volunteers. It is estimated that the costs of this effort (above the current limited expenditures on tuberculosis research in the US and globally) would be approximately $800 million dollars over a twenty year period.

1. Vaccine-targeted Laboratory Research

- Development of improved animal models of tuberculosis, including models of persistent infection and reactivation disease. Will likely require additional animal facilities (Biosafety Level 3).

- Elucidation of the mechanisms by which: 1) *M. tuberculosis* bacteria, and the host response to those bacteria, cause tissue damage and 2), model animals and the human host protect themselves immunologically from disease. May require development of a primate model.

- Identification of immunologic correlates of animal and human protection against *M. tuberculosis*.

- Identification of protective antigens and virulence genes of *M. tuberculosis* in order to rationally develop candidate vaccines.

- Development of diagnostic tools that distinguish individuals infected with *M. tuberculosis* infection from individuals with active tuberculosis disease from individuals previously vaccinated with BCG.

Necessary expertise for this research will likely be drawn largely from the academic community with contributions from interested industry scientists. To effectively streamline the vaccine development process, the above areas of basic research should be pursued simultaneously with limited empiric testing of vaccine candidates

in the best available animal models.

1. Production Of Vaccine Candidates for Animal and Human Testing

- Establish pilot manufacturing facilities that meet Good Manufacturing Practice (GMP) standards for products to be delivered to human subjects. GMP facilities may be most readily found in industrialized countries, but developing country scientists should be involved in the manufacturing process to increase trust in the product in countries where efficacy trials may be held.

- NOTE: A successful scale-up manufacturing plan should be developed for each candidate that will enter a large efficacy trial before the start of the trial.

- Establish repositories for human and animal samples acquired during trials.

- Identify and develop adequate reagent sources and supplies.

- Develop assays for the efficient evaluation of vaccine candidates in animal and human trials.

Manufacturing expertise will likely be drawn primarily from industry.

1. Testing in Human Subjects

Efficient translation of basic research findings into the clinical arena and rapid movement of developed vaccine candidates into human trials will be crucial, and will require a focused, coordinated effort involving multiple types of expertise. The needed participants might include mycobacteriologists, animal model developers and vaccine testers, epidemiologists, clinical trials specialists and vaccine biologists, on-site physicians, nurses and support staff, regulatory personnel, and local tuberculosis control officers. One way to create effective collaborations of this type might be to establish Tuberculosis Vaccine Research Units (TVRUs). TVRUs could be charged with developing needed diagnostic and laboratory assays, establishing and maintaining trial sites, conducting appropriate field and epidemiologic research, soliciting promising vaccine candidates from investigators worldwide, and rapidly moving these candidates into clinical trials, while also using trials to begin evaluating correlates of protection as potential surrogate markers of vaccine efficacy. (Such markers would be invaluable in subsequent large efficacy trials). Establishing multi-disciplinary teams or networks to accomplish these goals could expedite progression from laboratory bench to clinical trial.

- Phase I (safety and immunogenicity) trials will require protocol development and preparation of trial sites. These could be in the US, other industrialized nations and/or developing countries. Such trials typically involve 10-60 human subjects. The necessary preparations may include infrastructure development, training, and epidemiological and surveillance groundwork, depending on the needs of the site.

- Phase II (expanded safety and immunogenicity) trials may require establishment of data coordinating centers, central laboratory facilities and/or standardized methodologies, a Data and Safety Monitoring Board and a coordinated mechanism for candidate vaccine selection. These trials typically involve a few hundred human subjects.

- Phase III (large efficacy) trials involving thousands of subjects will additionally require more substantial infrastructure, sophisticated trial design, and intensive pre-trial epidemiologic studies and surveillance to determine the local prevalence (total number of cases) and incidence (number of new cases identified per year) of tuberculosis disease, as well as the prevalence of BCG administration and exposure to non-pathogenic environmental mycobacteria.

  > Phase III trials will need to occur in populations with high prevalence and incidence of tuberculosis, and therefore are likely to involve sites in developing (as well, perhaps, as in industrialized) countries.

  > Phase III trial sites may be used initially (while new candidate vaccines are in earlier stages of development) to learn more about BCG and what factors are responsible for its variable efficacy against tuberculosis in different settings and in childhood extrapulmonary versus in adult pulmonary tuberculosis. Understanding the failure of BCG in some parts of the world would contribute a great deal to the ability to create a more effective tuberculosis vaccine.

  > Successful Phase III trials will likely require a pre-established agreement and cooperative effort among international and US funding and regulatory agencies, industry, academic scientists, tuberculosis control programmes, and involved governments.

- All phases of vaccine testing in human volunteers will likely require:

  > Staff training at clinical trial sites located in developing and industrialized countries.

- IRB and ethical reviews by all involved countries.

- Optimization of promising vaccine candidates and delivery parameters through expanded animal model testing.

- Disease monitoring and treatment.

- HIV testing and subsequent counseling of human volunteers.

- Workshops for government and health care staff in trial site countries.

- Adequate sources of reagents and supplies.

- Core laboratory facilities for development and use of standardized methods and assays.

- Sample and strain repositories.

- Productive collaborations between developing and industrialized countries at the government as well as scientific and health care levels.

Most importantly, successful development of effective tuberculosis vaccines will require a sustained commitment and extensive collaboration among participating governments, scientists, vaccine manufacturers and health care personnel both within the US and internationally, including developing and industrialized nations as full partners.

Research Plan for
Malaria Vaccine Development
National Institute of Allergy and Infectious Diseases

AREAS OF RESEARCH CURRENTLY SUPPORTED

NIAID supports research on basic parasite biology, diagnosis, immunology and vaccine development, pathogenesis, drug discovery and development, and vector biology. In FY96, the Institute spent $19.2 million on malaria research (intramural plus extramural).

Within the *Division of Microbiology and Infectious Diseases* (DMID), the extramural portfolio currently consists of:

- unsolicited investigator-initiated research grants (approximately 95 percent of which focus on laboratory-based studies in vitro or in animal models).
- 3 ICIDR awards and 1 TMRC award for research in endemic areas.
- 1 research contract, supporting a clinical trial of adjunct therapy.
- 2 Phase I/II vaccine trials in DMID Vaccine and Treatment Evaluation Units (VTEUs).

NIAID currently has four active solicitations which may impact on malaria research but are not specific to malaria:

- PA 96-048, Expanded Research on Emerging Diseases.
- PA 96-067, Molecular Correlates of Pathogenesis in Parasitic Diseases.
- PA 97-002, Human Immune Resistance to Malaria in Endemic Areas
- PA 97-027, Immunologic Interventions in Infectious Diseases.

Within the *Division of Intramural Research* (DIR), the Laboratory of Parasitic Diseases conducts the NIAID intramural vaccine research effort, including:

- the Recombinant Protein Expression Unit.
- a collaborative program with Malian scientists at the Malaria Research and Training Center of the National School of Medicine and Pharmacy to develop a vaccine testing unit.

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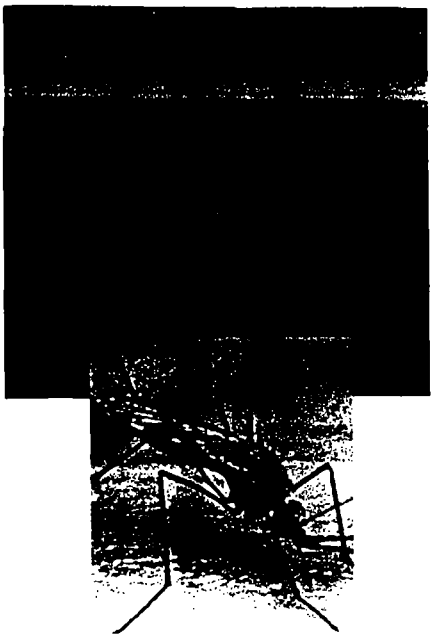

MALARIA RESEARCH

AN AUDIT OF INTERNATIONAL ACTIVITY

PRISM Report no. 7

J Anderson, M MacLean and C Davies

September 1996

MAIN FINDINGS

Funding

Total identifiable global expenditure on malaria research in 1993 was approximately US$84 million. Over half the total came from the USA (especially the US Agency for International Development, USAID, and the National Institute of Allergy and Infectious Diseases, NIAID). Much of the remainder came from Europe (notably the Wellcome Trust and the Medical Research Council, MRC, in the UK), or from the Programme in Research and Training in Tropical Diseases (TDR) which is cosponsored by the United Nations Development Programme, the World Bank and the World Health Organization (WHO), as well as several governments, especially in Scandinavia.

Funding has declined in some organizations over the past decade, most notably in USAID. However, there have been increases elsewhere, especially at the Wellcome Trust, NIAID and the US Department of Defense (DoD). Support went mainly to researchers in Europe and the USA. The exceptions were to be found in the funding initiatives of the TDR programme, the Wellcome Trust, the UK MRC, the European Union (EU) and USAID, which encouraged international cooperation. Notable among these were the overseas units supported in malaria-endemic countries by the Wellcome Trust and the UK MRC.

The overall conclusion to be drawn is that global investment in research is very low compared with other disease areas over the past 10 years, and appears to be declining further. Expressed as investment in research per death, malaria research (at approximately US$42 per fatal case) receives markedly less funding than other diseases such as cancer, HIV/AIDS or asthma.

Research outputs

International publishing activity largely reflected the pattern of funding and was very low compared with other biomedical fields. The USA is currently the largest single contributor to the malaria research literature (34 per cent of the global total in 1994), but its world share of publications has been declining over the past 10 years (from 42 per cent in 1984). Meanwhile, the trend from the UK is up, from 14 per cent of the world total in 1984 to 18 per cent in 1994. The world share of malaria publications from France, Australia and Thailand also increased.

UK centres for collaborative research located in malaria-endemic countries appeared to foster international coauthorship. A total of 38 per cent of UK output was internationally coauthored and largely reflected the work at the overseas units of the Wellcome Trust and UK MRC.

Citations to papers supported by the six funding bodies contributing most to malaria research were more numerous than citations to papers supported by other organizations. In 1989, the most recent year for which citation analysis was conducted, NIAID and the UK MRC appeared to have the greatest citation impact. For five organizations, the production of high-citation-impact papers remained more or less stable over time. These were the NIAID, the US DoD, TDR, the Wellcome Trust and the UK MRC. For one funding body (USAID), there was an apparent decline in its proportion of high-impact papers over time.

Activity in different subfields of malaria research

The field of malaria research was divided into 14 subfields, and research publications were assigned to each of these. 'Clinical' research papers accounted for 42 per cent of the world total, describing studies of malaria in humans ranging from clinical management and pathophysiology to human immune response and genetic susceptibility. 'Non-clinical' papers accounted for 58 per cent of the world total, describing studies of malaria in animal models or *in vitro* and basic studies on mosquito vectors.

Table 2.1 Summary of identified funding support for malaria in financial year 1993 (FY 1993)

Funding organization	Funding for malaria research ($ million 1992 base year)
United States Agency for International Development (USAID)[7]	15.1
National Institute of Allergy and Infectious Disease (NIAID) (USA)	13.1
Department of Defense (DoD) (USA)[8]	~11.6
Research and Training in Tropical Diseases (TDR) Programme[9]	9.0
Wellcome Trust (UK)[10]	7.1
Medical Research Council (MRC) (UK)	6.8
European Union (EU)	2.6
National Institute of Health and Medical Research (INSERM) (France)	2.3
Centers for Disease Control (CDC) (USA)[11]	2.2
National Health and Medical Research Council (NHMRC) (Australia)	1.8
Overseas Development Administration (ODA) (UK)[12]	1.6
International Development Research Centre (IDRC) (Canada)[13]	1.4
The Mexican government[14]	1.2
Directorate General for International Cooperation (DGIS) (The Netherlands)	1.1
MacArthur Foundation (JCM) (USA)	1.0
Institute for Scientific Research for Development and Cooperation (ORSTOM) (France)	1.0
Others	~5
Total	**~84**

[7] The USAID figure is for research and field programmes

[8] DoD data for FY 1993 were not available. The data presented here are for 1995 (adjusted to 1992 US dollars).

[9] The TDR programme is supported by voluntary contributions from governments, international organizations, charities, other non-governmental bodies and the three co-sponsors of the programme – the World Health Organization (WHO), the World Bank and the United Nations Development Programme (UNDP). The figure of $9 million given represents malaria funding only, and not the additional tropical diseases covered in the Programme.

[10] Funding for malaria research at the Wellcome Trust increased markedly in FY 1994 to $10.6 million.

[11] The CDC figure is for research and control activities.

[12] ODA data for FY 1993 were not available. The data presented here are for FY 1992, which is to say April 1992–March 1993

[13] IDRC reported that its funding of malaria in FY 1993 was unusually high.

[14] This figure, which is for FY 1994, is believed to be an underestimate of government expenditure as it represents the support given to one research organization only.

allocation, the MVD portion fluctuated and has decreased by more than half in FY 1994. This reflected the overall decrease in malaria funding in that year, although the large loss of funds to MVD was partially offset by a small increase in funds to other central projects.

A geographical analysis of USAID's support for malaria research and field programmes is made difficult by the fact that the Agency's funding organization structure does not directly reflect the location of expenditure. For example, central funds managed by Washington may, and often are, reallocated and spent at the country level. Consequently, the specific allocation of malaria support on a geographical basis is not readily available.

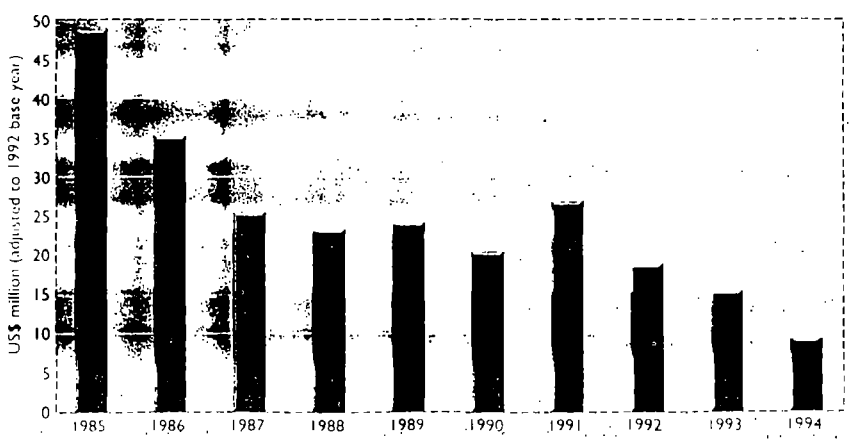

Figure 2.1: Funding for malaria research and field programmes by USAID