A Proposed National Strategy for Tuberculosis Vaccine Development

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The global tuberculosis epidemic causes ~5% of deaths worldwide. Despite recent concerted and largely successful tuberculosis control efforts, the incidence of tuberculosis in the United States remains 74-fold higher than the stated elimination goal of <1 case per million population by the year 2010. Current bacille Calmette-Guérin vaccines, although efficacious in preventing extrapulmonary tuberculosis in young children, have shown widely variable efficacy in preventing adult pulmonary tuberculosis, confound skin test screening, and are not recommended for use in the United States. The Advisory Council for Elimination of Tuberculosis recently stated that tuberculosis would not be eliminated from the United States without a more effective vaccine. Recent scientific advances have created unprecedented opportunity for tuberculosis vaccine development. Therefore, members of the broad tuberculosis research and control communities have recently created and proposed a national strategy, or blueprint, for tuberculosis vaccine development, which is presented here.

Introduction

From 1985 through 1992, there was an 18% increase in tuberculosis cases in the United States. In 1989, in response to this resurgence, the Advisory Committee for Elimination of Tuberculosis (ACET), in collaboration with the Centers for Disease Control and Prevention (CDC), published “A Strategic Plan for the Elimination of Tuberculosis in the United States” [1]. This plan set a goal of tuberculosis elimination (defined as a case rate of <1 per million population) by 2010. In 1996, the incidence of tuberculosis in the United States was 8.0 per 100,000 population [2]. Although this represented the fourth consecutive year that the number of tuberculosis cases had decreased in the United States and a 7% decrease from the previous year, 21 of the 50 states and the District of Columbia reported either no change or an increase in the number of tuberculosis cases [2]. The United States’s tuberculosis incidence was 80-fold higher in 1996 than the year-2010 elimination goal; in 1997, it remained 74-fold higher [3].

This somewhat disappointing, although significant, level of progress toward eliminating tuberculosis in the United States, as well as recognition of the worsening global tuberculosis epidemic and its impact on the United States, led ACET in 1996 to delineate for the Secretary of the US Department of Health and Human Services (DHHS) 4 major concerns regarding the United States’s program to control tuberculosis, as follows (Jeffrey R. Starke, M.D. [Chairman, ACET], in a letter to the Honorable Donna Shalala, 11 October 1996, personal communication). (1) Because an increasing percentage of patients with tuberculosis in the United States are foreign-born, the United States will need “to invest overseas and domestically to improve international tuberculosis control efforts.” (2) “Appropriate standards” for tuberculosis services in a managed care setting will have to be “developed and enforced.” (3) The national “focus and strategy” of CDC-based cooperative agreements through categorical funding of tuberculosis control activities “must be maintained.” (4) “Tuberculosis elimination probably cannot be achieved in the United States without the development of an effective vaccine.”

The research effort to develop the vaccine must be a federal priority, with adequate research funds made available. The only hope for tuberculosis control throughout the world is an effective vaccine.” ACET has recently expanded on the urgent need for new, more effective tuberculosis vaccines and has called for the development of “a comprehensive, consensual strategy” to achieve this goal [4].

To initiate creation of a broad-based strategy for tuberculosis vaccine development, the National Institute of Allergy and Infectious Diseases (NIAID), ACET, and the National Vaccine Program Office (NVPO) convened a workshop in March 1998 entitled “Blueprint for Tuberculosis Vaccine Development.” The Workshop was chaired by Dr. Barry Bloom, then of Albert Einstein College of Medicine and the Howard Hughes Medical Institute. Participants included representatives of the academic tuberculosis, vaccine development, and clinical trials research communities, vaccine manufacturers, ACET, CDC, the World Health Organization (WHO) Steering Committee on the Immunology of Mycobacteria, the International Union Against Tuberculosis and Lung Disease (IUATLD), the US Food and Drug Administration (FDA), the NVPO, and NIAID.

This group discussed the global burden of tuberculosis; current opportunities in tuberculosis vaccine research; strategies for developing tuberculosis vaccines; and the risks, uncertainties, and concerns inherent in a major effort to develop tuber-
culosis vaccines. Participants agreed that (1) effective tuberculosis vaccines are urgently needed and that (2) the development of these vaccines will require long-term commitment and sustained international, as well as national, collaboration. A draft document (“Blueprint for Tuberculosis Vaccine Development”) that summarized these deliberations was presented and discussed with a broad audience of tuberculosis researchers, controllers, and vaccine manufacturers at the NVPO’s International Symposium on Tuberculosis Vaccine Development and Evaluation, held in San Francisco in August 1998. Input gathered at that meeting was used to further develop the blueprint, and a final draft was endorsed by the National Vaccine Advisory Committee and ACET in October 1998 and November 1998, respectively. These 2 advisory groups are currently in the process of presenting the blueprint to the Secretary of the DHHS and her staff for consideration as a national priority.

Two points deserve extra emphasis. First, there are fears that a concerted effort to develop a tuberculosis vaccine will distract resources from the urgent necessity of treating current patients. My personal view is that this is not and should not become an “either/or” situation; vaccine development and tuberculosis control that use currently available tools are not competing priorities but are complementary ones. The intention of the blueprint report is 2-fold: to lay out a strategy for an efficient and effective tuberculosis vaccine development effort and to raise the profile of tuberculosis as an important problem in this country, as well as in other nations.

Current control strategies and development of improved vaccines should be synergistic efforts that benefit today’s tuberculosis patients and the tuberculosis patients of tomorrow. Second, the extended period often required for vaccine development must not discourage us from undertaking this challenging but urgently needed task. As William Shakespeare wrote, “Our doubts are traitors / And make us lose the good we oft might win / By fearing to attempt” [5]. Fearing to attempt to develop an effective tuberculosis vaccine may unnecessarily consign our children and grandchildren to a world still plagued by tuberculosis.

The Blueprint for Tuberculosis Vaccine Development and the list of participants in the March 1998 blueprint workshop follow.

**Blueprint for Tuberculosis Vaccine Development**

On 5–6 March 1998, the ACET (DHHS), NVPO, and NIAID (National Institutes of Health [NIH]) 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 world’s leading cause of death from any single infectious disease. It is a major killer of adults and the major attributable cause of death of people with HIV disease/AIDS. In addition to its immense human burden, it is a major economic burden in the United States and globally. Antituberculosis 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 United States. Despite limited resources for research on tuberculosis, new scientific advances encourage the view that the development of an effective vaccine to prevent tuberculosis is scientifically feasible and worthy of a significant national and international effort.

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; it also will lead to improved approaches to the development of diagnostic tools and the design of complex clinical vaccine trials. 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 are 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, which links the expertise of organizations (NIH in biomedical research, CDC in epidemiology, FDA in regulatory affairs and interactions with industry, USAID in international health, WHO, and 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 to it in animals. 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 bacille Calmette-Guérin (BCG) vaccine.

Expanding 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 ones 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 or good manufacturing practice, which are required to ensure that products used in human vaccine trials are as safe and effective as possible.

The ability to conduct vaccine trials will require establishing facilities in the United States that have the immunologic and microbiological expertise to develop useful end points 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 rates of tuberculous infection and disease will have to be identified that can provide the statistical power necessary for obtaining definitive results and can ensure value for money in the conduct of human trials.

Long-term international scientific collaborations need to be encouraged and initiated, with training and infrastructure development, to enable the study of tuberculosis epidemiology and the 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 United States by projected reductions in risk of 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 United States for a single year, currently estimated to be $700 million [6]. 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 due to 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, just as streptomycin in the 1940s 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 United States 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 deaths among adults aged 15–59 years. Tuberculosis kills more women worldwide than all other causes of maternal mortality. The case fatality rate for tuberculosis is high; ~50% of untreated patients 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 United States 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 that probably began >70 years previously, due in large part to improved living conditions and public health measures. Then, starting in 1986, there was a dramatic increase 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, increasing 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 United States, but the economic costs of this tuberculosis control have been and continue to be enormous. New York City alone spent $750 million from 1993 through 1996 to protect hospitals and jails, to ensure compliance with treatment, and to reduce the incidence of multidrug-resistant tuberculosis. The increase in cases above the expected number in the United States during the 1980s and early 1990s (excess cases) was 68,000, which on average cost $25,000 per case. The cost of multidrug-resistant cases was found to be as high as $250,000 per case [7]. The current cost of tuberculosis control in the United States is estimated to be $700 million to $1 billion per year [6].

Although the United States has controlled tuberculosis more...
successfully in recent years, a number of factors point toward future increased tuberculosis risk, even in the United States. Over the course of this century, there has been a steady increase in population density in the United States (3.4-fold since 1900), and tuberculosis rates are highest in urban areas. Although 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 United States and abroad. In the United States, multidrug-resistant strains were detected in 43 states and the District of Columbia from 1993 through 1997, compared with only 13 states in 1991. In countries such as South 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 coepidemic 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 one-third of patients with AIDS in Africa. Although the lifetime risk of developing tuberculosis is ~10% for immunocompetent individuals in the United States, for individuals infected with HIV the risk is markedly higher, 4%–8% annually.

With 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 United States each year. Although the majority of patients with tuberculosis in the United States are native to this country, an increasing percentage of cases in the United States (now ~39%) involve foreign-born persons. The failure to develop measures to prevent and treat tuberculosis everywhere threatens our ability to control the disease anywhere, including in the United States.

The tools (drugs and, in low-endemicity 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 strategy against tuberculosis, directly observed treatment (short-course; DOTS), has been adopted by the WHO for the global control of tuberculosis. DOTS requires that drug therapy be supervised to ensure compliance. Unfortunately, this requirement and other significant barriers limit implementation of DOTS; it is currently available to only 12% of patients with active disease worldwide. In addition, chemotherapy is expensive and has significant side effects, and a cure requires 6–9 months of directly observed therapy. As a consequence, compliance of patients is difficult to maintain, even in countries with strong tuberculosis control programs.

Moreover, current DOTS drugs are largely ineffective against multidrug-resistant tuberculosis, 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, difficulties in ensuring 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 protects children from disseminated and meningeal tuberculosis, 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 United Kingdom 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 United States because the vaccine has low efficacy and interferes with skin test screening.

In 1989, ACET published a strategic plan for tuberculosis elimination in the United States by the year 2010. Tuberculosis incidence in the United States 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 tuberculosis vaccine), the global toll of tuberculosis will not be reduced substantially, nor will the disease be eliminated in the United States and other low-incidence countries” [4]. Current models [8, 9] demonstrate the beneficial effect that would result from combining effective vaccination with antituberculous treatment.

Opportunities in Tuberculosis Research

With the increase of tuberculosis in the United States and Europe in the 1980s and 1990s and the emergence of drug resistance as a major problem, support for tuberculosis research at NIH and for disease control at the CDC increased in recent years. Despite the difficulties of working with the tubercle bacillus, including 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 2 strains of M. tuberculosis is 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, 50–100 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 for use in human trials. Vaccine concepts currently being investigated in experimental animals include the following.

- **Live attenuated vaccines.** These include genetically modi-
fied BCG vaccines that express protective antigens of *M. tuberculosis* and genetically engineered mutants of *M. tuberculosis* that are attenuated and have lost the ability to both produce disease and revert to virulence. Other live attenuated vaccines would use 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 immunologic 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.

**Subunit vaccines.** These consist of proteins or peptides and possibly lipids and carbohydrates that are expressed in *M. tuberculosis*. 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 the duration of immunity is relatively short-lived. Booster shots and complex adjuvants or delivery systems are likely to be required.

**Naked DNA vaccines.** These consist of DNA-encoding protective antigens and can be produced and purified relatively inexpensively in *Escherichia 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, these responses 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 use in 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 ones. Mice are intrinsically resistant to tuberculosis and as models do not readily distinguish among candidates that have efficacies about 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 immunologic correlates and surrogate end points for protection. The development of correlates of protection and, ultimately, surrogate end points 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 animal and 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 epidemiological 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 ideal vaccine.** An ideal vaccine against tuberculosis should be safe; should have demonstrated protection in animal models; should protect against disease and infection; should be protective after a single dose or, if necessary, a small number of doses, preferably not requiring administration by injection; should be long-lasting and able to engender immunologic memory; should not compromise the tuberculin skin test for diagnosis; be inexpensive to manufacture; should be heat stable and have a long shelf life; should not interfere with protection engendered by other vaccines; and should be capable of being integrated into existing immunization schedules. However, a candidate that falls short by ≥ 1 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 measles-mumps-rubella and diphtheria-pertussis-tetanus vaccines, 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 to establish what immunologic responses are elicited by the vaccine. For example, this might include T cell proliferative responses to antigen or induction of lymphokines such as IFN-γ and TNF, cytotoxic T cells, and antibodies to specific antigens of the pathogen.

Phase II trials represent the first opportunity to examine easily measured immunologic parameters in humans that may be correlates of protection and may ultimately be used as surrogate end points 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 7000–300,000 subjects) to determine vaccine efficacy and for search even lower-frequency adverse effects can be undertaken.

At least 3 different phase III trial designs for tuberculosis vaccine candidates have been suggested and are described below.

Preinfection vaccine trial. The test of a preinfection 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 of infection to disease, as well as to prevent the establishment of a latent or persistent infection. Questions that need to be addressed are (1) 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 (2) whether antibodies and mucosal immune responses to the tubercle bacillus can prevent infection. The advantage of this strategy is that one can generate an immune response in an individual before an infection that would be sufficient to provide full protection in most subjects. A disadvantage of this strategy is that it could require 20–30 years to fully evaluate protective efficacy against adult tuberculosis.

Postinfection 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 infection 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 from studies of BCG vaccination of animals or humans that indicate whether BCG vaccine is effective in already infected individuals.

Total-population vaccine trial. One strategy that would take advantage of the best features of both of the other strategies would be to carry out vaccine trials for efficacy in total populations in regions of the world where the risk for infection is high. If the recipients were first given a skin test 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 in 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 to be 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 end points of protection.

Phase II trials provide the critical opportunity to identify immunologic correlates of protection that can be measured simply and quickly. These correlates will then be tested in efficacy trials to determine whether they represent valid surrogate end points 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 end points and in which standardized databases are developed for doses, dosing 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 phase 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 end points (e.g., cases of active tuberculosis) expected to be observed in the control group. Trials designed to observe ~60–100 end points 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 postinfection vaccines, populations with annual infection rates of 1%–2% would be required, and a 20-year trial involving 20,000–130,000 people. In addition, the likely dropout rates must be taken into account in long-term trials, and more subjects must be enrolled in the study to ensure the power of the final results. The history of BCG vaccine 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 United States and Western Europe are sufficiently low that phase III efficacy trials would need to be very long and expensive (if feasible at all) 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 necessary 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-endemicity 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 epidemiological knowledge of the tuberculosis problem at the sites selected for trials, as well as competent laboratory facilities for diagnosis, immunologic studies, and evaluation of surrogate end points. Independent of the protective efficacy of any particular vaccine candidate, such large-scale trials provide an extraordinary opportunity to develop new techniques to analyze and measure immunologic 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; these 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, CDC, FDA, USAID, and academic and industrial researchers will be critical, in addition to close links with the WHO and the International Union Against Tuberculosis and Lung Disease, as well as scientists and health workers in countries that have both the need and the infrastructure to evaluate vaccines against tuberculosis.

Logistics. To obtain definitive results, there must be consensus regarding case definitions; defined end points; 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 their 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 immunologic 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 end points 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, the willingness of public and private sectors to pay for such vaccines, and the possibilities for economic returns. Finally, the extraordinary effectiveness and low cost of childhood vaccines such as those against polio and measles 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 M. 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 de-
As the host response to those bacteria, cause tissue damage and by which model animals and the human host protect themselves immunologically from disease must be elucidated. This may require development of a primate model.

Immunologic correlates of animal and human protection against *M. tuberculosis* must be identified, as should the protective antigens and virulence genes of *M. tuberculosis*, in order to rationally develop candidate vaccines.

Diagnostic tools should be developed that distinguish individuals infected with *M. tuberculosis* infection from individuals with active tuberculosis disease and individuals previously vaccinated with BCG.

Necessary expertise for this research will probably 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 empirical testing of vaccine candidates in the best available animal models.

**Production of vaccine candidates for animal and human testing.** Pilot manufacturing facilities that meet good manufacturing practice standards must be established in order for products to be delivered to human subjects. Such facilities are mostly found in industrialized countries, but scientists in developing countries should be involved in the manufacturing process to increase trust in the product in areas where efficacy trials may be held (a successful scale-up manufacturing plan should be developed before the start of the trial for each candidate that will be included in a large efficacy trial). Repositories for human and animal samples acquired during trials must be established. Adequate reagent sources and supplies must be identified and developed. Assays must be developed for the efficient evaluation of vaccine candidates in animal and human trials. Manufacturing expertise will likely be drawn primarily from industry.

**Testing of 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 of people with several 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 epidemiological research, soliciting promising vaccine candidates from investigators worldwide, and rapidly moving these candidates into clinical trials. The TVRUs also would use trials to begin evaluating correlates of protection as potential surrogate markers of vaccine efficacy. (Such markers would be invaluable in subsequent large efficacy trials.)
trials.) Establishing multidisciplinary 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 United States, 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 pretrial epidemiological 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 vaccine administration and exposure to nonpathogenic environmental mycobacteria.

Phase III trials will need to be undertaken in populations with high prevalence and incidence of tuberculosis and therefore are likely to involve sites in developing countries (and perhaps 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 vaccine and what factors are responsible for its variable efficacy against tuberculosis in different settings and in childhood extrapulmonary versus adult pulmonary tuberculosis. Understanding the failure of BCG vaccine in some parts of the world would help enable the creation of a more effective tuberculosis vaccine.

Successful phase III trials will likely require a preestablished agreement and cooperative effort among international and United States funding and regulatory agencies, industry, academic scientists, tuberculosis control programs, and involved governments.

All phases of vaccine testing in human volunteers will likely require (1) staff training at clinical trial sites located in developing and industrialized countries; (2) institutional review board involvement and ethical reviews by all involved countries; (3) optimization of promising vaccine candidates and delivery parameters through expanded animal model testing; (4) disease monitoring and treatment; (5) HIV testing and subsequent counseling of human volunteers; (6) workshops for government and health care staff in trial site countries; (7) adequate sources of reagents and supplies; (8) core laboratory facilities for development and use of standardized methods and assays; (9) sample and strain repositories; and (10) productive collaborations between developing and industrialized countries at the government as well as scientific and health care levels.

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

Participants in the Blueprint for Tuberculosis Vaccine Development Workshop

Workshop participants included the following (in alphabetical order): Barry R. Bloom, chair (Howard Hughes Medical Institute and Albert Einstein College of Medicine; currently Harvard University School of Public Health); Robert F. Breiman (National Vaccine Program Office); Michael J. Brennan (Center for Biologics Evaluation and Research, Food and Drug Administration); Mary Lou Clements-Mann (Johns Hopkins University); George T. Curlin (National Institute of Allergy and Infectious Diseases [NIAID], National Institutes of Health [NIH]); Bruce Davidson (National Tuberculosis Controller’s Association, ACET member); Ann M. Ginsberg (NIAID, NIH); Mark Grabowski (NIAID, NIH); Gail G. Jacobs (NIAID, NIH); John L. Johnson (Case Western Reserve University); Wendy Keitel (Baylor College of Medicine); John R. La Montagne (NIAID, NIH); Bess I. Miller (CDC); Christopher Murray (Harvard University School of Public Health); Charles Nolan (chair, Advisory Committee for Elimination of Tuberculosis); Ian Orme (Colorado State University); Peter Paradiso (Wyeth-Lederle); Lee B. Reichman (NJMMS National Tuberculosis Center); Daniel Salmon (National Vaccine Program Office); Steven G. Self (Fred Hutchinson Cancer Research Center); Jeffrey R. Starke (Baylor College of Medicine); and Douglas B. Young (Imperial College School of Medicine).

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