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Development of New Vaccines for Tuberculosis

Recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET)

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NOMINEES TO THE ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS (ACET)

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Development of New Vaccines for Tuberculosis

Recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET)

Summary

Tuberculosis (TB) remains a major, global public health problem, particularly in low-income countries. Better application of current diagnostic, treatment, and prevention strategies could lead to gradual decreases in the disease, but eliminating TB completely in the United States and internationally will require new tools. The greatest impact could come from a new vaccine, and recent technological advances have provided the basis for new vaccine development. However, sustained support is required to move the research from the laboratory to field trials of vaccines and to implement new vaccine programs. Recognizing the importance of TB vaccines, the Advisory Council for the Elimination of Tuberculosis (ACET) recommends that public agencies and vaccine manufacturers develop a comprehensive, consensual strategy to achieve these goals. This report outlines the elements that should be considered in devising a strategic plan for vaccine development.

INTRODUCTION

Interest in the development of new vaccines for tuberculosis (TB) has increased in recent years as the disease continues to be a major, global public health problem. *Mycobacterium tuberculosis* kills more adults each year than any other single pathogen, according to the World Health Organization (WHO) Global Tuberculosis Programme (*1*). The World Bank estimates that the disease accounts for >25% of avoidable adult deaths in developing countries (*2*). Moreover, the global number of TB cases is expected to continue to increase (*3*), particularly in countries where the human immunodeficiency virus (HIV) infection is epidemic, unless diagnostic and treatment strategies are applied widely and effectively.

This pandemic is contributing to the TB burden in the United States. In 1997, nearly 40% of new U.S. cases occurred in persons born in other countries (*4*). Like Canada and several European countries, the United States is expected soon to have more TB cases among foreign-born persons than native-born persons.

CURRENT CONTROL MEASURES

Some TB control strategies, including widespread use of bacille Calmette-Guérin (BCG) vaccine and the provision of drugs without supervised treatment, have had little impact on the disease and have worsened it in some cases. The most effective control measure is curative treatment of patients with infectious pulmonary tuberculosis (i.e., those with acid-fast bacilli [AFB] found on microscopic examination of sputum smears). Although WHO estimates that widespread application of its directly

observed treatment, short-course (DOTS) strategy* could decrease the global TB burden by 50% within 10 years (*5*), data to support this proposition are lacking. The DOTS strategy also requires a largely vertical, complex system (e.g., specialized staff at the central level, a system of diagnostic and treatment centers, and frequent training and supervision of field staff) that could be difficult to sustain in many areas without continuing donor assistance. This drawback, as well as reliance on antiquated tools (e.g., microscopy and chest radiography for diagnosis and treatment regimens of at least 6 months' duration) suggests that this approach might not have the anticipated impact. In 1995, programs that had implemented the DOTS strategy covered <25% of the world's population (*6*), and WHO announced this year that its Year 2000 TB objectives would not be met because of slow implementation of DOTS (*7*).

Although BCG vaccine is the most widely administered of all vaccines and has the highest coverage of any vaccine in the WHO Expanded Programme on Immunization, it appears to have had little epidemiologic impact on TB (*8*). Both randomized placebo-controlled clinical trials and retrospective case-control and cohort studies have demonstrated a wide variation in vaccine efficacy, ranging from 80% to zero (*9*). The largest and most recent prospective randomized trial, the Chingleput study in southern India, failed to demonstrate any protection overall (*10*). These studies have indicated, however, that BCG confers protection against serious forms of childhood TB (e.g., disseminated and meningeal TB) that are associated with high mortality rates. More recent studies have demonstrated that BCG vaccine also protects against the development of leprosy (*11,12*). Despite its shortcomings and because of its beneficial effect in children and against leprosy, BCG vaccine likely will remain a component of childhood vaccination strategies in low-income countries. However, because of questions about the vaccine's efficacy and because it induces dermal hypersensitivity to purified protein derivative (PPD) tuberculin in most recipients, BCG has never been recommended for programmatic use in the United States.

ELIMINATING TUBERCULOSIS

During the past decade, several countries with low TB incidence rates, including the United States, have embarked on plans to eliminate the disease as a public health problem (*13,14*). In CDC's 1989 Strategic Plan for the Elimination of Tuberculosis in the United States, ACET defined elimination as achieving an incidence rate of reported cases of fewer than 1 per million (i.e., a 74-fold reduction from the 1997 U.S. case rate). During development of the U.S. plan, CDC recognized that new diagnostic, treatment, and prevention technologies would be needed to achieve this goal because of the limitations of current methods.

For example, even when current screening and diagnostic technologies are applied optimally, many patients with newly diagnosed TB already have spread the infection to their closest contacts before they are identified and treated. Environmental control methods (e.g., ventilation and ultraviolet radiation) have reduced TB transmission in some settings, most notably hospitals, but these measures cannot be applied easily

*The essential elements of the DOTS strategy are a) political consensus that tuberculosis control should be given a high priority; b) passive case-finding based on sputum smear microscopy; c) use of standardized, short-course treatment regimens administered under direct observation; d) a secure supply of drugs and equipment; and e) supervision with regular monitoring of treatment and case-finding results.

in environments where most transmission likely occurs (e.g., households of infectious patients, nursing homes, prisons, jails, homeless shelters, and other community settings).

CDC also has advocated preventive chemotherapy — treating persons with *M. tuberculosis* infection at risk for developing active disease — as an important intervention strategy. Theoretically, preventive therapy could play a major role in TB elimination. However, the problems of nonadherence and drug toxicity and the difficulties in identifying those infected persons at highest risk for disease limit the effectiveness of this strategy. Some progress has been made, as exemplified by the recent studies of rifampin-based, short-course preventive therapy, but curative treatment and preventive therapy as practiced are not likely to eliminate TB.

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 where TB cases continue to emerge from the pool of previously infected persons. Research advances of the recent past have increased the likelihood that a new vaccine will be developed soon.

PROGRESS IN VACCINE DEVELOPMENT

A major research effort is being made to develop new tuberculosis vaccines. Much of this work is aimed at improved understanding of the immunopathogenesis of TB by studying both the infecting organism and its human host. Researchers have sequenced the complete genome of *M. tuberculosis* (*15*), which will provide new opportunities to address questions of virulence, pathogenesis, and persistence (i.e., the ability of bacilli to achieve long-lasting dormancy following infection). Researchers also have more knowledge of both host and microbial genetic factors related to increased resistance and susceptibility to TB (*16,17*) and are working to better understand the human protective immune response to the disease (*18*).

At the same time, new vaccine candidates (e.g., subunit vaccines, DNA vaccines, and attenuated strains of living mycobacteria) are being developed and tested in animal models (*19*). Within the next few years, several candidate vaccines should be available for human testing.

NEEDS AND RECOMMENDATIONS

Several critical steps must be taken to reach the goal of developing a new vaccine and establishing its use in public health programs. ACET recommends the following initial actions:

- Develop a consensus among public funding agencies and vaccine manufacturers that a new TB vaccine is an urgent public health priority.
- Establish a sustained commitment of both private and public-sector funds over several decades to support intramural and extramural research.

  Much of this work logically will fall within the scope of the National Institutes of Health (NIH), but also should be supported by CDC; the Food and Drug Administration (FDA), which is part of the Public Health Service (PHS); and the U.S.

Agency for International Development (USAID). International partners like WHO should be involved so that research initiatives can be expanded to focus on all aspects of TB vaccine development.

To achieve these goals, dialogue must be increased between U.S. public funding agencies, international health organizations, vaccine manufacturers, and other interested parties (e.g., public health and medical communities). Although a new vaccine could be developed largely through public-sector support, the ultimate feasibility of production and global distribution depends on establishing an ongoing partnership with the pharmaceutical industry. Collaborations should be sought domestically and internationally with private and public-sector partners to advance a vaccine development strategy. Establishing a TB vaccine task force composed of these partners could provide guidance and advocacy in this area.

- Develop a comprehensive strategic plan for vaccine development. Although several national and international meetings have addressed vaccine development in recent years, a comprehensive strategy has not been formulated. The PHS should play a major role in developing this plan by establishing a projected timeline and estimates of resource needs, outlining specific steps that need to be taken, and defining the roles and responsibilities of the interested parties (e.g., the public sector, industry, and academia). This process was started earlier in 1998 when the NIH's National Institute for Allergy and Infectious Diseases sponsored the Blueprint for TB Vaccine Development Workshop.

- Establish close collaboration between CDC, FDA, and NIH to support implementation of clinical vaccine trials, as recommended in the 1992 National Action Plan to Combat Multidrug-Resistant Tuberculosis (*20*).

  Relationships also must be developed and fostered with international organizations (e.g., WHO and the International Union Against Tuberculosis and Lung Disease), funding agencies (e.g., USAID and the World Bank), and vaccine manufacturers. Representatives of these organizations should form a working group to develop protocols for field-testing candidate vaccines. Vaccine trial sites should be identified in both the United States and high-incidence countries, and preparations for clinical testing should begin as soon as possible. However, major expenditures should not be committed too far in advance of the availability of appropriate vaccine candidates.

- Increase basic research. Researchers need to define what host factors protect persons from TB infection and disease development, and they need to discover how the properties of the tubercle bacillus permit it to survive years after the establishment of infection. Researchers should organize studies in the United States that use hypothesis-generating protocols to link specific epidemiology, human immune status and response, and other physiological responses to TB infection, TB disease, and the bacteriology of infecting organisms.

  To facilitate vaccine trials, researchers need to determine human correlates of protection against TB. The major endpoint for clinical trials would be the development of TB, which would make the trials long and costly to conduct. Correlates

of protection (e.g., lymphocyte proliferation or cytokine production in response to antigenic stimulation) have never been validated in humans. Although researchers have long thought that induction of responsiveness to PPD by BCG vaccine correlated with vaccine efficacy, an analysis of clinical trials has disproved this theory (*21*). However, putative surrogate markers of protection could be evaluated in initial vaccine trials and, if shown to correlate with protection, could be used to select and test newer vaccine candidates for further study. Trials also are needed to establish vaccine safety and efficacy in persons with HIV infection.

- Establish consensus on what characteristics are desirable in a new vaccine. For example, any new vaccine should be relatively free of side effects and safe when administered to immunocompromised persons (e.g., persons with HIV infection). It should be, but does not have to be, non-living. Ideally, the vaccine should not lead to hypersensitivity to PPD, which would make tuberculin testing invalid in vaccinated persons. The vaccine should protect against disease resulting from subsequent infection (i.e., preexposure), as well as endogenous reactivation of earlier infection (i.e., postinfection). Although it is commonly thought that a new preexposure vaccine is needed to replace BCG, a postinfection vaccine could be more effective, especially in countries like the United States where the majority of TB cases occur in persons with remote infection. Given the limitations of preventive therapy, an effective postinfection vaccine could be the most important new tool to help eliminate TB in the United States. In high-incidence countries, a postinfection vaccine could be administered to adults in high-risk groups (e.g., health-care workers), and wide application could have a major global impact.

Before a new vaccine can be tested on humans, researchers must prove that it is safe in animals and that it induces an immune response. Although not an absolute requirement, a new vaccine also should demonstrate protection against TB in animal models. No surrogate marker of protection has been validated in animal models, so protection can only be demonstrated by response to a challenge from a dose of virulent tubercle bacilli. Because no models of dormant TB infection exist to test postinfection vaccines, additional research is needed in this area.

CONCLUSION

Signs of progress are appearing in TB vaccine development. To build the needed consensus for a strategic approach and the partnerships required for success, the National Vaccine Program Office (NVPO) is sponsoring an international symposium on TB vaccine development and evaluation in 1998. The primary objectives of the meeting are to stimulate the field of TB vaccinology, build partnerships among organizations essential to the successful development of vaccines, and help implement a universal strategy for vaccine development and evaluation. These objectives represent important first steps to eliminating TB as a global health problem.

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