Clinical Considerations in Designing Trials of Vaccines for Tuberculosis

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Despite remarkable strides in the treatment of tuberculosis, the disease continues to be a major public health problem in many parts of the world, a situation that is projected to remain unchanged for years into the future. The development of a highly effective vaccine could substantially reduce the magnitude of the tuberculosis problem. A tuberculosis vaccine could theoretically prevent initial infection by Mycobacterium tuberculosis and enhance host response to prevent the progression from infection to disease or even to augment response to treatment in cases of established disease. Assessment of candidate vaccines will require clinical trials. This article suggests how traditional end points of morbidity and mortality, a number of newer measures of disease impact, and surrogate markers of tuberculous infection and disease might be used in such studies.

Despite the remarkable strides that have been made in treating patients with tuberculosis over the past 50 years, the disease continues to be a major public health problem in many parts of the world. There are many reasons for this, including the relatively long period of treatment required to cure tuberculosis, the emergence of drug-resistant strains of Mycobacterium tuberculosis, and the emergence of HIV infection as a cofactor that facilitates the transmission and progression of tuberculosis in many parts of the world. Although an effective vaccine for tuberculosis could theoretically overcome these problems, the currently available vaccine, BCG, has proved to be limited [1].

Trials of new candidate vaccines will be greatly influenced by the natural history, clinical manifestations, and diagnostic algorithms of tuberculous infection and disease. Although many of the clinical aspects of tuberculous infection and disease are insensitive and/or nonspecific for the purpose of diagnosis or end-point definition, our evolving diagnostic armamentarium may obviate some of these problems. Although the current cost or complexity of some of the relevant technology may preclude widespread application of certain techniques, continued evolution of these tools and thoughtful subgroup analysis of vaccine trial participants may permit their use in future studies. This presentation will review briefly the natural history of exposure to M. tuberculosis, as well as the general clinical manifestations of tuberculosis, and will suggest their implications for tuberculosis vaccine development.

A number of factors, both environmental and host-related, can affect the outcome of exposure to tubercle bacilli. Among the latter are age, immune status, genetic factors, comorbid conditions (especially those affecting immunity) and BCG immunization status. It is possible to schematically represent these influences and the potential outcomes of exposure to tuberculosis (Figure 1).

On average, ~30% of persons with protracted exposure to M. tuberculosis–contaminated aerosol (e.g., household contacts of a person with infectious tuberculosis) will become infected after exposure; other exposed persons, because of host (particularly genetic) factors and environmental circumstances of the exposure, remain uninfected. Among those infected, a number of events have been traditionally thought to occur. These include skin test sensitization and conversion, lymphohematogenous dissemination of tubercle bacilli to anatomic sites beyond the lungs, and development of relative resistance to exogenous reinfection. However, each infected individual has some risk of developing active disease (i.e., tuberculosis). In fact, only ~10% of all infected persons with a normal immune system will develop active disease, roughly half within the first several years after infection and the other 5% at some time later in life, after a period of latent infection.

A vaccine for tuberculosis might theoretically work by (1) blocking the initial infection, (2) preventing early progression to disease by facilitating the eradication of latent infections, or (3) limiting the severity of illness or enhancing response to treatment in persons who develop disease. Moreover, currently available vaccines (i.e., BCG) frequently cause conversion of the tuberculin skin test, making it impossible to study its impact on subsequent virulent infection by wild strains of M. tuberculosis. Ideally, new vaccines would not have this effect or would provide the opportunity to study other markers of infection (or prevention of infection). This, in turn, would facilitate trials by reducing the number of study subjects needed and would provide insight into how such vaccines provide protection from tuberculosis.

Although infection is usually equated with tuberculin skin test conversion, this correspondence does not always hold. Reaction size among persons ill with tuberculosis and therefore known to be infected by M. tuberculosis will vary. The majority
Figure 1. Risk of tuberculous infection is determined by many factors, such as intensity and duration of exposure to tuberculosis (TB); it is likely that host factors (both acquired and genetic) are involved. Likewise, the course of these infections and whether tuberculous disease develops are also impacted by host factors. Vaccines theoretically can affect each of these steps, including the manifestations of disease. Quotation marks indicate relative susceptibility or resistance.

of reactions will be \(~10\) mm to perhaps \(20\) mm of induration, with some larger reactions and some smaller; some individuals will have no reaction (i.e., anergy). The exact distribution, again, will depend on host factors. For example, among HIV-coinfected individuals, the entire distribution would be shifted toward more small reactions, and the proportion of anergic individuals would be substantially increased.

It has also long been appreciated that skin test reactivity and conversion can occur in the absence of virulent infection with *M. tuberculosis*, most importantly after BCG vaccination. Thus the tuberculin skin test must be recognized as problematic with regard to both sensitivity and specificity when used for the diagnosis of tuberculous infection or disease.

There are many parameters that might be considered to define tuberculous disease. Before considering several potential clinical definitions, it is useful to note epidemiological approaches to defining the impact of tuberculosis. Murray and Lopez [2] used disability-adjusted life-years (DALYs) as a measure of the worldwide impact of tuberculosis and other conditions, now and into the next century. It is clear that different measures of disease (e.g., death, DALYs, and years of productive life lost) will produce different rankings for various diseases, depending in part on their severity, chronicity, and the age groups that they effect. Measures such as DALYs may be especially helpful for the purpose of describing the potential social and economic impact of tuberculosis and the effect of deferring tuberculosis (rather than completely preventing it) by use of a vaccine.

When tuberculous disease occurs, it can affect any anatomic site. For example, in one recent year (1996) in the United States, \(>15\)% of tuberculosis was extrapulmonary, with lymphatic, pleural, and bone/joint being the most common nonlung sites. If the analysis were confined to certain subgroups (e.g., children or HIV-infected persons), the proportion of extrapulmonary disease would be much higher. It is also important to note that the morbidity may be different for different sites of involvement (e.g., meningeal > pulmonary > lymph node). Thus there may be particular value in the prevention of some forms of disease, even if other forms are not as effectively prevented.

It is also important to recognize that confirmation of extrapulmonary tuberculosis by culture is usually more difficult than confirmation of pulmonary tuberculosis, a circumstance that creates potential difficulty with the use of extrapulmonary tuberculosis as an end point in vaccine trials. Although conventional diagnostic criteria that emphasize clinical judgment and response to tuberculosis therapy, supplemented by culture confirmation, may be used as end points for defining extrapulmonary disease, it is in this area that new technology may be most helpful. For example, techniques for expanding the small amounts of mycobacterial nucleic acid typically present in specimens of infected CSF or surrogate markers described below may prove most useful in the setting of extrapulmonary disease.

Regardless of the site, when tuberculosis does occur, certain systemic manifestations may be encountered. These include fever (35%–80%), weight loss, anemia (10%), leukocytosis (10%), and hyponatremia. Acute-phase reactant levels and the sedimentation rate may be elevated. These are all, of course, nonspecific manifestations. When tuberculosis occurs in the lung, it has classically been thought of as producing upper-lobe and superior-segment lower-lobe infiltrates, often with cavitation (so-called postprimary disease).

If one considers the traditional diagnostic armamentarium for tuberculosis, it is apparent that the tools have long been imperfect and, until recently, have changed little over many years. The “gold standard” has been culture identification of
**M. tuberculosis** in clinical specimens. A positive acid-fast stain for bacilli has been useful but is both less sensitive and less specific than culture. After these comes an array of tests, including tissue histology, chest radiography, and tuberculin skin testing, with the limitations previously noted. Recent scientific and technologic developments have provided potential new clinical tools, and some may be useful for assessing candidate vaccines.

CT scanning of the chest has been reported to show a variety of patterns with respect to pulmonary tuberculosis [5]. Some findings (e.g., centrilobular nodules, branching linear structures, tree-in-bud patterns, and cavities) are especially common in untreated tuberculosis and resolve with therapy, whereas others (e.g., bronchovascular distortion, fibrotic bands, and bronchiectasis) develop as active disease resolves. If these patterns are confirmed as being specific, or if other (i.e., nontuberculous) conditions can be excluded, CT changes might serve as surrogate markers of prior tuberculosis when one is assessing, for example, bacteriologically negative “cases” given antituberculosis treatment as a “therapeutic trial.”

Developments in the mycobacteriology laboratory have been proceeding rapidly in recent years. Various procedures for nucleic acid amplification and gene probing are now available. At the current state of the art, these are highly accurate in confirming smear-positive disease. With refinement, they may enhance our ability to diagnose smear-negative (i.e., paucibacillary) disease.

For a number of years, some laboratories have been studying adenine deaminase (ADA), a byproduct of lymphocyte activation, to identify extrapulmonary tuberculosis. Ribera et al. [6] in Spain have been leaders in this area of study. They have reported, for example, ADA systems with sensitivities of 1.0 and specificities of 0.98 for detecting tuberculosis involving the meninges and CSF.

More recently, attention has focused on the production of certain cytokines and chemokines during the course of tuberculosis. A report from Australia of a study that used whole blood tested under field conditions for production of IFN-γ suggested that levels of this cytokine increase both with **M. tuberculosis** infection and with active tuberculosis. Moreover, levels of IFN-γ decline to intermediate values in persons treated with regimens that include rifampin [7]. Finally, other cytokines have been identified as being released in increased amounts from cells in the lavage from tuberculosis-involved areas of lung but not from uninvolved lungs or from healthy controls [8]. It is possible that one or another of these tests, alone or in combination with other studies, could be helpful in confirming the diagnosis of tuberculosis in certain settings or in helping to define vaccine effect.

One can contemplate a series of tuberculosis-diagnostic criteria that could be used for purposes of a vaccine trial. Table 1 presents one such set of criteria. In all situations, clinical judgment should point to the diagnosis. The highest level of certainty involves definitive confirmation by culture of the organism or by a new approach to specific identification of **M. tuberculosis** (category A). This would be used especially when access to the infecting organism is readily available and concentrations are high (e.g., with pulmonary tuberculosis).

Alternatively, and if available, sensitive and specific surrogate markers of tuberculosis might be used to define a probable diagnosis (category B). This would be especially helpful in situations where the organism is not readily available (e.g., tuberculosis infection or miliary tuberculosis). When direct confirmation is not feasible, a “therapeutic trial” (category C) might be used to define likely tuberculosis. To prevent dilution of cases, consideration should be given to requiring a minimum proportion of diagnoses to satisfy a definitive end point (i.e., category A). In addition, plans should be made to carefully review or otherwise investigate at least some predetermined subset of less definitive cases (i.e., category B or C) to determine actual case rates.

The duration of follow-up and schedule of study during a vaccine trial cannot be fully defined until the specific conditions of the trial are described. However, certain general comments can be made. Depending on the rate of new tuberculous infections, the age of the population to be studied, and the size of the study population, it is entirely possible that a study of the efficacy of a candidate vaccine in preventing infection and/or disease during the period after vaccination could be accomplished over several years. As a practical matter, such studies will be greatly facilitated by accurate registries that promptly record new cases of disease and by end points that require minimal postvaccination testing.

Studies of a vaccine’s safety would be conducted in parallel

### Table 1. Diagnostic criteria for tuberculosis disease.

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<tr>
<th>Diagnosis category</th>
<th>Criteria</th>
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<tr>
<td>A, definite</td>
<td>Clinical picture consistent with tuberculosis; bacteriologic confirmation (culture, gene probe/NAA ± AFB smear); histologic findings</td>
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<tr>
<td>B, probable</td>
<td>Clinical picture consistent with tuberculosis; exclusion of other diagnostic considerations; presence of highly specific tuberculosis (surrogate) marker</td>
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<tr>
<td>C, likely</td>
<td>Clinical picture consistent with tuberculosis; exclusion of other diagnostic considerations; typical response to antituberculosis treatment (in absence of other treatment)</td>
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NOTE: AFB, acid-fast bacilli; NAA, nucleic acid amplification.
with the assessment of immediate or short-term efficacy. Much longer surveillance would be required in order to fully define the duration of protection. Establishment of comprehensive disease registries, performance of tuberculosis case-control studies, and similar techniques will be needed to address this important issue. Such studies will, in turn, require dependable mechanisms for identifying persons receiving candidate vaccines, even years after vaccination.

Any clinical trial has potential ethical issues associated with it. With respect to a tuberculosis vaccine trial, the issue of preventive treatment of those potentially infected by virulent *M. tuberculosis* will be especially important. In fact, despite the proven efficacy of isoniazid and other prophylactic regimens, the logistic problems associated with sustaining months of treatment, coupled with resistant strains of *M. tuberculosis*, have made preventive therapy impractical in many parts of the world. It is presumed that vaccine trials would most likely be conducted in such regions with high rates of tuberculosis and no preventive-therapy programs.

As candidate tuberculosis vaccines emerge over the coming years, their safety and efficacy will need to be tested in clinical trials. An understanding of the natural history of tuberculous infection and of the clinical, social, and economic impact of the disease, perhaps coupled with technologic developments in clinical medicine, should facilitate the design and implementation of these studies. The end points used in such studies have important implications for the size, cost, and duration of such trials. Thoughtful consideration of the issues described above will enhance the chances of a successful trial.

References


