Editorial

Bacillus of Calmette and Guérin Vaccination for Tuberculosis Prevention in Healthcare Workers: How Good Is Good Enough?

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The reemergence of tuberculosis as a major public health threat in the United States during the past 12 years[1] and the emergence of multiply drug-resistant tuberculosis as a significant public health problem have rekindled interest in the development of a vaccine to prevent tuberculosis. In the absence of a new vaccine, renewed interest has surfaced in the utility of immunization with the strain of *Mycobacterium bovis* known as bacille Calmette Guérin (BCG) as a strategy to reduce the risks for transmission of tuberculosis.[2,3] In the United States, aggressive public health interventions in the past 3 years apparently have had a substantial beneficial effect on the rate of new cases of tuberculosis. Despite the efficacy of these public health strategies, developing countries lack the resources to invest in such labor-intensive interventions as directly observed therapy. Thus, tuberculosis presents, and undoubtedly will continue to present, a formidable global public heath challenge. In the absence of effective public health interventions, the very factors that contributed to the resurgence of tuberculosis in the United States are likely to fuel the fire of tuberculosis worldwide during the next 2 decades.

The use of BCG as a public health tuberculosis prevention measure has been a matter of substantial controversy since the vaccine's initial availability in the 1920s. The literature is replete with studies attempting to evaluate the efficacy of BCG for preventing tuberculosis and for preventing the severe sequelae of tuberculosis in different study populations. The history of the use of BCG is convoluted and complex.[4] Studies attempting to measure the efficacy of BCG have yielded protective efficacy estimates that have ranged from 0% to 80%.[5] In addition to the limitations of the vaccine itself, several factors have clouded the interpretation of the studies designed to evaluate the utility of this candidate vaccine. The lack of precise diagnostic tools for tuberculosis exposure, infection, and active disease, the lack of specificity of the BCG vaccine, strain variation of BCG vaccines, and the fact that immunization with BCG results in a positive tuberculin skin test, thereby rendering ineffective the one available study that can be used in an epidemiological investigation, are only four of the factors that have made definition of the role of BCG extremely problematic.

The issue of the efficacy of BCG was clarified, at least to a certain extent, with the publication in 1993, 1994, and 1995 of three meta-analyses[5-7] of the large family of studies that have, over the past several decades, addressed this perplexing question. These meta-analyses demonstrated that, on average, BCG was 50% effective in preventing clinical tuberculosis and in preventing the severe sequelae of tuberculosis in infants and young children. Although the meta-analyses demonstrated the modest protection afforded by BCG immunization, these studies

raised as many questions as they answered. Among the questions that remain as yet incompletely addressed are the reason or reasons for the vast differences in efficacy in the published studies, a definitive explanation as to why the efficacy of BCG varied substantially by geographic latitude,[8] and the extent to which strain variations among BCG vaccines influence efficacy.[9,10]

Nonetheless, because vaccination often is the least expensive and most cost-effective intervention available to public health authorities, a vaccine that could prevent or reduce the severity of 50% of cases of tuberculosis—although far from ideal—still appears quite appealing. For this reason, public health authorities in areas with high prevalences of tuberculosis typically support the use of BCG.

The argument for the use of BCG has been somewhat more complex, however, in lower risk settings. Specifically, in countries such as the United States, where the prevalence of tuberculosis has remained reasonably low, some authorities have argued that the use of this only modestly effective vaccine for relatively low-risk populations (eg, for healthcare workers) is not warranted. These experts argue that the use of BCG, in effect, clouds the investigation of potential epidemics.[11] The fact that the use of the vaccine produces a positive tuberculin skin test is seen as a substantial impediment to the investigation of potential outbreaks and case-clusters of tuberculosis.

Conversely, in a decision-analysis model, Greenberg and colleagues suggested that BCG immunization of house staff would result in fewer cases of tuberculosis among house officers.[12] Similarly, Nettleman and her colleagues recently published a decision analysis demonstrating that the use of a vaccine that was 50% effective likely would be less costly and more effective in preventing cases of tuberculosis in healthcare workers than tuberculin–skin-test surveillance programs.[13] These authors caution, however that the role of vaccination would have to be defined carefully if the vaccine interfered with the use of tuberculin skin testing.[13] Several studies have attempted to address the question of the protective efficacy of BCG for healthcare workers. In 1995, Brewer and Colditz evaluated these studies to determine if a meta-analysis of these data was possible. Although they favor the use of the vaccine, their careful analysis of the studies that have evaluated the use of BCG in healthcare workers found so many substantive methodological problems that they thought a meta-analysis was not scientifically feasible.[3] Thus, based on available data, I cannot find

definitive evidence that demonstrates BCG would provide 50% protective efficacy in the US healthcare worker population.

In this issue of *Infection Control and Hospital Epidemiology*, Jenney and Spelman argue for the use of BCG in US healthcare workers and suggest that the current United States Public Health Service guidelines concerning the use of BCG vaccination of healthcare workers are inadequate.[14] Although they cite the studies noted previously that demonstrate the modest efficacy of BCG immunization, they provide only cursory discussions of the limitations of these studies and of the downside of the use of BCG in the healthcare worker population. They discuss none of the studies (of the several such published series) that failed to find any effect of BCG and provide no rationale for the wide variation in study outcomes. Further, they provide only a cursory discussion of the side effects and risks associated with this vaccine.

Currently available data concerning the use of BCG in healthcare workers are conflicting, and the reasons for the conflict are unclear. Respected authorities disagree on the role of BCG for healthcare providers. I suspect these are the very issues considered by the crafters of the Centers for Disease Control and Prevention (CDC) guidelines, who were unwilling to make a definitive recommendation for the use of this vaccine without substantive data supporting the recommendation. In my own view, it is clear that the questions of the efficacy and the appropriateness of BCG immunization of healthcare workers in low-prevalence areas remain unanswered.

In 1986, Dr. Laurence Farer, then the Senior Program and Policy Advisor for the Division of Tuberculosis Control at the CDC, wrote, "When the turn of the next century arrives, both BCG vaccination and [isoniazid] INH preventive therapy may have become nothing more than curiosities of medical history."[15] As 1998 begins, medicine has a great deal to accomplish to realize Dr. Farer's prediction. An effective vaccine for tuberculosis continues to elude us. Tuberculosis has proven to be a most resilient foe; isoniazid preventive therapy soon may be something of a medical curiosity, but not for the reason that Dr. Farer had anticipated. Two achievements likely would have a profound impact on tuberculosis prevention efforts: the development of a truly effective tuberculosis vaccine and the development of sensitive, specific tests that detect exposure to, or infection with, *Mycobacterium tuberculosis*. If both were accomplished, the risk for occupational infection with *M tuberculosis* likely would be reduced to an

undetectable level. Several new approaches to the development of a vaccine for tuberculosis are under investigation, including the use of recombinant DNA technology to express mycobacterial genes in mammalian cell systems,[16] the use of specific recombinant BCG vaccines that may be extremely potent inducers of cytokines important to host defense,[17] and the use of subunit vaccines.[18]

As Jenney and Spelman[14] correctly point out, tuberculosis continues to present occupational risks to healthcare providers; the presence of multiply drug-resistant tuberculosis in the healthcare setting increases that risk. Nonetheless, the role of BCG immunization for US healthcare workers remains ambiguous at best. Although certain circumstances may warrant the use of BCG in healthcare workers,[1] we eagerly await a more effective vaccine or a vaccine that may not compromise epidemiological investigation of exposure to *M tuberculosis*. The modest efficacy of BCG and the imprecise tools available to diagnose infection make the determination of efficacy in low-prevalence populations difficult to determine. Further, in the absence of an effective vaccine or more precise tools to detect tuberculosis infection, the literature on BCG immunization of healthcare workers likely will continue to be confusing, and opinion will be far easier to find than fact.

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