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Novel Vaccines Against Tuberculosis

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THE TB PROBLEM AND NEED FOR A VACCINE

Tuberculosis (TB) is responsible for two million deaths and nine million new cases of pulmonary TB each year. Although these numbers place TB among the most important global health problems, active disease only represents the tip of the iceberg as it has been estimated that one-third of the world's population is latently infected with *Mycobacterium tuberculosis* (MTB), the primary causative agent (1). TB is particularly prevalent in developing regions of the world such as sub-Saharan Africa and Southeast Asia, where it is further fuelled by the human immunodeficiency virus (HIV) epidemic, and is overwhelming the limited resources that many countries have available to identify and treat active contagious pulmonary disease. As both HIV and TB target primarily the adult working part of the population, these two diseases represent major roadblocks to healthy economic development in many developing countries. Drugs against MTB have been available for more than 50 years, but treatment demands a complicated and exceedingly long-lasting treatment regimen. The World Health Organization (WHO) has initiated the directly observed therapy (DOTS) campaign in many regions, but so far this program has failed to control the global TB epidemic or prevent the rising rates of multidrug resistant (MDR) strains of MTB, which in some regions, for example, parts of Russia, are responsible for a large proportion of TB cases (1).

M. bovis Bacille Calmette–Guérin (BCG), the only vaccine currently available against TB, is named to honor Albert Calmette and Camille Guérin who developed this vaccine strain between 1906 and 1919 (2), attenuating it by passaging it 230 times on potato slices first with and then without ox gall. The strain was found to be both safe and effective in guinea pigs, rabbits, and nonhuman primates. We now know that during its attenuation, BCG lost a large number of gene segments clustered in numerous regions of difference (3). This ancestral BCG strain was distributed to numerous institutions all over the world; as a result of different culture and preparation conditions over several decades, current strains of BCG differ from each other (3,4). Today, approximately 4 billion people have received BCG, which makes this vaccine the most widely used vaccine worldwide. Because of its proven efficacy in preventing miliary TB in toddlers, BCG is part of the expanded program of immunization (EPI) promoted by the WHO. However, while the vaccine is well-established, discussion of its benefits and drawbacks has never ceased and includes safety aspects, interference with the tuberculin skin test as a diagnostic reagent and, in particular, the fact that although it is credited with helping to end the TB epidemic in Europe, the efficacy of this vaccine generally has been very disappointing in trials conducted in the developing world (5). In various trials, estimates of its efficacy against adult pulmonary TB have ranged from 0% to 80%, and in general, the lowest efficacy has been found in the countries with the highest incidence of skin test positivity to tuberculin, presumably due to latent TB and exposure to atypical mycobacteria in the environment (5,6). Initially, BCG vaccinations were restricted to tuberculin-negative individuals, but studies coordinated by the WHO indicated that it was safe to give BCG to those who had already converted their skin test; consequently, there was approval for mass vaccination of all age groups in TB-endemic areas. Today, a consensus has developed that BCG, although safe in all immunocompetent individuals, efficiently protects only skin-test negative individuals (primarily children) (7,8). Many explanations have been suggested, but recent studies in animal models have demonstrated that a preexisting immune response against mycobacterial antigens shared in BCG prevents the necessary BCG replication and vaccine take (6). Therefore, vaccine protection against adult pulmonary TB in high endemic countries is very limited, as was most clearly demonstrated by the 15-year follow-up data from the large multicenter trial of BCG in Chingleput, India (9). This unresolved problem has highlighted the need for novel TB vaccines. With increasing investment from public funds such as the European Union (EU), National Institutes of Health (NIH), and the Gates Foundation in recent years, TB vaccine research, development, and testing has now become a very active area, conducted mostly by public research organizations and public/private partnerships. Recent reanalysis of the commercial value of a novel TB vaccine may result in a larger investment from private industry in the future and thereby a more efficient and streamlined development of novel vaccines for this global health emergency (10).