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Review

Preventive vaccines for tuberculosis

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ABSTRACT

There are nearly ten million new cases and 1.4 million deaths from tuberculosis (TB) each year, and the 90-year old bacille calmette-guérin (BCG) vaccine in widespread use appears to have minimal impact on the worldwide incidence, despite demonstrating reasonable efficacy against complications of infant TB and death. Novel vaccine development has accelerated in the past ten years, with at least 16 candidates entering human trials, and a few vaccines have entered into Phase 2b efficacy studies. However, different vaccines may be needed due to the varying disease states (naïve, latently infected, or active), the ages affected (infants, adolescents and young adults, the elderly), and patient health status (HIV and immunocompromised patients especially). Modeling has shown that mass vaccination of latently infected populations, especially adolescents and young adults, will likely have the largest impact on new infection rates. At present, research and development of TB vaccines is hampered by the lack of validated animal models, the absence of correlates of immunity and a human challenge model, as well as by the size and cost of Proof-of-Concept clinical trials. Nonetheless, ongoing research and clinical studies should remove many of these barriers over the next five years, and lead to an increased understanding of the pathogenicity of *Mycobacterium tuberculosis* and what may constitute protective immunity during various stages of infection and disease.

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1. Background

In March 1993, the World Health Organization (WHO) designated tuberculosis (TB) a global public health emergency. Currently, TB is a leading cause of mortality worldwide and a leading cause of death in HIV-infected individuals and women of childbearing age. Ninety-nine percent of the TB deaths and 95 percent of the over nine million new cases each year occur in the low- and middle-income countries that comprise 85 percent of the world's population. Many of the tools for the diagnosis, treatment, and prevention of TB are antiquated and considered inadequate for global TB control. The epidemic of TB in Africa has been fueled by HIV disease, and the increasing incidence of diabetes in Asia further threatens attempts at control. Highly effective vaccines could eventually help diminish or eliminate the disease, as has been done for polio and measles and for smallpox, respectively.

Consequently, one of the highest priorities of TB research is to develop vaccines that are more efficacious for preventing TB than BCG [1]. Better control of TB than that provided by BCG could be achieved by vaccines that protect individuals from initial infection, prevent those recently infected from progressing to active disease, or decrease the capacity for transmission by those with active disease. Different vaccines may be required to induce immune responses in diverse populations, such as infants *vs.* young adults, or those already infected with *M. tuberculosis* (Mtb). Effectiveness of a vaccine may also be dependent on HIV infection status. The

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decision to focus on specific age groups and/or sub-populations during development is also complicated by multiple interacting factors. These include the potential disease and transmission impact, the feasibility of performing studies in geographical regions most in need, and the likelihood that more effective vaccines will actually be implemented in the target groups studied. Nonetheless, experts in TB prevention and control mostly agree that the strategy with the largest vaccine impact would be to mass vaccinate all adolescents/young adults in high-burden countries, regardless of their latency status, even with a vaccine that is only 60 percent efficacious [2].

2. Current situation

Mycobacterium bovis bacillus Calmette-Guérin (BCG) is a live, attenuated vaccine that is widely administered to infants in most areas endemic for TB, and is the only vaccine available to protect against TB. After its introduction in Paris in 1921, BCG was distributed around the world and maintained for decades by numerous independent serial passages of distinct stocks of bacteria. Accordingly, there are now a number of BCG substrains which exhibit striking genotypic and phenotypic heterogeneity [3,4]. BCG has been shown to be effective for the prevention of more serious extrapulmonary TB in children, such as tuberculous meningitis and miliary TB [5]. However, reviews of data from clinical trials suggest that there is not much protective efficacy of the vaccine in adults when it is given at birth, as recommended by WHO. A meta-analysis of prospective trials and case-control studies concluded efficacy at about 50 percent, with a range from a low of zero to a high of 80 percent [6].

Most successful, licensed vaccines available today induce neutralizing antibodies which provide protective immunity; however, in TB animal studies, gene disruptions of the human INF-γ pathway and clinical use of anti-TNF antibodies both suggest that a robust TH1 cellular immune response is likely required for protection against Mtb infection and disease [7,8]. For this reason, the majority of current clinical vaccine candidates are based on a variety of vectors, adjuvants, and antigens that induce classical TH1 cytokines such as IFN-γ and TNF-α from either CD4+ or CD8+ T cells. As summarized in the annually updated TB vaccine pipeline found on the website of the Stop TB Partnership Working Group on TB Vaccines, 16 of these candidates have moved forward into clinical studies over the last ten years (http://www.stoptb.org/wg/new_vaccines/) [9].

The clinical candidates are based on a variety of immune induction strategies, such as inactivated whole cell or whole cell extracts, or modified non-pathogenic mycobacteria (Mw, *M. vaccae*, RUTI, and *M. smegmatis*) [10–12], viral-vectored candidates (MVA85A, AERAS-402, and AdAg85A) [13–17], fusion protein subunits with TH1-inducing adjuvants (M72/AS01, Hybrid 1/CAF01, Hybrid 1/IC31, and HyVac 4) [18–21], and live recombinant BCG vaccines (VPM 1002, Aeras 422, rBCG30) [22–25] and attenuated *M. tuberculosis* (MTBVAC). DNA TB vaccines are being developed in different countries, notably in emerging economies, but have not yet entered into human clinical trials [26]. To date, clinical trials characterizing these candidate vaccines have included studies of safety and immunogenicity in diverse populations, including healthy, TB-naïve adults and infants, latently infected (PPD+ or Quantiferon+) adolescents and adults, HIV-positive adults, as well as patients undergoing drug treatment for TB. Despite initial concerns about vaccines eliciting reactive pulmonary inflammatory reactions (Koch reactions) in persons harboring active or non-symptomatic infection with Mtb (latent TB or undergoing treatment), none of these reactions have been clearly observed to date.

BCG vaccine is the most widely administered neonatal vaccine worldwide, and due to its short-term protective effectiveness, most of the new candidate vaccines are being studied as boosters following a priming immunization with BCG [27]. In parallel, however, recombinant BCG vaccines are also being studied as replacements for BCG to improve its safety in HIV-exposed infants and to induce better efficacy as well as better priming. Currently, BCG, being a live vaccine with the potential to elicit disseminated disease in HIV-infected babies [28], is no longer recommended by WHO for use in this population. Recombinant BCG vaccines have been generated using diverse approaches, such as attenuation through specific gene deletions, improved immunogenicity by removal of immune evasion genes or addition of genes to improve antigen presentation, as well as the over-expression of specific antigens for a "matched" BCG-priming, followed by boosting vaccines presenting the same recombinant antigens. Attenuated live Mtb strains, which have shown acceptable safety in immune-suppressed animal models, have also been developed preclinically with human studies initiated with the MTBVAC candidate [24].

Phase 2b proof-of-concept efficacy trials are currently under way in infants and HIV-positive adults, which use BCG priming followed by boosting vaccines that induce CD4+ T cell (*e.g.*, MVA-vectored) or CD8+ T cell (*e.g.*, adenovirus-vectored) immune responses. A large Phase 2b trial in HIV-negative adults in Africa and India using the GSK M72 adjuvanted fusion protein vaccine is also being initiated. These efficacy trials may yield the first clues about potential correlates of protective immunity, and, at a minimum, will help to better define disease risk factors, if no protection is observed. The number of participants in these trials (1400–7000) is likely to be insufficient for licensure, but these ongoing studies are a significant advancement for the TB vaccine field. Not only will they provide the samples to study correlates of risk of disease or correlates of protection, but they will help identify and define endpoints in large trials that will be acceptable for submission to regulatory authorities. They will also inform the field on the data needed to estimate sample sizes and subgroups required for adequate power of Phase 3 studies. Most likely, these Phase III studies will need to be performed at many sites in varying geographies and continents, in order to analyze potential effects of host immunological variability, co-morbidities and co-infections that are representative of diverse global communities, as well as assess the vaccines ability to protect against different circulating Mtb strains [29]. On this note, most clinical studies of TB vaccines to date have been performed in sub-Saharan Africa, but there is a clear need for clinical studies in other high-burden regions, such as China and India, which have unique epidemiological patterns and country-specific challenges for approving and introducing TB vaccines.

3. Challenges of new TB vaccines

Despite the recent advances in the field, developing a TB vaccine for any chosen population is fraught with considerable obstacles. First, there is no correlate of protection that can guide vaccine design or animal experiments, or that can be used as a credible endpoint in early human studies. Second, without a known efficacious vaccine that prevents pulmonary TB, it is impossible to validate an animal model as a potential surrogate. Third, due to the relatively low regional incidence of TB, despite the high worldwide prevalence, Proof-of-Concept trials that use clinical endpoints are by necessity very large (1000–35,000 subjects) and expensive ($10–$50 million).

The gaps remain large in our understanding of TB and the role of the natural human immune response following infection and colonization. For example, we have no clear models upon which to identify the "best" Mtb antigens for a vaccine, as many TB vaccine animal models use attenuated strains, short timing to challenge, and have a narrow dynamic range of responses that do not allow for easy differentiation among candidates. Likewise, these Mtb