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Review Article

Tuberculosis Prevention and Treatment: Achievements and Challenges in the Vaccine Development Process

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Abstract

Although vaccines have been the most effective tools for eradication of the infectious diseases such as smallpox and polio, they have not been that successful for obliteration of tuberculosis so far. BCG vaccine has been globally utilized in infants and children; however, its limited variable efficacy in prevention of pulmonary tuberculosis and transmission of *Mycobacterium tuberculosis* (*M. tuberculosis*) has been reported. Imperative to developing new tuberculosis vaccines has been due to the threat of multidrug resistant *M. tuberculosis* strains. Current vaccines in clinical development include whole cell derived vaccines, viral vectored vaccines and adjuvanted protein subunit vaccines. In this review, a number of challenges regarding the recently developed TB vaccines and vital approaches recommended to tackle them have been addressed.

Keywords: *Tuberculosis; Vaccine; M. tuberculosis*

Introduction

Tuberculosis (TB) is infectious disease caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*). TB has been the deadliest infectious disease and has killed one billion people over the past two hundred years [1]. Throughout the 20th century, TB fatality rate declined notably in industrialized countries, with interruptions over the second World Wars, as a result of enhanced living standards and development of antibiotics as main TB control policies [1]. With the appearance of the HIV/AIDS pandemic and the rise in drug resistance, TB returned in the early 1990s and turned into a salient case of mortality, particularly in sub-Saharan Africa [1]. In 2008, 1.4 million new cases of TB was estimated amongst persons with HIV infection, and relative risk of TB amongst HIV-infected individuals was up to 37 times greater than amongst HIV-uninfected persons [2]. In 2014 and 2016, there were respectively 9.6 and 10.4 million new TB cases along with 1.5 and 1.7 million deaths globally [3,4].

The implementation of directly observed therapy, short course (DOTS) strategy, which centered on direct supervision of drug intake by patients, was initiated in 1995. By 1999, 127 countries responsible for 80% of global TB mortality, had implemented DOTS programme. However, the appraisal of DOTS programme by 2004 indicated its unsatisfactory effectiveness, which led to the development the new Stop TB Strategy in the mid-2000s in order to allowing wider access for all TB-infected persons, especially in the poorest countries. The new STOP TB Strategy, particularly for addressing the new challenges of TB-HIV co-infection and MDR-TB, was formally launched on World TB Day in 2006 and provided the basis for the Global Plan to Stop TB 2006 - 2015 [1].

From late 1990s, research and development for proficient diagnosis, prevention and treatment of TB in individuals of all ages was required, primarily in developing countries. Foundations together with academic groups, research institutes and public-private partnerships were set up for research and development on new TB diagnostics, drugs and vaccines. As the behavior of the immunity system towards *M. tuberculosis* is unlikely to change by drug resistance mutations in the bacterium strains, TB vaccines are expected to be effective against both drug-sensitive and drug-resistant strains [3].

Traditional and modern tuberculosis vaccines' situation

The first TB vaccine was developed after 231 subculture of a virulent bovine strain of *Mycobacterium bovis*, isolated by Edmond Nocard in 1902 from a cow with tuberculous mastitis (namely Lait Nocard strain), carried out on bile, glycerin and potato medium during 11 years, from 1908 to 1919. The obtained bacterium strain was hindered from producing progressive tuberculosis in animals and named Bacillus Calmette-Guerin (BCG). In 1921, a trial of BCG vaccine was initiated and thousands of infants were orally vaccinated with the vaccine by 1928, without serious complication [5]. The main producers of BCG vaccine have been Pasteur-Merieux-Connaught, the Danish Statens Serum Institute, Evans Medeva (which has taken over the old Glaxo vaccine), and the Japan BCG Laboratory in Tokyo. The quality of BCG vaccine (e.g. the proportion of viable cells per vaccine dose) manufactured by these producers have varied (Milstien and Gibson, 1990]. BCG vaccine strains used by various manufacturers may be characteristically different from the original Paris strain [6]. However, due to limited information on protective efficacy of the BCG vaccine strains, it is difficult to recommend one BCG vaccine strain.

Prophylactic BCG vaccine has protective effect in infants' population and there is general agreement that the vaccine provides trivial protection in adults. Due to inconsistent efficacy of BCG vaccine and its weak protective effect during adulthood, the development of new commercial vaccines has been entailed for combating TB. A number of new TB vaccines have been devised to replace or boost BCG [7,8]. Improved grasp of immunological mechanisms has been the road map for designing new TB vaccines. For instance, the immune system compromisation in HIV-infected individuals leads to reactivation of *M. tuberculosis*, latent infection of which was previously deterred by robust immune response. For latent *M. tuberculosis*, suitable post-exposure vaccines are therefore required to prevent the bacterium reactivation, particularly in areas with soaring tuberculosis incidence. New vaccine candidates against *M. tuberculosis* have been developed based on stimulation of T cells, including Th_1 cells activating anti-mycobacterial ability of macrophages [9], memory T cells producing cytokines (interferon γ, tumour necrosis factor and interleukin 2) [10], Th17 supporting Th1 response [11] and CD8 cells attacking *M. tuberculosis* directly by perforin and granolysin [12].

Pre-exposure vaccines (e.g. hybrid H1 and H4 vaccines) are mostly faced with metabolically-active *M. tuberculosis*; therefore, chosen antigens for this type of vaccines are derived from those expressed during metabolically-active stage of the bacterium [13]. Post-exposure vaccines, in contrast, are given to individuals with dormant *M. tuberculosis* and these types of vaccines contain antigens expressed during latent-phase of *M. tuberculosis* infection. It is preferable to use multistage vaccines, such as H56, M72 and ID93, designed based on a combination of the antigens to deal with both active and latent stages on *M. tuberculosis* infection [13].

Live tuberculosis vaccines have been also developed, based on either improvement of BCG vaccine via overexpression of proteins (such as Ag85B) responsible for the pathogenesis of *M. tuberculosis* [14] or attenuation of *M. tuberculosis* through deletion of virulence genes. Improved recombinant BCG vaccines (rBCG), such as rBCG30 overexpressing Ag58B and rBCGΔUreC:Hly (VPM1002) secreting listeriolysin, have passed preclinical studies which advocating their greater potency and safety than the conventional BCG vaccine, and started their clinical trials [15,16]. Entered into clinical trials, MTBVAC01 is a live attenuated *M. tuberculosis* MT103 strain with an inactivated *phoP* and *fad26* genes, which are respectively responsible for intracellular growth of *M. tuberculosis* and fatty acid biosynthesis [17,18].

Whole heat-inactivated *M. vaccae*, an environmental nonpathogenic mycobacterium, and fragmented detoxified *M. tuberculosis*, namely RUTI, have been also prepared as immunotherapeutic agents and have been successfully assessed in clinical trials [8]. Inactivated *M. vaccae* (Vaccae™) has been already assessed in the most advanced stage of clinical trials for safety and efficiency in preventing adults and approved in China for the adjunctive treatment of TB [19,20].

Subunit and viral vector-based vaccines that boost BCG prime have been developed. Subunit vaccines supply antigens which are recognized by T-cells of individuals with latent or cured tuberculosis. Recombinant fusion antigens from *M. tuberculosis* and BCG (such as Ag85B-ESAT-6, Ag85B-TB-10.4 and M72) have been built up in adjuvant (like IC31) as well as live viral vectors (like vaccinia and adenovirus) [21-26]. The efficiency of live viral vectors vaccines in human may be however reduced by previous exposure or vaccination with the vector.

Viable live attenuated vaccines (e.g., VPM1002 and MTBVAC) and inactivated vaccines, which are named whole cell vaccines, are poly-antigenic and have a greater opportunity, compared to subunit vaccines, for generating a more diversified immune response (i.e. both humoral and cellular immune responses to a range of protein and lipid antigens). Strategy of utilizing whole cell vaccines for TB has gained increased attention due to difficulties in discovering antigens integral to inducing protective immune response to *M. tuberculosis* [3,13].

New ideas in TB vaccine development have been addressed in literature [3]. Firstly, due to the sophistication of a large number of protein, lipid and glycolipid antigens, all immunogenic in humans, the whole cell mycobacterial vaccines have the potential advantage of inducing a broader immune response, in comparison to other vaccine candidates. It has been reported that the humoral immunity can modulate the immune response to *M. tuberculosis* [27-34]. Non-classical T-cells, having receptor to bind non-protein antigens, can also play an integral role in developing adaptive immune response [35,36]. Thus, broadening immune responses, having been CD4 and CD8 T-cell responses for the current TB vaccine clinical pipeline, by induction of unconventional T-cells (e.g. CD1, MR1, HLA-E and γδ T-cells) and antibody responses has been argued in order to expand TB vaccine candidates' immunogenicity.

There are two strategies to reduce tuberculosis by the near future vaccine candidates. Given that BCG vaccination does not promote immune response to dormant *M. tuberculosis*, in the first strategy, post-exposure vaccines eliminate the latent bacterium and deter its later reactivation. Therefore, the discovery of stage-specific genes [37,38] and expression of latency antigens [39] would help eradicate dormant *M. tuberculosis*. In the second strategy, application of new boost vaccines (considered as replacements for BCG) eradicates *M. tuberculosis*.

In an inclusive tuberculosis vaccination approach, three types of vaccines ought to be involved [8]. First, BCG or a BCG substitutes to prepare the immune system for consequent boost subunit vaccination. Second, subunit vaccines have to be administered repeatedly during an individual lifetime to boost the initial level of the BCG- or BCG substitute- induced memory response. Third, post exposure administration of boost vaccines to adolescents and adults in order to eradicate latent infection.

TB vaccines trials' issues

There are integral issues to be considered relevant to clinical trials. Co-infection with pathogens is a factor proved to modulate the immune response [40]; consequently, this issue can influence the response to TB vaccines during trials. The participants in TB vaccines trials should be therefore monitored for active infections. The clinical trials for some tuberculosis vaccines, such as MVA85A, has shown good vaccine safety but no vaccine efficacy [41] and the later caused important disputes. There are several issues to be addressed before drawing firm conclusions from clinical trials. For instance, masking the effect of new vaccines by BCG and other mycobacterial antigens might be the reason for inefficiency in clinical trials. Also the characteristics accountable for *M. tuberculosis* high burden in a clinical trial's site, such as the South African Tuberculosis Vaccine Initiative (SATVI), may resist against vaccination [42]. Based on BCG vaccine efficacy history, it is surmised that the efficacy results for the new developed vaccines would be also troublesome. To generate data that can be extrapolated to countries with genetically, culturally, and environmentally diverse populations, new vaccines' clinical trials should be completed in several countries and in various regions of the globe.

There are further concerns to be addressed regarding trials. For example, the major weak points for TB vaccine candidates include the lack of standardization of the testing protocols (for efficient induction of memory or effector immunity, based on the kind of vaccine candidate), the choice of the challenge strain (i.e. the selection of current clinical isolates-inducing regulatory T cells- instead of laboratory-adapted challenge strains), the doses of vaccines and the routes of vaccination, vaccine to challenge intervals and the route of the challenge strain administration. A rational process for preclinical testing of TB vaccine candidates is the progressive evaluation from small-animal (mouse, guinea pig) models to nonhuman primates (NHPs), and the common consensus is that the NHP models, mostly macaques) should be endpoint for non-clinical tastings, due to their close similarities to humans. However, there are major limitations with NHP models, including different immune responses and different patterns of disease outcome in various subspecies of NHP models. Hence, it would be prudent for the field to use smaller-animal models to avoid such limitations.

Conclusions

The recent high global morbidity and mortality for tuberculosis has been happening in the presence of recent devices of interventions (including drugs, diagnostics and a vaccine), proving the inadequacy of such tools and the urgent need for much more efficient ones. Despite the continuous development of antimycobacterial agents for the treatment of multidrug-resistant tuberculosis and immense optimism arisen from their introduction into the health centers, patients bearing resistant-strains to such novel drugs (such as bedaquiline and delamanid) have been reported [43]. Therefore development of better vaccines for enhancing wide immune protection against pulmonary TB in all age groups (i.e. children and adults) is a goal worth pursuing, with the hope that vaccination can manage the problem derived from multidrug- resistant tuberculosis. An effective vaccine preventing pulmonary TB can significantly contribute to the goal of reducing TB morbidity and mortality by the year 2035.

BCG is the only licensed vaccine available today and has been used for more than 95 years with significantly safety proofs, although its efficiency has been controversial and no universal BCG vaccination plan subsists. Diverse efficacy results for BCG vaccines might be attributed to the dissimilarities in microbiological characteristics between strains of BCG used by different vaccine manufacturers [44,45], the genetic variation in the studied populations [46] and the exposure to various environmental mycobacteria providing a context protection that BCG could not improve it against tuberculosis [47,48].

Although the public health benefits of an improved TB vaccine would be high, TB vaccine development looks unattractive to industry mainly owing to the risk of failure and the low commercial cost. Destructive effect on the TB vaccine development endeavors could happen through funding shortfall for research and development on this field. With the renewed investment of funders the dedicated funding for TB vaccines development from the Bill and Melinda Gates Foundation and the European & Developing Countries Clinical Trials Partnership (EDCTP), restoration of the TB vaccine development pipeline has been possible so far. Broadening antigen selection and expanding the range of vaccine immune response, via inducing both non-conventional T-cells and antibody responses, are factors which can be considered for increasing TB vaccine efficacy.

Overall, attempts made over the past two decades on development of novel TB vaccines-including prophylactic, therapeutic and post-exposure tries-appear to be slow-moving, and several of the vaccine candidates have not been moved toward clinical trials [49]. In spite of this fiasco, the obtained experience deems to be fruitful for future designing and testing tuberculosis vaccines. There are poorly-understood issues regarding the host response (such as memory immunity and inhibitor role of regulatory T cells promoted by current clinical strains) which make the elimination program dubious. Immunodominant antigens (e.g. Ag58 family) are only made in large quantities during certain times in *M. tuberculosis* life cycle; however, it is recently argued that weakly immunogenic subdominant proteins of *M. tuberculosis* are superior vaccine candidates and deserve future attention [49].

Conflict of Interest

No conflict of interest is declared.

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