Austin Journal of Clinical Immunology

Open Access

Austin Publishing Group

Special Article - Vaccine Development

Vaccine Development: Highlighting Development of Tuberculosis Vaccines

Bhawna Sharma*

Department of Immunology, National JALMA Institute for Leprosy and Other Mycobacterial Diseases (ICMR), India

***Corresponding author:** Bhawna Sharma, Department of Immunology, ICMR-National JALMA Institute for Leprosy and Other Mycobacterial Diseases (ICMR), Tajganj. Agra. Uttar Pradesh, India

Received: November 07, 2019; **Accepted:** December 10, 2019; **Published:** December 17, 2019

Abstract

Vaccine development is a complex strategic plan for the development of vaccine for infectious diseases. Vaccine development today faces a number of significant challenges. There exist tremendous public health needs to address major well-known pandemic diseases, including Acquired Immunodeficiency Syndrome (AIDS), Tuberculosis (TB), and malaria. Delivery of a vaccine in a programme such as Expanded Program on Immunization is the end result of years of discovery and development. Only a few vaccines candidates progress to licensing as making the costs of vaccine research and development is extremely high. Development of vaccines can be simplified into two broad stages: Preclinical and Clinical trials. Tuberculosis remains a global dilemma for a number of reasons, one of them is the lack of a highly efficacious vaccine, and an incomplete understanding of what controls transmission, infectivity, reactivation, and progression of disease. Insights of the immune response needed for protective immunity is critical for the development of an effective vaccine. The lack of validated immune correlates of protection, together with the uncertain predictive value of animal models, is the most important challenges to successful vaccine development. The development pathway for TB vaccines remains a challenge due to a lack of guideposts, including immune correlates of protection against disease or infection, animal challenge models that are known to reliably predict vaccine efficacy in humans, or an established controlled human infection model.

Keywords: Tuberculosis; Vaccines

Background

Vaccine development involves the process of taking a new antigen or immunogen identified in the research process and developing a test antigen into a final vaccine that can be evaluated through preclinical and clinical studies to determine the safety and efficacy of the resultant vaccine candidate. Vaccine development today faces a number of significant challenges. There exist tremendous public health needs to address major infectious for which natural immunity does not provide a helpful guide for vaccine development. During this process, the product's components, in process materials, final product specifications, and manufacturing process are defined. The manufacturing scale used during development is usually significantly smaller than that used in the final manufacturing process. Vaccine development has been a very successful strategy in the prevention of highly contagious or serious disease. An excellent example is that of smallpox, which a threat to human health is no longer. The development of vaccines for all infectious agents would be an ideal, but sometimes there are difficulties with immunogenicity and the protective nature of vaccines. WHO's Initiative for Vaccine Research (IVR) facilitates vaccine Research and Development (R&D) against pathogens with significant disease and economic burden, with a particular focus on low and middle income countries.

Stages of vaccine development

Delivery of a vaccine in a programme such as Expanded Program on Immunization is the end result of years of discovery and development. Only a few vaccines candidates progress to licensing as making the costs of vaccine Research and Development extremely high. Development of vaccines can be simplified into two broad stages:

1. Pre-clinical development is research carried out in lab assays and on animals. It includes:

- Identification (discovery) of relevant antigens (e.g. screening)
- Creation of the vaccine concept
- Evaluation of vaccine efficacy in test tubes and animals
- Manufacture of the vaccine to Good Manufacturing Practice standards

2. Clinical development is when the vaccine is first tested in humans. It covers four stages over several years, from initial clinical trials in humans (phase I) right through to introduction and beyond (phase IV). Clinical development is built on rigorous ethical principles of informed consent from volunteers, with an emphasis on vaccine safety as well as efficacy.

Phase I clinical trials: They are small-scale trials to assess whether the vaccine is safe in humans and what immune response it evokes. For diseases of poverty this covers trials in European volunteers (phase Ia) and then in populations in Developing Countries (phase Ib).

Citation: Sharma B. Vaccine Development: Highlighting Development of Tuberculosis Vaccines. Austin J Clin Immunol. 2019; 6(2):1039.

Phase II clinical trials: These trials are larger and look mainly to assess the efficacy of the vaccine against artificial infection and clinical disease. Vaccine safety, side-effects and the immune response are also studied.

Phase III clinical trials: Vaccines that progress to phase III clinical trials are studied on a large scale of many hundreds of subjects across several sites to evaluate efficacy under natural disease conditions. If the vaccine retains safety and efficacy over a defined period, the manufacturer is able to apply to the regulatory authorities for a licence to market the product for human use.

Phase IV clinical trial: The final phase IV happens after the vaccine has been licensed and introduced into use. Also called post-marketing surveillance, this stage aims to detect rare adverse effects as well as to assess long term efficacy.

Tuberculosis vaccine development

Tuberculosis (TB) remains a major infectious cause of mortality and morbidity globally. It is estimated that about a third of the world's population are infected with *Mycobacterium tuberculosis (M. tuberculosis)*. Despite significant advances in reducing mortality in recent decades through improved diagnosis and drug treatment regimens, Ten million people developed TB disease in 2017 and 3.5% of new TB cases and 1.7 billion people, 23% of the world's population are estimated to have a latent TB infection and are at risk of developing active TB disease during their lifetime [1]. In addition to enormous human suffering, TB causes substantial economic burden and is one of the major drivers of global inequity. *M. tuberculosis* can cause a spectrum of clinical manifestations, from latent asymptomatic infection and asymptomatic sub-clinical disease to the full spectrum of symptomatic clinical disease affecting any organ of the body. Thus the true burden of TB remains difficult to quantify. There are many obstructions in the way to the control of TB which mainly include difficulties and delays in diagnosis, lengthy treatment regimens, drug resistance, the most important is the lack of a highly efficacious vaccine, and an incomplete understanding of what controls transmission, infectivity, reactivation, and progression of disease [2].

There are three main conditions that make it scientifically more practical to eradicate a disease: (1) Epidemiological vulnerability, (2) effective interventions, and (3) feasibility of elimination. In case of TB, the disease is not vulnerable to eradication for the following reasons: it is transmitted simply by means of air; transmission occurs throughout the year and is not linked to a cyclical disease cycle, there is no natural immunity to prevent re-infection; it is not easily diagnosed, disease relapse is documented in a proportion of patients who complete treatment; and there is an LTBI reservoir that can re-activate at any time in an infected individual's lifetime. In addition, TB elimination has never been documented from any country in the world, indicating that the likelihood of achieving global TB eradication is low.

On May 19, 2014, the 67th World Health Assembly adopted the World Health Organization (WHO) Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015 [3]. The post-2015 global tuberculosis plan, known as the End TB Strategy [4] was formed and developed through consultation with a wide range of stakeholders. The strategy sets ambitious goals for global TB eradication in post-2015 agenda. A 90% reduction in TB-related mortality, an 80% decline in TB incidence, and the elimination of catastrophic expenditures for TB-affected people by 2030 are targeted in the strategy. The vision of strategy has making the world free of TB, with zero deaths, disease, and suffering due to the disease.

The other face of the deadly disease is different from the active form of disease and known as Latent TB infection. It is estimated that one-quarter of the world's population are latently infected with *M. tuberculosis* and are at risk of reactivation of this latent infection. *M. tuberculosis* employs multiple mechanisms to inhibit innate and adaptive immune responses and to establish a chronic persistent infection. The primary focus of TB vaccine efforts thus far has been to prevent cases of active TB disease. Shifting the goal to preventing infection offers several advantages for countering the immune evasion strategies of *M. tuberculosis*. In regards to effective preventive interventions, a safe and effective *M. tuberculosis* vaccine is not available till date, despite intense research efforts over the past two decades. The only licensed vaccine against TB, Bacille Calmette Guerin (BCG), that was first developed in 1921 and is an attenuated strain of *Mycobacterium bovis*. When administered at birth, BCG confers consistent and reliable protection against TB meningitis and other forms of disseminated disease. However, the protection conferred against pulmonary disease is very variable and is lowest in low and middle-income settings, where the current burden of disease is greatest [5]. This BCG vaccine does not prevent infection but may reduce mortality in young recipients. BCG has been implemented for nearly a century, and despite its widespread use, TB continues to be a major global problem. A vaccine to prevent *M. tuberculosis* infection or disease remains an important tool for elimination, but the development of such a vaccine is considerably hindered by the complex biology of *M. tuberculosis* and the lack of basic information on protective immune responses [6]. *M. tuberculosis* is a complex intracellular pathogen capable of subverting the host immune response for its own survival. Understanding the immune response needed for protective immunity is critical to the development of an effective vaccine. The lack of validated immune correlates of protection, together with the uncertain predictive value of animal models, is the most important challenges to successful vaccine development.

TB vaccine development strategies: TuBerculosis Vaccine Initiative (TBVI) and Aeras initiated TB vaccine community that has published a Blueprint for TB vaccine development in 2012 It includes a global, integrated strategy, outlining major scientific challenges, critical activities and crucial questions [7]. This Blueprint summarized the current situation of global TB vaccine development and identified key areas of research which are critical for the development of a new, effective TB vaccine. A more diverse and dynamic pipeline is needed to accelerate towards our goal of a new TB vaccine. It is needed to test a broader range of vaccine technologies against a broader range of antigens and we need to move vaccine candidates more rapidly through the pipeline. Vaccine technologies that have shown promise in pre-clinical studies include the Cytomegalovirus (CMV) vector, which is a live, attenuated, persistent viral vector able to express multiple MTB antigens. It has been shown that the engineering of the CMV vector leads to constant, low-level replication of the virus,

giving sustained antigen expression and long-term immunity, making this technology highly attractive for TB vaccine development [8,9].

The strategy which is under development for the pandemic flu response could also be applied to TB vaccine development. One such approach uses mRNA as a vaccine vector [10]. TB disease manifestations in Non Human Primates (NHPs) are very similar to those observed in humans, and this model is therefore regarded as the most reliable for testing TB vaccines in product development. However, final validation of the NHP model is possible only after successful efficacy testing of a novel TB vaccine in humans, when results can be backtranslated to the NHP [11]. It has been shown in a series of NHP experiments that mucosal or intravenous vaccination with whole cell mycobacterial vaccines provides better protection than parenteral vaccination, by inducing more T Helper (TH) TH17 cells, more resident memory T cells [12] and more effector T cells [13]. The challenge ahead is to increase the rate at which candidate vaccines enter the pipeline and the rate at which candidates move through the pipeline. There are promising new approaches, although obstacles need to be overcome for the use of intravenous inoculation or viral vectors which integrate into the host genome. Transparent and robust criteria for moving vaccines from one stage of vaccine development are currently being reviewed and will be used to increase the pace of TB vaccine development.

TB Vaccine research and Development: As discussed previously, BCG can provide decades of protection against TB, still inadequate but, it gives evidence that vaccine mediated protection against TB is a possibility. A new TB vaccine is, therefore, inevitability. Novel vaccine platform technologies alone will not lead us to a new TB vaccine. In TB there is no doubt that immunity can prevent disease and no doubt that protective immunity can be induced by vaccination. Evidence for this includes the long lasting immune protection found following immunisation with BCG [14,15] and natural immunity found in those latently infected with *M. tuberculosis* [16] and in those who either clear infection or resist disease [17]. A key activity in research and development is the identification of target antigens for insertion into vaccine candidates *M. tuberculosis* has distinct phases of growth, which may be associated with active mycobacterial replication, persistence and dormancy [18]. Antigens associated with active bacterial replication include the early secreted antigens, such as the Ag85 family, ESAT-6 and CFP-10. These antigens have been used extensively in TB vaccine development as they are highly immunogenic and have shown protection in animal models. Antigens in the DosR regulon, however, are associated with dormancy and their use offers the possibility of designing vaccines to more specifically target Latent MTB Infection (LTBI). The broader range in antigen choice has been matched with the development of novel adjuvants, including synthetic and bio-inspired molecules, which mimic naturally occurring cellular processes for more efficient delivery of vaccine components to the cell.

STRATEGIC GOALS: Developing a safe, effective and affordable TB vaccine

For adolescents and adults with active pulmonary TB disease: Given the central role that adolescents and adults with active pulmonary TB disease play in spreading *M. tuberculosis* infection, the prevention of pulmonary TB disease in adolescents and adults is the priority strategic target in TB vaccine development. It may represent an effective means of preventing *M. tuberculosis* infection and TB disease in infants and young children, as well as in adolescent and adult contacts [19]. The vaccine should be protective in people with or without evidence of *M. tuberculosis* infection, and prevent progression to TB disease following primary infection, as well as following re-infection(s) and reactivation in subjects with latent infection.

For neonates and infants: While infants and young children with TB do not represent an important source of Mtb transmission, they represent an important, vulnerable group, and there is a need to improve upon the BCG vaccines currently in use. The possibility that past mycobacterial exposure may impact the vaccine response in a negative way [20], which would impact the technical feasibility of vaccine development success, also calls for continued efforts for early life TB vaccine research. A new TB vaccine intended for administration in early life, providing both a superior degree and longer duration of protection as compared to the current BCG vaccines, that could be safely administered to infants with HIV infection or other causes of immune suppression, would represent an important public health advance.

The development pathway for TB vaccines remains a challenge due to a lack of guideposts, including immune correlates of protection against disease or infection, animal challenge models that are known to reliably predict vaccine efficacy in humans, or an established Controlled Human Infection Model (CHIMs). Despite extensive efforts, no correlates of immune protection have been reliably identified for TB vaccines. Identifying immune correlates of protection remains a high priority given the potential for such biomarkers to advance the development and selection of future vaccine candidate selection. Animal challenge models represent a mainstay of the TB vaccine development pathway. Controlled Human Infection Models (CHIMs) have proven valuable in advancing vaccine development for influenza, malaria, enteric diseases and other infectious diseases. Efforts are ongoing to develop a CHIM to assess TB vaccines, and overcome a number of challenges.

References

1. World Health Organization (WHO). Global tuberculosis report. Geneva: WHO/HTM/TB. 2018.
2. Zumla A, Raviglione M, Hafner R, von Reyn CF. Tuberculosis. N Engl J Med. 2013; 368: 745–755.
3. World Health Organization. Documentation for World Health Assembly 67. Geneva: WHO; 2014.
4. World Health Organization. The End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: WHO. 2015.
5. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet. 2006; 8; 367: 1173-1180.
6. Moliva JI, Turner J, Torrelles JB. Prospects in Mycobacterium bovisbacille Calmette et Gue´rin (BCG) vaccine diversity and delivery: why does BCG fail to protect against tuberculosis? Vaccine. 2015; 33: 5035–5041.
7. Brennan MJ, Stone MR, Evans T. A rational vaccine pipeline for tuberculosis. Int J Tuberc Lung Dis. 2012; 16: 1566–1573.
8. Früh K, Picker L. CD8+ T cell programming by cytomegalovirus vectors: applications in prophylactic and therapeutic vaccination. Curr Opin Immunol. 2017; 47: 52–56.

9. Greene JM, Dash P, Roy S, McMurtrey C, Awad W, Reed JS, et al. MR1-restricted mucosal associated invariant T (MAIT) cells respond to mycobacterial vaccination and infection in nonhuman primates. Mucosal Immunol. 2017; 10: 802–813.

10. Zhang C, Maruggi G, Shan H, Li J. Advances in mRNA Vaccines for Infectious Diseases. Front Immunol. 2019; 10: 594.

11. Laddy DJ, Bonavia A, Hanekom WA, Kaushal D, Williams A, Roederer M, et al. Toward tuberculosis vaccine development: recommendations for nonhuman primate study design. Infect Immun. 2018; 86: e00776-00817.

12. Aguilo N, Alvarez-Arguedas S, Uranga S, Marinova D, Monzón M, Badiola J, et al. Pulmonary but Not Subcutaneous Delivery of BCG Vaccine Confers Protection to Tuberculosis-Susceptible Mice by an Interleukin 17-Dependent Mechanism. J Infect Dis. 2016; 213: 831–839.

13. Sharpe S, White A, Sarfas C, Sibley L, Gleeson F, McIntyre A, et al. Alternative BCG delivery strategies improve protection against Mycobacterium tuberculosisin non-human primates: Protection associated with mycobacterial antigen-specific CD4 effector memory T-cell populations. Tuberculosis (Edinb). 2016; 101: 174–190.

14. Harris RC, Dodd PJ, White RG. The potential impact of BCG vaccine supply shortages on global paediatric tuberculosis mortality. BMC Med. 216; 14: 138.

15. Mangtani P, Nguipdop-Djomo P, Keogh RH, Trinder L, Smith PG, Fine PE, et al. Observational study to estimate the changes in the effectiveness of bacillus Calmette-Guérin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK. Health Technol Assess. 2017; 21: 1–54.

16. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. Clin Infect Dis. 2012; 54: 784–791.

17. Esmail H, Barry CE, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Philos Trans R Soc Lond B Biol Sci. 2014; 369: 20130437.

18. Schubert OT, Ludwig C, Kogadeeva M, Zimmermann M, Rosenberger G, Gengenbacher M, et al. Absolute Proteome Composition and Dynamics during Dormancy and Resuscitation of Mycobacterium tuberculosis. Cell Host Microbe. 2015; 18: 96–108.

19. White R, Harris R, Knight GM. Potential public health impact of new TB vaccines: Prevention of disease, infection and immunotherapy. TB Vaccine 4th Global Forum. 2015; 21–24.

20. Poyntz HC, Stylianou E, Griffiths KL, Marsay L, Checkley AM, McShane H. Non-tuberculous mycobacteria have diverse effects on BCG efficacy against Mycobacterium tuberculosis. Tuberculosis (Edinb). 2014; 94: 226–237.