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AN UPDATE ON NEW VACCINES FOR TUBERCULOSIS

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ABSTRACT

Tuberculosis (TB) is one of the most common and deadly communicable diseases in the world, infecting approximately one-third of the total human race. The number of drug-resistant TB cases are increasing. The spectrum of resistance varies from single to multidrug and from multidrug to total drug resistance varieties. Human Immunodeficiency Virus (HIV) infection is also responsible for the recent re-emergence of tuberculosis infection worldwide. When drugs are becoming ineffective against Mycobacterium tuberculosis, there is a need to focus more on preventive strategies. Though Bacillus Calmette–Guérin (BCG) vaccine is efficient in preventing miliary and meningeal tuberculosis in children, it is not effective against pulmonary tuberculosis. For prevention of pulmonary tuberculosis, development of new vaccines is the need of time. Several new vaccines are under clinical trials either to replace old BCG or act as a booster for the current BCG vaccine. New vaccines include live Mycobacterial vaccines, its subunit, live vector-based vaccines and killed whole or fragmented vaccines. This review recaps the status of development of pre-clinical tuberculosis vaccines.

Keywords: Vaccine, Mycobacterium tuberculosis, Tuberculosis, Trials, Anti TB vaccines, BCG vaccine.

Contribution/ Originality

This study reviews current knowledge regarding the status of development of new vaccines for tuberculosis.

1. INTRODUCTION/BACKGROUND

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*).The DNA of *Mtb* had been recovered from the tissues of Egyptian mummies [1].

During 2010; the World Health Organization (WHO) had declared that approximately one-third of the world's population was infected with *Mtb.* Recent data of WHO estimates that worldwide in 2013 almost nine million cases and 1.5 million deaths per year were reported [2]. In recent years, there is an increasing trend of multidrug-resistant (MDR-TB) and worldwide about 480,000 people developed MDR-TB in 2013. Among MDR-TB patients, 9% were diagnosed with extensive drug-resistant (XDR-TB) [2]. Some cases with total drug resistance (TDR-TB) to first and second line anti-tubercular drugs have also been reported [3].

Immuno-compromised individuals, especially HIV-infected patients, are more prone to tuberculosis infection. The Joint United Nations Programme on HIV and AIDS (UNAIDS) estimated that among 2.6 million new cases of HIV infection, 1.8 million were associated with tuberculosis [4].

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According to the WHO, Asia region has been most severely affected by TB. The burden of tuberculosis in South-East Asia and Western Pacific Regions together accounts for 58% of total TB cases worldwide in 2012. Among top five countries with the high burden of incident cases, India ranked first (2.0 million) followed by China (0.9 million - 1.1 million), South Africa ().4 million-0.6 million), Indonesia (0.4 million-0.5 million) and Pakistan (0.3 million- 0.5 million) [5]. Based on Malaysian Association for the Prevention of tuberculosis (MAPTB), Tuberculosis is an important public health challenge in whole Malaysia with 24,071 new cases reported in 2013 [6]. The evidence confirmed that TB was the second highest communicable disease in Malaysia after dengue fever [6]. It was estimated by WHO that the incidence rate of TB in Malaysia was 81/100,000 population during 2013 [6]. Following this re-emergence and drug resistance trends, the WHO was forced to declare Tuberculosis as a global public health emergency during 1993 [2, 7].

1.1. Immunology

Mtb is the causative organism of tuberculosis. It is transmitted through the air as suspended droplets and inhaled by individuals into lungs. The organism reaches the deepest of alveoli in their lungs, where the organism avoids destruction by alveolar macrophages and maintains itself in the intracellular environment [7-9].

Once *Mtb* causes initial infection in the lungs; innate immunity will be activated. Dendritic cells and alveolar macrophages are transported to the infected site to control the pathogen. Active TB occurs when the organism is released from the granuloma. This is because dendritic cells and the macrophages fail to control the pathogen and causes necrosis of granuloma [10].

In many cases of TB, humans are infected by the organism but they do not develop the disease. These cases are classified as latent TB infection (LTBI) where the people are the vast reservoir for the organism. Such LTBI will reactivate when the immune system of the person weakens, most notable in individuals with HIV infection [11].

LTBI occurs when immune system restrains the spread of *Mtb* by the formation of granuloma. However, it does not kill all the pathogen where the organism survives inside the granuloma.

In some studies, it is believed that the CD4+ Th1-cells are also involved in controlling TB infection. However, due to some unknown reasons, the T-cell response is muted within the granuloma with limited antigen presentation and recognition [8].

Th17 that is produced by IL-17 received attention lately due to some evidence suggesting that Th17 cells are involved in controlling TB infection. Besides that, apoptosis of the cells is caused by CD 8+ T-cells also plays an important role in TB infections [7]. Though the mechanisms of the immune system controlling the TB bacilli are not well understood, scientists believe it is the cell-mediated immunity that plays an important and critical role [12].

1.2. Previous old BCG Vaccine

The only vaccine that was available for tuberculosis till date is the *M.bovis* BCG vaccine, isolated by Calmette and Guérin in Lille, France [7]. This vaccine was first administered to a human infant in 1921. Since then more than 100 million of BCG vaccines are administered to infants annually. It is well-known fact that BCG can protect the infant from meningeal and miliary tuberculosis. However, the efficiency of BCG vaccine in preventing TB is reduced in old age group.

1.3. Limitations of BCG Vaccination

Although BCG can prevent meningeal and miliary tuberculosis in infants, it cannot provide immunity in adults to prevent pulmonary tuberculosis. This vaccine also cannot be administered to HIV-infected children. Studies have revealed that when BCG was given to children who were infected with HIV, there was a high risk of developing systemic or disseminated tuberculosis [13].

The Global Advisory Committee on Vaccine Safety has already issued warning that HIV-infected infants should not be given BCG injection [14]. Another limitation of BCG is that it does not provide protection against reactivation of LTBI [15].

Researchers are still investigating the reasons that why BCG vaccine is unable to prevent pulmonary tuberculosis in adolescents. Recent findings propose that the current BCG vaccine has lost more than 100 genes in regions of difference (RD) from its original genome [16, 17].

Helminth infestations are also associated with increased incidence of TB by interference with the protective anti-TB responses [7, 12]. The helminth infestations affect the immune responses by inducing Th 2 or increased regulatory T-cell (Treg) activity [18].

1.4. Role of New Vaccines

Limitations of the old BCG vaccine have urged the scientists to develop new effective vaccines in preventing tuberculosis. The primary goal of the new vaccines is to provide immunity to TB for all age groups and also in patients with HIV [13].

Some of the vaccines in clinical trials are designed to be safer in HIV-infected individuals [19, 20]. The new TB vaccine also needs to be safe, stable, inexpensive and should be able to provide long-lasting immunity [21].

Another role of new TB vaccine is its ability to combine with other vaccines that are given in childhood. This is because the large percentage of the world population is infected with *Mtb*. Thus, a booster is also required to protect against various types of *Mtb* infections. A new BCG vaccine booster with minimum 50-70% efficacy can save about one-quarter of the TB population [12].

1.5. New Vaccines for *Mycobacterium Tuberculosis*

The aim of developing new TB vaccines is either to replace the old BCG or act as a booster for the current BCG vaccine. The new TB vaccines that are being undergone clinical trials can be differentiated into a viral vector, subunit, bacterial vector and heat-inactivated Mycobacterium [22].

1.6. Live Mycobacterial Vaccines

The development of new TB vaccines is either to improve the recombinant (r)BCG or to acquire a more efficient and genetically attenuated *Mtb* to be used to prevent TB [7, 17].

In rBCG is the recombinant strain of BCG that uses BCG as a backbone to express T-cell immunity from *Mtb* [22].

In rBCG, antigens can act together to maximize the protection and at the same time, researchers expect rBCG to have a prolonged life time in the tissues thus ensuring the immunological memory [21]. To construct rBCG, immunodominant *Mtb*-specific antigens i.e. RDI and RD2 loci are introduced into BCG [17]. A study shows that the ESX-1-complemented BCG vaccine provided better protection than BCG against TB [23].

The rBCG30 is engineered for over-expressing the gene Ag85B. This antigen is a protein that secreted by *Mtb* [22]. It is found that rBCG30 secretes more over-expressing Ag85B as compared to BCG. Thus, it induces a greater Th1 immune response towards *Mtb*. Another recombinant BCG vaccine is VPM 1002. It uses protein, listeriolysin that is derived from *Listeria monocytogenes* to escape from phagolysosomes to the cytosol of the host. Listeriolysin can only work at acidic pH 5.5. However, listeriolysin cannot carry out its activity in the presence of BCG because BCG neutralises the phagosomal pH. Thus, the modification was done by deleting the urease C (ureC) gene in BCG by virtue of which microbial antigens are released into cytosol with better CD8+ T-cells stimulation [20]. Recently phase 2 trials have been completed comparing rBCG with BCG in newborn babies, however, results are still pending [24].

1.7. Subunit and Live Vector-Based Vaccines

Subunit vaccines are dead or non-replicating vaccines that can be delivered safely into the human body [7]. Most of the subunit vaccines are based on recombinant fusion proteins with attenuated viral vectors and are used as a BCG booster [7]. M72/MTB72F is the recombinant fusion protein consisting of *Mtb*32 and *Mtb*39 antigens developed by GlaxoSmithKline (GSK). This vaccine was mixed with either liposomal formulation (AS01) or proprietary oil-in-water emulsion (AS02) with monophosphoryl lipid A and *Quillaja saponaria* fraction 21 (QS21) [9, 19].

Based on clinical trials studies, M72 demonstrated high levels of CD4 T-cells in individuals with primed-BCG [11]. Another recombinant fusion protein is Hybrid I (HI) which consists of early secreted antigenic target 6 (ESAT-6) and Ag85B. HI is combined with adjuvant IC31 that consists of oligodeoxynucleotides and polycationic aminoacids [9]. Based on preclinical data, this vaccine increases Th-1 responses against *Mtb* in mice and guinea pigs [9, 19, 22].

The viral vector is also used to develop new TB vaccine, for example, the modified vaccinia virus Ankara 85A (MVA85A) which utilizes poxvirus to express Ag85A while Aeras 402 uses a recombinant adenovirus-35 to express Ag85A, 85B and TB10.4 [8]. Both of these vaccines are to act as a booster for BCG. MVA85A, shows strong T-helper cells responses by boosting specific CD4+ and CD8+ in the experiment with mice. Evidence also shows that MVA85A is safe and immunogenic in HIV and infected adults in the TB-endemic region [25].

1.8. Killed Whole/Fragmented Cell Vaccines

Therapeutic vaccines are being developed as a treatment for patients who are already infected with *Mtb*. The aim of therapeutic vaccines is not only to destroy pathogen in active disease but also in LTBI. However, extra cautions are needed in developing a therapeutic vaccine because the high dosage of *Mtb* antigens is likely to cause potential risk such as tuberculin shock [12]. This phenomenon was described by Robert Koch over 100 years ago, and it is also known as Koch's phenomenon [9]. Two heat-inactivated strains (*Mycobacterium vaccae* and *Mycobacterium indicus pranii*) has been tested with a combination of chemotherapy for *Mtb* infection. RUTI® or therapeutic vaccine is a heat-inactivated *Mtb* cellular bacterial fragment. It is grown under stress condition and is fragmented and detoxified by Triton X-11. This vaccine is designed to shorten the chemotherapy of LTBI and direct observed treatment short-course (DOTS) [12, 22].

1.9. Multistage, Multi-Antigenic Subunit Vaccine

The multi-antigenic, multistage subunit vaccine can be a very useful tool against complex microbes invading host cell by various pathways [26]. For *Mtb*, AID4 polyprotein, multistage subunit vaccine has been developed as a novel vaccine. A study published in 2015 compared AID4 emulsified in adjuvant monophosphoryl lipid A (MTO) with BCG showed promising initial results [27].

Another study studied Mtb10.4-HspX (MH) as multistage subunit fusion vaccine as a potential candidate for clinical use [26].

Table provides the summary of important tuberculosis vaccines that are undergoing human clinical trials.

1.10. Ethical Issues

All new TB vaccines are currently passing through different stages of clinical trials. The Clinical trials of new TB vaccines are mostly carried out in TB endemic areas. The populations in these areas are mostly poverty-stricken and poorly educated. They often have limited knowledge about the research and not familiar with human rights [9]. The concept of informed written consent becomes an ethical concern as the study population mostly does not fully understand the content of research protocol. In order to address this issue of grave concern, the WHO is now trying to introduce regulatory challenges for testing new TB vaccines in these under-developed and developing countries.

Table. Tuberculosis vaccines in human clinical trials

Types of Vaccine	Name	Description	Clinical Trial Phase
Recombinant BCG	rBCG30	Over expressing antigen 85B (Ag85B)	Phase I completed
	VPM 1002	Used listeriolysin produced by *Listeria monocytogenes* to support an acidic phagosomal for listeriolysin activity. Allowing BCG antigens to access to MHC I (20).	Phase IIa ongoing
	Aeras 422	Over expression of Ag85A and Ag85B.	Phase I
Viral Vector	MVA85A	Act as a BCG booster by expressing CD4 T cell responses.	Phase IIb ongoing
	Aeras 402	Uses a replication-deficient adenovirus serotype 35 expressing antigens 85A, 85B and TB10.4 (20).	Phase IIb
Recombinant fusion protein	M72/MTB72F	Recombinant fusion of *M.tb*39 and *M.tb*32 in AS01 (10, 16)	Phase II
	Hybrid 1 (H1)	Ag85B-ESAT-6 fused with strong Th1 adjuvant, IC31 (12, 16) Have prolonged Th-1 immunity.	Phase I
Bacterial fragments	RUTI®	Detoxification, fragmentation of *M.tb* (16).	Phase II
Heat-inactivated *Mycobacterium* (Inactivated whole/ fragmented mycobacteria)	*Mycobacterium vaccae* (MOD-901)	Multiple-dose of vaccine shown to be safe and give protection in Tb-HIV infected adults who have been given BCG injection during childhood (12, 22).	Phase III
	Mycobacterium indicus pranii (MIP)	Applied with chemotherapy for *M.tb* infection and results shown that it decreases response of inflammatory system (16, 20) .	Phase III

2. CONCLUSION

Even after so many decades, tuberculosis remains one of the major causes of mortality and morbidity in most of the under-developed and developing countries. This is due to the absence of any safe, stable and inexpensive vaccine providing life-long immunity. The scientists are still trying to solve the mystery of how the *Mtb* evades and escapes from the host adaptive immune responses. The only vaccine for TB which is BCG that has been existing for almost 100 years is losing its potency. Based on the evidence reviewed in this article, most of the new TB vaccine candidates have shown good efficacy and safety in trials on animals. However, the search for new TB vaccines will continue, even though, there is still no potent vaccine successfully passing through all stages of clinical and field trials. This is because the vaccines in clinical trials will prevent and reduce the number of TB cases around the world, but not completely destroy the pathogen. Thus, the next generation of vaccines that can fully eradicate Mycobacterium tuberculosis would always be required.

3. FUTURE OUTLOOK

More than 12 vaccines are currently undergoing clinical trials in various parts of the world. However, we are not sure whether these vaccines can fully prevent TB in the population. This is because there are gaps in scientific knowledge in TB and its vaccine development. A research into lung immunity may provide some information whether the regulatory T cells play an important role in modifying the susceptibility of *Mtb* [10]. The advanced technologies and development in Bioinformatics have increased the possibility of finding novel candidate antigens based on the genomic sequence [22]. A biomarker is one of a valuable tool in developing TB vaccine. The clinical endpoints can be determined with the help of biomarker. This could also reduce the cost and at the same time accelerate the clinical trials by providing useful information. The TB biomarker also can be used in the early diagnosis of active TB and the prediction of reactivation risk, latent infection as well as treatment outcome [9, 28].

REFERENCES

[1] D. M. Thomas, "The history of tuberculosis," *Respiratory Medicine*, vol. 100, pp. 1862-1870, 2008.

[2] World Health Organization, "Global tuberculosis control report 2014." Available http://www.who.int/tb/publications/global_report/en/ [Accessed 18th February 2015], 2014.

[3] A. A. Velayati, P. Farnia, and M. R. Masjedi, "The totally drug-resistant tuberculosis TDR-TB," *International Journal of Clinical and Experimental Medicine*, vol. 6, pp. 307–309, 2013.

[4] UNAIDS, *Report on the global AIDS epidemic 2010*. US: UNAIDS, 2010.

[5] World Health Organization, "Global tuberculosis report 2013." Available http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf, 2013.

[6] MAPTB, "Stop TB in my lifetime [Internet]. 2014 August (1)." Available http://www.maptb.org.my/files/MAPTB_newsletter_Aug2014.pdf, 2014.

[7] T. H. M. Ottenhoff and S. H. E. Kaufmann, "Vaccines against tuberculosis: Where are we and where do we need to go?," *PLos Pathog.*, vol. 8, p. e1002607, 2012.

[8] C. W. Charles, B. D. Zhu, X. L. Fan, B. Gicquel, and Y. Zhang, "Systems approach to tuberculosis vaccine development," *Respirology*, vol. 18, pp. 412-420, 2013.

[9] S. H. E. Kaufmann, "Future vaccination strategies against tuberculosis: Thinking outside the box," *Cell Press Immunity*, vol. 33, pp. 567-77, 2010.

[10] S. Schwander and K. Dheda, "Human lung immunity against mycobacterium tuberculosis: Insights into pathogenesis and protection," *American Journal of Respiratory and Critical Care Medicine*, vol. 183, pp. 696-707, 2011.

[11] B. Beresdord and J. C. Sadoff, "Update on research and development pipeline: Tuberculosis vaccines," *Clinical Infectious Diseases*, vol. 50, pp. S178-S183, 2011.

[12] S. Svenson, G. Källenius, A. Pawlowski, and B. Hamasur, "Towards new tuberculosis vaccines," *Human Vaccines*, vol. 6, pp. 309-317, 2010.

[13] M. Hatheril, "Prospects for elimination of childhood tuberculosis: The role of new vaccines," *Archives of Disease in Childhood*, vol. 96, pp. 851-856, 2011.

[14] Global Advisory Committee on Vaccine Safety, "Safety of BCG vaccine in HIV-infected children," *WHO Weekly Epidemiological Record*, pp. 18-24, 2007.

[15] U. Mack, G. B. Migliori, M. Sester, H. L. Rieder, S. Ehlers, D. Goletti, and D. M. Cirillo, "LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement," *European Respiratory Journal*, vol. 33, pp. 956-973, 2009.

[16] J. Hess and S. H. E. Kaufmann, "Development of novel tuberculosis vaccines," *C R Acad. Sci. III*, vol. 322, pp. 953-958, 1999.

[17] C. M. Montañésa and B. Gicquel, "New tuberculosis vaccines," *Enfermedades Infecciosas y Microbiología Clínica*, vol. 29, pp. 57-62, 2011.

[18] S. H. E. Kaufmann, G. Hussey, and P. H. Lambert, "New vaccines for tuberculosis," *Tuberculosis Series*, vol. 375, pp. 2110-2119, 2010.

[19] H. McShane, "Tuberculosis vaccines: Beyond bacille calmette-guerin," *Philos. Trans. R Soc. Lond. B Biol. Sci.*, vol. 366, pp. 2781-2789, 2011.

[20] A. C. Hesseling, B. J. Marais, R. P. Gie, H. S. Schaaf, P. E. Fine, P. Godfrey-Faussett, and N. Beyers, "The risk of disseminated bacille calmette-guerin (BCG) disease in HIV-infected children," *Vaccine*, vol. 25, pp. 14-18, 2007.

[21] P. Andersen, "TB vaccines: Progress and problems," *Trends in Immunology*, vol. 22, pp. 160-168, 2011.

[22] M. J. Cayabyab, L. Macovei, and A. Campos-Neto, "Current and novel approaches to vaccine development against tuberculosis," *Frontiers in Cellular and Infection Microbiology*, vol. 2, pp. 1-16, 2012.

[23] D. Bottai, W. Frigui, S. Clark, E. Rayner, A. Zelmer, N. Andreu, and R. Brosch, "Increased protective efficacy of recombinant BCG strains expressing virulence-neutral proteins of the ESX-1 secretion system," *Vaccine*, vol. 33, pp. 2710-2718, 2015.

[24] C. Da Costa, B. Walker, and A. Bonaviz, *International Journal of Infectious Diseases*, vol. 32, pp. 5–12, 2015.

[25] T. J. Scriba, M. Tameris, E. Smit, L. Van Der Merwe, E. J. Hughes, and B. Kadira, "A phase IIa trial of the new tuberculosis vaccine, MVA85A, in HIV- and/or mycobacterium tuberculosis-infected adults," *Am. J. Respir Crit Care Med.*, vol. 185, pp. 769-778, 2012.

[26] H. Niu, L. Hu, Q. Li, Z. Da, B. Wang, K. Tang, and B. Zhu, "Construction and evaluation of a multistage mycobacterium tuberculosis subunit vaccine candidate Mtb10. 4–HspX," *Vaccine*, vol. 29, pp. 9451-9458, 2011.

[27] X. Wang, J. Zhang, J. Liang, Y. Zhang, X. Teng, X. Yuan, and X. Fan, "Protection against mycobacterium tuberculosis infection offered by a new multistage subunit vaccine correlates with increased number of IFN-γ+ IL-2+ CD4+ and IFN-γ+ CD8+ T cells," *PloS One*, vol. 10, p. e0122560, 2015.

[28] S. D. Lawn and A. I. Zumla, "Tuberculosis," *Lancet*, vol. 378, pp. 57-72, 2011.