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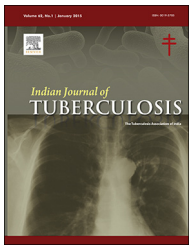

Review Article

Vaccines against tuberculosis: A review

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ABSTRACT

Tuberculosis (TB) has taken toll of many lives, therefore a need of effective TB vaccine, which can provide sufficient immunity to prevent developing of disease has been felt for a longer time.

BCG, the only available vaccine, though prevents against severe form of primary tuberculosis in paediatric population, failed to have its efficacy in pulmonary patients. Few candidates are in the pipeline undergoing clinical trial. An extensive research is needed to ensure their safety and efficacy before their acceptance as a TB vaccine to be incorporated in national immunization programmes.

1. Introduction

Tuberculosis (TB) is one of the oldest diseases known to mankind having its description in Vedas. The causative organism, a rod-shaped, non-spore forming aerobic bacilli engulfs about two million lives worldwide annually. Despite highly effective available pharmacotherapy, the control programmes are being blocked by accelerating effect of HIV co-infection and development of MDR strain. *Mycobacterium bovis* based BCG vaccine, available for last 90 years, has shown some protective efficacy in combating serious paediatric TB like tubercular meningitis and disseminated tuberculosis. But it proved to have poor outcome in terms of protecting pulmonary disease and especially the non-paediatric population.[1] Therefore, improved TB control strategy is of utmost importance and a more effective TB vaccine is a major public health priority.[2]

2. Problem and magnitude of tuberculosis

As per WHO global TB report 2014, almost 9 million people developed the disease worldwide with 1.5 million mortality, of whom 3,60,000 were tested positive for HIV. About one-third of world population is infected asymptomatically with tubercular bacilli,[3] and at the risk of reactivation. India accounted for one-fourth of total global incidence of TB cases annually which equals 2.3 million out of 8.6 million total cases in 2012. National Tuberculosis control programme was launched almost 50 years ago and revised in 1993 with country-specific goals and objectives. In the history of TB control in India, there are three important setbacks: first, BCG was found to be ineffective in TB control in 1979; second, the rapid spread of HIV, with TB as its commonest opportunistic infection since 1984 and third, the emergence of MDR and its prevalence since 1992. TB drains national economy worth US $ 23 billion

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annually. Therefore, it warrants a structural renovation to cover loop holes and incorporation of de novo ideas in control programmes for a better TB control.[4]

3. Presently used vaccine-BCG

Mycobacterium bovis bacillus Calmette–Guerin (BCG), the only licensed TB vaccine, is a live attenuated strain of *M. bovis* which was passaged by Calmette and Guerin almost hundred years ago. *M. bovis* was isolated by Nocardia in 1902. Two French Scientists – Calmette, a Physician and Guerin, a Veterinarian – sub-cultured the organism for 230 generations using culture media containing glycerol, potato and beef bile. BCG was thus developed after a long series of passage of virulent *M. bovis* strain from year 1908 to 1921 and it took almost 13 years to obtain a safe TB Vaccine. It was then first administered orally in 1921 in Paris and injected intradermally in 1927. In India, first intradermal BCG vaccine was administered in Madanapalle, Andhra Pradesh in 1948. Since 1921, many clinical trials in different parts of the world have evaluated the efficacy of BCG in preventing TB disease. These trials demonstrated that BCG confers consistent protection against severe forms of childhood TB like meningitis and disseminated TB, and leprosy, in endemic zones.[5–9] However, it provides highly variable protection against pulmonary disease, which alone accounts for the major burden of global TB, and is an important cause of morbidity and mortality.[10] Furthermore, revaccinating with BCG during adolescence in a population already vaccinated at birth, does not improve the protective efficacy as shown in a large, randomized controlled trial (RCT) in Brazil.[9] BCG is currently being administered to neonates of high-risk populations as part of the World Health Organization (WHO) Expanded Programme on Immunization (EPI).[11]

BCG is indicated for the infants living in high endemic TB areas or to the infants and children at risk of TB exposure in otherwise low endemic areas. BCG efficacy varies from 0% to 80%. It protects neonate and children against serious forms of primary disease such as meningeal and disseminated TB and saves 40,000–70,000 children a year. BCG vaccination also prevents massive lympho-haematogenous dissemination of the disease.

4. Limitations of BCG

Despite its record of being the most widely used vaccine in the world, BCG has no apparent impact on the growing global TB epidemic and the latter still remains the second leading cause of infectious disease deaths. It is not well in protecting TB in adults or the cases of latent TB (due to which nearly two million people die each year). BCG is not reliable against pulmonary TB, which accounts for most of the TB disease worldwide. It is also not recommended for use in infants infected with HIV for the fear of increased risk of severe BCG-related complications. Apart from these, it has got some negative recommendations or contraindications too. BCG vaccine should not be given to persons with impaired immunity, symptomatic HIV infection, known or suspected congenital immunodeficiency, leukaemia, lymphoma, or generalized malignant disease. It is also contraindicated in patients taking immunosuppressive treatment (e.g. corticosteroids, alkylating agents, antimetabolites and radiatiotherapy) and should be avoided in pregnancy.[11] Revaccination with BCG in adolescents does not improve protective efficacy.[5]

5. Future vaccines

Vaccines are known to be an incredibly efficient health tool, and TB vaccines that prevent adolescents and adults from developing infectious TB would be the single greatest advancement in the global fight against the disease.[2]

5.1. *Expectations from TB vaccine*

Future vaccine should be safe and effective in preventing TB in children, adolescents and adults, including people living with HIV. It should provide protection against all forms of TB – including LTBI MDR and XDR TB.[2] It should reduce the cost and burden of TB on patients, health care systems and national economies. Safety and efficacy in at-risk infants, children and adults (including people living with HIV) should be assured.[5] Timing of vaccination should not interfere with other childhood immunizations. It should be feasibly manufactured on a mass scale and should be stored and administered under low-technology conditions.[5]

5.2. *Science behind future vaccine*

To achieve the effective protection against *M.tb* by vaccination, there is a need to induce the relevant arm of the immune system. *M.tb* is an intracellular bacillus and primarily remain inside the macrophages. Therefore, humoral immunity is unlikely to play a major role in protection against *M.tb* and intact cellular immunity response is essential,[11] especially the Class II restricted CD4+ T cells.[2] The increased susceptibility to TB disease in HIV infected patients signifies the importance of Class II restricted CD4+ T cells in protective immunity to *M.tb* Class I restricted CD8+ T cells also play an important role probably in maintaining the latent state, although the precise mechanism by which they work is yet not clearly elucidated. Interferon gamma (IFN-g) secreted by both CD4+ and CD8+ T cells may have a role by inducing the activation of the infected macrophages and by increasing expression of MHC Class I and II proteins on antigen presenting cells. Defect in IFN-g gene in mice has shown to markedly increase the susceptibility to *M. tb*[2] and treatment with exogenous recombinant IFN-g delayed the infection in these mice. In humans, mutation in IFN-g receptor 1 gene, makes individual more susceptible to severe atypical mycobacterial infections[11] and perhaps also to TB. Therefore, as far as currently available information is concerned, an ideal vaccine against TB should seek to induce both CD4+ and CD8+ protective T cells.[5]

5.3. *T cell inducing vaccines*

In general, induced antibody level has been used as a potency marker in new vaccine development. However, in the last