Vaccines for Tuberculosis

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Vaccines have played a major role in our efforts to control many bacterial and viral infectious diseases. Smallpox is the classical example of a viral disease that has been eradicated primarily by using an effective vaccine.

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India has a comprehensive immunization programme for infants and children under the National Health Mission (1). The Expanded Programme on Immunization launched in 1978 was renamed as Universal Immunization Programme (UIP) in 1985 and has been an integral part of the National Rural Health Mission from 2005. It is one of India's largest public health programmes targeting close to 2.67 crore newborns and 2.9 crore pregnant women annually. Under the UIP, immunization is providing free of cost against 12 vaccine preventable diseases: diphtheria, pertussis, tetanus, polio, measles, rubella, severe form of childhood tuberculosis (TB), hepatitis B, meningitis & pneumonia caused by Hemophilus Influenza type B, rotavirus diarrhoea, pneumococcal pneumonia and Japanese Encephalitis. The two major milestones of UIP have been the elimination of polio in 2014 and maternal and neonatal tetanus in 2015.

Unfortunately, for TB, an ancient scourge that has afflicted mankind since antiquity and that still affects more than 10 million persons annually with 1.4 million deaths (2) we do not have an effective vaccine.

BCG (Bacillus Calmette Guerin), the only licensed vaccine for TB currently, was developed by Frenchmen Albert Calmette, a physician and microbiologist and Camille Guerin, a veterinarian, by attenuating Mycobacterium bovis over 230 cycles between 1908-1919 (3). BCG was first used for human immunizations as early as a century ago in 1921 by the oral route. The League of Nations, the precursor of the World Health Organisation (WHO) adopted BCG as a standard vaccine for human TB in 1928. However, the use of BCG suffered a setback in 1930 when 207 of 252 children who received the vaccine in Lubeck, Germany, developed active TB And 72 of them died. The vaccine came from Pasteur Institute in Paris but was contaminated with Mycobacterium tuberculosis in the TB laboratory in Lubeck. Although BCG vaccine itself was eventually exonerated, its use declined for several years thereafter.

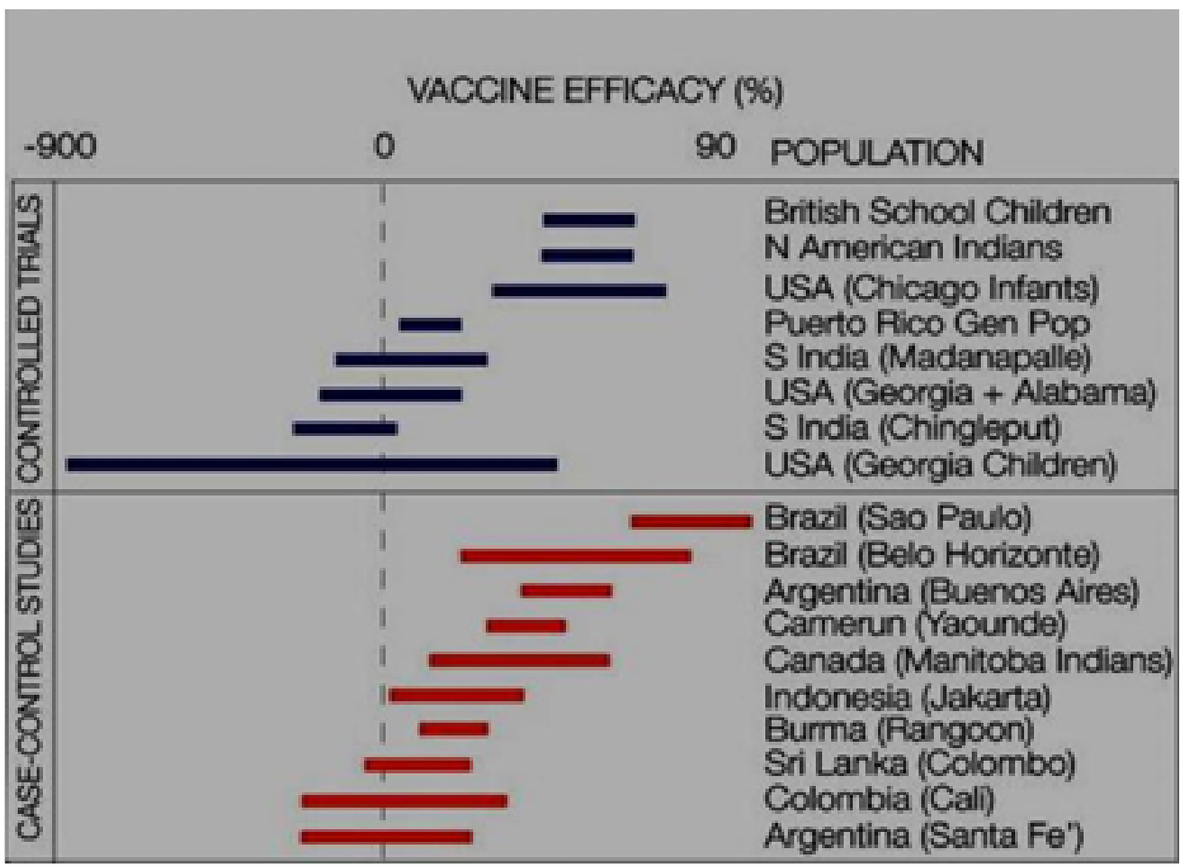
In India, BCG vaccination was first introduced on a limited scale in May 1948. The BCG Vaccine Laboratory was set up in Chennai (then called Madras) in the same year and in 1949 BCG vaccination was extended to schools in almost all the States of India. The International TB Campaign helped to scale up by conducting BCG vaccination demonstrations in five centres starting with Madanapalle in Andhra Pradesh. The Programme was expanded through mass campaigns in 1951 supported by the United Nations International Children's Emergency Fund (UNICEF) and WHO. By 1956 the campaign covered all the States of India. BCG became part of the National TB Control Programme in 1962.

Even though BCG is the most widely used vaccine (120 million/year) in the world, its efficacy against TB is one of the most debated issues. To test its efficacy in the Indian population a randomized clinical trial (RCT) was started in Chengleput in South India by the Tuberculosis Chemotherapy Centre (TCC), later renamed the Tuberculosis Research Centre (TRC) and subsequently as the National Institute for Research in Tuberculosis (NIRT) of the ICMR, in 1968. The Chengleput trial was the world's largest BCG vaccine study. It was a double blind, parallel-arm, placebo controlled RCT covering a population of 3,66,000 individuals in Chengleput district of South India close to Madras. Two strains of BCG (French and Danish) and 2 doses (0.1 mg; 0.01 mg) of each were used and compared to a placebo. The study population was followed up for 15 years by resurveys every 30 months. Two reports (7.5 years and 15 years) were published (4,5).

The results of the study came as a surprise to the Indian and international community. It showed overall, that neither of the two strains of BCG in either dose offered protection against adult forms of pulmonary TB. However, a modest protection of 21-32% was seen in children 1-9 years of age. These results were hugely disappointing and prompted further research to identify the causes of the failure of the vaccine. A rigorous evaluation by Indian and International experts of the methodology of the trial did not reveal any methodological flaws.

The efficacy of BCG vaccination has varied in different populations ranging from 0-80% (Figure 1). In RCTs in British school students, infants in Chicago and in North American Indians the efficacy has been as high as up to 80% whereas in other states in the USA (Georgia, Alabama) and in South India the vaccine has offered no or little protection. However, case control studies over different geographic locations have shown modest to significant protection, especially against military and disseminated TB.

Figure 1: Efficacy of BCG vaccine in randomized clinical trials and case-control studies in different populations



A systematic review and meta analysis of RCTs in pulmonary and meningeal and miliary TB showed higher protection with increasing latitude. Protection was greater when BCG was given in infancy or at school age, when prior sensitization was excluded. Protection against meningeal and miliary TB was greater than for pulmonary TB. Protection was also higher with a lower likelihood of diagnostic detection bias. There was little evidence that other study characteristics or vaccine strain was associated with protection (6).

It was assumed that the possible reasons for the variable efficacy of BCG could be:

a) Genetic variability among the strains of BCG. Six BCG strains are in use in international immunization programs (BCG Pasteur 1173 P2, BCG Danish1331, BCG Glaxo 107, BCG Tokyo 172-1, BCG Russia-I and BCG Brazil). These six BCG strains exhibit different characteristics of attenuation and protection in animal models.

b) Genetic variation in populations.

c) Prior exposure to non-tuberculous mycobacteria could result in a nonspecific immune response against mycobacteria that could interfere with efficacy of BCG by a process of either 'Masking', as already there is a level of immunity and BCG is not adding to this, or by 'Blocking' that prevents BCG from replicating and stops it from producing an immune response

d) Interference by concurrent parasitic infection. Th1 response is required for an effective immune response to TB infection. Concurrent infection with parasites can produce a simultaneous Th2 response that could blunt the effect of BCG.

In view of these varied responses the WHO has made the following recommendations (7):

a)In high TB burden countries, a single dose of BCG vaccine should be given to all infants soon after birth. Revaccination is not recommended.

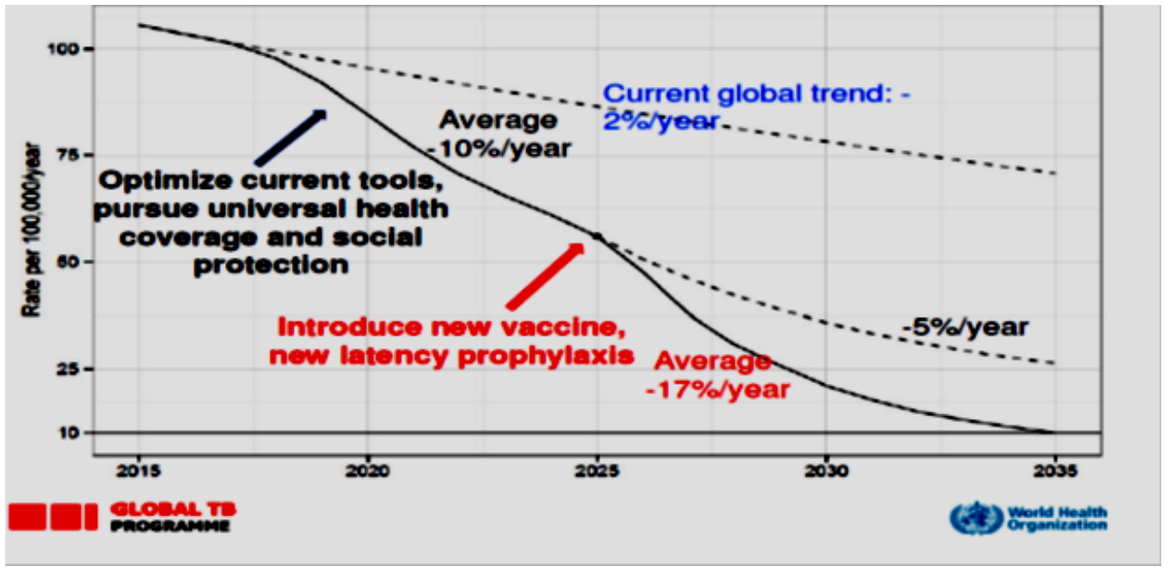
b) BCG vaccine should not be used in HIV infected children, even if they are asymptomatic.

c) Low TB burden countries may choose to limit BCG vaccination to neonates and infants of high-risk groups for the disease or to skin-test negative older children.

d) BCG vaccination of adults is not recommended.

The End TB Strategy of the WHO based on the United Nation's Sustainable Development Goals (SDGs) envisages a Vision of a world of 'zero' deaths, disease and suffering due to TB', and aims at a 95% reduction in deaths, 90% reduction in the incidence of the disease by 2035 compared to 2015 (8). The National Strategic Plan of the Government of India to eliminate TB (9) is even a more ambitious, planning to reach these goals set by WHO by the year 2025. The current rate of decline of TB incidence globally is a mere 2% per year (Figure 2). To reach these goals set by the WHO this rate of decline has to be steeply increased and for this to happen new vaccine(s) against the disease are desperately and urgently needed. However this is easier said than done as there are many challenges to be faced for the development of a new TB vaccine. Our knowledge and understanding of the immune system in TB is still inadequate. As yet there is no good correlate for protection and there is no suitable animal model. Funding is available primarily from governments and charitable organizations as TB is not high priority for pharmaceutical companies that are profit oriented. And many TB endemic countries lack the infrastructure for large-scale clinical trials that will be required to evaluate vaccine candidates.

Figure 2



New TB vaccines:

However, driven by the compulsions and urgency of the global need to rein in and reverse the TB epidemic there has been a welcome and concerted effort in the research and development of new vaccines against TB in the last two decades (10). Under the aegis of Aeras and later the International AIDS Vaccine Initiative (IAVI), funded in main by the Bill and Melinda Gates Foundation,many thousands of potential TB vaccine candidates were identified and have gone through the stages of preclinical evaluation in animal models and a handful have qualified for clinical studies in humans to date. Similarly in Europe, the research promoted by the different European Commission Framework Programs has resulted in several potential TB vaccine candidates. The European TB Vaccine Initiative (TBVI) is a non-profit organization that facilitates the discovery and development of new, safe and effective TB vaccines and biomarkers that are accessible and affordable for global use.

Efficacy trials of new prophylactic TB vaccines could target either the prevention of infection against Mycobacterium tuberculosis (POI), or the prevention of acquiring TB disease (POD) and the prevention of recurrent TB disease (POR). POR trials evaluate therapeutic vaccines administered as an adjunct to drug treatment to increase the effectiveness and shorten the duration of TB treatment in patients undergoing TB treatment for active disease.

New TB vaccine candidates in clinical trials can be either whole cell vaccines, consisting of a) live or attenuated Mycobacterium tuberculosis strains, b) Mycobacterium bovis BCG, c) recombinant BCG, d) killed mycobacterial vaccines formulated from other saprophytic mycobacterial species or Mycobacterium tuberculosis; or subunit vaccines that contain Mycobacterium tuberculosis antigens expressed as a) recombinant proteins formulated with different adjuvants or b) expressed by recombinant viral vectors used as vehicles for the administration of antigens.

Currently,14 TB vaccine candidates are beingbeing studied in Phase 1 to Phase 3 RCTs in children and adults (11). Of these, eight are based on whole-cell mycobacteria and six on subunit candidates (Table). Of the whole-cell mycobacterial candidates, four are based on live attenuated mycobacteria (BCG revaccination, recombinant BCG (VPM1002), attenuated Mycobacterium tuberculosis (MTBVAC) and GamTBVac), and four are based on inactivated/ extracts of mycobacteria (MIP, DAR-901, RUTI, AEC/BC02). Of the subunit candidates, three are mycobacterial fusion protein(s) in new adjuvant formulations (ID93:GLA-SE, H56:IC31 and M72:ASO1E) and three are based on recombinant live-attenuated or replication-deficient virus-vectored entities expressing one or more Mycobacterium tuberculosis proteins (Ad5Ag85, ChadOx1.85/MVA85A and TB/FLU-04L).

Recently there has been encouraging news that in infected adults, the adjuvant vaccine M72/AS01E has shown 54% protection against active pulmonary tuberculosis disease, without evident safety concerns (12). Of particular interest to us in India is a Phase 3 multicentre double blind, placebo controlled RCT that is studying the safety and efficacy VPM1002 andMycobacterium indicus pranii(MIP) in preventing TB in household contacts of TB patients on treatment. VPM1002 is a live-attenuated, recombinant BCG and results from phase 1 and 2 clinical trials have confirmed the pre-clinical data and have shown that VPM1002 is at least as safe and immunogenic as BCG. MIP, earlier known as Mycobacterium w, is a non pathogenic mycobacterial species known to be protective against leprosy. The origin of the proposed name is a combination of the site of isolation of the bacterial species from India (indicus), discovery by Pran Talwar (pranii) and characterization at the National Institute of Immunology, India (pranii). The trial has completed recruitment of 12000 participants (13). Results are eagerly awaited.

Table: TB vaccines currently in clinical trials in children and adults (11)

Category	Phase 1	Phase 2a	Phase 2b	Phase 3
Infants/		MTBVAC		VPM1002
Adolescents & Adults	Ad5Ag85A	MTBVAC	M72+ASO1E	VPM1002
	ChadOx1.85A	TBFlu04L	DAR-901	MIP
	AEC/BC02	GamTBVac	H56:IC31	
		ID93/GLA-SE	BCG	
Therapeutic	ID93/GLASE	RUTI		VPM1002
	H56:IC31	TBFlu04L		

	Live attenuated
	Whole cell
	Protein/
	Viral vectored

References:

1. https://nhm.gov.in/index1.php?lang=1&level=2&sublinkid=824&lid=220

2.https://www.who.int/publications/i/item/9789240013131

3.https://thorax.bmj.com/content/thoraxjnl/38/11/806.full.pdf

4. Trial of BCG vaccines in south India for tuberculosis prevention: first report.Bull World Health Organ. 1979; 57(5): 819–827

5.Fifteen year follow up of trial of BCG vaccines in south India for tuberculosis prevention. Tuberculosis Research Centre (ICMR), Chennai. Indian J Med Res,1999; 110: 56-69

6. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials.Clin Infect Dis. 2014 Feb;58(4):470-80

7. https://www.who.int/immunization/policy/position_papers/PP_BCG_summary_2018.pdf?ua=1

8.https://www.who.int/tb/End_TB_brochure.pdf

9. https://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020.02.2017%201.pdf

10.Update on TB Vaccine Pipeline. Appl. Sci. 2020, 10, 2632

11. https://www.tbvi.eu/what-we-do/pipeline-of-vaccines/

12.N Engl J Med 2019; 381:2429-2439

13. http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=27411&EncHid=&userName=VPM1002