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REVIEW ON TUBERCULOSIS VACCINE: DEVELOPMENT AND IMPLEMENTATION A CHALLENGE

Nishtha Singh*[1], Nidhi Bhatnagar[1], Sheetal Agarwal[1], Kalpana Kuntal[2], Amit Kumar[3]

[1]*Assistant Professor, Hind Institute of Medical Sciences, Barabanki
[2]Senior Resident, King George Medical University, Lucknow
[3]Assistant Professor, Autonomous State Medical College, Kanpur Dehat

***Corresponding author:** Nishtha Singh
*E-mail: nishsingh422@gmail.com

ABSTRACT
Tuberculosis continues to be among the leading causes of morbidity as well as mortality. It is appreciated that our aim of eliminating TB in the foreseable future will not be realized until we have a new vaccine with significant efficacy among diverse populations and all age-groups. Although impressive strides have been made in more refined development of new TB vaccines based on learnings from past experiences, the substitute or a booster vaccine for the BCG vaccine is not available yet. This article puts in perspective the recent efforts in re-positioning BCG, development of newer vaccines based on novel approaches, the current TB vaccine pipeline, and the unmet challenges faced in vaccine development, exploring newer ideas in vaccine development and what the future holds for it.

INTRODUCTION
A total of 1.25 million people died from tuberculosis (TB) in 2023 (including 161 000 people with HIV). Worldwide, TB has probably returned to being the world's leading cause of death from a single infectious agent, following three years in which it was replaced by coronavirus disease (COVID-19). It was also the leading killer of people with HIV and a major cause of deaths related to antimicrobial resistance. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. Only about 2 in 5 people with drug resistant TB accessed treatment in 2023. [1] Revised National Tuberculosis Control Programme (RNTCP) from 1997 further scaled up to a National TB Elimination Program (NTEP) from 2018. [2] Modelling studies suggest that to achieve an accelerated decline, a new TB vaccine will be required in addition to a shorter treatment regimen for active TB as well as latent TB, a point-of-care diagnostic test and greater efforts at preventing transmission of infection. [3] It has been envisaged to reduce TB incidence rate by 80 per cent and TB mortality rate by 90 per cent by the year 2030. [4] An ideal TB vaccine would be the one that induces a high level of long-lasting immunity, protects against sustained infection as well as progression of infection to disease (all forms) and recurrence among all age groups, has high safety profile including among key populations like people living with HIV to active disease that involves symptoms like persistent cough or fever and weight loss. Therefore, timely and accurate diagnosis is essential to effective management microscopy and culture-based techniques, but these lack sensitivity, speed and complexity. But the past several years has seen great improvements in techniques for movements. Mycobacterium tuberculosis is a very adaptable and control of TB. [5]

TUBERCULOSIS VACCINE DEVELOPMENT AND PIPELINE

The STOP TB Partnership Working Group on New TB Vaccines regularly compiles and updates the growing pipeline of TB vaccine candidates being developed and evaluated for use in humans.[6] Currently, there are 17 candidate TB vaccines in the developmental pipeline.[7] Multiple candidate vaccines demonstrating proof of concept of protection against TB in animal models are currently under evaluation in clinical trials. They are based on a variety of technological approaches that include live attenuated mycobacteria, killed whole-cell mycobacteria, mycobacterial extracts, adjuvanted protein vaccines, and viral vectored vaccines. There have also been advances in development of vaccines for use in infants and children as alternatives to BCG vaccination, and other vaccines are in development for co-administration or booster vaccines with BCG. The BCG vaccine has non-specific beneficial effects associated with reductions in neonatal and adult morbidity and mortality.[8], [9] BCG vaccine is found to introduce trained immunity. Two of the new TB vaccine candidates, MTBVAC and VPM1002, appear to harness the beneficial non-specific effects associated with BCG. [10], [11] The current vaccine developmental pipeline includes candidates for prevention of infection, prevention of recurrence, prevention of disease, and adjunctive treatment for TB disease. The current TB vaccines are applied intradermally and elicit clusters of differentiation (CD)4+, CD8+ T-cell responses, and B- cell responses. [12], [13] Future research in vaccine development will need to clarify whether live bacteria are indeed needed for a long-lived immune response directed against a broad array of biologically relevant targets expressed by *M*tb.

Newer vaccines

A major part of these efforts focused on designing subunit vaccines that deliver immune-dominant *Mycobacterium tuberculosis* (MTB) antigens using viral/protein adjuvants. The first vaccine to enter efficacy trial was MVA85A which expresses MTB antigen 85A considered among the most important MTB antigens required for cell wall synthesis on an attenuated vaccinia Ankara viral vector. Whole-cell mycobacterial vaccines that contain a broader range of immunogenic molecules are expected to induce a more diverse immune response to a range of protein and lipid antigens. [14] The ongoing VPM1002 and Immuvac vaccine trial in India is expected to provide further insights.

Efficacy of MIP as an adjunct to anti-TB drug therapy was demonstrated among erstwhile so classified category-II (CAT-II) pulmonary TB cases (unfavorable treatment outcome after treatment as a new TB patient and re-treated with a streptomycin containing re-treatment regimen of first line anti-TB drugs). [15]

The summary of various tuberculosis vaccine with their technology of development is summarize in table 1.

Table 1: Showing various tuberculosis vaccine phases

Candidate vaccine	Technology	Protective immune response	Target Population	Phase
TB/FLU-05E	Influenza strain with ESAT-6 or in combination with Ag85A	Enhanced protection in BCG primed individuals	Adolescents, Adults	I
DAR 901	Mycobacterial inactivated whole cell	Enhanced Th1 cytokine response	Adolescents, Adults	IIb
RUTI	Mycobacterium inactivated within liposomes	Induction of mixed Th1, Th2 and Th3 multiantigen responses	Adolescents, Adults	IIb
VPM 1002	Recombinant genetically modified vaccine	Enhances production of CD4 and CD8 T-cells	Infants; Neonates; Adolescents; Adults	III
MTBVAC	Based on genetically modified TB vaccine	Induces protection with CD4-Tcells	Infants; Neonates; Adolescents; Adults	III

TUBERCULOSIS VACCINE POLICY

As global anticipation around these new TB candidate vaccines continues to build, even if one of these vaccines is successful, the translation of it into global policy recommendations will require careful consideration and must seek WHO policy recommendation and prequalification for their products before rollout. Pertaining to vaccine indications, target populations, use case(s), and immunization strategies, as well as preliminary consideration of data that should be collected for

safety, efficacy, and policy evaluation. [16] Guidance on characteristics pertaining to vaccine presentation, packaging, storage requirements, and disposal are also important issues in WHO PPCs. [17] Current preparedness discussions and initiatives on TB vaccine pipeline are considering two streams of activity: (i) a scientific pipeline composed of candidate vaccines under study and running alongside it and (ii) a policy pipeline leading to vaccine introduction. This will require defining and comparing definitions and addressing supply concerns related to availability, affordability, local manufacturing, and universal procurement in bulk for effective global distribution. [18]

CHALLENGES IN VACCINE DEVELOPMENT

There is a lack of a validated animal model that can predict vaccine efficacy in humans with certainty. Many of the newer vaccines found highly immunogenic turned out to be ineffective in preventing clinical TB implying that the currently known immunological markers do not correlate with clinical efficacy. Lack of reliable biomarkers impedes rational decision making for proceeding to the next stage/phase of vaccine development pathway.

CONCLUSION

Although new effective TB vaccines could be a major transfor- mative tool in the global fight against TB, vaccines alone will not eradicate all clinical forms of TB worldwide. For new vaccines to become an additional powerful additional tool for enhancing exist- ing global TB control activities, they will need to be made avail- able and scaled-up widely at a low cost and used in parallel with existing diagnostics and drug treatment and prevention regimens. Long-term political and funder commitment through sustainable more effective global partnerships will be essential for this to happen.

CONFLICT OF INTEREST

Authors have no conflict of interest

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