Newer Vaccines for Tuberculosis Prevention

Sumitha Nayak

ABSTRACT
As per the latest data from World Health Organization, in the year 2019, a total of 10 million people fell ill with tuberculosis, of which 1.2 million were children, while 1.4 million people died due to tuberculosis. Eight countries account for two-thirds of the total, with India leading, followed by Indonesia, China, the Philippines, and four other countries. Multidrug-resistant (MDR-TB) and rifampicin-resistant TB (RR-TB) pose a serious public health threat with over 200,000 cases globally, half of which are in India, China, and Russia. Prevention of this disease needs to be seriously re-looked at, as the world works toward the end TB strategy of WHO, part of the Sustainable Development Goal SDP Target 3.3, to be achieved by the year 2030.

Keywords: BCG vaccine, Multidrug-resistant TB, Newer TB vaccines, Tuberculosis.

Introduction
As per the latest data from World Health Organization, in the year 2019, a total of 10 million people suffered from tuberculosis, of which 1.2 million were children, while 1.4 million people died due to tuberculosis.¹

There are 30 high burden countries that are responsible for 87% of new TB cases. Eight countries account for two-thirds of the total, with India leading, followed by Indonesia, China, the Philippines, and four other countries.

Multidrug-resistant (MDR-TB) and rifampicin-resistant TB (RR-TB) pose a serious public health threat with over 200,000 cases globally, half of which are in India, China, and Russia. Prevention of this disease needs to be seriously re-looked at, as the world works toward the end TB strategy of WHO, part of the Sustainable Development Goal SDP Target 3.3, to be achieved by the year 2030.

TB Prevention
An important cog in the wheel of tuberculosis progression is the risk of TB infection progressing to TB disease. To break this wheel, active intervention is essential. A vaccine given to all children can help to confer protection, especially against severe disease forms. Currently, the role of the available BCG vaccine is limited to protection against disseminated TB and miliary TB. Currently, there are at least 15 candidate vaccines at different stages of clinical trials, while one vaccine has entered phase III. These newer vaccines have the potential of combating the disease as we forge ahead to end TB.

Immune Response against TB
The nature of the response to tuberculosis is immune-mediated. Both the CD4+ and CD8+ T cells play a role in the immunity against TB. The dendritic cells (DCs) migrate from the site of infection in the lung alveoli toward the draining lymph nodes.² These infected DCs produce interleukin 12 (IL-12), which are responsible for the production of interferon-gamma secreting CD4+ cells. In persons with a deficiency of IFN-gamma and IL-12 receptors, there is extreme susceptibility to mycobacterial infection. The most effective

Challenges in Prevention of TB and Limitations of Currently Available BCG Vaccine
There continues to be a large pool of TB infected populations globally. Also, treatment of TB does not preclude re-infection. Studies have shown that re-infection with new strains of mycobacteria are commoner than previously believed.³ The efficacy of the currently available BCG vaccine is variable across the globe. Studies from the UK have shown a 60–80% protection against pulmonary TB, while populations in Malawi and other tropical countries, including India, have shown no protection.² It is postulated that the pre-exposure of these populations to the environmental mycobacteria could interfere with the response elicited to BCG vaccine.³ People living with HIV (PHIV) have a 15–21 times higher likelihood of developing TB infection as current data show almost 69% of HIV patients co-infected with TB.¹ This diversity in the efficacy together with the need for better protection, especially of PLHIV has thrown up questions regarding the usefulness of this 100-year-old vaccine, and the need for new anti-TB vaccines.

Attributes of Newer Anti-TB Vaccines
While one-third of the population globally is considered to be infected with TB, any new vaccine that is developed should be...
Newer BCG Vaccines

capable of preexposure protection, postexposure prevention of disease occurrence as well as act as an immunotherapeutic to enhance the rate of clearance of mycobacteria. The newer vaccines should also be capable of protecting HIV-infected population who are more prone to TB infection and also protecting those who have already received childhood BCG. The vaccines need to be safer than BCG and provide long-lasting protection against pulmonary TB from the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.

**Need for Newer TB Vaccines in the Current Scenario**
The emergence of MDR and RR TB has been a game-changer in the control of TB disease, morbidity, complications, and mortality. As a 100-year-old vaccine, the BCG has stood the test of time. However, the elucidation of genetic manipulation of the genome sequence of the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.

**Need for Newer TB Vaccines in the Current Scenario**
The emergence of MDR and RR TB has been a game-changer in the control of TB disease, morbidity, complications, and mortality. As a 100-year-old vaccine, the BCG has stood the test of time. However, the elucidation of genetic manipulation of the genome sequence of the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.

**Need for Newer TB Vaccines in the Current Scenario**
The emergence of MDR and RR TB has been a game-changer in the control of TB disease, morbidity, complications, and mortality. As a 100-year-old vaccine, the BCG has stood the test of time. However, the elucidation of genetic manipulation of the genome sequence of the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.

**Need for Newer TB Vaccines in the Current Scenario**
The emergence of MDR and RR TB has been a game-changer in the control of TB disease, morbidity, complications, and mortality. As a 100-year-old vaccine, the BCG has stood the test of time. However, the elucidation of genetic manipulation of the genome sequence of the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.

**Need for Newer TB Vaccines in the Current Scenario**
The emergence of MDR and RR TB has been a game-changer in the control of TB disease, morbidity, complications, and mortality. As a 100-year-old vaccine, the BCG has stood the test of time. However, the elucidation of genetic manipulation of the genome sequence of the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.

**Need for Newer TB Vaccines in the Current Scenario**
The emergence of MDR and RR TB has been a game-changer in the control of TB disease, morbidity, complications, and mortality. As a 100-year-old vaccine, the BCG has stood the test of time. However, the elucidation of genetic manipulation of the genome sequence of the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.

**Need for Newer TB Vaccines in the Current Scenario**
The emergence of MDR and RR TB has been a game-changer in the control of TB disease, morbidity, complications, and mortality. As a 100-year-old vaccine, the BCG has stood the test of time. However, the elucidation of genetic manipulation of the genome sequence of the newborn period until adolescence and adulthood.4

Some of the major challenges in newer vaccine development are listed in Table 1.

**COVID-19 and TB Control**
The ongoing COVID-19 pandemic has disrupted the diagnosis and management of tuberculosis patients. As the pandemic rages on, the disease burden could worsen, with an increase of 0.2–0.4 million deaths from TB in 2020 alone.5 India is one of the four countries that contribute to 44% of global TB cases and yet has shown a large drop in the number of cases of TB that were diagnosed and treated between January and June 2020. Besides India, Indonesia, the Philippines, and South Africa have shown similar trends. This is worrisome, as it could translate into over 1 million new cases of TB per year between 2020 and 2025.2 Better protection against disease by a more effective vaccine would certainly be an important tool to mitigate TB disease.
TB. All vaccines currently in the development pipeline may be used as prime, boost, or immunotherapeutic vaccines.

The vaccines in phase III trials have shown great promise in protection against tuberculosis, both as prophylactic and as post-exposure vaccines. They are also being tested for efficacy in PLHIV (Tables 2 and 3).

**Phase III Vaccine—VPM1002**

The VPM 1002 is a recombinant BCG vaccine. It contains the listeriolysin encoding gene (hly) in place of the urease C gene.\(^8\) This listeriolysin is a cholesterol-dependent cytolysin. It forms transmembrane barrel pores in the phagolysosome membrane. Release of antigens and bacterial DNA into the cytosol occurs, results in autophagy, inflammasome activation, and subsequently apoptosis and cell death.\(^8\) In mice trials, VPM1002 has been shown to protect a post-exposure vaccine. It showed stronger efficacy and is safe for use in immunocompetent and immunodeficient mice.\(^9\)

Phase I and II trials have shown good immunogenicity, efficacy, and safety of this vaccine.\(^8\) Phase IIb trials in South Africa compare VPM 1002 with BCG in HIV exposed and uninfected and HIV unexposed BCG naive newborns.\(^8\) Multicentric randomized placebo-controlled phase II/III trials in India on 2,000 adults have been ongoing since 2017. These assess if VPM1002 can prevent recurrence of TB within 1 year after completion of treatment and safety and efficacy in HIV-infected newborns.\(^8\) This vaccine holds the potential for the prevention of TB in the future.

**Phase III Vaccine—MIP**

Also known as Immunovac, this is a heat-killed non-pathogenic *Mycobacterium (Mycobacterium indicus pranii)* containing vaccine.\(^11\) This is being investigated as a prophylactic TB vaccine. It is immunogenic and safe. This vaccine has been approved by DCGI and FDA as an immunoprophylactic and immunotherapeutic in multibacillary leprosy patients as well as for disease prevention in close contacts of patients.\(^12\) Current trials are underway to assess disease prevention in close healthy household contacts of sputum smear-positive TB patients.\(^11\)\(^,\)\(^12\)

**Table 2: Global pipeline of vaccines**

| Target               | Phase I  | Phase IIa | Phase IIb | Phase III |
|----------------------|----------|-----------|-----------|-----------|
| Newborn adolescents  | M.tbVac  | M72/AS01E | VPM1002   |           |
| Adults               | M.tbVac  | M72/AS01E | VPM1002   |           |
| ChadOx MVA 85 A      | TBFlu 04L| DAR-901   | MIP       |           |
| GamTBVac             | BCG Revaccination BMGF | H56:1C31 | M. Vaccae |           |
| Therapeutic          | ID 93/ GLASE | RUTI     | VPM1002   |           |

| Vaccine Characteristics |
|-------------------------|

**Phase III Vaccine—M. Vaccae**

This is a whole-cell, heat-inactivated vaccine that is undergoing phase III trials in China.\(^4\)\(^,\)\(^11\) This is safe and immunogenic for use in patients with HIV.\(^4\) This has already been licensed for use as adjunctive therapy for the treatment of TB in China.\(^11\) A large trial covering over 10,000 individuals with latent TB infection, given the vaccine in a six-dose schedule as a disease preventive, has been recently completed in China, and results are awaited.\(^11\)\(^-\)\(^13\)

**Conclusion**

This independent review has looked into the limitations of the currently available BCG vaccine, which are overcome by the novel vaccines. As the disease demographics change, accelerated by the COVID outbreak, the challenges in managing TB seem humungous. These newer anti-TB vaccines that are now in the pipeline at different stages of study offer some hope as we race to achieve the SDG goals of the World Health Organization. Almost a hundred years after the introduction of the BCG vaccine, the newer anti TB vaccines undergoing efficacy trials, take us a step forward in the development of efficacious protection against and eradication of tuberculosis.

**Table 3: Characteristics of vaccines in phase II and phase III trials**

| Phase II trials | Type of vaccine | Characteristics |
|-----------------|-----------------|-----------------|
| MtbVac          | Live attenuated | Improved safety. Trial as a replacement for BCG |
| TB/Flu04L       | Viral vector vaccine | Phase IIa trials as a BCG booster in Quantiferon positive adults |
| ID93/GLASE      | Adjuvanted sub-unit vaccine | Phase II immunogenicity and safety trials in patients on treatment for active TB |
| M72/AS01E       | Adjuvant fusion subunit vaccine with 2 Mtb antigens | Phase IIb trials in patients with latent TB infection |
| DAR-901         | Whole-cell inactivated | Phase IIb trials in BCG primed adolescents |
| H56:C31         | Adjuvanted subunit vaccine | Phase IIb trials for safety in reducing recurrence of TB: HIV |
| MIP             | Whole-cell inactivated | As a prophylactic vaccine |

| Phase 3 trials | Type of vaccine | Salient features |
|----------------|-----------------|-----------------|
| VPM1002        | Recombinant, live vaccine | Trials as a post-exposure vaccine |
| MIP            | Whole-cell inactivated vaccine | As a prophylactic vaccine |
| M. Vaccae      | Whole-cell inactivated vaccine | As a disease preventive vaccine; efficacy in PLHIV |
REFERENCES
1. World Health Organization, Tuberculosis. Key facts. Available at https://www.who.int/news-room/fact-sheets/detail/tuberculosis. Accessed on 16.12.2020.
2. World Health Organization, Global tuberculosis report 2020: executive summary. Available at: https://apps.who.int/iris/bitstream/handle/10665/337538/9789240016095-eng.pdf Accessed on 16.12.2020.
3. Martin C. The dream of a vaccine against tuberculosis: new vaccines improving or replacing BCG? Eur Respir J 2005;26(1):162–167. DOI: 10.1183/09031936.05.00109904.
4. Ahsan MJ. Recent advances in the development of vaccines for tuberculosis. Ther Adv Vaccines 2015;3(3):66–75. DOI: 10.1177/2051013615593891.
5. World Health Organisation, Global Tuberculosis report 2020: executive summary. Available at https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf. Accessed on 28.4.2021.
6. World Health Organisation, WHO preferred product characteristics for new tuberculosis vaccines. Available at https://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1 Accessed on 28.4.2021.
7. Martin C, Aguilo N, Marinova D, et al. Update on TB vaccine pipeline. Appl Sci 2020;10(7):2362. DOI: 10.3390/app10072632.
8. ICMR, Need for effective TB Vaccines. Available at https://itrc.icmr.org.in/index.php/our-work/thematic-areas/vaccines. Accessed on 16.12.2020.
9. Nieuwenhuizen NE, Kulkarni PS, Shaligram U, et al. The recombinant Bacille Calmette-Guerin vaccine VPM1002: ready for clinical efficacy testing. Front Immunol 2017;8:1147. DOI: 10.3389/fimmu.2017.01147.
10. Nieuwenhuizen NE, Kaufmann HES. Next generation vaccines based on Bacille Calmette-Guerin. Front Immunol 2018;9:121. DOI: 10.3389/fimmu.2018.00121.
11. US National Library of Medicine. Clinical trials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT03152903. Accessed on 11 Feb2021.
12. Bharathi K. Tuberculosis vaccine development: current status and future directions. J Clin Diagn Res 2019;13(9):AB01–AB04. DOI: 10.7860/JCDR/2019/17230.13164.
13. Weerasuriya CK, Clark RA, White RG, et al. Review symposium. New tuberculosis vaccines: advances in clinical development and modelling. J Intern Med 2020;288(6):661–681. DOI: 10.1111/jiom.13197.