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A Review on creation of novel therapeutic and preventive vaccinations for Tuberculosis(TB)

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ABSTRACT:

The causal agent of tuberculosis (TB), Mycobacterium tuberculosis, remains a concern to global health, particularly in regions with high HIV infection rates, poverty, and overcrowding. The lack of efficacy of the currently available Bacillus Calmette-Guérin (BCG) vaccine, especially in adults, emphasizes the urgent need for innovative preventive and therapeutic immunization strategies. This study offers a critical overview of global TB epidemiology, highlighting the challenges posed by extensively drug-resistant (XDR) and multi-drug-resistant (MDR) TB strains, as well as the disproportionate burden in countries such as North Korea and South Korea. It talks about new developments in pharmacological treatments, such as innovative and repurposed anti-TB medications, and diagnostic techniques like interferon-gamma release assays (IGRAs). Despite their multiple roles in disease and immunity, special attention is paid to vaccine innovation, ranging from booster candidates that incorporate ESAT-6 antigens to priming vaccines like VPM1002 and MTBVAC. This study highlights the need for integrated research techniques to design effective vaccines that can battle latent TB, enhance immunity, and address diagnostic interferences by weighing the benefits and drawbacks of existing candidates. The long-term objective of TB eradication requires sustained international cooperation and investment.

Keywords: Tuberculosis (TB), Mycobacterium tuberculosis**,** BCG vaccine**,** Vaccine development**,** MDR-TB (Multidrug-resistant tuberculosis)**,** XDR-TB (Extensively drug-resistant tuberculosis)**,** Latent TB infection (LTBI)**,** ESAT-6 antigen**,** TB diagnostics**,** Interferon-gamma release assays (IGRAs)**,**VPM1002, MTBVAC**,** Immunotherapy**,** TB epidemiology**,** Tuberculosis drug resistance**.**

Introduction

Airborne particles containing Mycobacterium tuberculosis are the main way that tuberculosis (TB), a dangerous disease, is disseminated. Approximately one billion people have died from tuberculosis (TB) during the last 200 years, and it continues to rank among the top 10 causes of mortality globally, including among those infected with HIV. An estimated 10.4 million people worldwide received a TB diagnosis in 2015, and 1.8 million of them passed away from the illness. TB susceptibility is influenced by a number of variables, such as HIV co-infection, poverty, overcrowding, malnutrition, and heavy alcohol use. About 12% of TB infections develop into active TB, whereas the majority stay in a latent form with no symptoms.

Prior to the Food and Drug Administration (FDA) approving two interferon-gamma (IFN-γ) release assays (IGRAs) in the early 2000s, the tuberculin skin test was the only way to diagnose tuberculosis (TB). Following stimulation with early secretory antigenic target-6 (ESAT-6), a crucial antigen of M. tuberculosis, these tests measure the amounts of IFN-γ released by T cells in patients exposed to the bacteria. The QuantiFERON-TB Gold In-Tube test, which detects IFN-γ levels in peripheral blood after exposure to ESAT-6, CFP-10, and TB7.7, was the first IGRA to be introduced. In the second test, T-SPOT.TB, peripheral mononuclear cells are extracted, stimulated with ESAT-6 and CFP-10, and their IFN-γ secretion is subsequently measured using whole blood. The findings of these diagnostic tests may differ because they use various antigens.

As a result, IGRAs are regarded as indirect diagnostic techniques and are advised to be used in conjunction with other clinical evaluations and radiographic imaging.

The effectiveness of conventional TB treatments, such rifampicin and isoniazid, against multi-drug-resistant tuberculosis (MDR-TB) is limited. Novel anti-TB drugs, such as bedaquiline (Sirturo) and delamanid (Deltyba®), which have shown promise in the fight against MDR-TB, are the subject of ongoing study. Repurposed medications such as metformin, imatinib, and linezolid are also being investigated as possible therapeutic alternatives.

The Bacillus Calmette-Guérin (BCG) vaccine, which is made from an attenuated strain of Mycobacterium bovis, is currently the only authorized vaccination against tuberculosis. The BCG vaccine does not successfully prevent initial infections or the reactivation of latent TB, but it does offer protection against severe types of TB, including tuberculous meningitis and disseminated TB in children. According to reports, the BCG vaccine has little effect on adult populations and a 0% to 80% efficiency rate in preventing pulmonary tuberculosis. New TB vaccinations must be developed in light of these restrictions. An overview of recent developments in TB vaccine research, the status of adjuvant studies, and creative approaches to vaccine development are the objectives of this paper.

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that 10.4 million cases of tuberculosis (TB) occurred globally in 2015, representing an incidence rate of roughly 142 cases per 100,000 persons. The TB burden varied significantly by region. In high-income nations, the incidence of tuberculosis (TB) was less than 10 cases per 100,000, whereas in 30 countries that the WHO identified as having a high TB burden, the incidence ranged from 150 to 300 cases per 100,000. With more than 500 cases per 100,000 people, South Africa, Lesotho, and Mozambique had among of the highest incidence rates.

With 80 cases per 100,000 people and 5.1 cases per 100,000, respectively, South Korea had the highest TB incidence and mortality rates among OECD member states. These rates were much higher than the OECD average of 11.4 cases and 1.0 deaths per 100,000 people. In response to the high burden of tuberculosis, the South Korean government launched a national campaign to reduce the disease's incidence to 50 cases per 100,000 people by 2020.

Formerly known as the Democratic People's Republic of Korea (DPRK), North Korea is listed as one of the 30 countries with the highest burdens of both tuberculosis and multidrug-resistant tuberculosis (MDR-TB). The nation is recognized as having a high risk of tuberculosis. It is also listed among the most severely affected TB-endemic countries by the WHO. The DPRK came in third place globally in 2015 with 561 TB cases per 100,000 people, behind South Africa (834 cases per 100,000) and Lesotho (788 cases per 100,000). According to the WHO's 2016 Global Summary, North Korea maintained a high percentage of baby BCG vaccine coverage, with 98% coverage from 2010 to 2014 and 97% in 2015.

However, because WHO was unable to directly verify the data, the accuracy of these numbers is questionable.

Figure 1 shows the Republic of Korea's total TB cases and new TB cases from 2001 to 2016. The statistic per 100,000 people represents the overall number of TB patient cases and new cases in the Republic of Korea between 2001 and 2016. The Korea Centers for Disease Control and Prevention's 2017 National Tuberculosis Management Guidelines provided the statistics.

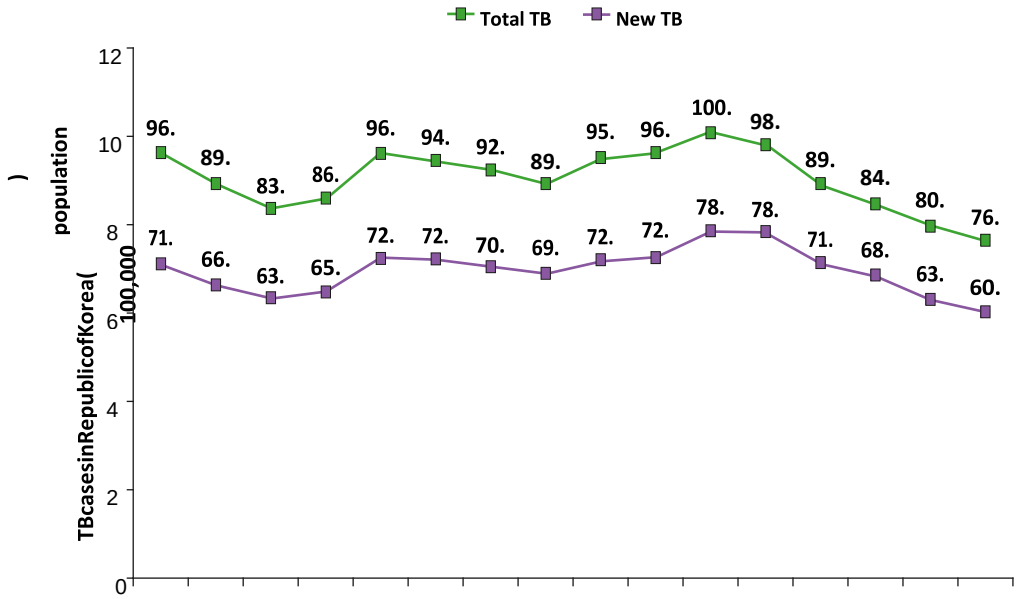

Table 1 shows the Republic of Korea's total TB cases and new TB cases from 2007 to 2016.

Cases found in years	Total TB cases in korea's	New TB cases in korea's
2007	45,637	34,750
2008	44,304	34,147
2009	43,312	35,845
2010	48,191	36,335
2011	50,351	39,657
2012	48,122	39,545
2013	45,272	36,089
2014	43,120	34,869
2015	40,857	32,191
2016	39,275	39,245

Source :- cited in The Korea Centers for Disease Control and Prevention's 2017 National Tuberculosis Management Guidelines.

Table 2. Number of deaths by TB in Republic of Korea (2006–2015)

Death cases in Year	Deaths cases
2006	2,626
2007	2,386
2008	2,333
2009	2,282
2010	2,365
2011	2,264
2012	2,566
2013	2,239
2014	2,385
2015	2,209

Source :- The Korean Statistical Information Service (KOSIS), Statistics Korea (http://kosis.kr) is the source.

Table 3 shows the incidence, mortality, and prevalence of tuberculosis in a few OECD nations from 2012 to 2014 (per 100,000). population

Country	2012			2013			2014		
	Prevalence	Incidence	Mortality	Prevalence	Incidence	Mortality	Prevalence	Incidence	Mortality
Chile	20.0	16.0	1.6	20.0	16.0	1.6	20.0	16.0	1.6
Estonia	27.0	24.0	2.4	26.0	22.0	2.3	25.0	20.0	2.1
Japan	24.0	19.0	1.8	24.0	19.0	1.8	23.0	18.0	1.8
Republic of Korea	118.0	96.0	5.5	106.0	90.0	4.0	101.0	86.0	3.8
US	4.5	3.7	0.2	4.1	3.4	0.2	3.8	3.1	0.1
Poland	27.0	21.0	1.7	26.0	21.0	1.5	26.0	21.0	1.4
Portugal	31.0	26.0	1.4	30.0	25.0	1.2	29.0	25.0	1.2
DPR Korea	521.0	417.0	30.0	536.0	429.0	25.0	552.0	442.0	20.0

Despite not being a member of the OECD, DPR Korea is included for comparison with the Republic of Korea (source: Estimated TB cases and deaths [WHO, 2016]).

TB therapeutic drug development

By triggering alternate survival strategies, Mycobacterium tuberculosis (MTB) adjusts to the host's harsh internal environment, including exposure to antibiotics and immune system stressors, which frequently results in dormancy. MTB can either cause active tuberculosis or go into a latent form, known as latent TB infection (LTBI), based on the situation of the host. Drug-susceptible TB is frequently treated with first-line medications including pyrazinamide (PZA), ethambutol (EMB), rifampicin (RIF), and isoniazid (INH). For the treatment of LTBI, the US Centers for Disease Control and Prevention (CDC) suggest two primary approaches: either INH monotherapy for 6–9 months or a combination therapy of rifapentine and RIF for 3–4 months. In some countries, LTBI regimens may contain PZA and EMB.

When MTB strains that are resistant to one or more of the standard therapies—known as extensively drug-resistant (XDR) or multidrug-resistant (MDR) strains—cause TB, second-line treatments are necessary. Pretomanid (PTM), bedaquiline (BDQ), and delamanid (DLM) are significant among them. Additionally, research and clinical trial developments for first-line and second-line anti-TB treatments have been successfully monitored.

Priming vaccines

The live attenuated Mycobacterium tuberculosis vaccine known as MTBVAC (ΔPhoPΔfadD26) is devoid of two essential virulence genes: fadD26, which is involved in the manufacture of a lipid essential to the bacterial cell wall, and PhoP/PhoR, which controls gene transcription and impacts the ESX-1 secretion system. These deletions improve the immune response while decreasing pathogenicity. Its enhanced effectiveness is associated with greater Ag85 protein secretion as a result of the noncoding RNA Mcr7 being silenced. MTBVAC is presently undergoing phase II clinical trials after demonstrating safety and immunogenicity in preclinical animal research. Its safety in comparison to BCG was evaluated in a completed phase I trial (NCT02013245), and a phase Ib research (NCT02729571) is scheduled in cooperation with other international institutions.

Boosting vaccines

The live attenuated Mycobacterium tuberculosis vaccine known as MTBVAC (ΔPhoPΔfadD26) is devoid of two essential virulence genes: fadD26, which is involved in the manufacture of a lipid essential to the bacterial cell wall, and PhoP/PhoR, which controls gene transcription and impacts the ESX-1 secretion system. These deletions improve the immune response while decreasing pathogenicity. Its enhanced effectiveness is associated with greater Ag85 protein secretion as a result of the noncoding RNA Mcr7 being silenced. MTBVAC is presently undergoing phase II clinical trials after demonstrating safety and immunogenicity in preclinical animal research. Its safety in comparison to BCG was evaluated in a completed phase I trial (NCT02013245), and a phase Ib research (NCT02729571) is planned in cooperation with other international institutions.
The heat-killed whole-cell Mycobacterium vaccae vaccine Vaccae (SRL-172), created by Biologic Pharmacy Co. in China, is authorized as a therapeutic adjuvant for tuberculosis patients. It is presently being evaluated for stability and effectiveness in high-risk TB patients after completing a phase III trial in people with HIV co-infection (NCT01979900). Phase III studies are currently underway for another vaccine made from Mycobacterium indicus pranii (formerly Mycobacterium w), a non-pathogenic, dead strain that shares antigens with M. leprae.

Advantages of ESAT-6

1. T-cell Activation ($CD4^+$ and $CD8^+$)
- ESAT-6 contains multiple T-cell epitopes, specially recognized by $CD4^+$ T-cells, leading to:
  - IFN-γ, TNF-α, and IL-2 production
  - Effective granuloma formation seen

2. Important in Latent and Active TB
   - ESAT-6 is expressed in early infection and reactivation stages, making it ideal for:
     - Vaccines targeting latent TB
     - Boosting responses in the therapeutic vaccines

3. Role in Novel Vaccine Platforms
- Used in various forms of formulation:
  - Recombinant proteins (e.g., H1, H56)
  - Viral vectors (e.g., Modified Vaccinia Ankara - MVA)
  - DNA-based vaccines
  - Fusion antigens (e.g., Ag85B-ESAT-6)

4. Vaccine Boosting Potential

Acts best in prime-boost strategies with the BCG or new subunit vaccines, increasing long-term memory T-cell responses.

Disadvantages of ESAT-6

1. Dubble Role in Virulence and Pathogenesis
- ESAT-6 disrupts host cell membranes (via pore formation), possibility contributing to:
  - Cell lysis
  - Tissue necrosis
  - Spread of bacteria between cells Immune evasion

2. Diagnostic Complications
   - Cause false positives in IGRA tests (e.g., QuantiFERON-TB Gold)
   - Required re-evaluation of current TB diagnostics

3. Immunosuppressive Properties

Inhibit MHC class II expression
Suppress macrophage activation
Modulate dendritic cell maturation

Conclusion:

Even with major improvements in detection and treatment, tuberculosis is still a major worldwide health concern, particularly in light of the emergence of extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains. Although it is successful in avoiding severe tuberculosis in children, the current Bacillus Calmette-Guérin (BCG) vaccine is not a dependable defence against latent TB infections or adult pulmonary tuberculosis. This restriction emphasizes how urgently novel vaccine approaches are needed. Promising candidates with the ability to augment immune responses and enhance long-term protection, including VPM1002, MTBVAC, and ESAT-6-based subunit vaccines, are being investigated as priming and boosting agents. There are still issues, though, such as the requirement for broad-spectrum efficacy, safety concerns, and diagnostic interference. To speed up the development of next-generation vaccines, therefore, strong clinical trials, ongoing investment in TB research, and ongoing international collaboration are necessary. Reaching these objectives is crucial to international efforts to eventually eradicate tuberculosis.

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