INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

A Review on Novel Approaches in Vaccine Development

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ARTICLE INFO

Published: 01 July 2025
Keywords:
Immunizations, Pathogens, mRNA Vaccines, DNA Vaccines, Clinical Trials, Tuberculosis (TB), Respiratory Syncytial Virus (RSV), COVID-19, BCG (Bacille Calmette – Guérin)
DOI:
10.5281/zenodo.15779379

ABSTRACT

Vaccines are critical tools for maintaining global health. Traditional vaccine technologies have been used across a wide range of bacterial and viral pathogens, yet there are a number of examples where they have not been successful, such as for persistent infections, rapidly evolving pathogens with high sequence variability, complex viral antigens, and emerging pathogens. Novel technologies such as nucleic acid and viral vector vaccines offer the potential to revolutionize vaccine development as they are well-suited to address existing technology limitations. In this review, we discuss the current state of RNA vaccines, recombinant adenovirus vector-based vaccines, and advances from biomaterials and engineering that address these important public health challenges. Novel approaches to vaccine development include structure-based immunogen design, gene-based vaccine platforms and formulation of recombinant antigens with potent adjuvants. These technologies are producing encouraging results in the development of vaccines for globally important diseases such as tuberculosis, influenza and respiratory syncytial virus. Here we highlight the most important developments in these areas over the past 18 months.

INTRODUCTION

Vaccines play a critical role in global health by preventing infection and transmission of multiple diseases worldwide. The World Health Organization estimates that vaccines prevent the death of 2–3 million people every year. Moreover, immunization have enabled the eradication of smallpox and are now close to eradicating polio. In addition, vaccines have a significant economic impact by reducing costs of illnesses and hospitalizations of over $500 billion. Although traditional vaccines have been tremendously successful there are many infectious diseases for which no efficacious vaccines have been developed. The development of vaccine for human pathogens such as Human Immunodeficiency Virus (HIV), tuberculosis (TB), respiratory

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

syncytial virus (RSV),Cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein Barr virus (EBV) has thus far been unsuccessful. HIV has caused 39 million deaths globally, and over 36 million people still live with virus today. Even with the availability of antiretroviral therapy (ART), approximately up to 2 million people become infected every year. Similarly, TB causes 1.6 million deaths annually. RSV is a major cause of lower respiratory tract infections and hospital visits during infancy and childhood, with 59,600 in-hospital deaths occurring in 2015 globally. In the United States alone, each year, more than 40,000 infants are born with congenital CMV infection, with nearly a 20% of these children developing permanent hearing loss, brain damage, or neurodevelopmental delays. In addition, emerging and re-emerging pathogens such as Ebola virus, Zika virus, and most recently, severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) have become major global health threats. Combatting outbreaks requires the rapid development of vaccines that has not typically been possible with traditional vaccine platforms. These challenges have sparked intense interest in the development of novel vaccine technologies. In this review, we will review three such platforms: mRNA vaccines, vector-based vaccines, and materials science approaches to vaccination. We will discuss the development of these platforms, including applications to the COVID-19 pandemic. Leishmaniasis is a neglected vector-borne disease caused by an obligatory intracellular parasitic protozoan called Leishmania. Leishmania (Kinetoplastida: Trypanosomatidae) is a unicellular eukaryotic organism with a distinct nucleus and kinetoplast. Around 20 out of 53 Leishmania species, that infect animals and reptiles, have been linked to human infections. According to WHO (2021), each year around 0.7–1 million cases are recorded throughout the world, with 20000–30000 deaths occurring annually and is one of the seven most significant tropical diseases with a wide range of clinical manifestations and potentially deadly outcomes. The disease is prevalent mainly in tropical and subtropical regions, particularly in Africa, Brazil, Algeria, Afghanistan, Columbia, Iran, Sri Lanka, and India. Leishmaniasis has three main clinical manifestations: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL). Brucellosis, a zoonotic disease caused by Brucella bacteria, is characterized by its ability to survive and multiply within host Macrophages. Afflicted animals commonly exhibit symptoms such as infertility, abortion, and reduced milk production, resulting in significant economic losses for the livestock industry [2]. Human infection typically occurs through direct contact with infected animals or consumption of contaminated dairy products, leading to clinical manifestations like intermittent fever, arthritis, orchitis, hepatosplenomegaly, and depression. Although rarely fatal, brucellosis can cause severe debilitation and disability. Recent research indicates a global annual incidence of 1.6 million to 2.1 million new cases, significantly higher than the previously estimated 500,000 cases [5,6], posing substantial threats to public health. Treatment usually involves a combination of antibiotics, but prolonged use may lead to side effects and the development of drug resistant strains, presenting significant therapeutic challenges. Vaccination remains the most effective preventive measure against Brucella infection. The current Brucella vaccines for animals consist of live attenuated vaccines, including S19, Rev.1, S2, SR82, and RB51 [8,9]. Among these, RB51 is the only officially approved attenuated vaccine. While these vaccines provide good immune protection in animals, there is a risk of residual virulence that could potentially lead to human infection and abortion complications in pregnant cows. According to a recent analysis, tuberculosis (TB) has killed one billion people over the last 200

years, more victims than from smallpox, malaria, plague, influenza, cholera, and AIDS together. Indeed towards the end of the 19th century, one in five of all deaths was caused by TB. Although TB is considered a disease of the past in some circles, it remains the deadliest contagious disease globally. In 2015, 10.4 million new cases of active TB were recorded, resulting in 1.8 million deaths (World Health Organization, WHO). Approximately two billion people are infected with the causative agent, Mycobacterium tuberculosis, but only a small proportion of those individuals living with a latent TB infection (LTBI) are at risk of developing active disease (somewhere in the order of 10% over a lifetime). This is because our immune system is capable of containing the pathogen in a dormant stage. However, since the immune response fails to achieve sterile eradication, individuals with LTBI are at risk of developing TB later in life. TB reactivation is greatly accelerated by co-infection with HIV. Of the 15 million individuals suffering from co-infection with HIV and M. tuberculosis, 1.2 million have developed TB in 2015, rendering HIV co-infection a major driving force in the TB pandemic. An additional complication is the increasing incidence of multidrug Resistant (MDR)-TB annually; this accounts for half a million new cases with only a 50% chance of cure by drug treatment. Globally some 50 million individuals are already latently infected with MDR M. tuberculosis, creating a remarkable resource for future cases of active TB with insufficient treatment options. Nevertheless, the WHO has vowed to reduce TB morbidity by 90% and TB mortality by 95% by 2035. This ambitious goal can only be accomplished successfully if more rapid diagnostics, new drugs for shorter therapy, and new vaccines to prevent pulmonary TB become available. Cancer vaccination strategies focus on initiating an immune response against cancerous cells. The discovery of tumour associated antigens (TAAs) and tumor specific antigens (TSAs) supported the development of vaccination strategies which can elicit robust immune responses capable of clearing cancer cells while simultaneously having limited toxicity. TAAs are germline encoded self-antigens re-expressed in cancers, e.g. cancer testis antigens of which the expression is normally exclusive to the testis or placenta. TAAs are expressed in a wide range of cancers and could be included in low cost off-the-shelf vaccination approaches, but are generally less immunogenic due to tolerance induction mechanisms specific for self-antigens. More promising are TSAs or neoantigens, as they are highly specific and arise from tumours-associated genomic aberrations or are encoded by viral genes involved in cancer development. Encouraging phase I trials have been performed using neoantigen-based vaccines, showing sustained progression-free survival, no tumor recurrence after resection or reduction in metastases in a subset of patients. Generally, cancer vaccines are composed of different combinations of tumor antigen, adjuvant and a delivery platform. Synthetic long peptide (SLP)-based vaccination has shown promising results in women with HPV16–positive vulvar intraepithelial neoplasia.

Vaccine

mRNA Vaccine

mRNA vaccines have gained considerable attention in the recent years, because they have the potential to expedite vaccine development, to have improved safety and efficacy, and to tackle diseases that have not been possible to prevent with other approaches. mRNA is non-infectious, nonintegrating, and is degraded by normal cellular processes shortly after injection, decreasing the risk of toxicity and long-term side effects. Intracellular expression of the antigen by mRNA

may lead to strong T cell responses typically seen with viral vector-based or replication defective virusbased vaccines. However, mRNA vaccines have the advantage that they do not induce vector-specific immunity and do not contend with either pre-existing or newly raised vector immunity that could interfere with subsequent vaccinations. More than 10 mRNA vaccines were already at different stages of clinical testing before the beginning of the SARS-CoV-2 pandemic. These studies have demonstrated the safety and immunogenicity of mRNA vaccines in thousands of vaccinated subjects including children and elderly subjects.mRNA vaccines enable precise antigen design and the generation of proteins with a ‘‘native-like’’ presentation (e.g., membrane bound with human glycosylation patterns), expression of proteins stabilized in a more immunogenic conformation or exposing key antigenic sites (e.g., prefusion stabilized) , and delivery of multiple mRNA to the same cell allowing the generation of multi-protein complexes or protein antigens from different pathogens thus creating a single vaccine against several targets. mRNA vaccines are manufactured using chemically defined, consistent processes, regardless of the antigen encoded by the mRNA, and this has the potential to simplify vaccine production, scale up, quality control, and the overall vaccine development timelines. These factors allow for multiple iterative cycles of antigen improvements and human evaluation thus shortening the overall development time to safe and efficacious vaccines (Figure 1). Finally, because this is such a rapidly developing field, there are many opportunities for innovation, improvement and new development.

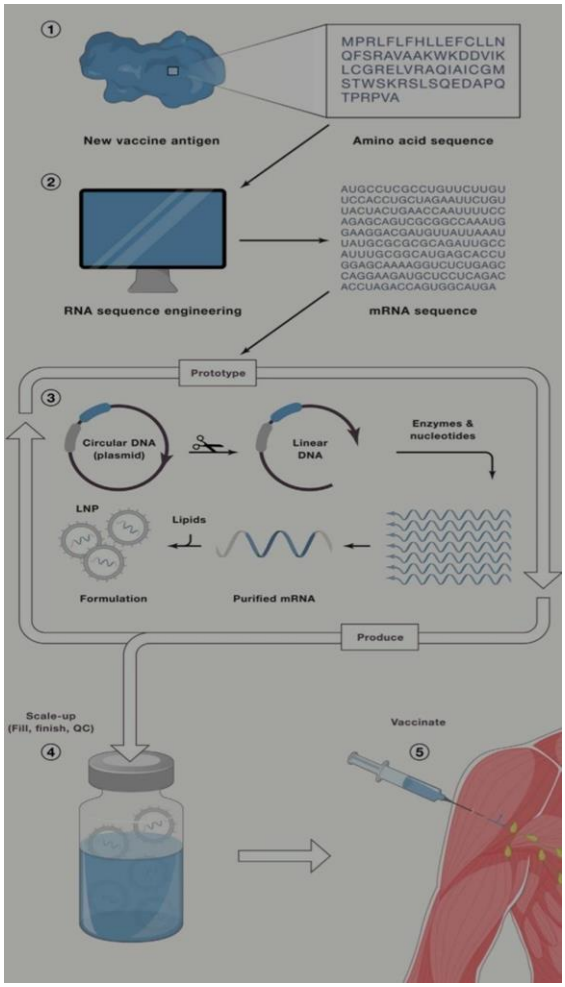
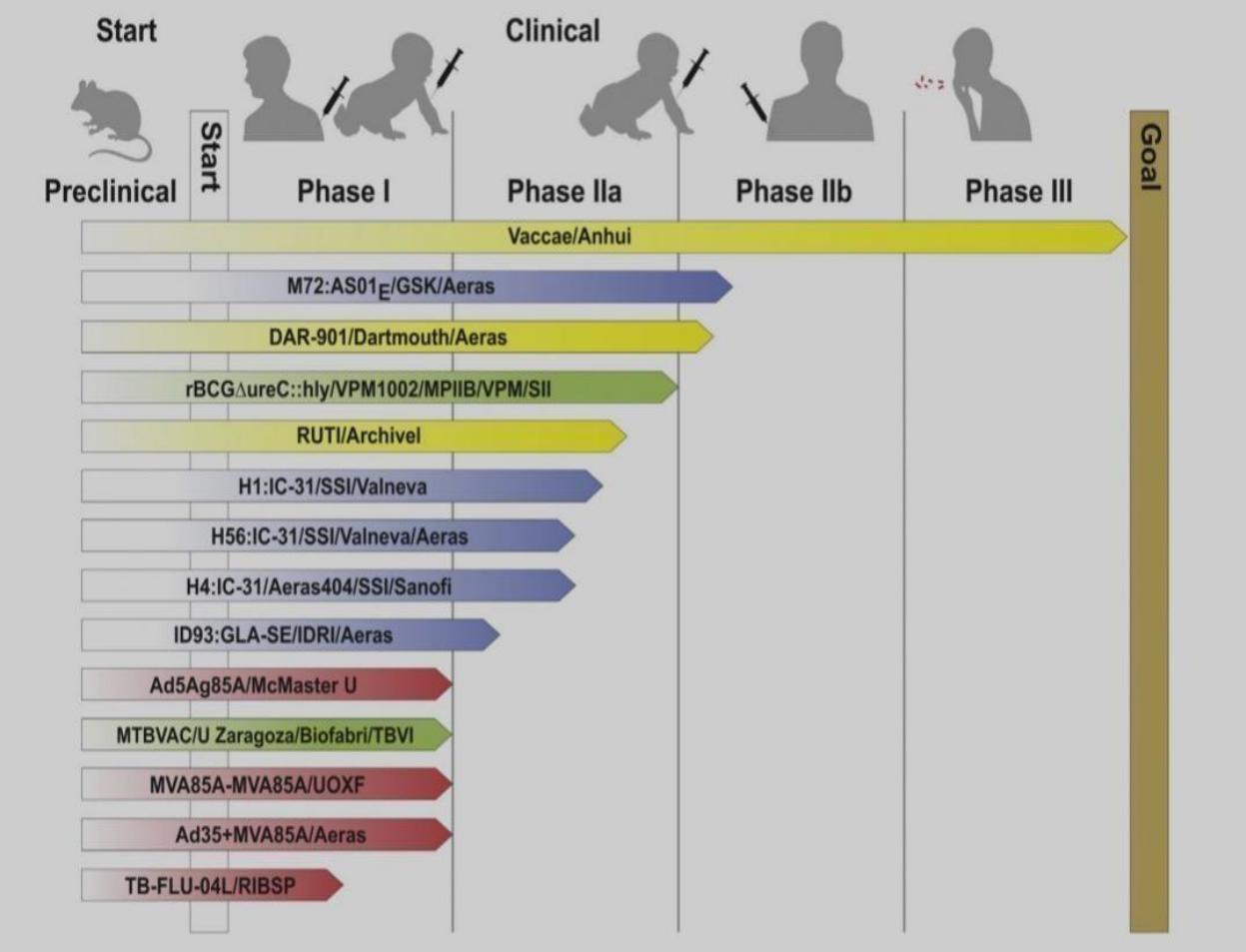


Figure 1. Process for mRNA vaccine development from target identification to vaccination. (1)It starts with the identification and design of a target antigen. (2) Digital sequence design based on propriety algorithm. (3) Manufacturing of plasmid, and lipid nanoparticle (LNP). (4) Fill, finish, and quality control (QC). (5) intramuscular injection, cellular uptake, protein expression, and immune activation. A unique feature of mRNA vaccines is that they can be produced and scaled up in a predictable and consistent fashion and with well-established processes and reagents within weeks regardless of the antigen. This feature is advantageous during outbreaks caused by new viruses or pandemic situations where a rapid response is needed. The COVID-19 pandemic has accelerated investment in manufacturing and scale-up of mRNA vaccines leading to commercial scale production. Two mRNA-based SARS-CoV-2 vaccines (Modern a mRNA-1273 and Pfizer/BioNTech BNT162b2) have been tested in large Phase 3 clinical trials and were demonstrated to be safe and highly efficacious in both adults and elderly subjects. Importantly, both manufacturers expect to produce hundreds of millions of doses of vaccine for deployment in 2021. These are the first licensed mRNA vaccines, and their wide acceptance and use wouldopen the way to other novel mRNA vaccines against infectious disease targets.

• Tuberculosis Vaccine Development

A vaccine against infant TB was introduced in 1921 by the French scientists Albert Calmette and Camille Gue´ rin, which was accordingly named bacille Calmette–Gue´ rin (BCG). This vaccine is now widely used to prevent severe forms of extrapulmonary TB such as miliary TB in infants.11,12 However, BCG fails to prevent the most common form of disease – pulmonary TB – at any age.11,12 BCG is an attenuated strain of Mycobacterium bovis, the etiological agent of TB in cattle. Although it is well tolerated, it can disseminate in immunocompromised individuals, notably HIV-infected persons, causing a disease termed BCGosis.7 Accordingly, BCG is not recommended for HI exposed neonates in several countries. Because of these limitations of BCG, novel TB vaccine candidates have been developed, of which several have reached the clinical trial pipeline. These TB vaccine candidates can be categorized into the following: (1) preventive pre-exposure vaccines, which are administered prior to first exposure to M. tuberculosis, typically to neonates; these are also known as priming vaccines; (2) preventive post-exposure vaccines, which are targeted at adolescents and adults with LTBI and prior BCG immunization; these are also known as boosting vaccines; (3) therapeutic vaccines, which are to be administered in adjunct with canonical TB drugs, notably to persons at higher risk of developing recurrent disease. Figure 1 provides an overview of the major TB vaccine candidates in the clinical pipeline. Preventive vaccines come in three generic types: subunit vaccines, viable whole-cell vaccines, and inactivated whole-cell vaccines. Subunit vaccines are composed of one or more antigens that are considered protective (Table 1). Often several antigens are combined to improve vaccine efficacy. Yet, protectivity is generally defined loosely and based on protection measured in one or more experimental animal models. To increase protectivity, antigens are either formulated with adjuvant or expressed by a recombinant viral vector (Tables 2 and 3). A number of current vectored vaccine candidates are based on recombinant adenovirus or vaccinia virus, many of which express the antigen 85A (Table 3).13–22 Another viral vectored vaccine against TB harnesses a replication deficient influenza virus expressing M. tuberculosis antigens. Some vectored vaccines are being developed not only as

BCG boosters, but also are prime boost strategies comprising different viral vectors and/or M.Tuberculosis antigen combinations.20 The recombinant modified Vaccinia Ankara (MVA) vector expressing antigen 85A (MVA85A) was one of the most advanced TB vaccines, but it failed to demonstrate protection in a preventive pre-exposure phase IIb Trial.23 Generally, these subunit vaccines are given as a boost after a BCG prime, with the aim of improving BCG-induced protection, i.e. to increase efficacy and prolong duration.



Figures 1. Pipeline of major TB vaccines in clinical trials. RUTI and Vacate are therapeutic vaccines; all other vaccines are preventive. For further explanations of antigens, adjuvants, and genetic modifications of the vaccines, see Tables 1–5. (Abbreviations: GSK, Glaxo Smith Kline; MPIIB, Max Planck Institute for Infection Biology; VPM, Vakzink Project Management; SII, Serum Institute India; SSI, Statens Serum Institute; McMaster U, McMaster University; TBVI, Tuberculosis Vaccine Initiative; UOXF, University of Oxford; RIBSP, Research Institute for Biological Safety Problems). Since pre-exposure vaccines are mostly confronted with metabolically active M. tuberculosis, antigens for this type of vaccine are chosen from those expressed during the stages of active replication and metabolism. These include the hybrid H1 and H4 vaccines.21,22 In contrast, post-exposure vaccines are administered to persons with M. tuberculosis in a dormant stage and need to include antigens expressed during latent infection. Ideally, a combination of antigens in the form of fusion proteins is administered to cover both active and

latent stages. These so-called multistage vaccines include H56, M72, and ID93. Viable vaccines were originally considered as replacement vaccines only and given instead of BCG. Hence, their first target population would be neonates (Table 4). The most advanced vaccine candidate is the recombinant BCG vaccine, VPM1002, which has shown a better safety and efficacy profile than standard BCG in preclinical models.25 It has completed clinical phase I and Phase II trials in adults and neonates and is currently being assessed in HIV-exposed neonates. It was shown that VPM1002 was well tolerated in adults with childhood BCG immunization, and protected against TB in an experimental post-exposure mouse model.26 Hence, this vaccine is currently being developed also as a preventive post-exposure vaccine for adolescents and adults. Accordingly, a vaccination protocol has been submitted to prevent recurrence of TB in previously cured TB patients. Even after successful completion of drug treatment for active TB, over 10% of patients experience recurrence and develop TB for a second time, thus presenting a high risk group for vaccine trials. The second viable vaccine candidate that has successfully completed a phase I clinical trial is a double deletion mutant of M. tuberculosis termed MTBVAC. Several vaccines are being developed to improve treatment outcomes in active TB (reduce mortality or relapse rates). This is a particular challenge in MDR-TB and extensively drug-resistant (XDR)TB with extremely low cure rates of less than 50%, providing a greater opportunity for identifying the therapeutic efficacy of an investigational vaccine. The biological hypothesis is that additional stimulation with mycobacterial antigens may further enhance the immune response and improve bacterial killing. However, there are experimental data suggesting that certain types of excessive immune response might be detrimental in the immune control of TB in humans.33,3 Mycobacterium indicus pranii (Mw) is an inactivated non-tuberculous mycobacterial vaccine that has been studied as an adjunct to therapy for leprosy35 (Table 5). A phase II study of Mw as an adjunct to therapy for TB has been completed and is being analyzed. A preclinical study of Mw administration by the aerosol route will examine immune responses in guinea pig and mouse models. RUTI is a vaccine being developed to improve the outcomes in the treatment of both LTBI and TB disease and to reduce exposure to antibiotics (Table 5). Its mechanism of action is based on the induction of a polyantigenic cellular response to non-replicating Bacilli contained in detoxified cell wall nano-fragments of M.Tuberculosis. A phase I trial demonstrated safety and immunogenicity and a phase II trial showed safety and immunogenicity in both HIV-negative and HIV-positive volunteers with LTBI.36 A Phase IIa trial is planned to investigate the safety and immunogenicity of RUTI therapeutic immunization in patients with MDR-TB.

ACKNOWLEDGEMENT

The authors thank Souraya Sibaei for excellent secretarial assistance and Diane Schad for graphics work.

Funding: SHEK acknowledges support from The European Union's Seventh Framework Programme (EU FP7) ADITEC (HEALTH-F42011-280873); the EU Horizon 2020 project TBVAC 2020 (grant number 643381); The Bill & Melinda Gates Foundation (BMGF) GC6-2013, #OPP 1055806 and #OPP 1065330; the Bundesministerium fu¨ r Bildung und Forschung (BMBF) project ''Infect Control 2020''. FvR acknowledges support from the Global Health Innovative Technology Fund (GHIT, grant number G2015-147) and the US National Institutes of Health (Fogarty International Center

D43-TW006807). Conflict of interest: SHEK is co-inventor of the TB vaccine VPM1002. CFvR is the sponsor for DAR-901.

CONCLUSION

Until recently the development of new vaccines against TB was directed towards containing M. tuberculosis by prolonging LTBI and blocking active TB disease.4,5 Although an effective vaccine to prevent TB disease would be an applaudable achievement, the sterile elimination or prevention of M. tuberculosis infection would ultimately be preferred. Although the biological mechanisms that might lead to sterile M. tuberculosis elimination or the prevention of M. tuberculosis infection are not known, recent evidence suggests that BCG immunization is capable of preventing infection at least in part.5,37 As a result, some new vaccine candidates are now being tested to determine whether they have efficacy in preventing M.Tuberculosis infection.38–40 These prevention of infection trials employ IGRAs, which are based on a simple blood test to detect Infection. Because TB is a poverty-related disease, cost matters. Hence, it is critical to accelerate clinical trials and at the same time reduce their cost. One option towards this goal is stratification based on High-risk groups.41 These include miners, who are at a markedly elevated risk of developing TB, and patients with successfully treated TB who have a high rate of recurrent TB, as described above. Alternatively, biomarkers that predict progression towards active TB would allow the stratification of study participants at greatest risk of developing active TB disease within the duration of a standard clinical trial.41,42 Indeed, bio signature so that can predict progression to active TB are currently being developed. These signatures comprise changes in the gene expression of defined markers at high sensitivity so that they most likely diagnose subclinical incipient TB.43 Even though the development of an improved vaccine against TB presents major challenges on several fronts, it is a goal worth pursuing. After all, an effective vaccine that prevents pulmonary TB could make amajor contribution to the goal of reducing TB morbidity and mortality by 90% and 95%, respectively, by the year 2035. Finally, the application of biomaterials and engineering enhances control of vaccine delivery has shown promise to enhance vaccine efficacy and to tune the nature of responses elicited. Taken together, these innovations in vaccine science have the potential to address many shortcomings of conventional vaccine technologies and will likely play a major role in the development of future vaccines for both existing and novel pathogens.

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HOW TO CITE: Shaikh Mujeeb Ur Rahman, Anwar Qamar Q.*, Shaikh Altamash A., Patel Aaref N., Shah Huzaif, Khan Ahetesham H., Faisal Khan, A Review on Novel Approaches in Vaccine Development, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 7, 01-11. https://doi.org/10.5281/zenodo.15779379