Review

Current Advances in the Development of Drug and Vaccine for Tuberculosis Prevention and Treatment

Biniam Moges Eskeziaw,[1] Temesgen Assefa Gelaw,[1] Gebiru Sinshaw Wondie,[1] Mesfin Dagne Worku[2]

[1]Department of Biotechnology, Debre Birhan University, College of Natural and Computational Sciences, Debre Birhan, Ethiopia
[2]Center of Food Science and Nutrition, Addis Ababa University, Addis Ababa, Ethiopia

Abstract

Tuberculosis remains a deadliest public health problem worldwide due to a single infectious agent, Mycobacterium tuberculosis. It demands more attention to combat its global impact. However, in addition to treatment with drugs, prevention attempts were done for the last many years through vaccination with Bacillus Calmette- Guerinvaccine (BCG). BCG is the only licensed and commonly used vaccine worldwide especially for protection against severe forms of pediatric TB, but not as a powerful vaccine because of unreliable against adult pulmonary TB which accounts for most of the disease global burden. Overall efforts to safe, efficient and greater immunogenic novel drugs and better vaccine development is must to combat, prevent and treatment of both drug-resistant and drug-sensitive MTB strains for all age groups and among people with HIV. Henceforth, currently there are 10 new or repurposed anti-TB drugs and 15 new Tb vaccines with a degree of diversity in terms of vaccine delivery platforms, ranging from whole cell vaccines to adjuvanted proteins, recombinant and vectored vaccines are developed and undergoes different phase of clinical trials. Overall, this review gives the basic idea of new drug and vaccine development approaches, and their effective role and clinical trial stuts in TB prevention and treatment.

Keywords: Antigen, drug, multi-drug resistant TB, mycobacterium tuberculosis, tuberculosis vaccine

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Tuberculosis (TB) is an infectious disease caused by the acid- fast bacteria bacillus *Mycobacterium tuberculosis* (MTB). It affects lungs (pulmonary TB) and other sites (extra pulmonary TB). The chance of developing TB upon infection with MTB is higher among people infected with other co-epidemic disease like HIV.[1] The acute stage of MTBinfection is characterized by its rapid growth and the development of an immune response targeted to bacterial antigens secreted in the first growth phase. The vaccines developed against these acute- phase antigens can minimize the severity of the disease but it can't prevent the initiation of infection.[2]

Mycobacterium tuberculosis has a mechanism for adaptation the hypoxic and hostile environment of host macrophages via undergoing a dramatic change in gene transcription and this change in gene expression make the pathogen to persist in the face of sturdy memory immune responses. [3] The regulatory proteins in the MTB genome are important for the pathogen's being able to adapt different environments during infection. In addition to adaptation, the flexibility of regulatory gene may help its ability to shift between acute progressive disease and long-lived latent infection. The burden of disease caused by MTB can be detected in terms of incidence, prevalence and mortality rate.[4]

According to,[5] more than 2 billion people have been exposed to MTB. Among this, above 8 million people show active disease and 1.5 million died from the disease. This shows the world foremost cause of death by a single infectious agent, *Mycobacterium tuberculosis*.[6] Due to the serious consequences at individual and societal level of the spread of all forms of TB, including drug-resistant strains, vaccine and anti-TB drugs are needed. Currently, Bacillus Calmette- Guerin (BCG) is the only licensed tuberculosis vaccine globally. It was developed in France in the early part of the 20th century and first used in humans in 1921. In addition to the BCG vaccine, the most effective first-line anti-TB drug, rifampicin, was available in the 1960s.[7] Bacille- Calmette-Guerin (BCG) vaccine for the prevention of TB was almost usedfor 100 years and the vaccine protects against severe forms of TB in children. Unfortunately due to the complex nature of *M. tuberculosis* and its pathology within the human host, genetic variation in BCG strains and nonspecific immune response against mycobacterium, its efficacy in pulmonary Tb is variable in adolescents and adults and it is also not recommended for use in infants known to be infected with HIV.[6] However, most of the disease burden and transmission is higher in latently infected adults and adolescents worldwide. Hence, the development of novel, safe and effective vaccine and drugs to prevent and treat all forms of TB, including drug-resistant strains at all age groups including those with HIV are needed.[2] Hereafter, to develop safe and effective vaccine, three approaches could be implemented. The first approach is to develop safe and long-acting recombinant BCG strains or attenuated *M.tuberculosis*, and the second strategy is a prime-boost strategy in which a viral vectoredvaccineas a booster dose is given at a later stage. The third scheme is to develop therapeutic vaccines to reduce the duration of TB therapy and it includes immunotherapeutic vaccines.[8] As the disease continues to be a major global public health problem, currently the development and research of new vaccines and drug to reduce TB infection reactivate latent TB. This limits the spread of (Multiple drug resistant TB (MDR) Extreme drug resistant TB (XDR) has increased to achieve the goal of TB elimination by 2050. Currently, there are nearly 10 new or repurposed anti-TB drugs and 15 TB vaccines developed and undergo different phase of clinical trials, including five protein or adjuvant vaccines, four viral-vectored vaccines, three mycobacterial whole cell or extract vaccines, and one each of the recombinant live and the attenuated *M.tuberculosis* vaccine.[9] Generally, this paper focuses on the review of current research resulting from the recent advancement in the development of TB vaccines and drug for prevention and treatment of tuberculosis. Firstly in the paper, an introduction to the overview of tuberculosis, their global impact, applicable anti TB drug and vaccine development is addressed to understand the fundamentals that explain the overall status of TB. Secondly, recently discovered/developed drugs for the treatment of TB, and current vaccines in various phases of clinical trials for prevention of tuberculosis are reviewed followed by opportunity and challenges for new drug and vaccine developments are also indicate.

The Global Problem of Tuberculosis and Status of Existing Control Efforts

According to[5] and the data collected from 202 countries and territories tuberculosis is found in all regions of the world and it becomes greater global public health problem.[1] Particularly in developing countries, due to the inadequate health service and health professionals, insufficient supply of anti-TB drug and vaccine, lack of awareness for the transmission way of TB and improper taking of the drug, absence of national vaccine and drug center, limitation of advance technology and fund for prevention and treatment of TB and other problems have contributed to increased occurrence of the disease. *Mycobacterium tuberculosis*, resistant to most of the available drugs (MDR TB) and the disease become one of the top 10 causes of death worldwide.[8] Accordingly, about 32% of the world population is infected with TB.[5] From these around 10.4 million of the infected people develop active TB (1.2 million among HIV positive) and near to 1.8 of these die from the disease (1.4 million are among HIV-negative people and 0.4 million among HIV positive people). Globally, 0.48 million new cases with MDR-TB were recorded and from these 9.7% developed XDR-TB. Thus, MDR and XDR-TB strains are already a serious global problem of tuberculosis that result in the use of more expensive, less effective, and more toxic drugs. Consequently, above 95% of deaths from the TB disease accounts in developing countries, like Africa and south-East Asia.[10] Globally, TB mortality, incidence, drug resistance TB strain status with different regions are given in Table 1.

In Africa region, Ethiopia is one of the 22 high in all form of TB/HIV and multidrug resistant TB (MDR TB) burden countries. According to the recent national estimate of tuberculosis incidence, mortality and TB drug resistance surveillance report,[5] 0.2% of the population were estimated as new TB incidence (0.02% among HIV positive TB incidence), 0.034% of the population was recorded as TB mortality (0.04% among HIV positive mortality). And also 2.3% of new TB and 17.8% of previously treated TB cases were estimated to have MDR-TB disease.[5]

To eradicate the global health problem of TB disease burden (incidence, prevalence, mortality and drug resistance TB strain) at international, regional and national level of measurement were taken by different countries. Some of

Table 1. Estimated incidence and mortality of TB report in 2015 by WHO Region[5]

Region	HIV negative TB Mortality	HIV positive TB Mortality	HIV positive TB	Incidence MDR-TB	XDR-TB	Total TB	Population
Africa	450.000	300.000	834.000	110.000	1.100	2.720.000	989.000.000
Americas	19.000	5.900	32.000	11.000	122	268.000	991.000.000
Eastern Med.	80.000	3.000	13.000	39.000	117	749.000	648.000.000
Europe	32.000	4.900	27.000	120.000	2.691	323.000	910.000.000
South-East Asia	710.000	74.000	4.740.000	200.000	3.099	227.000	1.930.000.000
Western Pacific	89.000	5.700	34.000	100.000	450	1.590.000	1.860.000.000
Global	1.400.000	390.000	1.170.000	580.000	7.579	10.400.000	7.320.000.000

the measurements that were taken by countries specially in industrialized countries are, adequate allocation health infrastructure, adoption and implementation of sound health policy (specially tuberculosis control policy), adequately producing of BCG vaccine and anti-TB drug with proper use and distribution, allocation of well-organized tuberculosis diagnostic and treatment services, funding to encourage the research and development of drug and vaccine. Many developing countries also apply the TB control practices based on their capacity.[11] Some of the efforts and effective system for tuberculosis control were developed by low-income developing countries. These are implementing directly observed therapy short-course (DOTS) strategy, using rifampin-based regimens, reliable supply of high- quality drugs and diagnostic supplies, reporting of treatment outcome for all patients and monitoring of program performance, and there was political commitment in the governments.[12]

Due to such global TB control measurement; TB mortality and prevalence rate fell by an estimated 45% and 41%, respectively, from 1990 to 2013. TB incidence also declined to at an average rate of about 1.5% within a year from 2000 to 2014. The incidence, prevalence and mortality rates declined much more in the Eastern Mediterranean and European Regions than the South-East Asia and African Region, but its failing rate not fast enough with wanted targets. For TB reduction strategy, Ethiopia has achieved the Millennium Development Goal that target on reducing the TB incidence. Nationally, the TB incidence, mortality and prevalence rate has decreased by 38.75%, 46% and 50.5% respectively from 1990 to 2016.[13]

Recent Advances in the Development of Drug and Vaccine for Tuberculosis Prevention and Treatment

Current Vaccines in Various phases of Clinical trials for Prevention of Tuberculosis

Vaccination is an important process for the prevention and control of TB incidence. As the BCG TB vaccine was devel-

oped and first used on humans in France, it gets widespread acceptance from US, Great Britain, and Germany after World War II. It was the only licensed and most widely used vaccine in most countries worldwide, with more than 90% of all children was being vaccinated.[14] The Bacille-Calmette-Guerin (BCG) vaccine against TB is almost 100 years old. However, the BCG vaccine has limitations and its efficacy in preventing pulmonary TB in an adults is highly variable and it is not recommended for use in infants with HIV infection. The slow globaldecline in TB incidence, the growing problem of MDR-TB and recently the disease continues to be a major, global public health problem. Thus, research to develop new effective TB vaccines for tuberculosis is ongoing.[15] For improvement of the available BCG vaccine three different approaches are being used. The first is to develop an improved BCG vaccine version with safe and long-acting recombinant BCG strains, the second approach is a prime- boost strategy in which a new vaccine usually viral vectored or protein adjuvant is given at later stage. The third method is to develop therapeutic vaccines with reducedTB therapy and inclusive to all immunotherapeutic vaccines.[8] Currently there are 15 vaccine candidates undergoing in clinical trials and designed for prevention of TB infection (pre-exposure and post-exposure). These are six AdAg85A, MTBVAC, ID93+GLA-SE, Crucell Ad35/MVA85A, DAR 901 and TB/FLU-04L in phase I trials, six vaccines including VPM 1002, H1/H56/H4+IC3 and Crucell Ad35/AERAS-402 in phase II trials, two vaccines including MVA85A and M72+AS01E are in phase IIb trials and one vaccine *M. vaccae* (MV) is in a phase III clinical trial.[7] The TB vaccines include protein or adjuvant, viral vectored, mycobacterial whole cell or extract, attenuated MTB and recombinant live, under clinical phases of development and their indications are given in Figure 1 and Table 2.

Mycobacterium Whole Cell or Extract Vaccines

Mycobacterium whole cell vaccine strategy is an important technique when it is impossible to identify the specific individual antigen of the mycobacterium for the generation of

protective immune responses to MTB.[16] In addition, using a whole cell as a vaccine induces diversified humeral and cellular immune response to a range of protein, lipid and antigens than using individual specific subunit-based vaccines. *M. Vaccae* and Dar-901 vaccine is a whole cell or extract.[7]

M. vaccae is a whole cell heat-killed immunotherapeutic agent in tuberculosis. Currently its phase 3 trials for safety and efficacy in preventing TB disease being assessed and it was harmless and immunogenic in adults with HIV positive and prompted CD4+ T-cell-expressing IFN-γ and IL- 10 responses in cultures from *M. vaccaetreated* mice compared with those from non-treated ones.

DAR-901 is another type of a whole cell vaccine, resulting from a heat-inactivated whole cell and developed in Dartmouth University, USA, to prevent TB disease in adolescents and adults. A phase 1 safety and immunogenicity trial recently was completed and now a phase 2 clinical trials are being assessed in Tanzania.[8]

RUT I is a killed fragmented vaccine developed by encapsulating detoxified *M.tuberculosis* bacteria in liposome. It is designed as immunotherapeutic vaccine to reduce the ex-

tent and duration of drug treatment of latent and active Tb infection (LTBI) with isoniazid (INH). Its PhaseI and II studies on safety, tolerability and immunogenicity aspect were tested and the result showed that it was safe, well tolerated and has a capacity to induce activation of IFN-γ, CD4+ cells and CD8+ cells against tuberculin purified protein derivative, ESAT6 and Ag85B. A phase III study for this vaccine candidate is yet not studied.[7]

Viral Vectored Vaccines

A Viral vectored vaccine comprises viral genes that code an antigen (Fig. 2). The most common viral vectors are Ad-5Ag85A, ChAdOx185A, MVA85A and TB/FLU-04L. All these viral vectors can prompt high levels of Ag85A antigen specific to CD4+ and CD8+ T-cells in those with pre- existing immunity to Ag85A primed by BCG vaccination.[16]

Ag85A vaccine is a recombinant replication-deficient adenovirus serotype 5 vaccine vector that induces a strong Th1 type cellular immune response to MTB antigen. Its phase I clinical trial studies were performed and the result showed, bit is safe, immunogenic and heightened protection against virulent MTB in murine, bovine and guinea pig models.[10]
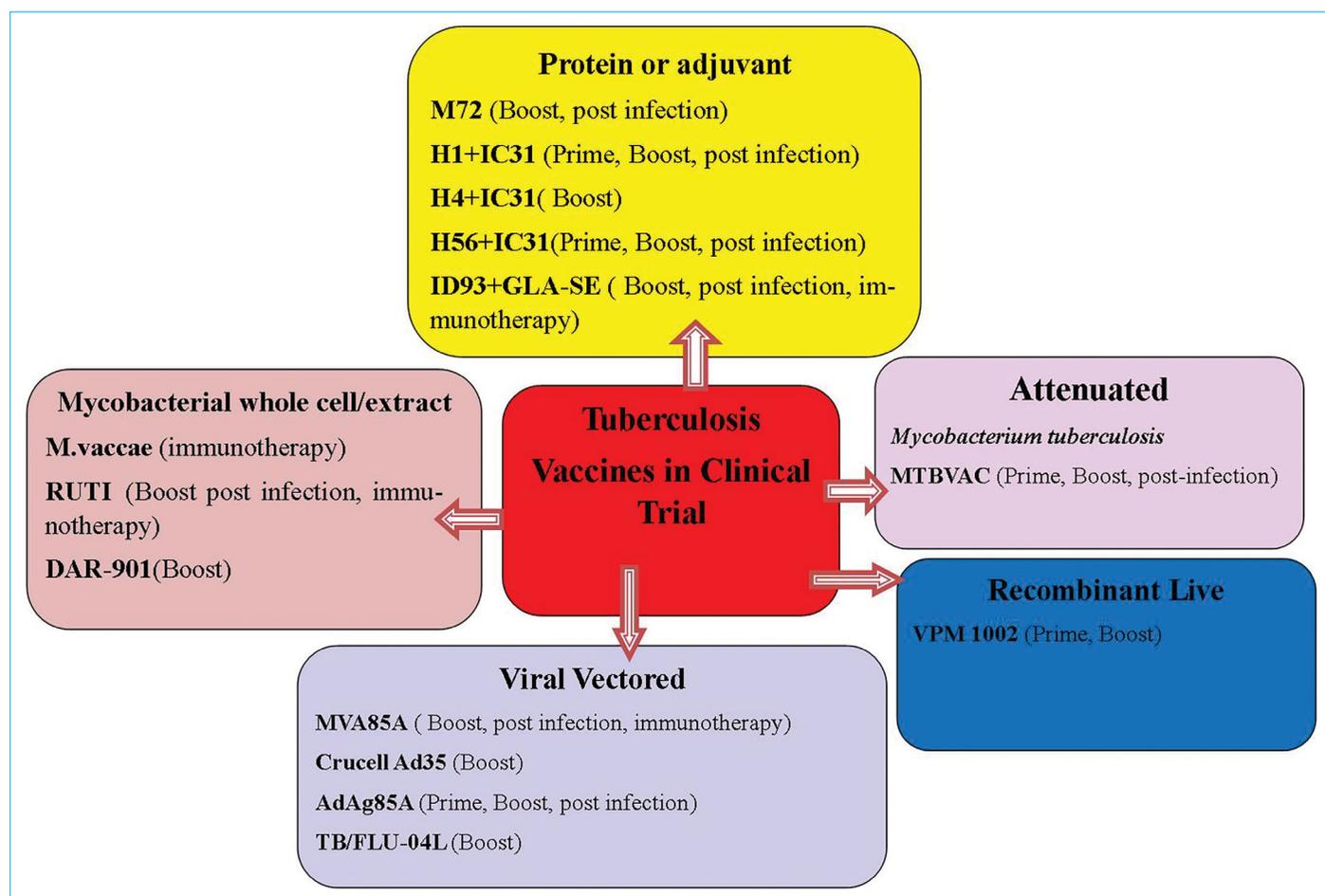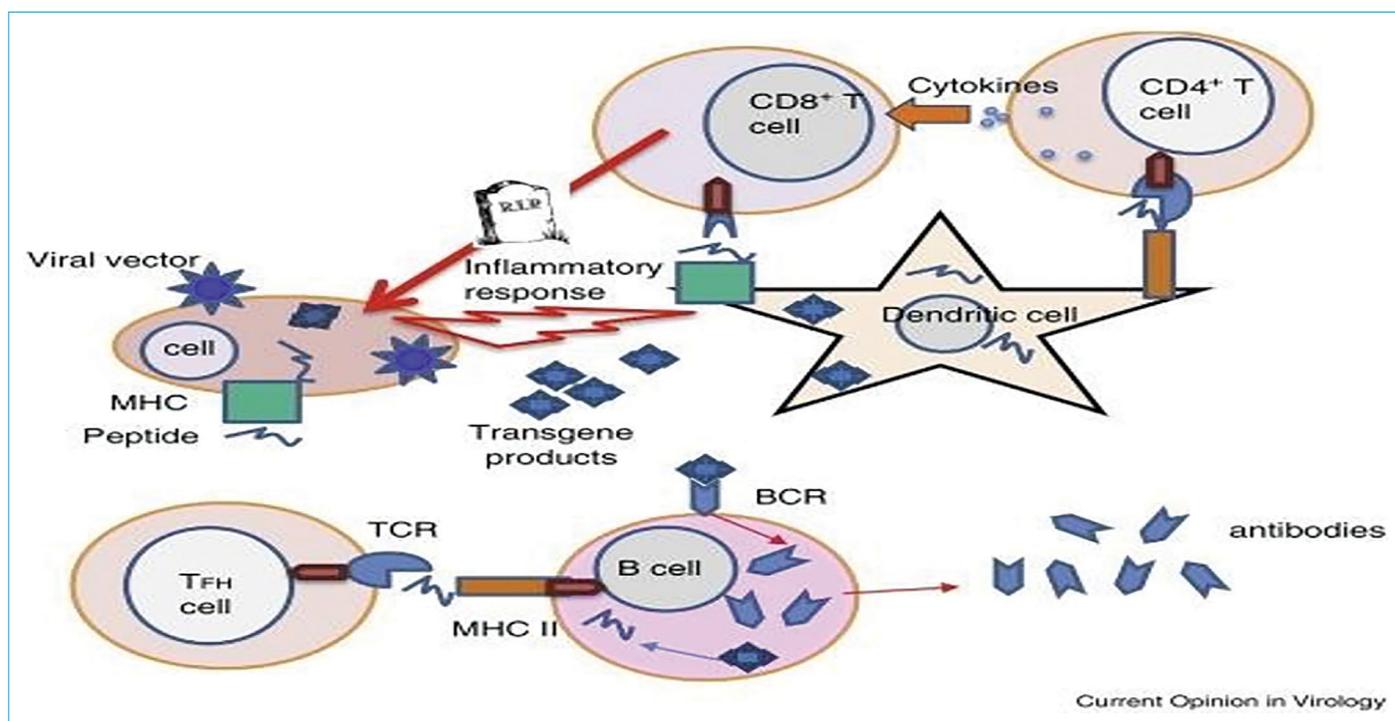
Protein or adjuvant

M72 (Boost, post infection)

H1+IC31 (Prime, Boost, post infection)

H4+IC31 (Boost)

H56+IC31 (Prime, Boost, post infection)

ID93+GLA-SE (Boost, post infection, immunotherapy)

Mycobacterial whole cell/extract

M.vaccae (immunotherapy)

RUTI (Boost post infection, immunotherapy)

DAR-901 (Boost)

Tuberculosis Vaccines in Clinical Trial

Attenuated

Mycobacterium tuberculosis

MTBVAC (Prime, Boost, post-infection)

Recombinant Live

VPM 1002 (Prime, Boost)

Viral Vectored

MVA85A (Boost, post infection, immunotherapy)

Crucell Ad35 (Boost)

AdAg85A (Prime, Boost, post infection)

TB/FLU-04L (Boost)

Figure 1. Different new developed tuberculosis vaccines in various phases of clinical trials.[8]

Table 2. The developmental pipeline for new tuberculosis (Tb) vaccines (2016)[8]

Tb vaccine/gent	Strategy	Tb vaccine type	Sponsorship	Status
M. Vaccae	Immunotherapeutic	Whole-cell M. vaccae	AnHuiLongcom	Phase III
M72/AS01	Prime-boost	Protein/adjuvant	GlaxoSmithKline, Aeras	Phase IIb
H4+IC31	Prime-boost	Protein/adjuvant	SSI,Sanofi Pasteur, Valneva, Aeras	Phase
IIaH56+IC31	Prime-boost	Protein/adjuvant	SSI, Valneva, Aeras	Phase
IIaMTBVAC	Prime	Live attenuated (MTB)	University of Zaragoza, Biofabri,	Phase
IIa	VPM1002	Prime	Live recombinant rBCG SSI, Valneva SSI, Valneva	Phase IIa
Dar-901	Prime-boost	Whole-cell M. obuense	Dartmouth University, Aeras	Phase IIa
ID93+GLA-SE	Prime-boost	Protein/adjuvant	Infectious Disease Research,Aeras	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	ArchivelFarma	Phase IIa
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
ChAdOx1.85A+MVA85A	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A-IMX313	Prime-boost	Viral vector	Oxford University, Imaxio	Phase I
TB/FLU-04L	Prime-boost	Viral vector	Research Institute for BSP	Phase I
MVA85A (aerosol)	Prime-boost	Viral vector	Oxford University	Phase I

Figure 2. Schematic diagram of mechanisms of Viral vectored as a vaccines.[17,25]

Crucell Ad35/AERAS-402 is an adenovirus-vectored vaccine that expressed three *M. tuberculosis* antigens such as Ag85A, Ag85B and TB10.4. It is designed as a booster vaccine for the prevention of TB in infants, adolescents and adults. Crucell Ad35 induced CD4+ and CD8+ T-cell immune response and mediate the role of IFN-γ. AERAS-402 also induced CD8+ T-cell response, by cells expressing IFN-γ and TNF-α. It's Phase I studies were completed and phase II studies with safety and immunogenicity were being reach to endpoints.[17]

MVA85A is a prime- boost designed types of viral vector vaccine derived from a modified recombinant strain of Vacicinia virus, that expressing strong immunogenic antigen 85A of *M. tuberculosis*. The safety and immunogenic performance of MVA85A vaccine was accompanied in animal models and the result showed a high induction of Poly functional CD4+ T cells expressing IFN-γ, IL-2, TNF-α, IL-17 specific to MVA85A antigen. The results from the first clinical trials show that it is immunogenic and safe in humans.[18]

Adjuvant Protein Subunit Vaccines

This type of vaccine is manipulated by selecting a specific antigen that stimulate the immune system rather than from the entire microbe or whole cell. This contains epitopes where the antibody or T-cell recognized and bind with their specific antigens. It is designed as a boost to BCG to prevent *de-novo* infection with TB and/or reactivation in those already infected. A major limitation of this vaccine is its requirement for adjuvant for vaccine delivery; however, because of using a specific antigen instead of the entire microbe the chance of adverse reaction is low.[14]

M72+AS01E is an advanced protein subunit vaccine. It contains a fusion protein antigen 32A and 39A of the *M. tuberculosis* which is designed as a prime-boost vaccine to prevent the development of active TB from a non-active TB infection. [16] Phase II and phase IIa clinincal trials were completed and the result showed clinically acceptable safety profile and highly induces immunogenic (CD4+ T-cell and humoral responses) for M72/AS01antigen and also the phase IIb studies is ongoing. Safety and immunogenicity of M72/AS01 in adults with TB infection and HIV are ongoing.[19]

H56+IC31, a prime-boost protein subunit adjuvanted vaccine which contains 85B, ESAT6 and AgRv2660c antigens, that is used to control late-stage infection with MTB and also used for TB therapy by combining with COX-2-selective inhibitors (non-steroidal anti-inflammatory drug) that improve the vaccine response to H56 and shorten the duration of chemotherapy for multidrug-resistant TB. Currently its phase II trial is being evaluated in Africa.[20]

H4:IC31 is another type of a prime- boost protein subunit adjuvanted vaccine that contains Ag85B and TB10.4 antigens and was developed by SSI in collaboration with Sanofi-Pasteur, France, Aeras and Intercell.[21] This vaccination strategy is to boost and prolong the immune response that induced BCG vaccine that increased the protection power against MTB to immune response dominated by IFN-γ, TNF-α, IL-2 or TNF-α, CD4+ cell. The safety and immunogenicity studies were completed and now a phase II study has being evaluated.[19]

ID93+GLA-SE are a recombinant fusion protein of novel adjuvant, GLA-SE. This vaccine expresses three *M. tuberculosis* virulence antigens (Rv2608, Rv3619 and Rv3620) and one *M. tuberculosis* latency antigen Rv1813.[21] When the GLA-SE (TLR4) combined with ID93, it induces a poly functional T-Helper type 1 immune response characterized by CD4+ T cells producing IFN-γ, tumor necrosis factor (TNF) and interleukin 2 (IL-2) for the rheostat of TB. In addition, their safety and immunogenicity Phase 1 trial assessment was completed in adult in South Africa.[22]

Recombinant (rDNA) live vaccines

Recombinant vaccines (Fig. 3) are experimental vaccines similar to DNA vaccines, but it uses an attenuated virus or bacterium as a vector to insert microbial DNA to cells of the body. It can be constructed by selecting a gene that code antigenic from the microbe and then transfer to the host organism for cloning and then passing through different process until to act as a delivery system for a DNA vaccine.[23]

VPM1002 is a recombinant BCG strain which has a gene of *Listeria monocytogenes* that code listeriolyisn protein, integrated into the genome with inactivated urease C gene for immunogenicity improvement and also it contains a hygromycin resistant marker gene. This vaccine is used as a BCG replacement for infants to prevent recurrent TB disease and in adults and for active pulmonary TB. A phase I and phase II study for the evolution of its safety and immunogenicity has been tested and that the vaccine candidate was safe and induced multifunctional CD4+ and CD8+ T-cell immunogenicity.[21]

Live Attenuated Vaccine

Live attenuated vaccines (Fig. 4) contain a version of the living microbe that has been weakened to eliminate its pathogenic character. MTBB VAC is the first and only live attenuated vaccine, which is developed as BCG replacement strategy in infant. Its safety, protective efficiency and immunogenicity in infants was tested in clinical trial and the result indicates MTBB VAC is safe for infants with enhanced immunogenicity and better protection efficiency against *M. tuberculosis* challenges in comparison to BCG vaccine.[24,25]

Interaction of Mycobacterium Tuberculosis Antigen and the Host Immune System for Tuberculosis Vaccine Development

The nature of the host cell responding to *M. tuberculosis* infection and their relative contribution changes over
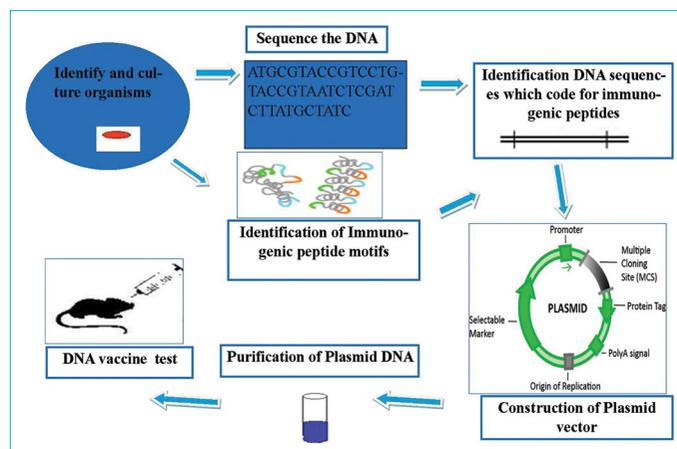

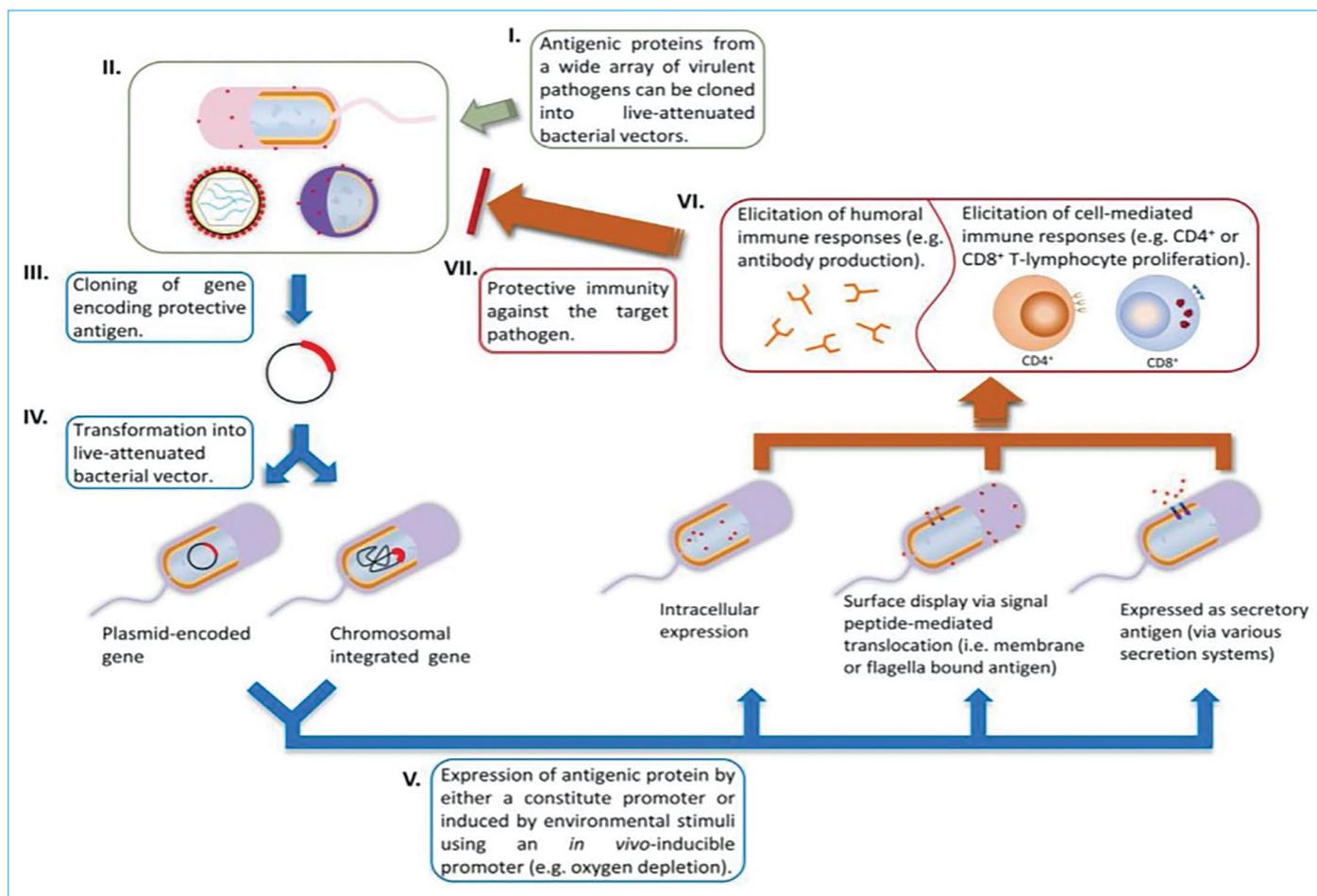**Figure 3.** Schematic diagram of recombinant (DNA) live vaccines.

Figure 4. Live Attenuated vaccine.[26]

time is an area of prominence for the development of TB vaccine. Humoral immune T cells such as CD4+, CD8+ and γ/δ T cells and their derived cytokines play a vital role to against MTB by making specific binding with the antigen of the *M. tuberculosis*.[27] The immunogenic (antigens) part of MBT is found on their cell surface that infects the host cell and induce host immune system; which is the most critical agent for the development of different vaccines against TB (Fig. 5).[28]

When the researcher wants to develop TB vaccine, an antigen has to be selected from the *M. tuberculosis* with same strain. Yet, TB antigens for vaccine development are not completely understood, which is an obstacle in finding effective vaccine against TB.[28] However, currently there are around 11 antigens that have been used for the development of Tb vaccines that are studies under various phases of clinical trials.[29] The *M. tuberculosis* antigens, their corresponding therapeutic vaccines for Tb in clinical trials (Table 3) and their immunological responses are indicated in Table 4.[8]

Recently Developed Drugs for the Treatment of Tuberculosis

The Need for New Tuberculosis Drug development

The anti-TB drugs currently used in first-line treatment are more than 40 years old on use. However these drugs require long treatment duration for first line and second line treatment of new cases. Drug resistance TB, and sometimes serious side-effects with low cure rates, health problem due to interactions between some anti-TB drugs and antiretroviral therapy (ART) for people living with HIV, occurrence of high rate of treatment failure associated with current tuberculosis regimens under different conditions are the most fundamental factors for the need of discovering and developing new drugs. The new drugs need to be more effective, and useful in shorter treatment regimens and other treatment improvement approaches for both drug-sensitive and drug-resistant tuberculosis.[12] Generally, there are numerous reasons considered for developing new TB drugs such as, to improve current treatment in terms of shortening treatment duration and dose minimization, mend the

Table 3. *Mycobacterium tuberculosis* antigens used in vaccines under various clinical stages of development

S. No.	Antigen	Vaccine candidate
1	Rv0125 (Mtb32A), Rv1196 (Mtb39A)	M72+AS01E
2	Rv0288 (TB10.4)	H4+IC31; H1+IC31; Crucell Ad35
3	Rv1813, Rv2608, Rv3619, Rv3620	ID93+GLA-SE
4	Rv1886 (Ag85B)	H4+IC31; H56+IC31; Crucell Ad35
5	Rv2660	H56+IC31
6	Rv3804 (Ag85A)	MVA85A; Crucell Ad35; Ad5Ag85A; TB/FLU-04L
7	Rv3875 (ESAT6)	H1+IC31; H56+IC31; TB/FLU-04L

Table 4. Therapeutic vaccines in clinical trials for Tb and their immunogenic response

Tb vaccine	Immune response
AdAg85A	IFN-γ, CD4+ and CD8+ T cells
ID93+GLA-SE	TH1 (IFN-γ, TNF-α and IL-2) CD4+ Tcell (IFN-γ and TNF-α)
Crucell Ad35/MVA85A	IFN-γ and CD4+ T cell
DAR 901	IFN-γ
VPM 1002	CD4+ and CD8+ T cell
H1+IC31	TH1 (IFN-γ, IL-2)
RUTI	TH1 (IFN-γ), TH2, TH3, CD4+ and CD8+ T cells
H56:IC31	CD4+ T cell
H4:IC31	CD4+ T cell (IFN-γ, TNF-α and IL-2)
Crucell Ad35/AERAS-402	CD4+ (IFN-γ, TNF-α and IL-2) and CD8+ T cell (IFN-γ and TNF-α)
MVA85A	IFN-γ, CD4+ T cell, CD4+T cell (IFN-γ and IL-2), CD4+ T cell (IFN-γ, TNF-α, IL-2 and IL-17)
M72+AS01E	CD4+ T cell, CD4+ and CD8+ T cell
Mycobacterium vaccae	IFN-γ and IL-10

IFN-γ- antigen-specific interferon γ; IL-interleukin; TH1- T helper 1; TNF-α- tumour necrosis factor α.

protective efficacy and tolerability of treatment for drug resistance TB (MDR-TB and XDR-TB), provide for more effective treatment of LTBI and to advance the treatment of TB among people living with HIV.[30] To address the above problems associated with the previous anti-TB drug, WHO and others responsible organizations and countries have advocated to the discovery and development of new, more effective anti- TB drugs for treatment of both drug-susceptible and drug-resistant TB. Hereafter, currently there are 10 new or repurposed anti -TB drugs developed and undergoes in Phase II and Phase III clinical trials.[31]

Drugs for the Treatment of Drug-Susceptible Tuberculosis

When someone is infected with TB bacteria that are fully drug susceptible TB, all commercially available TB drugs will be effective as long as they are taken properly. According to the WHO recommendations a six month treatment regimens are being used as standard for the treatment of drug susceptible TB.[12] However, a series of new combination regimens are currently being tested and the result
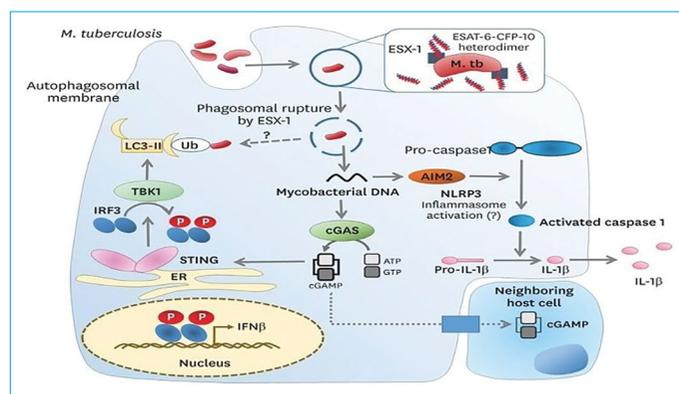

Figure 5. Mechanism of host cell responses in Mycobacterium tuberculosis-infection. In infected host cells, the bacterium is internalized through phagocytosis. M. tuberculosis replicates and secretes its peptides that induce pathogenic effects in the endosome.

indicates an encouraging prospects for treatment of drug susceptible TB. Currently fluoroquinolones and pyrazinamide drugs being tested as new treatment regimens for drug-susceptible TB. Based on the effect of these drugs assessing the feasibility of the introduction of new drugs and shorter regimens for TB treatment is critical point.[32]

Drugs for the Treatment of Latent Tuberculosis Infection

Latent tuberculosis infection is a state of persistent immune response to induce by *M. tuberculosis* antigens without indication of clinically sign of active TB. There is infection with *M. tuberculosis*, but do not have TB disease and can't spread TB infection to others. But it can be detected by tuberculin skin test or TB blood test positive.[33] Globally one-third of the world's population is estimated to have LTBI without active TB disease. However, without treatment like immunosuppressive drugs, the lifetime risk (HIV, malnutrition, and inflammatory diseases) of TB reactivation about 5 to 10% of infected persons will develop TB disease within the first five years after initial infection.[34] Latent tuberculosis infection can be effectively treated to prevent its development in to active TB. Currently four treatment regimens are recommended by WHO for the treatment of LTBI. These are 6-month or 9-month isoniazid with daily, 3-month rifapentine plus isoniazid with weekly, 3- or 4-month isoniazid plus rifampicin daily, and 3-or 4-month rifampicin alone with daily. These drug treatments allow to reducing the risk of progressing LTBI in to active TB by above 60%.[35]

Drugs for the Treatment of Drug-resistant Tuberculosis (MDR-TB and XDR-TB)

TB disease can be treated by different line anti-TB drugs; the first line TB drugs were isoniazid (H), streptomycin (S), rifampicin (R), pyrazinamide (Z), and ethambutol (E). However, due to different reasons *M. tuberculosis* strain becomes resistant to more than one antibiotic, in particular to isoniazid and rifampicin, the strain is considered MDR. The most common means for people to get drug resistant TB are, firstly when their TB treatment is inadequate (due to patients fail to keep to proper TB treatment regimes, wrong or sub-standard TB drugs are prescribed and used for treatment). Secondly, it could be due to the direct transmission of drug resistant TB from one person to another.[36] According to WHO report 580,000 (7.9% of the population) incident cases of MDR/RR-TB were estimated in 2015, from this near to 3.4% death with MDR/RR. The regions South-East Asia, Europe and Africa are the first, second, and third region where high incidence of MDR/RR-TB in 2015 are recorded. Globally a total of 51% of patients with MDR-TB have resistance to all first-line and second-line drugs are considered to be XDR TB. An estimated 9.7% of people with MDR-TB have XDR-TB and above 7,500 XDR-TB patients were started on treatment in 2015, but the treatment success rate was around 26%.[5]

To overcome the problems of drug resistant TB, recently, two new effective molecular drugs were approved by stringent regulatory authorities for the treatment of MDR-TB under particular conditions. The first, bedaquiline, was approved by the US Food and Drug Administration (FDA) in December 2012, for the combination therapy to treat adults with multi-drug resistant pulmonary TB. The second drug, delamanid, was formally approved for use MDR-TB in children patients by the European Medicines Agency in April 2014.[30] Their phase II studies in a series of new combination regimens treatment in bactericidal activity or two-month sputum- culture conversion efficiency were being tested and the result showed they have potential for treatment of drug-susceptible and drug-resistant TB.[37]

Drugs for Treatment of HIV-positive Tuberculosis Patients (Co-epidemics of TB with HIV)

Tuberculosis and HIV co-infection implies when people have both HIV infection with either latent or active TB disease. Several studies show that TB co-infection increases the risk of HIV progression and death, particularly in persons with untreated HIV disease.[38] HIV-infected individuals with latent TB are approximately 20-30 times more likely to develop TB disease than those who have no HIV infection, in the first 1-2 years after infection.[4] Globally in 2015 there were an estimated 10.4 million new cases of active TB incidence worldwide and 11% of the incident TB cases in 2015 are estimated to have been among people living with HIV. From this 0.4 million deaths result from TB disease among people living with HIV. While TB and HIV co- infection remains a major public health problem in many parts of the world.[5,38] The WHO guidelines recommend that a person having TB with HIV infection has to start HIV anti- retroviral therapy between 2 and 8 weeks after starting TB treatment for those individuals who have a CD4 count of less than 200mm.[39] Medication or treatment for the burden TB patient infected with HIV requires 6 months of therapy. The first 2 months (intensive phase) with 4 drugs--rifampin (or other rifamycin), INH, pyrazinamide, and ethambutol treatment are applied and followed by 4 months (continuation phase) rifampin and INH alone. In addition to that all HIV-infected patients with active TB should receive trimethoprim-sulfamethoxazole prophylaxis treatment.[40]

Opportunities and Challenges for TB Drug and Vaccine Discovery and Development

Tuberculosis is the most neglected but a very deadly disease next to HIV-AIDS and malaria; despite the fact that; governments or public private partnership support is not as such. On top of this; there are a lot of challenges for new drugs and vaccine development such as, lack of adequate finance for research development, complexity of the pathobiology of *M. tuberculosis*, lack of understanding about the mechanisms of mycobacterial metabolism, the

length of the treatment and clinical development of tuberculosis drugs is not simple, lack of appropriate data and information on the epidemiology of the bacteria are some to mention.[21] But perhaps; there are some recent progress opportunities for the new drug and vaccine discovery like the willingness of the newly emerging economy countries the < BRICS>. Especially china has the capacity and the novel approach technology to develop new vaccine; on the other hand, the advancement of detection and diagnosis technologies like gene expert has shown a significant role on revealing of the sequence of a gene,[15] good progress of the traditional medicine and medical herbs for farmacology formulation practice, there are also countries that adopt and implement sound health policy specially that encourage conducting research development on vaccine and drug, advance technology for the production of broad-spectrum antimicrobials.[41]

Conculusion

Tuberculosis is a main leading, global health problem and cause of death due to a single infectious agent, *Mycobacterium tuberculosis*. According to WHO TB report in 2015, about 32% of the world population is infected with TB and from these around 10.4 million of the infected peoples are develop active TB (1.2 million among HIV positive) and near to 1.8 million of death occurred worldwide (1.4 million among HIV-negative people and 0.4 million among HIV positive people); 3.3% of these belongings resulted from MDR-TB and XDR-TB strains. So developing a novel safe and effective vaccine and drugs to prevent and treat all forms of TB, including drug-resistant strains, at all age groups, including those with HIV are critical components of a strategy to achieve the WHO goal in TB eradication by 90% by 2050. A major challenge to TB vaccine and drug development is the lack of diversity in both the antigens included in TB vaccines, and the immune responses induced by TB vaccine candidates; this challenge indicates conducting a further research on different approaches regarding to the selection of the best antigens, adjuvant use, antigen dose, and immunization strategy. Currently there are nearly 10 new or repurposed anti-TB drugs including recently approved anti-Tb drugs (bedaquiline and delamanid to treat MDR-Tb) and 15 new Tb vaccines are developed and undergoing different phases of clinical trials.

Since *Mycobacterium tuberculosisisis* manifested with strain changes throughtime due to horizontal gene transfer and improper drug and vaccine usage thereby the leads to resistance to currunt commercially available drugs and vaccines, new drug and vaccine shall be designed as per strain based further researches.

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