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RECENT TREATMENT ON TUBERCULOSIS: A SYSTEMIC REVIEW

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Abstract:
Tuberculosis (TB) is an infectious illness spread through the air that poses a global health issue. TB was the largest cause of death due to a single infectious agent worldwide until the introduction of COVID-19, which is caused by the SARS-Cov-2 virus. It's caused by Mycobacterium, a bacterial genus with a diverse range of hosts, susceptibilities, and infection path physiology. The conflict is fought on the basis of genuine knowledge, with mankind armed with past experience and modern medicine to defeat this ancient foe in all of its forms. This collection of review articles is an honest attempt to raise TB awareness.

Key words: *Tuberculosis, Treatment, Review*

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INTRODUCTION:

Tuberculosis (TB) is an airborne infectious disease that threatens public health worldwide. Until the advent of COVID-19, which is caused by the SARS-Cov-2 virus, TB was the leading cause of death due to a single infectious agent worldwide, exceeding that due to HIV/AIDS [1]. It is caused by Mycobacterium, a bacterial genus with a wide spectrum of hosts, and differing host susceptibility and infection path physiology [2]. To differentiate TB in humans and animals, "human tuberculosis" usually refers to Mycobacterium tuberculosis (MTB) infection, whereas "zoonotic tuberculosis" refers to infections in human and animals mainly caused by a closely related species, Mycobacterium bovis [3]. Together these and other TB species comprise Mycobacterium tuberculosis complex (MTBC). Most patients with TB (approximately 90%) are adults, and fewer cases occur in women than men. The World Health Organization (WHO) has estimated that 10 million people (range: 8.9–11.0 million) developed TB in 2019, of which 140,000 had new cases of zoonotic TB (range: 69,800–235,000). Although the disease has slightly declined in recent years, in 2019 alone, approximately 1.2 million people died from TB, and approximately 500,000 people developed rifampicin-resistant TB [4].

Trends in Global TB

Human TB control and prevention the history of human infection with TB dates to 3 million years ago. MTB can cause disease in almost any part of the body, but it primarily invades the respiratory tract. Most patients with TB are diagnosed with active pulmonary TB. MTB has infected approximately one-third of the population worldwide. Human TB continues to be among the top ten causes of mortality globally, and it is the leading cause of death due to a single infectious agent [5].

After decades-long neglect in mitigating this disease, renewed global efforts to control TB began in 1991, when the WHO declared TB a major global public health problem, which was subsequently declared a global emergency in 1993. Recommendations were released in 1994 for TB control based on directly observed therapy strategy (DOTS) with a short-course regimen [6]. In response to the 2000 United Nations (UN) Millennium Development Goals, with targets to be reached by 2015, the WHO and the global advocacy organization Stop TB Partnership launched historic firsts with the Global Plan to Stop TB 2001–2005 in 2001 and the Stop TB Strategy 2006–2015 in 2006. Importantly, the latter focused on patient-centered care for all TB-infected individuals, rather than on directly observed therapy with a short-course strategy [7].

To better address the global TB epidemic in the post–Millennium Development Goal era, the UN began developing Sustainable Development Goals (SDGs) in 2012. These goals include a target of a TB-free world. The World Health Assembly, in 2014, formulated the End TB Strategy, which was launched by the WHO in 2015. The WHO and the Stop TB Partnership also published the Global Plan to End TB 2016–2020: The Paradigm Shift and the UN subsequently released the SDGs in 2015, which became official on January 1, 2016. In 2018 the UN held a high-level meeting to address TB and garner strong political support for strengthening TB control measures in the coming years, as well as to define targets and responsibilities to facilitate the End TB Strategy. Accordingly, in 2019, the WHO and the Stop TB Partnership published an updated version of their global plan, the Global Plan to End TB.

Human TB is a global public health emergency. Globally in 2020, approximately 9.9 million people were estimated to have contracted TB, which is equivalent to 127 cases per 100,000 people (detailed information in Fig 1). The epidemic slightly decreased after 2019, and a slow downward trend has continued since 2000. Worldwide, an estimated additional 100,000 deaths occurred among HIV-negative people in 2020, compared with 1.2 million deaths in 2019, and an additional 214,000 deaths occurred among HIV-positive people, representing a small increase from 209,000 in 2019. The global decrease in the absolute number of TB deaths until 2019 was followed by an increase in 2020 in four of the six WHO regions and most of the 30 high-TB-burden countries, because of the COVID-19 pandemic. Risk factors are critical at the population level, including poor working and living conditions, which increase the risk of TB transmission, as well as factors that impair immunity to TB infection and disease (e.g., malnutrition, HIV infection, diabetes, alcohol abuse, smoking, and indoor air pollution). However, TB continues to be overshadowed by diseases such as HIV, malaria, and now COVID-19 [8].

Advances in human TB treatment

Innovation is crucial for TB control and prevention. The vaccine currently in use was developed in the 1930s, the basic treatment for TB was developed in the 1960s, and the last new anti-TB drug was introduced in many countries approximately three decades ago. The global TB situation is critical, but now is also a time of great promise and discovery for TO BE treatment and prevention. Many substantial changes are on the horizon. For example, the efficacy of M72/AS01E, an adjuvanted protein subunit vaccine, has been demonstrated by clinical trials to prevent the development of active TB in latent TB infection, thus bringing some hope for ameliorating this disease [9].

Furthermore, dramatic changes in the treatment landscape for TB occurred with the introduction of three new drugs and drug regimens over the past decade. For instance, the Nix-TB clinical trial has indicated that an all-oral regimen of bedaquiline, pretomanid, and linezolid (BPaL) has favorable outcomes at 6 months post-treatment, thus suggesting that, if safety management is adequate, the BPaL regimen is a feasible option for patients with highly drug-resistant forms of TB. The BPaL regimen has also been recommend by the WHO for the treatment of multidrug-resistant TB with additional fluoroquinolone resistance, thus providing hope for patients with drug-resistant TB[10].

Finally, system innovations such as digital health technologies are influencing the entire TB patient journey . Digital health and other innovations, if deployed at scale, could help end human TB in the SDG era[11].

Zoonotic TB control and prevention

Several MTBC organisms, which are present in both animals and the natural environment, can cause zoonotic TB, including M. bovis, M. caprae, M. microti, M. pinnipedii, and M. orygis. However, M. bovis is the main causal agent of zoonotic TB in humans. In general, cattle are considered the natural hosts of M. bovis; however, zoonotic TB due to M. bovis and other MTBC pathogens has been reported

in other species of domesticated animals and wildlife, and remains a major zoonosis. The most common pathways of transmission to humans are inhalation, consumption of unpasteurized milk, and close contact with infected animals or untreated animal products. For example, in recent years, M. bovis has been confirmed in pastoralists in Nigeria . Reverse zoonoses due to M. tuberculosis, which is transmitted from humans to goats, pigs, and cattle, have also been reported in Nigeria , owing to close human and animal contact in most pastures, factories and communities in the country[12].

After the WHO recognized the implications of zoonotic TB to public health in 1950, TB in animals has been controlled and nearly eliminated in several developed countries but in only very few low- and middle-income countries , where zoonotic TB has substantial economic effects and can simultaneously affect the health of humans, livestock, and ecosystems. This threat of zoonotic TB spurred development of a resolution in 1983 by the World Organization for Animal Health, or OIE (formerly the Office International des Epizooties), calling for eradication of M. bovis for both public health and economic reasons [13].

In the past decade, zoonotic TB has attracted new attention from international health authorities, such as the WHO, the Food and Agriculture Organization (FAO), and OIE. The WHO and Stop TB Partnership's Global Plan to End TB 2016–2020: The Paradigm Shift first included communities and people at risk of contracting zoonotic TB as a key population. In October 2017, the WHO, FAO, and OIE developed the first roadmap for efforts against zoonotic TB under the One Health (i.e., animal, human, and environmental health) umbrella, which was launched at the 48th Union World Conference on Lung Health that year [14].

A recent study has noted that zoonotic TB is reemerging as an infectious disease in high-income countries and as a neglected disease in low- and middle-income countries. Furthermore, because the burden of M. bovis–associated zoonotic TB is unknown, it is likely to be underestimated. The prevalence estimates of zoonotic TB are also inaccurate, because current laboratory tests cannot distinguish the species of MTBC infecting humans or animals. The WHO has estimated the zoonotic TB burden according to scientific studies since 2016 [49] and has proposed strengthening the surveillance of zoonotic TB to more accurately determine the disease burden. Of the 10 million people in 2019 with new cases of active TB, 140,000 (range: 69,800–235,000) have been estimated to have zoonotic TB (1.4%), and approximately 11,400 (range: 4,470–21,600) ultimately died (8.1%). For zoonotic TB in cattle, studies have reported a prevalence of confirmed M. bovis zoonotic TB ranging from 0% to 28%; however, some of the culture methods and the array of molecular methods currently used in laboratories are inappropriate for the diagnosis of zoonotic TB [15].

Concerns regarding zoonotic TB, as reported for decades, still remain valid . Post-mortem examination and the single intradermal comparative cervical tuberculin test are the major diagnostic tools for bovine TB . However, these tests have biosafety issues, are time-intensive, and lack both political commitment and high-quality surveillance data. Together, these hurdles have contributed to an increase in TB incidence worldwide. To address this challenge, efforts are underway to adapt human TB diagnostics to detect potentially zoonotic TB organisms in cattle . However, because M. bovis cannot be eradicated from livestock while continued transmission occurs between domestic animals and wildlife, controlling M. bovis infection with detect and cull policies remains the backbone of zoonotic TB risk reduction. Animal vaccination is also proving beneficial in certain circumstances. Accordingly, oral bacillus ChalmetteGuerin vaccine should be administered to animals at large scale as a complement to traditional control measures to induce protection against TB and decrease host reservoirs. An even more troubling prospect involves animal carriers of drug-resistant MTB contributing to reverse zoonotic at the human-animal interface. Despite these concerns, the zoonotic TB in humans, compared with other diseases, might have received a disproportionately low allocation of scientific attention and resources in recent years [16].

Effects of the COVID-19 pandemic

The pandemic has created unprecedented global socioeconomic disruption. Its influence on TB control is likely to extend worldwide, particularly in terms of case detection and short-term TB mortality : the number of TB cases is projected to increase by 6.3 million in the next 5 years, together with a 20% increase in deaths from TB in the same period [17], thus delaying achievement of the WHO End TB target.

Before COVID-19, a large decline had been observed globally in the number of new human TB diagnoses and reports, from 7.1 million in 2019 to 5.8 million in 2020. The numbers returned to 2012 levels after an 18% decline, far below the approximately 10 million TB cases in 2020. In China, for example, a marked decrease in case notifications was associated with COVID-19 interventions: in the 11 weeks during and immediately after the COVID-19 lockdown, the case notification rate was 20% lower than that in the corresponding period in 2019. Similar findings have been reported in other countries. Empirical evidence regarding the long-term effects of the pandemic on TB outcomes has been limited to date, and further study is required [18].

Tuberculosis treatment

Nowadays, TB treatment is long, possesses important side-effects and people often interrupt it. The first line treatment is based on six drugs: isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol and thiacetazone (Table 1), which are available in cheap generic forms and are effective if taken as prescribed. These drugs complement each other and are used in various combinations, which is very important to prevent the emergence of multiple drug-resistant organisms, which can lead to ineffective treatment. Unfortunately, these drugs have some disadvantages such as important sideeffects and weak sterility problems and must be administered for 6–9 months. When standard treatments fail, second-line TB drugs (Table 2) are used, but these drugs have a far lower efficacy and require even longer administration periods (18–24 months) with higher cost (US$2500–3000), higher rates of adverse effects and low cure rates (around 60%) [19].

Table 1: Recommended doses of essential anti-tuberculosis drugs

Drugs	Year of introduction	Mode of action	Recommended dosage (mg/kg)			
			Daily	Range	Three times per week	Range
Isoniazid	1951	Bactericidal	5	4–6	10	8–12
Rifampin	1970	Bactericidal	10	8–12	10	8–12
Pyrazinamide	1954	Bactericidal	25	20–30	35	30–40
Ethambutol	1970	Bacteriostatic	15	15–20	30	25–35
Streptomycin	1944	Bacteriostatic	15	-----	30	25–35
Thioacetazone	1962	Bacteriostatic	2.5	Not applicable		

Table 2: Second-line anti-tuberculosis drugs

Drug	Mode of action	Recommended daily dosage(mg/kg)		
		Average (mg/kg)	Minimum (mg)	Maximum (mg)
Amikacin (A)	Bactericidal	15	750	1000
Capreomycin (Cm)	Bactericidal	15	750	1000
Ciprofloxacin (Cx)	Bactericidal	10–20	1000	1500
Cycloserine (Cs)	Bacteriostatic	10–20	500	750
Ethionamide (Et)	Bactericidal	10–20	500	750
Kanamycin (Km)	Bactericidal	15	750	1000
Ofloxacin (O)	Bactericidal	7.5–15	600	800
p-Aminosalicylic acid (PAS)	Bacteriostatic	150	8 g	12 g
Protionamide (Pt)	Bactericidal	10–20	500	750

Another important strategy in TB treatment is the directly observed treatment short-course (DOTS), which is considered to be the most cost-effective of all the health interventions. This strategy started in the 1990s, and at that time TB management was disorganized and ineffective. According to WHO, DOTS is based on five key principles: government commitment to sustained TB control activities; case detection by sputum smear microscopy among symptomatic patients self-reporting to health services; standardized treatment regimen of 6–8 months for at least all sputum smear-positive cases, with DOTS for at least the initial 2 months; a regular, uninterrupted supply of all essential anti-TB drugs; and a standardized recording and reporting system that allows assessment of treatment results for each patient and of the overall TB control programme. This strategy, now covering 180 countries, is accessible by over 70% of the world population, and DOTS has shown excellent results in countries using the strategy on a large scale. For example, DOTS has prevented 30 000 deaths a year in China; in the case of Peru the TB incidence has decreased by 6% each year over the past decade and DOTS is responsible for the decrease of TB drug resistance in New York [19].

New drugs against tuberculosis

To overcome the problems with available treatments, new drugs to treat TB are urgently required, specifically more potent therapies, with fewer side effects, to be used in shorter treatment regimens and to be employed to treat MDR TB and latent disease. To date, however, the improvement in TB drug development has been obstructed by two major factors: the opinion that there was little need for new agents and the high cost of development associated with the prediction of insufficient return on investment. In this context, different new initiatives have been created to obtain promising drug candidates (Table 3) . For example, in the discovery research field there are different class of compound that are under study, such as, ethambutol analogues, deazapteridines, imidazo(4,5-c)pyridines, fulleropyrrolidines, thiolactomycin and analogues, 9-benzylpurines, benzoxazines, mefloquine and analogues, diterpenoids, tryptanthrin and analogues, clofazimine and other phenazines, 1,2,4 triazoles, isoniazid analogues, toluidine derivatives, saccharides, quinolones and miconazole analogues, as well as the natural product calanolide . In 2005 other classes of compounds were identified against TB, such as trisubstituted and nucleoside pyrimidines, bis-glycosylated diamino alcohols, triketones , lamivudine prodrugs, phenanthrenes , aryloxyphenyl cyclopropyl methanones, ferrocenyl diamines , 5-deoxy-5-phospho-Dribonohydroxamic acid, halogenobenzimidazoles and 1-benzoyl-isothiosemicarbazide . An important study published in 2005 in the field of drug discovery was that of Protopopova and co-workers in collaboration with Clif Barry (NIH/NIAID). The group built a library of 63238 compounds based on the pharmacophore of ethambutol, 1,2-ethylenediamine. These compounds were evaluated against Mycobacterium tuberculosis and demonstrated in-vitro activity equal to or greater (up to 14-fold) than ethambutol. The compound named SQ-109 (Fig. 1) was selected for further development due to its potent activity (minimum inhibitory concentration 0.7– 1.56 mM, an SI of 16.7 and 99% inhibition activity against intracellular bacteria). Additionally, it demonstrated potency in vivo and limited toxicity in vitro and in vivo.

Table 3: Important compounds in clinical study

Compound	Class of compound	Developer	Clinical phase
Rifalazil	Rifamycin	Kaneka Corporation	Phase II, aborted
Rifametane	Rifamycin	Societa Prodotti Antibiotici	Phase I
Moxifloxacin	Fluoroquinolone	Bayer	Phase II
Sitafloxacin	Fluoroquinolone	Daiichi Pharmaceutical	Phase III
Gemifloxacin	Fluoroquinolone	LG Chem, SmithKline Beecham	Phase III
Linezolid	Oxazolidinone	Pharmacia Corporation, Peapack, NJ	Phase I
PA-824	Nitroimidazol	PathoGenesis Inc	Phase I
R-207910	Quinoline	Johnson and Johnson	Phase I

It is also important to mention that after almost a gap of 35 years, in which no new TB drug was introduced on the market, the rifampicin analogue rifapentine (Fig. 2) was obtained. This semisynthetic drug was developed by Hoechst Marion Roussel under the trade name Priftin. Approved by the US Food and Drug Administration in 1998, this drug in comparison with rifampicin possesses higher lipophilicity with an elimination half-life almost fourfold greater [20].

Inhaled therapy

Inhaled therapy is an important treatment route under study for delivering antitubercular drugs directly to the lungs [21].The advantages of this route are fewer sideeffects, reduced risk of systemic toxicity, improved patient compliance, and targeting to alveolar macrophages, which are used by the mycobacteria as a safe site for their prolonged survival. There are different modes of respiratory drug delivery, such as aerosolization of the drugs as fine powders, liquid aerosolization or nebulization, which consists of the solubilization or a suspension of the drug in an aqueous medium using a device called a nebulizer. The drug can also be transported to the lungs directly without prior aerosolization, using an instrument called an insufflator.

Inhaled nitric oxide

Long and co-workers [22] demonstrated in a series of invitro experiments that nitric oxide is a promising defence against M. tuberculosis. These experiments showed that exogenous nitric oxide exerts a potent dose and time dependent killing action against M. tuberculosis. Due to these results, Long and co-workers evaluated the clinical application of exogenous nitric oxide, which was administrated in 18 patients (over 18 years old) at 80 ppm for 72 h with the standard anti-TB drugs. At this concentration, nitric oxide was safely delivered to patients with pulmonary tuberculosis without adverse effects, but does not accelerate airway disinfection.

Solid lipid particles

A nanoparticle is defined as a microscopic particle, sized from 10 to 1000 nm. This field is currently an area of intense scientific research, due to a wide range of potential applications such as, biomedical, optical, and electronic. Solid lipid nanoparticles are a new strategy in nanotechnology. They are defined as nanocrystalline suspensions in water, which are prepared from lipids. This nanotechnology associates the advantages of other colloidal carriers such as emulsions, liposomes, microparticles and nanoparticles without their disadvantages. The advantages of nanotechnology include good tolerability, better bioavailability, stability, low toxicity, scaling-up feasibility and the ability to incorporate hydrophobic as well as hydrophilic drugs. Due to all these advantages, Kuller and Pandy[23]evaluated in vivo the chemotherapeutic potential of solid lipid particles enclosing rifampicin, isoniazid and pyrazinamide against M. tuberculosis. The experiments were based on a single nebulization toinfect guinea pig, and have resulted in no tubercle bacilli in the lungs/spleen after seven doses of treatment with no biochemical hepatotoxicity. In comparison, with the orally administrated drugs, 46 daily doses were required to obtain an equivalent therapeutic benefit, which demonstrates the promising potential of this nanomethodology to improve the bioavailability and reduce the dosage frequency.

Tuberculosis vaccine feasibility

The existence of natural human defences against tuberculosis suggests that it should be possible to discover and develop a preventive vaccine. Approximately 85–95% of people infected with M tuberculosis can control the infection, never developing any manifestation of tuberculosis disease. Observational studies have shown that harbouring latent M tuberculosis infection provides some protection against tuberculosis disease developing from new exposure to the pathogen. Additionally, some individuals never acquire M tuberculosis infection despite long-term exposure to people with active pulmonary tuberculosis, such as household contacts and health-care workers, raising the possibility of intrinsic resistance. Moreover, the possibility that some become infected with M tuberculosis but then naturally clear their infection has been raised by documented accounts of individuals who convert their tuberculin skin tests or interferon-γ release assays (IGRAs), but later revert to negative, although these reports should be interpreted with caution. The reality of the ongoing tuberculosis epidemic, however, illustrates that many people are incapable of independently generating sufficient immune control of M tuberculosis infection, underlining the importance of developing a vaccine[24].

The BCG vaccine, first used in 1921, is an attenuated form of Mycobacterium bovis, the primary cause of bovine tuberculosis, and is currently the only tuberculosis vaccine that is licensed for use globally. BCG is the most widely used vaccine in history, with more than 4 billion doses administered since that first vaccination. BCG is routinely given to infants within days of birth, or when they first interact with health services, in most countries[25].

Multiple studies have shown that vaccination of infants with BCG is effective at preventing severe forms of tuberculosis in children. BCG has been shown to protect infants and young children, up to approximately 10 years of age, from developing pulmonary and extrapulmonary tuberculosis, although the degree and duration of protection has been variable, with increased protection in areas farther from the equator.Some observations also indicate that BCG seems to induce better protection in those who are not tuberculosis skin test positive[26].

Some degree of protection against active tuberculosis might last for up to 20 years following school-aged BCG vaccination and as long as 50–60 years following infant vaccination. Studies of BCG revaccination of adolescents have not consistently shown a protective effect against tuberculosis disease. Although a 2018, completed, placebo-controlled study of BCG revaccination in South African adolescents showed a significant degree of protection against sustained, de novo M tuberculosis infection as defined by an IGRA conversion of 6 or more month's duration relative to the placebo arm, the clinical significance of these results will require further study[27].

The clinical pipeline of tuberculosis vaccine

The tuberculosis vaccine candidates currently in clinical trials (figure) can be grouped into two general categories: mycobacterial whole cell-derived vaccines (table 1) and subunit vaccines, directed against a limited number of selected antigens (table 2).

Mycobacterial whole cell-derived vaccines

Whole cell vaccines are derived from M tuberculosis, BCG, or closely related strains of non-tuberculous mycobacteria. This class of vaccines can be further broken down into live vaccines that have been attenuated through genetic modification (VPM 1002, MTBVAC), or vaccines derived from killed or fractionated whole mycobacteria (Mycobacterium vaccae [Vaccae], Mycobacterium indicus pranii [MIP], DAR-901, RUTI31; table 1). Using a whole cell-derived vaccine represents an attractive vaccine strategy for several reasons. Chief among them is the proven efficacy of BCG, a live, attenuated whole cell vaccine that provides a solid proof-of-concept. Additionally, whole cell-derived vaccines comprise many different antigenic components and offer the possibility of stimulating a more diverse immune response than subunit vaccines due to the presence of non-protein antigens such as lipids and glycolipids prevalent in the outer layers of M tuberculosis, microbial metabolites, and phosphoantigens [28].

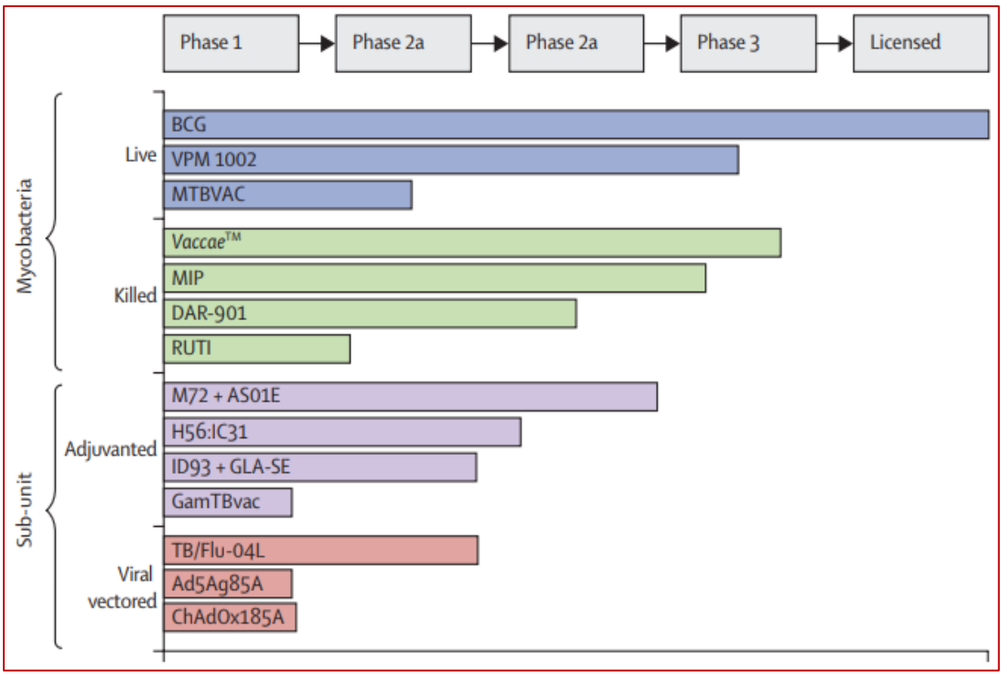

Figure 3: Tuberculosis vaccine candidates in clinical development

The indicated clinical development stages of vaccine candidates are based on an extrapolation from data in ClinicalTrials.gov.

Subunit vaccines

Subunit vaccines can be further subcategorised into adjuvanted protein subunit vaccines and recombinant viral vectored vaccines. By contrast with whole cell vaccines, subunit vaccines target a small number of selected antigens, usually six or less. Accordingly, a major challenge to developing protein subunit vaccines is the need to identify the optimal antigens to include in such vaccines. Intense efforts have been underway to identify the key antigens, expressed from approximately 4000 genes associated with M tuberculosis, that could elicit a protective immune response against the organism. Some researchers have specifically selected antigens for inclusion in vaccine candidates according to their expression profile at various stages of mycobacterial infection, on the basis of metabolic activity and protein expression thought to affect vulnerability to the immune system[29].

The antigens included in current vaccines in clinical trials have all been tested for their ability to induce some form of protective immunity against tuberculosis in an animal model of tuberculosis vaccination. However, most of these antigens have been selected for their capacity to induce the release of the Th1 cytokines interferon-γ and tumour necrosis factor. This choice is informed by the clinical observation that individuals with innate or acquired immunodeficiency in these immune pathways are highly susceptible to tuberculosis.Whether these characteristics will result in the generation of protective immunity, however, is uncertain. A component of the advancement of these purified protein antigens to clinical trials involves evidence of their ability to elicit classical T-cell responses. Non-classic T cells are intriguing in that they use host molecules that do not vary between individuals, such as CD1, MR1, and HLA-E. The ligands for these molecules are lipid, glycolipid, vitamin metabolite, and peptide and glycopeptide antigens.The T-cell receptors from the nonclassic T cells can recognise these ligands presented in the context of the non-classic molecules. How these nonclassic T cells might best be used as vaccines remains to be determined. Vaccine strategies targeting the non-classic responses could possibly enhance the development of more traditional T-cell or B-cell responses. Additionally, cells using the γδ T-cell receptor can recognise glycolipidantigens and phosphoantigens. Tuberculosis vaccination strategies predicated on the generation of antibodies remain relatively unexplored but represent a valid area for further investigation[30].

Adjuvanted protein subunit vaccines

Four adjuvanted protein subunit vaccines are in clinical trials: M72/AS01E,ID93+GLA-SE, H56/IC31 and GamTBvac (table 2 and appendix pp 1–4). Adjuvanted protein subunit vaccines consist of an antigenic protein, or a linked series of antigenic proteins, administered along with an adjuvant—an agent that is designed to potentiate immune system stimulation in such a way as to maximise the immunological impact of the antigens incorporated in the vaccine[31].

Table 4: Composition of whole mycobacterial cell-derived vaccines in clinical trials

Live attenuated	Parental mycobacterium	Modification or inactivation
VPM1002 (BCG ΔureC::hly)	Mycobacterium bovis BCG-Prague	Integration of listeriolysin encoding gene insert, urease gene deletion
MTBVAC	Mycobacterium tuberculosis	Transcription factor phoP and fadD26 (phthiocerol dimycocerosate synthesis) gene deletions
Killed or extract		
Vaccae	Mycobacterium vaccae	Heat-killed
MIP	Mycobacterium indicus pranii (formerly: Mycobacterium w)	Heat-killed
DAR-901	Mycobacterium obuense	Heat-killed
RUTI	M tuberculosis	Cell wall fragments of M tuberculosis grown under stress conditions, in liposome suspension

CONCLUSION:

It's been more than 100 years since the discovery of tubercle bacilli and the words of Robert Koch are still true, “amidst the persistently great variety in the ways and means of combating tuberculosis, it is yet necessary to ask what measures do indeed best satisfy the scientific requirements”. Tuberculosis continues to challenge physicians, pathologists and microbiologists in every possible way and dilemma persists till today in early diagnosis and treatment of every form of it.

WHO END TB strategy wishes to achieve 95% reduction in absolute number of tuberculosis deaths by 2035 which needs thorough understanding of tuberculosis and systemic filling of gaps in TB detection and treatment. The war is set on a platform of real knowledge; mankind equipped with experience of past and armed with present medicine to win against this ancient foe in its all forms. This review articles is a sincere effort towards increasing awareness about TB.

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