

The History of Tuberculosis and Bacillus Calmette–Guérin Vaccine in Iran

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Context: Tuberculosis (TB) disease caused by *Mycobacterium tuberculosis* (Mtb) remains as one of the leading infectious causes of death and disease throughout the world. The history of tuberculosis as a worldwide fatal illness traces back to antiquity, being a well-known disease in ancient civilizations.

Evidence Acquisition: Presented here, is a brief review of the history of tuberculosis and Bacillus Calmette–Guérin (BCG) vaccine development in the world as well as its historical background in Iran, mainly during the 19th and 20th centuries using a wide range of published information sources until the last months of 2013.

Results: TB causative agent remained unidentified until the last decade of the 19th century, when Robert Koch discovered it. At present, preparation of the BCG vaccine, application of the Mantoux intradermal diagnostic tuberculosis test and administration of proper antituberculosis medications have eventually controlled tuberculosis.

Conclusions: However, despite these significant advancements, tuberculosis remains a major concern, particularly in developing countries including Iran after the emergence of both multidrug-resistant tuberculosis and HIV co-infection.

Keywords: Tuberculosis; BCG Vaccine; Iran

1. Context

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (Mtb). Currently, tuberculosis is one of the greatest problems for public health, and worldwide is the most prevalent cause of death from infectious diseases, after HIV (1).

2. Evidence Acquisition

In this descriptive review, we searched a wide range of published information sources, consisting of local and national books related to tuberculosis and Bacillus Calmette–Guérin (BCG) vaccine; Iranian and foreign databases and the ministry of health database (Center for Disease Control and Prevention, and Vaccine Preventable Diseases Office), during the last months of 2013. We used the last version and the most complete sources, in order to retrieve the history of tuberculosis and development of the only effective vaccine against this disease, the BCG vaccine.

3. Results

Six to eight million people are infected with TB, annually, worldwide (2). A point of great concern is that over 80% of all cases are from developing countries (1). Tuberculosis is a complicated disease with multiple infectious sites and a wide range of clinical disease manifestations (3). Most infected individuals are malnourished, have

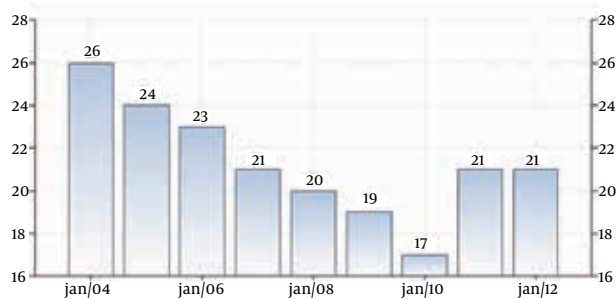
underlying diseases or are from lower socioeconomic classes (2). Approximately 70% of Mtb-exposed individuals will clear the bacteria, while the remaining 30% will get infected. In about 90% of those infected, Mtb either gets controlled by the immune response or remains viable but physiologically inactive or dormant in the host. People infected with dormant Mtb are diagnosed as having latent TB or non-clinical TB infection (LTBI). It is thought that 5-10% of LTBI cases progresses to active disease (3). In Iran, during the Islamic period, Iranian physicians were aware of TB. Ali ibn Sahl-e Rabbān Tabari, in his book, "Firdous al-Hekmah" (paradise of wisdom) described TB of both the skin (lupus vulgaris) and the lymph nodes (4). Razi, reported in "Al-Hawi" that a patient's medical history who had bloody sputum was most probably due to pulmonary TB (5). In addition, he described TB of the joints (6). In the "Canon of Medicine", Avicenna devoted a chapter to TB. He said that pulmonary TB should be differentiated from asthma, because both disorders may result in cough and shortness of breath. Avicenna added that in advanced cases of pulmonary TB, a potential danger would be lung hemorrhage and may ultimately lead to death (7). Avicenna believed that TB has three stages including pre-inflammatory, ulcerative and cavernous (8). In another famous Persian medical text, "Zakhireh-ye Kharazmshahi" (Treasure of Kharazm Shah), Ismail Jorjani expressed TB as a contagious illness with prolonged fever (9).

Antimicrobial therapy with various regimens is used to treat TB. However, their inadequate and inappropriate use has triggered an increase in multi drug resistant (MDR-TB), extremely drug resistant (XDR-TB), and total drug-resistant (TDR-TB) cases worldwide, adding to the challenges of TB eradication and healthcare cost (10). In a research by Metanat and colleagues in Zahedan, south-eastern of Iran with an almost high TB incidence (compared with other regions of Iran), 12.2% of patients had MDR-TB (11). Although multidrug combinations treat TB successfully, the used multidrug regimens are ineffective against MDR-, XDR- and TDR-TB and have not prevented transmission of disease in endemic regions, due to high infectivity rate, the ability of the mycobacterium to enter latency with no clinical symptoms of disease and lack of rapid diagnostic tests to detect active TB infection. Thus, vaccination is an important measure for controlling tuberculosis and is recommended by the World Health Organization (WHO) for all countries. The BCG vaccine was developed by Albert Calmette and Camille Guérin and first administered to infants in 1921. It is now given annually to more than 120 million people worldwide, with 4 billion people vaccinated to date. The BCG vaccine protects against disseminated forms of the disease including miliary TB and TB meningitis, while meta-analyses from several clinical studies have shown that BCG has reduced the risk of disease development by 50% in infants and neonates (12-14). However, mass vaccination with BCG has also been implicated as a selective force in the emergence of new pathogenic *Mtb* genotypes (15). The vaccine has traditionally been given intradermally, while recent refinements involving 'needle-free' vaccine patches may offer prospects for increased vaccine coverage without compromising immunogenicity (16). There are different rates of BCG efficacy in different parts of the world from 0 to 80% (17). Factors responsible for the variable efficacy of BCG vaccine in adults, particularly in developing countries such as Iran, include; virulence of different *Mtb* strains, storage conditions and resultant viability, strain differences, loss of genes and the methodology of studies conducted in different regions (12, 14, 18). The BCG vaccine has different efficacies in endemic and non-endemic areas. Meta-analysis of 14 prospective and 12 case-control studies revealed that the protective efficacy of BCG against pulmonary disease varies significantly with geographical latitude (14). This vaccine also appears to generate CD4+ central memory T cells rather poorly, potentially compromising control of subsequent TB infection (19, 20). Another factor that may underlie BCG failure is the unusually high concentrations of IL-4 that have been found in patients from developing countries (21, 22). IL-4-producing Th2 cell responses may predominate in these patients due to exposure to non-tuberculous mycobacteria (NTM) and/or helminth infections. Resultant IL-4 production and regulatory T-cell development may negatively regulate generation of Th1 type cells that could potentially contain TB infection, thereby leading to

active disease and vaccine failure (12, 18, 21-23). In recent mouse studies, CD4+ regulatory T-cells induced by BCG appeared to down-regulate effector T cell activity in mice infected with a virulent W-Beijing TB genotype; a finding with implications for BCG vaccination against highly virulent circulating TB strains (24).

Iran is located in a critical region of the TB world. According to the Dutch contemporary historian, W. Floor, at the end of the Qajar period (1796-1925) TB was a widespread disease in Tehran and other cities; one of the major causes of death in the 1920s (25). Dr. Jacob Eduard Polak from Austria who was the first European medical teacher in Iran wrote: "pulmonary TB could not be regarded as an endemic disease of Iran but I have seen nine cases in nine years of my medical practice in Iran, mostly among white women who developed signs of disease, short period after delivery and died soon." Then, he added that TB was more prevalent in the Azarbaijan Province, in the north-east and along the Caspian Sea, in the north of Iran (26). During the last decade of the Qajar period, in 1921, the Pasteur Institute of Iran was established which in due course played a major role in TB control (27) and the first TB sanitarium, known as Shah Abad TB Patients' Hospital was established in 1937 (28). In due course in 1944, "the Society Against TB and for the Support of TB Patients" was established. The main objectives of this society were to combat TB, as well as to support TB patients and public preventive measures education (29). Later, 30 members of this society founded a TB medical center named Bou-Ali Hospital in Tehran, in 1945 (30). Since its beginning, BCG department of the Pasteur Institute of Iran has established an effective collaboration with BCG service, BCG laboratory and the reference laboratory of mycobacteria at Pasteur Institute of Paris and BCG vaccine production center of Statens Serum Institute in Copenhagen. Since 1974, after several investigations and international inspections, BCG department of Pasteur Institute of Iran has been recognized as a BCG vaccine producer in accordance with international rules and regulations (31). At that time, the prevalence of TB was evaluated in 120 cities and districts and 1071 villages by a team of experts of the Pasteur Institute of Iran in collaboration with WHO. Tuberculosis skin tests were performed on 845061 individuals, of which 4% were positive (31). In 1988, BCG vaccine was produced in the large scales, according to GMP rules in a new building (current BCG department) of the Production and Research Complex of Pasteur Institute, located outside of Tehran, at the Tehran-Karaj Highway, and distributed and administered across the country (27). However, in the mid-20th century, TB was still a common disease. Between 1992 and 1999, rate of TB at the national level decreased in Iran. In 1997, the TB incidence rate per 100000 individuals in Sistan and Baluchistan Province was the highest compared to the other parts of Iran (73.5) and the lowest rate at 33 per 100000 individuals belonged to the Semnan Province (32). In 2001, the majority of TB patients in Iran were more than 50 years old and the rate of TB was more

Figure 1. Incidence of Tuberculosis (Per 100000 People) in Iran From 2004 to 2012 According to the World Health Organization



Incidence of tuberculosis is the estimated number of new pulmonary, smear positive, and extra-pulmonary tuberculosis cases.

in women than men. In 2001, there were over 9000 new cases of TB in Iran, mostly identified in Sistan and Baluchistan Province in southeastern Iran, especially in the city of Zabol, and in Golestan Province in northern Iran, along the Caspian Sea (probably because of the immigration of people from Zabol to Golestan Province). In addition, the prevalence of TB in the eastern and western provinces as well as in Gilan Province along the Caspian Sea was more than the average rate of the country. In 2003, the least detected cases of TB were from Fars and Isfahan provinces. The notification rate of TB in the Afghan population was significantly higher than the Iranian population (33). In 2006, Rafiee et al. reported that the incidence and prevalence of TB were 20.88 and 38.15 per 100000 individuals, respectively, in northeast of Iran including 141 cases of extrapulmonary TB, with a significant predominance in women. The gap between incidence and prevalence in this study may be explained by cases of TB relapse, long-term treatment for extrapulmonary TB, treatment failure or withdrawal, and multidrug resistant TB (1). According to the "Administration of Tuberculosis and Leprosy Control" of the Ministry of Health and Medical Education in Iran, in 2010, a total of 10,485 old and new cases of TB were reported in Iran and of these cases, 326 patients (around 2.2%) were HIV positive (34). Thus, due to the low prevalence of HIV infection in Iran, routine HIV testing may not be required for newly detected pulmonary TB patients (35). Bordering on Afghanistan, Pakistan and Iraq, with severely disrupted health services due to war and newly established countries to the north of Iran, have led to high TB infection rate in our country. The incidence of tuberculosis from 2004 to 2012 is shown in Figure 1.

In 2014, a research by Nasiri et al., involving five different provinces of Iran, revealed that of 252 TB cases, 41 (16.3%) were resistant to at least one drug and 16 (6.3%) were MDR, underscoring the need for further enforcement of TB control strategies including BCG vaccination in the country (36). Genetic variety of BCG vaccine strains may change the resulting immunological response to it. Four common sub-strains that are currently in use are BCG-Pasteur (1173P2), BCG-Japan (Tokyo-172), BCG-Danish

(Copenhagen-1331) and BCG-Glaxo (1077) (35). Although in the majority of countries with high TB incidence, the vaccine is supplied by UNICEF/WHO and the Global Alliance for Vaccines and Immunization (GAVI); in Iran as one of those countries with high TB incidence, a local unknown BCG vaccine strain is being used (37). For vaccine production purposes, different passage conditions have been used in different laboratories between 1921 and 1961, which have led to the emergence of different BCG vaccine strains, with genetic variations, including deletions, duplications and point mutations (37, 38). These genetic events can affect the immunogenicity of BCG and therefore ineffective immune response against BCG vaccine. Hence, it is important to evaluate the genetic variations of sub-strains of BCG vaccine during various periods of time. For this purpose, control methods recommended by the European Pharmacopoeia (PhEur) (European Pharmacopoeia Commission, 2008) and World Health Organization (WHO) for confirming the identity of BCG vaccine are used; including microscopic examining the bacilli in stained smears (by Ziehl-Neelsen staining), demonstrating their acid-fast property and determining the characteristic appearance of colonies grown on solid medium. The recommended methods can confirm the presence of mycobacteria in the vaccine, yet are not able to differentiate BCG sub-strains and other members of the *Mtb* complex (39, 40). In order to differentiate BCG strains, applying nucleic acid techniques followed by phenotypic based methods, is essential. Various molecular methods such as *gyrB* PCR and multiplex PCR have been applied to differentiate sub-strains of BCG (41-43). Amongst the molecular approaches, multiplex PCR is considered reliable and much more applicable to discriminate BCG strains within and with other members of the tuberculosis complex. Some studies have shown that multiplex PCR can be used as a diagnostic approach and has significant advantages over existing methods, such as being rapid, simple and effective (42, 44). Also, multiplex PCR is used to detect mycobacterial infection, which occurs due to BCG vaccine introduction (45, 46). Thus, further studies are needed to investigate the molecular characteristics of current BCG strains being used in Iran, taking benefit from the multiplex PCR method in the hope of producing an efficacious TB vaccine.

4. Conclusions

Despite the fact that BCG vaccine development in our country dates back to the mid-19th century, the incidence and prevalence of TB has been higher in Iran in comparison with many European and American countries, even in the last five decades. Two countries with a high prevalence of TB on the east of Iran, and disrupted health services in Iraq on the west of Iran are the major causes of the continuation of this high prevalence rate during the recent years. Furthermore, the emergence of multidrug-resistant TB, TB-HIV co-infection and the genetic variety of BCG vaccine have made tuberculosis a challenging issue

for many developing countries including Iran, highlighting the necessity for global and formularized programs for TB control.

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Authors' Contributions

Fatemeh Fallah developed the study concept and design; both authors contributed to the acquisition of data, analysis and interpretation of data and statistical analysis; Hamed Abdolghafoorian prepared the manuscript and Fatemeh Fallah was the study supervisor and critical reviewer of the manuscript for important intellectual content.

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