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# *Mycobacterium tuberculosis*: A Pathogen that Refuses to be Tamed

**Priyanka Chauhan***

*Neurovirology Laboratory, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA*

***Corresponding Author:** Priyanka Chauhan, Neurovirology Laboratory, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA.

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*"In the future the fight against this terrible plague of mankind will deal no longer with an undetermined something, but with a tangible parasite, whose living conditions are for the most part known and can be investigated further" …Robert Koch, 1905.*

More than 2000 years ago in ancient Greece, Hippocrates described a common illness that he called "phthisis". This was the same disease that we today call tuberculosis (TB). At the dawn of the new millennium, we are still mute witnesses to the silent yet efficient march of this sagacious disease, its myriad manifestations and above all its unequalled vicious killing power. In 1993, WHO declared TB as a global health emergency. TB, in its myriad devastating forms, has continued to afflict the humanity even in 21st century and ranks as foremost killer. Even though, a decline in incidence rate was registered and an estimated 53 million lives were saved during 2000-2016, TB took 1.7 million lives out of which 0.4 million people were HIV-positive and an estimated 10.4 million people fell sick with the disease in 2016 [1]. Globally in 2016, there were an estimated 490 000 new cases of multi drug resistant (MDR)-TB and an additional 110 000 people with rifampicin-resistant TB [1]. In addition, approximately, 6.2% of people with MDR-TB accounted for extensively drug resistant TB (XDR)-TB [1]. With the identification of *Mycobacterium tuberculosis*, the causative agent of TB by a German physician Robert Heinrich Herman Koch on 24th March 1882, development of Bacillus Calmette-Guérin, BCG developed in 1906 by Albert Calmette and Camille Guérin, the only licensed vaccine against TB as well as anti-tubercular drugs of 20th century, there were some early promise. However, the TB pandemic is facing additional complications due to the emergence of MDR and XDR *M. tuberculosis* strains. The deadly synergy between *M. tuberculosis* and HIV has made the situation even more precarious. The impact of this cursed duet on human suffering has been enormous. WHO has initiated "End TB Strategy" with the aim to end TB epidemic by 2030 [2].

*M. tuberculosis* has developed a 'hit-and-stay' strategy based on the slow growth, long incubation time and delayed onset of disease. TB is a contagious disease, which is transmitted when aerosols expectorated from an active TB patient are inhaled by a new host in close contact and shelters itself in the lungs and various extra-pulmonary parts of the body [3]. Individuals who are infected with *M. tuberculosis* exhibit three possible outcomes. (i) ~5 - 10% of individuals develop clinically active TB due to overwhelming *M. tuberculosis* replication following infection. In such individuals, caseating lesions cause dissemination to extra-pulmonary sites and transmission to new host. (ii) Out of the remaining ~90% of the cases, in a very small percentage of individuals, the ensuing immune response is able to completely eradicate the pathogen. (iii) Neither the pathogen is eradicated nor the infection transform into disease but *M. tuberculosis* escapes into non-replicating state termed as Latent tuberculosis infection. When a close contact inhale the droplet nuclei carrying the bacteria, series of events pursue that encompasses coordinated host innate and adaptive immune responses to control bacillary multiplication. *M. tuberculosis* employs various survival strategies to exploit the cellular niche for its own advantage and is able to grow in a relatively unrestricted manner during this phase [3].

In the year 1998, the genome sequence of *M. tuberculosis* was published and this initiated global efforts to accelerate research in the specific areas of TB/HIV co-infection, expansion of DOTS, novel drugs, novel vaccines and diagnostics. In spite of constant efforts, the battle against TB has been won and lost several times and TB continues to haunt the humanity. Hence, to change the current trajectory of TB, an intensified research for novel preventive interventions along with diagnosis and therapy are required. There has been tremendous

progress to eradicate TB over the past decade and currently there are more than a dozen anti-TB drugs and TB vaccine candidates that have entered clinical trials, and many more are in the pre-clinical pipeline to be considered for testing in phase I clinical trials [4,5]. However, constant efforts in the direction of diagnostics, drugs and vaccines are required to tame this noxious pathogen.

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