

Guest Editorial

The Looming Menace of Drug Resistant Tuberculosis and the Quest for the Elusive Vaccine

The malady which took away the life of the protagonist in John Bunyan's book of 1680 "The life and death of Mr Badman" was consumption and it was described as "The captain of all these men of death". Tuberculosis (TB), which was a major killer in the mediaeval times, still remains a formidable disease to reckon with, causing substantial mortality in the economically less developed countries in the world.

In 2015, there were an estimated 10.4 million new TB cases worldwide and six countries, India, Indonesia, China, Nigeria, Pakistan, and South Africa, accounted for 60% of the new cases. [1] With this huge burden, the additional menace of drug resistant tuberculosis is threatening to derail the gains already achieved till now in the control of TB. Multidrug drug resistant (MDR) TB refers to resistance to at least isoniazid and rifampicin and a shift of therapy to second line of agents. Extensively drug resistant (XDR) TB is MDR-TB which is also resistant to the fluoroquinolones and second line injectables, thus signifying the failure of second line of treatment. Approximately 20% of isolates globally are estimated to be resistant to one or more major drugs and about 10% are isoniazid resistant.[2]

According to the WHO report[1], in 2015, there were an estimated 480,000 new cases of MDR-TB and an additional 100,000 with rifampicin resistant TB. India, China, and Russian Federation accounted for 45% of the combined total of 580,000. Sadly, only 20% of this total population with MDR-TB were enrolled for second line treatment regimen, the gap being highest for India. Our country with its population of 1311 million as of 2015, had an incidence rate of 217/100,000 population, and a mortality rate of 36/100,000 with total death due to TB being 480,000 in 2015. In India, with treatment coverage of 59%, only 46%

of the MDR-TB cases were started on second line treatment as of 2013. The Global Preserving Effective TB Treatment Study investigators have done a mathematical modelling study to estimate the future burden of MDR- and XDR-TB in India, the Philippines, Russia and South Africa, published recently in the May, 2017 issue of The Lancet Infectious Diseases.[3] Their model estimates that a third of tuberculosis cases in Russia (32.5%) would be multidrug resistant by 2040, as well as 12.4% of tuberculosis cases in India, 8.9% in the Philippines, and 5.7% in South Africa; and an increase to 8.9% for XDR-TB in India. In effect, by 2040, a third of tuberculosis cases in Russia are predicted to be drug resistant; compared with one in ten in India and the Philippines, and one in 20 in South Africa. The availability of the new drugs bedaquiline and delamanid will have little impact since resistance to both the drugs have already been reported.

Against this seemingly bleak scenario, an effective vaccine remains the only hope to contain the global menace of TB. The existing BCG vaccine is almost a century old, being introduced in 1921. A number of trials to test its efficacy have been conducted across the world. It is a well known fact that this vaccine is particularly valuable in preventing severe forms of TB in children. The efficacy in preventing tuberculous meningitis and military TB are 73% and 77% respectively [4], and this is the main reason for continuation with this vaccine. On the other hand, the usefulness of this vaccine in preventing pulmonary TB is a controversial issue, with variable efficacy ranging from 0% in South Indian trial to 84% in UK trials in 1950s and 60s.[5]

The same met-analysis has also found that BCG vaccination affords protection against pulmonary and extra-pulmonary TB for up to 10 years, and possibly 15 years. The efficacy

and duration of protection is greater in latitudes away from the equator.

The limited protection offered by the current vaccine and its reduced efficacy in those already infected with TB in the past has spurred the development of new vaccines for TB. A total of 19 candidate vaccines are in various phases of development and clinical trials, and these new vaccine candidates belong to one of the three categories; namely cell derived vaccine, viral vectored subunit vaccine, and adjuvanted protein subunit vaccines.^[6] Of these, two are in advanced clinical trials. The first one is *Mycobacterium vaccae*, a non tuberculous mycobacterium, which is in phase III clinical trial for safety and efficacy in tuberculin positive adults in China. It has already been licensed in China as an adjunct to therapy in patients with TB.^[7]

The other vaccine candidate in pipeline is VPM1002. This is a joint venture of Serum Institute of India and Vakzine Projekt Management (VPM, Germany). It is a recombinant BCG mutant expressing listerolysin O, and lacking the urease C gene. Listerolysin O facilitates the perforation of the phagosomal membrane leading to the exit of BCG antigen into the cytoplasm leading to efficient MHC-mediated CD8+ T cell priming. In addition, there is induction of apoptosis and autophagy which leads to cross-priming, resulting in further stimulation of CD4+ and CD8+ T-cell responses. Furthermore, VPM1002 has been shown to expand CD4+ central memory T cells, as well as both T helper 1 (TH1) and TH17 cells, at a more profound level than BCG.^[8] This vaccine is intended to replace BCG as a pre-exposure vaccine for infants and also to prevent recurrent TB in adults after successful completion of treatment for active TB. It is also intended to replace conventional BCG in the treatment of bladder carcinoma.^[6] After successful Phase Ia, Ib and Phase IIa trials in Germany and South Africa, the Phase IIb trial on newborns with or without exposure to HIV has just concluded in South Africa. In this year, from the month of June, the Phase III trial will commence in India and South Africa. Initially, successfully treated adult TB patients will be vaccinated, and later on newborns will be included in the trial. If

everything is on track, the first market entry for this vaccine is slated for 2018 or 2019.

With the emergence of drug resistant TB, vaccination remains the only viable alternative in our fight against TB. But we should not forget that TB still remains a disease driven by socio-economic factors, and any strategy to control this global disease must also address this important and disturbing issue. The scientific, social, and economic interventions should complement each other in the strategy to fight tuberculosis.

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