Repurposing anti-tuberculosis and anti-leprosy vaccine against COVID-19 disease: an Indian experience

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COVID-19 caused due to SARS-CoV2 infection is a rapidly spreading pandemic with about 32 million cases worldwide and accounting for 1 million deaths. The USA is currently top in the list, with about 1.2 million active cases accounting to about 291 deaths per million[1]. Surprisingly, India, with a population size 4.2 times larger and population density 12.8 times more than the USA, has just 65 COVID-19 related death per million. Even the number of active cases in India is approximately 26 times less as compared to the USA. Taking into consideration the fact that USA has performed approximately six times more tests compared to India; still, it is hard to explain remarkably less mortality in COVID-19-related death in India, despite having a higher population density, low health care budget and relatively underdeveloped health care system. The precise cause for less COVID-19 related mortality in India is a matter of separate study. We speculate a few contributing factors like the timely implementation of nationwide lockdown by Indian Government, strict compliance of social distancing, a predominantly large youth population (65% age <35 years) who are less susceptible and lastly, a possible advantageous immune modulatory role of BCG vaccine conferred to the community during birth as part of the National BCG vaccination programme; a combination effect that might have contributed to the risk mitigation.

Bacille Calmette-Guérin (BCG) is the vaccine of choice for Tuberculosis (TB). WHO recommends neonatal BCG vaccination in countries or settings with a high incidence TB. These six countries (USA, Spain, Italy, UK, Russia, France and Germany) top the list with the highest number of COVID-19 cases. We looked into the national BCG vaccination programme in these countries[2]. The USA, with one of the lowest TB incidences (3 per 100,000) has no BCG vaccination programme, has 291 COVID-19 deaths per million (total cases 1,303,544). Spain, with a TB incidence of 12 per 100,000, BCG vaccination started in 1965 but stopped in 1981, has reported 558 COVID deaths per million (total cases 256,855). Italy, with a TB incidence of 6 per 100,000, BCG recommendation is limited and only for specific groups, has 491 deaths per million (total cases 214,458). The Russian Federation with TB incidence 80 per 100,000 has an active BCG vaccination recommended for all at birth, has surprisingly just 11 deaths per million (total cases 177,160); France, with a TB incidence of 8 per 100,000, BCG vaccination started in 1950 but stopped in 2007, has 395 deaths per million (total cases 174,191); Germany with TB incidence of 8 per 100,000 has no current BCG vaccination programme (started in 1961, but ended in 1998) has 87 deaths per million (total cases 168,245). India (with a TB incidence of 217 per 100,000 and has a national BCG vaccination policy for all at birth) has a mere 3 death per million (total cases 53,045). Thus, it appears that nations with an ongoing/active BCG vaccination programme in place due to high TB burden seems to have a low COVID-19 related mortality. Further, Pakistan (5 deaths per million), Singapore (4 deaths per million), Japan (4 deaths per million), Qatar (4 deaths per million), Bangladesh (2 death per millions), Nigeria (1 death per million), all has an active national BCG vaccination programme in place, and also reported a low number of COVID-19 related death. We want to exercise caution that a combination of several different factors like socio-economic status, population-specific genetic backgrounds, accessibility to health care facility, etc. could potentially influence the mortality rates and hence could not be directly associated with BCG vaccinations alone; however, the above observation seems to indicate a pattern.

BCG vaccine was developed about 80 years ago from an attenuated strain of *Mycobacterium bovis.* Though the precise protective mechanism (if at all) is currently not known, except the fact that BCG can function as a non-specific immune modulator and can protect newborns against a broad range of infections and death from sepsis[3]. This involves imparting heterologous immunity by engaging B and T cells in an antigen-independent manner, in addition to priming the circulatory monocytes to rapidly respond to pathogens, enabling them to release protective cytokines like IL1β, TNF-α and IFN-γ. This is called 'trained immunity'[4]. However WHO has cautioned the use of BCG vaccine in the COVID-19 pandemic due to the absence of rigorous scientific evidence. Clinical trials are underway to study the efficacy of this vaccine as prophylaxis amongst health care workers in the Netherlands, Australia and elsewhere. With BCG production line in place, a repurposing of this agent against similar pathogenic diseases can be quickly undertaken. Further, the initial findings from a preliminary investigation conducted by a Mumbai (India) based research institute raised the hope of treating the COVID-19 patients using BCG vaccine. Amid search of therapeutics for COVID-19, the focus was also concentrated on another mycobacterium-based vaccine, namely *Mycobacterium indicus pranii* (MIP) (earlier named as *Mycobacterium w* which is an anti-leprosy vaccine developed and named in honour of Indian immunologist Gursaran Pran Talwar). Functionally, MIP is also an immunomodulator and substantial scientific evidence so far showed that it could evoke cell-mediated response against infection, thereby acting as immunotherapeutics. Acting through the toll-like receptors (TLRs) pathway, MIP enhances the host-T cell responses and cytokine response[5]. Using this vaccine under the National Leprosy Eradication Programme (NLEP), India has effectively reduced the prevalence of leprosy. Recently, in a hospital-based study conducted in Chandigarh (India), MIP was found safe as adjuvant therapy in COVID-19 patients[6]. Using an intradermal MIP (heat-killed Mw) for three consecutive days, in addition to the standard treatment, a significant clinical and radiological improvement was observed in four COVID-19 positive patients in addition to standard medical care. It is conceivable that MIP might not be a stand alone choice but to be used in combination with other treatment modalities (remdesivir, tocilizumab and other antibiotics). Recently, the Council of Scientific and Industrial Research (CSIR) in collaboration with Cadila Pharmaceuticals (Ahmedabad, India) is planning to develop MIP-based immune modulator called Sepsivac to enhance innate immunity and to expedite the recovery of the patients of COVID-19 (ref. 7). With the approval from the Drug Controller General of India, CSIR is now initiating a randomized, blinded, two arms, active comparator-controlled clinical trial to evaluate the efficacy of the drug in greater detail against COVID-19 (ref. 8). As of now, several other studies are also in progress in India to evaluate the effectiveness of MIP against SARS-CoV-2.

In the present ongoing debate focusing on exploration of the future use of BCG vaccine in COVID-19, no formal conclusion is made except making assumptions from the current observation. BCG vaccination might confer additional protection against nSARs-CoV2 in COVID-19 disease as there seems a logical correlation between nations having an active BCG vaccination programme and reduced COVID-19 related death. Rigorous clinical trials and mechanistic details need to be elucidated to find the beneficial role of BCG vaccination in COVID-19 infection. Even then, there could be a spectrum of response due to genetic variation within the population as well as in the BCG stains, prior exposure to TB, etc. The protective role of BCG could be a standalone or in combination with other medications. More research is needed to investigate this possibility.

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Prospective of Indian agriculture: highly vulnerable to huge unproductivity and unsustainability

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With merely 2.4% arable land resources and 4% water resources[1], Indian agriculture is feeding nearly 1.3 billion people, which implicates huge pressure on land and other natural resources for continuous productivity. Excessive use of chemical fertilizers and pesticides since the green revolution has increased crop productivity several folds, but the late phase of the green revolution has darker shades. Imbalanced and indiscriminate use of chemicals consequently resulted in detrimental impact on crop productivity and soil fertility[2,3]. Intensive cropping system involving injudicious use of fertilizers is the major culprit in deteriorating soil health and inducing secondary micronutrient deficiencies in the soil and nutrient immobilization in the soil and plants[4]. In such a scenario the soil microbial population is majorly impacted and we do not know how many microbial species have gone extinct or are in the endangered stage due to such agricultural practices[5]. In addition, such misuse of fertilizers is currently contaminating surface and underground water bodies through nitrate leaching[6], further causing serious health hazards to humans and animals. India achieved food security through the green revolution; however, we have gradually moved to an unsustainable agricultural system nationwide.

Balanced and judicious fertilizer application rates were used till mid 1960s; however, due to the green revolution inorganic fertilizer consumption increased tremendously and reached a maximum of 18.07 million tonnes (mt) of nutrients in 2000; from then on, the nation is facing a gradual decrease in growth and productivity. Similar amounts, viz. 16–18 mt of nutrients was incorporated in the soil year after year[7]. Most preferable cereal crops of India are wheat and rice, and it is evident from research that their cultivation mined huge quantity of nutrients from the soil. Recent studies showed that organic matter was depleted from nearly 3.7 M ha soil, and there was clear evidence for land degradation due to indiscriminate use of inorganic fertilizers and pesticide[8]. Intensive and continuous use of inorganic fertilizers is one major cause for depletion of soil organic matter (SOM) and consequently nutrient immobilization. Moreover, in India, in general, blanket fertilizer recommendations are followed for N, P and K which rarely match soil fertility needs. Secondary and micronutrients are also often ignored in different cropping systems. Many studies report that the use of inorganic fertilizers has a suppressive impact on SOM mineralization[9]. Soil carbon and nitrogen are indirectly linked biologically; quality and quantity of soil carbon improve soil microbial functions, abundance and diversity though impact of long-term fertilization on soil microorganism-mediated carbon mineralization is not studied extensively[10]. However, the crucial role of soil microbes on carbon mineralization cannot be denied. As most of the nutrients are immobilized in the soil and reduce soil nutrient release potential, Indian agriculture needs another revolution to attain maximum productivity without