

Review Article,

BCG Vaccination: A Beacon of Hope with a Word of Caution – An Overview on the Current Consensus in nCOVID-19

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Abstract:

The world is witnessing a great toll on human lives and economy due to the nCOVID-19 pandemic. The newly emerged strain (SARS-CoV-2) is spreading rampantly with no regional barriers. No proven vaccination or a proven drug exists to pulverize SARS-CoV-2. Few studies have linked BCG vaccination policy to the differences in nCOVID-19 morbidity and mortality in countries experiencing an avalanche as against those with moderate to mild disease. Apart from its prime discovery for combating TB infection, BCG vaccination holds a wide array of clinical utility because of its immunomodulatory potential. This serves as a ray of hope for extrapolating its use in nCOVID-19 for a greater and immediate response. However, at present, it is shrouded with a fear of overutilization without proven efficacy against this contagion and may further result in a shortage of vaccines for children who are covered under immunization policy. A number of clinical trials are underway to enlighten upon BCG and its effectivity parameters to combat this scenario. These outcomes will surely be more significant for countries not following universal vaccination policy. In the interim, containment strategy along with supportive care is the mainstay to battle the prevailing scenario with a positive outlook on the results of ongoing clinical trials.

Keywords: nCOVID-19; BCG; SARS-CoV-2; Tuberculosis; Immunomodulatory

Level of Evidence: Level I

Abbreviation: BCG: Bacillus Calmette Guerin;
BUD: Buruli Ulcer Disease; CFU: Colony
Forming Unit; nCOVID-19: Novel Coronavirus

Disease-19; NSE: Non-specific Effects; TB:
Tuberculosis; TUR: Transurethral Resection;
WHO: World Health Organization

Introduction:

nCOVID-19 cases are escalating from its outset and continue to cast a devastating impact on human lives and economy globally. The World Health Organization declared this rampantly spreading condition as a pandemic on 11th March 2020. The prevailing scenario has not only brought human lives to a standstill but has also questioned the cohesion of a multitude of disciplines across the globe. As per the WHO report dated 3rd May 2020, there are 34,62,682 confirmed cases with 2,44,911 deaths globally.¹ Geographical variation has been observed, in terms of incidence rates and mortality which can be adjudicated to varying cultural norms and standards of medical care. Presently, neither any vaccine nor any drug is particularly available to subjugate this contagion. Quarantine and social-distancing have been adapted as principles to deterrence.

In the interim, studies linked BCG vaccination policy with the reduction in morbidity and mortality due to nCOVID-19, and this has drawn the attention of researchers and scientists all around the world. Expert views in this connotation are emerging rapidly. However, mixed views are popularising without any proven effectivity. BCG vaccine was discovered primarily to combat tuberculosis. But with advancing time, it has been found to have non-specific beneficial effects against other infections.² A systematic review of epidemiological studies provided evidence for the non-specific beneficial effects of BCG vaccine on all-cause mortality.^{3,4} Induction of cytokines associated with '*trained immunity*' is proposed to underlie such protection against viral infections.⁵ The range of NSEs (non-specific effects) includes a reduction in the incidence of respiratory tract infections in children, antiviral effects and reduced viremia in experimental animals.⁶ For several viruses such as respiratory syncytial virus, yellow fever, herpes simplex virus and human papillomavirus, a favourable in vitro or in vivo effect has indeed been observed in various studies.⁶ In addition to this, a growing number of studies have shown that BCG vaccination offers protection against certain malignancies, allergy and asthma⁷ and non-mycobacterial infections.⁸

Considering this newer aspect, clinical trials are afoot to prove its efficacy in nCOVID-19. This

has created a ray of hope, but at the same time caution must be exercised during the clinical trials while extrapolating it to nCOVID-19. These adduced documentations surely call for undertaking clinical evaluation; but it is not substantial enough to direct BCG vaccination for nCOVID-19 utility immediately. If this occurs, it will result in a sudden shortage of BCG vaccine which is presently being utilised against TB and in turn will be worrisome due to an increase in other infectious conditions; further escalating the disease burden. This article aims to outline how the wide array of BCG utility can also be counted on for nCOVID-19 with respect to recently emerged substantiation, which in turn offers a ray of hope to confront the prevailing scenario. At the same time; it recommends to act responsibly and cautiously in this regard.

Materials and methods:

Between March 2020 and May 2020, a scoping review was done from PubMed, Google Scholar, Scopus, PubMed Central and Medline using the following search terms namely BCG & nCOVID-19, vaccination & nCOVID-19, BCG, Diabetes Mellitus, BCG & Bladder cancer and BCG & Antivirals. A total of 179 articles were found. Two independent reviewers collected the articles, and a total of 72 articles were finally chosen for the review. A framework was developed for the analysis of these articles and then the various diseases were classified based on the mode of action of BCG in them.

Results:

A scoping review showed a number of plausible uses of BCG in various systemic diseases and viral infections.

BCG Vaccine- Brief Account of Current Clinical Utility:

BCG Vaccine in Tuberculosis (TB):

BCG vaccine was discovered as a preventive strategy for TB infection. It was developed by Albert Calmette and Camille Guerin in France between 1908 and 1921 from a virulent M.bovis strain, with more than 230 serial passages in vitro.⁹ Humans have been infected with M. tuberculosis (M.tb) for millennia. TB infection is characterized by a complex immunologic response, which leads to a unique host-pathogen interaction, therefore making it difficult to treat

and control. Moreover, TB is a poverty related disease and has severe social implications.¹⁰ BCG vaccination is used as a preventive measure for disseminated and life-threatening Mycobacterium tuberculosis infection, and it is injected intradermally in new-born infants at birth in endemic regions of the world.¹¹ The BCG based vaccine can provide stimulation of both innate and acquired immunity.¹²

BCG is considered a 'self-adjuvanted' vaccine, as components of the formulation are capable of engaging multiple Pattern Recognition Receptors (PRRs), including TLR2 and TLR4 (Heldwein et al., 2003), TLR8 (Dowling et al., 2017), as well as the C-type lectin receptors, Dectin-1 and Mincle (Yadav and Schorey, 2006; Matsunaga and Moody, 2009; Schoenen et al., 2010) are thought to enhance vaccine induced immunity. A study by Marchant et al. demonstrated that BCG-induced protection against TB is, at least in part, attributed to Th1 response. BCG elicits a Th1 cell response in adults, and overcomes the Th2 immune bias present in infants, by inducing adult-like IFN- γ responses.¹³ Finally, besides the different sub-strains themselves, it is known that the effectiveness of BCG vaccine is also influenced by factors such as the age, history of pre-exposure to certain diseases and nutritional status of the patients.¹⁴⁻¹⁵

Till date, BCG remains the most widely used vaccine worldwide and has been administered to more than 4 billion individuals with astonishing safety records.¹⁶⁻¹⁷ Currently, intradermal injectable and intravesical BCG formulations are available.¹⁸

BCG vaccine in Leprosy:

In 1939, Fernandez was the first to demonstrate the induction of a positive Mitsuda reaction – a marker for improved cell-mediated immunity against leprosy – following vaccination with BCG.¹⁹ It was the first vaccine to be considered against leprosy following the report of Fernandez in 1939 on lepromin conversion among lepromin-negative healthy children following BCG administration.¹⁹

The protection afforded against leprosy by BCG vaccination is highest in younger individuals and

wanes over time.²⁰⁻²² Systematic meta-analyses indicate that BCG has a protective efficacy of around 50%, and that protection appears to be better against the multibacillary than the paucibacillary forms,^{23,24} although the degree of protection against leprosy has varied dramatically. The reason for the wide-ranging protection percentages reported across studies is unclear, but BCG vaccines have never been standardized and thus the use of different vaccine strains may be a contributing factor.^{25, 26}

BCG Vaccine in NTM (Non-tuberculous mycobacterium) Infection:

Pathogenic NTM can cause pulmonary infections, skin disease and lymphadenitis.²⁷ A recent systematic review of randomized controlled trials (RCTs) on the effectiveness of BCG against Buruli ulcer has revealed ~50% efficacy.²⁸

BCG Vaccine in Cancer Therapy:

- **For Urinary Bladder** – About 70–85 % of patients with bladder cancer are initially diagnosed with non-muscle invasive bladder cancer (NMIBC), wherein the standard and most successful treatment of NMIBC is transurethral resection (TUR) followed by intravesical instillation of BCG as an immunotherapeutic agent to reduce the risk of recurrence and progression into muscle-invasive bladder cancer (MIBC).²⁹⁻³³ The mechanism of action of BCG as an immunotherapeutic agent against bladder cancer involves both innate and adaptive immune responses,³⁴ even though the immunotherapeutic responses induced by BCG are usually not memory responses, which may explain the need of maintenance schedules for a better immunotherapeutic outcome. It has been shown that the predominance of Th1 cytokines (e.g. IFN- α , IFN- γ , IL-2, IL-12) is associated with beneficial BCG response and tumour destruction,^{35,36} while high levels of Th2 cytokines (e.g. IL-10) may be associated with treatment.
- **For Melanoma** – In 1970, Morton et al. injected 36 patients of melanoma with BCG intralesionally and reported complete lesion regression in 684 out of 754 lesions injected, with some patients showing

regression of non-injected lesions that are close to the injected lesions.^{37,38}

- **For Stomach, Colonic & Pancreatic cancer** – In a randomized clinical trial in patients with stomach cancer, colon cancer, and pancreatic cancer, Falk et al. reported that when BCG was administered intraperitoneally to patients followed by several cycles of BCG and chemotherapy, prolonged survival was achieved with gastric cancer patients and, to a less extent, with colonic cancer patients, as compared to oral chemotherapy alone, however, the survival of pancreatic cancer patients became surprisingly shorter.³⁹

BCG Vaccine in Type I Diabetes:

BCG vaccine has been proposed to activate the reprogramming of immune cells and alter cell metabolism. This includes accelerating the process of glycolysis as well.⁴⁰⁻⁴² Some studies on non-obese diabetic (NOD) murine models revealed that this vaccine initiated the immuno-modulatory process and suppressed insulinitis.^{43,44} Shehadeh et al. in his pilot trial reported that a single injection

of BCG induced clinical remission in recent onset T1DM patients (65%) compared to 7% of control.⁴⁵ However, studies on human population remain scarce at present.

BCG Vaccine in Multiple Sclerosis:

BCG yields favourable effects with a reduction of disease activity by potentially modulating T-cell-mediated autoimmunity.⁴⁶

BCG Vaccine – Evidence of Antiviral Attribute

Substantiations have outlined the preventive role of BCG vaccination in respiratory infections (Influenza and pneumonia) among children and the elderly. These effects are regarded as ‘Non-Specific Effects’ (NSEs) which are driven by the innate immune memory response in the affected individual. This concept is governed by the principle called ‘trained immunity’.³⁻⁶ This represents an interplay of natural killer cells (NK Cells), cytokines, innate lymphoid cells and pattern recognising proteins which further involves transcriptional modifications and epigenetics reprogramming.⁸ Summary of correlation of BCG vaccine with Acute Respiratory Infection is discussed under table 1.

Table 1: Summary of Correlation of BCG Vaccination with Acute Respiratory Infection (Evidences)

Authors (Country)	Studies
Cruz, et al., 2017 (Brazil) ⁴⁷	A systematic review studied all-cause mortality in children after BCG vaccination and found that it approximately halved all-cause mortality in children under five years in lower income countries, due to pneumonia and sepsis. Effect size 0.56 (95%; CI 0.46-0.69)
Zimmermann, et al., 2018 (Australia) ²⁸	A systematic review on influence of BCG on vaccine responses found that it was associated with higher levels of antibodies against pneumococcus (serotype 9V, p<0.01; 18 C, p=0.04) and Influenza A (H1N1) pdm09 virus vaccines (p=0.04)
Aaby, et al., 2011 (West Africa) ⁴⁸	A Randomized Controlled Trial with a sample size of 2,320 on Infant mortality after early vs. Delayed BCG vaccination in low-birth-weight children; found reduction in infant mortality by 17% (mortality rate ratio [MRR] 5.83 [0.63-1.08] at 12 months after receiving this vaccination at the earliest. This was mainly attributed to fewer cases of respiratory infection and neonatal sepsis.
Biering-Sorensen., et al., 2012 (West Africa) ⁴⁹	A Randomized Controlled Trial with a sample size of 105 on early administration of BCG vaccine vs. Control in low-birth weight children concluded that its administration at first contact after birth may contribute to lower mortality [mortality rate ratio was 0.41 (0.14-1.18) (P=0.098) in infancy]. This was largely because of fewer deaths from pneumonia and sepsis in high mortality regions.
Leentjens, et al., 2015 (Netherlands) ⁵⁰	A Placebo Controlled Randomized Trial with a sample size of 40 on the influence of BCG vaccination on immune responses to influenza vaccination in adults concluded that BCG vaccination prior to influenza vaccination results in a more pronounced increase and

	accelerated induction of functional antibody responses against the 2009 pandemic influenza A (H1N1) vaccine.
Kjaergaard, et al., 2016 (Denmark) ⁵¹	Multicentric Randomized Controlled Trial with a sample size of 4,262 on impact of BCG vaccination at birth on parent-reported incidence of childhood infections during first year of life found that there is no overall impact of BCG vaccination on pneumonia [IRR 0.50 (95% CI 0.17-1.46, p=0.2) and cold [IRR 0.91 (95% CI 0.71-1.16, p=0.46)] in children < or= 13 mo. Further found that there was no support for the use of BCG to reduce the burden of the infectious diseases in high-income settings in which the mothers have not had BCG themselves.
Wardhana, et al., 2011 (Indonesia) ⁵²	A Prospective study (experimental) with sample size of 34 on efficacy of BCG vaccinations in elderly on the prevention of acute upper respiratory tract infection (AURTI) concluded that it can increase the IFN- γ level [treatment 0.07 pg/ml, control 0.04pg/ml, p=0.007] and IL-10 [treatment 0.30 pg/ml, control 0.027 pg/ml, p=0.043], and may protect from influenza and viral infection.
Hollm-Delgado, et al., 2014 (Global study of 18 countries) ⁵³	Prospective Cohort study (2 cohorts) including 58,021 and 93,301 sample size respectively on impact of BCG vaccine on acute lower respiratory infection (ALRI) in children globally; concluded (a) It lowered the risk of suspected ALRI (RR:0.83, 95% CI: 0.7-0.9) and (b) BCG vaccination was associated with a 17%-37% risk reduction for suspected childhood ALRI in both cohorts.
De Castro, et al., 2015 (Spain) ⁵⁴	A retrospective cohort in 4,64,611 hospitalized patients on heterologous protective effects of BCG vaccination against respiratory infection (RI) and sepsis in children (not attributable to TB); concluded that an average of 40% decrease in HR due to RI in BCG vaccinated children compared to unvaccinated cases, preventive fraction (PF) of 52.8% (43.8-60.7; P-value <0.001).
Haahr, et al., 2016 (Greenland) ⁵⁵	A retrospective cohort study involving 19,363 as sample size on nation-wide hospitalization rates due to infectious diseases (other than TB) among BCG vaccinated and unvaccinated children concluded that there was no association between BCG vaccinated and unvaccinated children's hospitalization rates due to respiratory infections [IRR (Incidence rate ratio) 1.07,95% CI: 0.96-1.20].
Stensballe, et al., 2005 (West Africa) ⁵⁶	A matched case-control study with sample size 386 on acute lower respiratory tract infection (ALRI) in children concluded that BCG vaccination may have a non-targeted protective effect against ALRI, the effect being more marked in girls.
Pollard, et al., 2017 (UK) ⁵⁷	A review article on Non-specific effects (NSE) of BCG vaccine concluded that there is a high plausibility that some vaccines do have non-specific effects, their magnitude and duration, and thus importance remain uncertain.
Moorlang, et al., 2019 (Netherlands) ⁶	A review article on Non-specific protection induced by BCG vaccine against viral infections concluded that BCG protects against DNA/RNA viruses in mice, such as influenza viruses. Further discussed that effect of BCG on an experimental viral infection in humans has been demonstrated which could be mediated via induction of innate immune memory.
Mukherjee, et al., 2017 (USA) ⁵⁸	Animal study on effect of pulmonary delivery of BCG on efferocytosis by alveolar phagocytes and concluded that BCG vaccine boosts efferocytosis in alveolar space in mice and protect host against influenza pneumonia.
Soto, et al., 2018 (Chile) ⁵⁹	Animal study on effect of recombinant BCG (rBCG) vaccine against human respiratory syncytial virus (hRSV) and human metapneumovirus (hMPV) in mice concluded that it reduces pneumovirus caused airway pathology by inducing protective humoral immunity and can be considered as effective approach against other respiratory viruses with similar biology of these viruses.
Yu, et al., 2007 (China) ⁶⁰	Animal study on effect of childhood vaccines (including BCG vaccine) on cross immunity against SARS-CoV virus in mice concluded that it doesn't induce cross reactivity against SARS-CoV virus.

Emerging Evidence for BCG Vaccination in nCOVID-19:

The emerging evidence has drawn our attention towards BCG induced immune re-programming for nCOVID-19 and further its imperative role in lowering associated morbidity and mortality (as shown in figure 1). On searching, a few non-peer reviewed works as pre-print version (on medRxiv)

revealed studies linking BCG vaccination policy and nCOVID-19 morbidity and mortality. A brief summary of the same has been tabularised in table 2. Of them all, 7 studies reported positive correlation in this connotation. Following adjusting to confounding factors; 4 studies tested it.

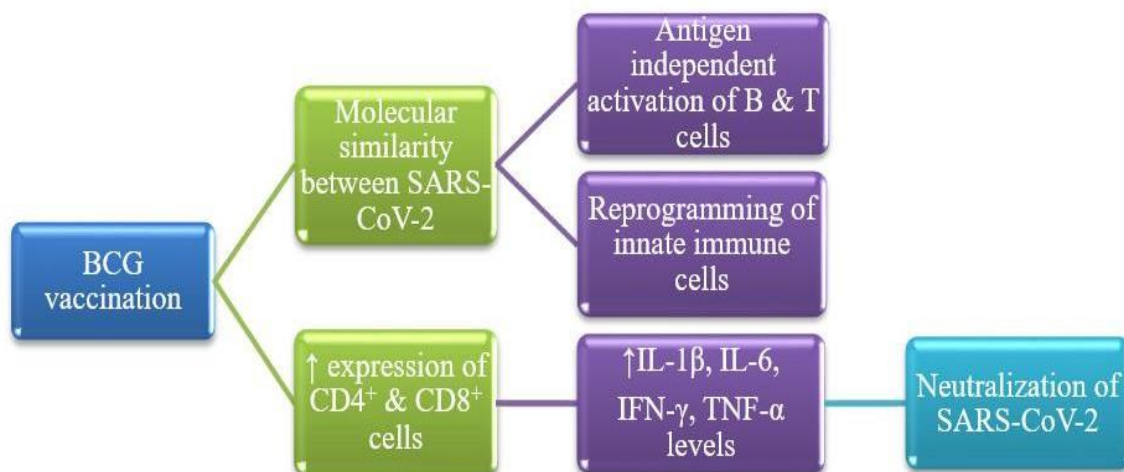


Figure 1: Schematic Representation of Plausible Role of BCG Vaccination in SARS-CoV-2 (Based on analysis of available studies)

Table 2: Emerging Evidences on BCG in nCOVID-19 (pre-print on medrxiv)

Authors (Country)	Studies
Miller, et al., 24 th Mar. 2020 (USA) ⁶¹	A retrospective correlational study on correlation between BCG vaccination policy with morbidity and mortality associated with nCOVID-19 concluded positive correlation suggesting that countries without universal BCG vaccine policies were more severely affected than those without BCG vaccine (p=8.64, e-04) and there was a positive significant correlation between the year of starting BCG vaccine and mortality rate.
Sala & Miyaka, 30 th Mar. 2020 (Japan) ⁶²	A retrospective correlational study on the association between BCG vaccine & the prevalence of nCOVID-19 and its associated mortality (per 1 million population) suggested that the number of total cases and deaths were significantly associated with the country's BCG vaccination policy.
Shet, et al., 1 st Apr. 2020 (USA) ⁶³	A retrospective correlational study on impact of BCG and nCOVID-19- attributable mortality per 1 million population (adjusted for confounders) found that nCOVID-19- attributable mortality among BCG using countries was 5.8 times lower than the non-BCG using countries. Lower middle income countries (LMIC), upper middle income countries (UMIC), high income countries (HIC) had median crude log-mortality of 0.4, 0.7 and 5.5 respectively. Limitations were included.
Goswami, et al., 3 rd Apr. 2020 (India) ⁶⁴	A cross-sectional study on relation between BCG vaccination and nCOVID-19 incidence & mortality per 1000 population found that areas in Europe and America which have higher BCG coverage had significantly less mortality compared to those with lower BCG coverage.

Hensel, et al., 4 th Apr. 2020 (USA) ⁶⁵	A retrospective correlational study between BCG vaccination policy and nCOVID-19 incidence and mortality, (adjusted for confounding factors) suggested positive correlation; nCOVID-19 testing rates as the significant confounding factor such that in countries with testing rate >2,500 test/million, these parameters were no longer associated with BCG policy.
Berg, et al., 5 th Apr. 2020 (USA) ⁶⁶	Correlated flattening of nCOVID-19 curve with BCG vaccination policies across countries (adjusted for confounding factors) and found that the presence of mandatory national policies for universal BCG vaccination is associated with flattened growth curves for confirmed cases of nCOVID-19 (b= -0.025, p= 0.020) and resulting deaths in the first 30-day period of country-wise outbreaks This effect was held after controlling for median age, gross domestic product (GDP) per capita, population density, population size, geographic region, net migration rate, and social distancing.
Kirov, 6 th Apr. 2020 (NA) ⁶⁷	A retrospective correlational study on impact of confounding factors on nCOVID-19 cases per 1 million & mortality rates concluded that the Median age of a population and income are the significant confounding factors of nCOVID-19 cases/million (R=0.774), while BCG vaccine may have little causal link to infection rates (R=0.21). Further mortality rates were greatly higher in countries with high BMI.
Dayal & Gupta, 7 th Apr. 2020 (India) ⁶⁸	Brief Report on impact of nCOVID-19 case fatality rates (CFR) between countries with high disease burden & those with BCG revaccination policies reported a significant difference in the case fatality rate between the two groups of countries (5.2% vs. 0.6%, p value <0.0001) and their data supports the view that universal BCG vaccination has a protective effect on the course of nCOVID-19 probably preventing progression to severe disease and death.
Szigeti, et al., 9 th Apr. 2020 (USA) ⁶⁹	A retrospective correlational study on association between daily rates of nCOVID-19 case fatality (Death Per Case)/Days of the endemic [dpc/d] and presence of universal BCG vaccination found that there was no significant association between nCOVID-19 dpc/d and BCG vaccination before 1980 (p=0.258), or with year of establishment of universal vaccination (rs= -0.03136, p= 0.852). Further suggested that physical distancing and use of PPE are the only epidemiologic measures which consistently associate with successful counteraction of morbidity/mortality during the pandemic.

The findings by Kirov⁶⁷ and Sziegti et al.⁶⁹ does not support this emergent linkage and calls for gathering strong evidence in this context. Further, the scientific report issued by the WHO (on 12th April, 2020) is in unison and explicably stated that no evidence exists currently to say that BCG vaccine confers protection against nCOVID-19 and is not recommended for nCOVID-19. However, it should be continued for neonatal

vaccination in countries with a high incidence of tuberculosis.⁷⁰

Discussion:

Currently, there are 6 studies registered (on Clinicaltrials.gov; 27th April 2020) of which 4 studies are currently recruiting participants. The details are tabularised in table 3.

Table 3: Clinical trials underway for BCG Vaccination in nCOVID-19⁷¹

NCT Number	Title	Study Type / Phase	Population	Study term	Location
NCT04328441	Reducing Health Care Workers Absenteeism in nCOVID-19 Pandemic Through BCG vaccine (BCG-CORONA)	Interventional/ Phase-3	1500	March 25, 2020 to December 25, 2020	Netherlands

NCT04347876	Outcome of COVID-19 Cases Based on Tuberculin Test: Can Previous BCG Alter the Prognosis?	Observational (Case-Control)	100	April 11, 2020 to June 30, 2020	Egypt
NCT04327206	BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE)	Interventional (open-label, randomized control trial)/ Phase-3	4170	March 30, 2020 to March 30, 2022	Australia
NCT04348370	BCG Vaccine for Health Care Workers as Defense Against COVID-19 (BADAS)	Interventional (Randomized control trial)/ Phase-4	1800	April 20, 2020 to November 20, 2021	United States

Analysing the strength and limitations; high-quality evidence corroborates the preventive role of BCG in acute respiratory infections (as discussed in table 1). However, how far BCG vaccination will be fruitful to combat the prevailing scenario lacks substantiation. The emerging evidence has limitations like a lack of consideration for the varying onset of the pandemic among different countries; not adjusting to significant confounding factors; not including limiting criteria; subjected to methodical error due to non-peer review and most important of all retrospective pattern. Further, due to the uncertainty of the benefits of BCG vaccination (NSE) in nCOVID-19 in terms of magnitude and duration, it is not worthwhile to make changes in practice and policy currently.^{57,70} The need of the hour is prospective RCTs in order to adduce solid evidence in this context.

On critical appraisal of the non-peer reviewed pre-print evidence, at the relationship between BCG and COVID-19 is being proven by looking at correlation/association among two data set (BCG vaccine coverage and nCOVID-19), without acknowledging the confounders. The variables like the difference in testing strategies, reporting bias, demographics, nation's ability to respond to the pandemic, prevalence of co-morbidities and different stages of the pandemic across various countries might have a significant impact on these associations / correlations and must be interpreted carefully. Therefore, at this stage, this association should be considered as a hypothesis only and

should be tested through appropriately designed studies. Though the epidemiological association between BCG and nCOVID-19 is striking, it does not prove causal relationship unless tested in well-designed clinical trials.⁷²

Conclusion:

The emerging evidence in view of BCG Vaccination as a preventive strategy serves as a ray of hope to combat the prevailing condition. Non-specific effects of BCG in respiratory infections are explicable substantiated, but its magnitude and duration are ill-defined. The later aspect raises concern and further warrants addressal with solid evidence from randomized controlled trials to be undertaken prospectively. It is imperative to not jump to an early immature conclusion in terms of utilising BCG for nCOVID-19 until proven otherwise.

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