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BCG vaccination. Moreover, the hot and humid climatic conditions resist intense transmission of respiratory viruses and may suppress the severity of the current pandemic. Another argument against this hypothesis is the waning of BCG-induced immunity. According to many studies, the BCG induced protection against TB wanes following infant immunization, and some studies have shown that it almost completely disappears by 10–15 years of age. There is still inadequate evidence to prove that the BCG induced non-tuberculous protective immunity persists for an exceedingly long time, i.e. till adulthood.

**BCG vaccine-induced heterologous, nonspecific effects**

BCG vaccine mainly works through induction of cell-mediated immunity whereas almost all other childhood vaccines offer protection primarily through induction of humoral immunity, i.e. production of antibodies. BCG is only moderately efficacious against pulmonary TB, but it is known to provide ‘nonspecific’ (heterologous) protection against certain respiratory infections and sepsis caused by viruses (e.g. vaccinia virus, herpes, and influenza), bacteria (e.g. Shigella flexneri), and protozoa (e.g. malaria). In Guinea-Bissau, vaccination with BCG reduced neonatal mortality in live birth weight babies by 48%. In Spain, the BCG vaccine reduced non-TB hospital admissions in infants by 32% for respiratory infections and by 53% for sepsis. Additionally, it has been shown that BCG vaccination was responsible for the reduction of all-cause mortality by approximately 50% among under-5-year old children.

Most of the studies on nonspecific effects of BCG were done by Abay P et al. mainly in Guinea-Bissau. Some of these studies were observational, non-randomized with questionable methodology, hence, with low-level evidence. The WHO had also reviewed these trials and concluded that BCG appeared to lower overall mortality in children but graded the evidence as ‘low’. It suggested the need for more randomized trials to demonstrate these effects. It was only after a few recent studies mainly by Netea MG et al. that provided evidence on the nonspecific effects of the BCG through human studies with the explanatory mechanism. In 2018, Netea MG et al. conducted a randomized placebo-controlled human challenge study in which it was shown that the BCG induced genome-wide epigenetic reprogramming of monocytes and offered protection against experimental infection with an attenuated yellow fever virus vaccine strain. Additionally, it has been shown that BCG administration enhances immune responses of other vaccines like hepatitis-B, poliovirus type-1, IPV, PCVs, with significantly higher production of antibodies.

**Protective effects of BCG in adults**

BCG is found useful in many non-TB conditions of adults also. This vaccine has been licensed for the treatment of superficial bladder cancer, for which it also exerts nonspecific effects. Thus far, it has not been surpassed by any other drug in terms of its ability to reduce disease recurrence and progression. BCG provides anti-tumor effects by a complex immune cascade that induces antitumor activity (via cytokine release) mediated by cytotoxic T lymphocytes, natural killer cells, neutrophils, and macrophages. BCG has also been shown to be useful in some autoimmune disorders such as Insulin-dependent diabetes mellitus (IDDM) and multiple sclerosis. In a study from Harvard Medical School, adults with longstanding Type-1 diabetes showed a remarkable recovery of serum HbA1c levels to near normal with no episodes of severe hypoglycemia at the end of three years which remained stable for the next five years. It has been previously documented that regulatory T cells (Tregs) play a key role in preventing various autoimmune disorders. The BCG vaccine probably works by upregulating these Tregs. Some observational studies suggest BCG-vaccination is associated with some protection against allergies, eczema, and asthma, although these findings have been inconsistent. Additionally, BCG has also been shown to be associated with protection against melanoma and may play a role in its treatment. Recently, a retrospective review has shown a lower risk of development of lung cancer among those who had received BCG vaccination during childhood.

**The mechanism behind the generation of BCG-induced nonspecific effects**

Unlike the ‘adaptive’ immunity, the ‘innate’ immune system is supposed to have no memory responses. But BCG, which can remain alive in the human skin for up to several months, triggers not only Mycobacterium-specific memory B and T cells but also stimulates the cells of the innate system (monocytes, neutrophils, macrophages, natural killer, dendritic cells, etc.) for a prolonged period. The process by which BCG imparts immune memory to the innate system is known as ‘trained innate immunity’ which in turn is elicited by a phenomenon known as ‘epigenetic effect’. The ‘epigenetic effect’ is produced by the modification of gene expression rather than alteration of the genetic code or nucleotide sequencing. This effect is brought about by two main mechanisms, DNA methylation and histone modifications, that alter innate immunity. BCG does epigenetic reprogramming in the training of innate cells, particularly monocytes. Upon pathogen X recognition by a receptor, ‘naïve’ monocytes undergo epigenetic reprogramming and a metabolic shift and convert into ‘trained’ monocytes, primed to respond more vigorously to nonspecific (Pathogens X, Y, and Z) secondary stimulation. Unlike antigen-specific memory of the adaptive immune system, the second stimulation does not have to be with the same pathogen or antigen. Later on, these ‘trained’ monocytes have a significantly higher production of several proinflammatory cytokines like interferon-gamma (IFN-γ), TNF-alfa, interleukins (IL-1β, IL-6, etc.) upon heterologous challenges, particularly T helper cell type 1 polarizing and typically monocyte-derived proinflammatory cytokines that helps in rapid clearance of infection (Figure 1). These modified, activated, ‘trained’ cells can be stimulated by various non-related infectious (viruses, bacteria, fungi and their components, parasites) or noninfectious agents such as nanoparticles which leads to potent immune memory responses. This response explains the BCG nonspecific protection against sepsis, pneumonia, and other pathogens. Both epigenetic changes and increased
nonspecific immune responses could be detected up to one year after BCG vaccination. 12

**Effect of BCG strains and scar rates on its nonspecific effects**

The BCG vaccine strains that are employed in the immunization programs of different countries vary widely. Over the years, more than 14 sub-strains of BCG have been used as BCG vaccine in different parts of the world. 11 Not all strains of BCG have similar potential to induce ‘trained immunity’ in vaccinated individuals; as a result, they have different propensities to induce ‘non-specific’ effects. 29 Most of the studies on beneficial effects of BCG against sepsis and pneumonia were done with Danish strain. 13–15 Whether other strains do have similar ‘non-specific’ responses is not yet ascertained. The ‘nonspecific effects’ of BCG are greater when there is a setback. Different strains of BCG have different scar rates. Scar formation rate is higher around >90% with BCG-Danish and BCG-Tokyo strains whereas it is only 52% with BCG–Moscow. 30 Among BCG-vaccinated children in a setting with low scar prevalence, having a scar is associated with lower mortality and morbidity. Revaccination with BCG confers little or no extra protection against TB, but it may increase the beneficial nonspecific effects of BCG. 30

**Can BCG offer any protection against ongoing COVID-19 pandemic?**

Even after almost 100 years of its invention, it is still a mystery, how exactly the BCG vaccine works. 31 It would be ironic if we were to discover that BCG protects against TB via a ‘nonspecific’ effect mediated by innate immunity. Nevertheless, at least we know that BCG elicits heterologous, ‘non-specific’ effects against a variety of infectious diseases, and SARS-CoV-2 shall not be an exception. Its beneficial effects are also well documented in adults albeit with some potential for toxicity. 23, 24 Notwithstanding the recent statement of WHO that there is no evidence of BCG-induced protection against SARS-CoV-2 infection, 32 still, the BCG may have some utility owing to the induction of strong, ‘non-specific’, innate immune responses in the vaccinated subjects. BCG may not be able to exert significant inhibitory responses against the SARS-CoV-2 virus, but even ‘stopgap’ protection and some attenuation of the disease may be expected. An extra dose of BCG to the healthcare workers and older people with comorbid conditions would be worth investigating. BCG is generally safe and well tolerated; however, it is contraindicated in immunocompromised individuals, so one needs to be extra careful while administering BCG to these individuals. Apart from safety, there are other issues like the selection of proper strain of the vaccine, and quantum of the immune responses elicited in older and high-risk individuals in comparison to the young and healthy population that need deliberation before employing the vaccine in these groups. One argument against the protective effects of childhood BCG vaccination on COVID-19 susceptibility is the waning of BCG-induced immunity. However, if the heterologous, ‘non-specific’ effects persist even for a few months, they should be able to offer some protection through modulation of innate immunity to the front-line health workers and high-risk individuals till a specific anti-SARS-CoV-2 vaccine becomes available.

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