Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

BCG vaccination strategy implemented to reduce the impact of COVID-19: Hype or Hope?

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ABSTRACT

The Bacillus Calmette-Guerin vaccine (BCG vaccine) designed to prevent tuberculosis in children has been shown to induce a adaptive immune response in the body to fight against bacteria as well as other parasites and viruses. This knowledge has been reciprocated to generate the idea that this vaccine can also offer protection against severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). Some recent pre-print articles have highlighted that countries with mass BCG immunizations seems to have a lower incidence of coronavirus disease 2019 (COVID-19) compared to those without BCG immunization. There are yet no experimental proof of any such association and the world health organisation (WHO) is currently testing the theory with clinical trials on selected cohorts. Epidemiologists and other scientific experts has expressed both their hope and concern simultaneously regarding the success theory of BCG vaccination to prevent COVID-19. Though its still not verified in any way whether the BCG vaccination can actually prevent COVID-19 or not but we believe a thorough analytical research in this regard is indeed worth a shot.

Contents

Abbreviations: **COVID-19**, Coronavirus Disease 2019; **SARS-CoV-2S**, Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein; **BCG**, Bacille Calmette-Guérin; **WHO**, World Health Organization; **MERS-CoV**, Middle East Respiratory Syndrome coronavirus; **NSEs**, Non-specific effects; **LFA-1**, Lymphocytes function associated antigens-1; **ICAM-1**, Intracellular adhesion molecule-1; **TCR**, T cell receptor; **IL-1β**, Interleukin-1β; **IFN-γ**, Interferon gamma; **TNF-α**, Tumor necrosis factor.

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1. Introduction

Currently, the whole world is busy with combating the coronavirus disease 2019 (COVID-19), whose causative agent is Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This virus poses a significant threat to both the economy and health across the globe. The novel virus spreads primarily via physical/close contact or via respiratory droplets released while coughing or sneezing by an infected individual. The new coronavirus has an irregular and non-uniform pattern of development. Due to this fact, it has infected more than 300,000 individuals in the first three months of the outbreak and has led to more than 13,000 deaths within the same period of time [1]. These figures are still on the rise.

SARS-CoV-2 consists of a single-stranded positive-sense RNA genome. It belongs to the Coronaviridae family and is the seventh of its kind known to have infected humans leading to ailments. The other six members of the family, including the SARS-CoV-1 and MERS-CoV (the Middle East Respiratory Syndrome Coronavirus), have also been encountered by the mankind previously, and have displayed relatively higher morbidity than of the novel SARS-virus.

SARS-CoV-2 is comprised of a genome that is approximately 30 kb long (29,903 nucleotides to be precise). *Orf1ab* gene known to encode for the non-structural proteins (NSPs) are present at the 5′ end of the genome. The genome also consists of genes encoding structural proteins like a spike (S), membrane (M), nucleocapsid (N), and envelope (E) along with genes encoding the accessory proteins like orf3a, orf6, orf7, and orf10 etc. [2,3].

Till date, any antiviral or antimicrobial treatments have not shown promising results or been proven to be useful to prevent SARS-CoV-2 infections. WHO does not recommends a treatment involving a combination of more than three antivirals. For now, the treatment options primarily rely on the promising results obtained from studies during previous encounters with SARS, Ebola, MERS, influenza, and other viral infections [4].

2. What is the BCG vaccine?

Bacillus Calmette-Guerin (BCG) vaccination has been used against tuberculosis from long back in many countires via their national tuberculosis programs. It holds an inconsistent position of being amongst the most broadly used and most controversial vaccines today. BCG vaccines were first used on man in the year 1921 [5]. The protective effect of BCG vaccine against meningitis and disseminated TB in children has been very well documented. The primary use of the BCG vaccine, obtained from *Mycobacterium bovis* isolate, is the treatment of tuberculosis (TB).

BCG vaccine is generally administered to infants intradermally after their birth. The most paradoxical and contended aspect of this vaccine is the varied efficacy found in several clinical trials. BCG vaccination was found to be protective in the case of young children who were not previously infected by the severe forms of tuberculosis [6].

3. Epidemiological studies

In a study carried out in Guinea Bissau, a country in West Africa, a 50% reduction in overall morbidity was observed in BCG vaccinated children. It was deduced that this curtailment in overall mortality rate was because of the administration of BCG vaccination, which reduced sepsis and subsequent respiratory infections [7].

Several epidemiological studies reached a parallel conclusion that the countries that adopted the universal policy of BCG vaccination had relatively a reduced death rate caused by COVID-19 to that of the countries which did not put this policy into effect [1,8]. It was conjectured that BCG vaccination rendering protection against COVID-19 was because of the vaccine's non-specific effects. Reduction in respiratory tract infections in children, antiviral effects, and reduced viremia in experimental animals were attributed to the non-specific effects of the BCG vaccine .

4. BCG vaccination: why is it hope against COVID-19?

4.1. Antiviral effects of BCG vaccine

Appurtenant results retrieved from clinicaltrials.gov and PubMed propounded that apart from preventing the propagated types of TB, some strains of BCG vaccine also induced protection against infection caused by other non-mycobacterial pathogens and non related causative agents [9]. Evidence obtained from clinical studies and laboratory experiments suggested that BCG vaccination may have non-specific preventive results against viral infections in the case of humans [10]. For example, in order to prevent the infection from the vaccinia virus, enhanced production of interferon-gamma (IFN-γ) from $CD4^+$ cells took place in the BCG vaccinated mice [11]. This phenomenon of overproduction of IFN-γ via stimulating the $CD4^+$ cells for the prevention of viral infection is essentially a form of 'adaptive immunity.'

Several epigenetic, as well as metabolic changes, are responsible for building adaptive immunity. Many genetic regions are promoted for encoding pro-inflammatory cytokines due to the build-up of adaptive immunity [12]. There is an enhanced secretion of pro-inflammatory cytokines like Interleukin-1β (IL-1β), which is also known as leukocytic pyrogen, upon BCG vaccination. IL-1β plays a crucial role in immunity against viruses [13].

4.2. Prime immune response and non-specific immune response attributed to BCG vaccine

BCG mediated prime immune response usually involves the release of chemokines and cytokines which further activates the immune cells at the site in the microenvironment. These mediators released are considered to function in a non-specific pattern or manner. The primary cytokines stimulated by BCG include Interleukin-2 (IL-2), TNF-α (tumor necrosis factor), and IFN-γ (interferon- γ), which are released upon the activation of $CD4^+$ T cells [14]. Antigen presentation to the APCs (antigen presenting cells) is the first and the most crucial step for BCG to act as a powerful therapeutic agent/vaccine resulting in an effective immune response. Activation of T helper cells occurs upon the internalization of BCG by APCs. The activation is carried out with the help of MHC class II molecules which are expressed on the surface of APCs and are recognized by the $CD4^+$ T cells via the T cell receptor (TCR). The interaction between MHC II molecules and TCR are regulated by the binding of co-stimulatory molecules (CD28) to B7–1 on the T cells. The binding of co-stimulatory molecules results in an upregulation of adhesion molecules like LFA-1 (lymphocytes function associated antigens-1) which binds to the macrophages via ICAM-1 (intracellular adhesion molecule-1) [15].

BCG vaccines are also known to have off-target effects since the 1970s. These non-specified immunomodulatory effects of BCG showed improved immunity in murine models against listeria and influenza [16,17]. The molecular mechanism of BCG vaccination and its non-specific effects were unveiled in recent studies. These non-specific advantages of the vaccine are mainly due to mTOR and NOD2 mediated changes in the epigenetic landscape of immune cells [12,18–20].

BCG priming induces a conformational change in the chromatin in adaptive as well as innate immune cells. Immune cells are assisted by these changes and augment immunity against fungal, mycobacterial, bacterial, and viral infections [12,18,19,21–24].

The production of pro-inflammatory cytokines like TNF-α and IL-1β (interleukin-1β) from mononuclear cells in the peripheral blood was increased strongly upon BCG vaccination in healthy human volunteers. This enhancement in the cytokine production continued for up to 3 months, even when exposed to unrelated pathogens *in vitro* [19]. As a result of this, human monocytes at the promoter sites of genes which encodes for pro-inflammatory cytokines underwent epigenetic reprogramming as well as the activation markers like CD11b, TLR4 and CD14 also increased. On the basis of these outcomes, it was hypothesized that increased cytokine

production in monocytes induced by BCG may give rise to some better clinical results during a subsequent viral infection [22].

It has been demonstrated in various controlled trials that BCG vaccination reduces the severity of infections by several viruses having a somewhat similar structure to that of SARS-CoV-2. For instance, yellow fever vaccine viremia was reduced by 71% due to the administration of the BCG vaccine in volunteers in the Netherlands [22]. The severity of encephalomyocarditis virus (mengovirus) was also significantly reduced in two studies conducted on mice [25].

A study was conducted on BCG vaccinated healthcare workers appointed to take care of the patients suffering from COVID-19. Several clinical trials were run on the healthcare workers using two registered protocols that aimed at perceiving the fact whether the BCG vaccination was enhancing their immunity against SARS-CoV-2 [24,25].

4.3. Clinical evidences supporting the strategy

4.3.1. Random Trials

The impact of BCG vaccine in reducing the chances of respiratory infections in old individuals as well as their prevention was tested in two intended studies. These studies revealed that the risk of pneumonia in old individuals, above the age of 65, was reduced due to BCG vaccination [26]. The acute infections in the upper respiratory tracts were prevented remarkably, when the elderly were administered with BCG vaccine, once a month for 3 months [27].

To study the potential non-specific effects of BCG vaccine in prevention from respiratory infections, four different randomized trials were carried out. In a randomized trial, conducted in West Africa, it was found that the infant mortality due to neonatal respiratory sepsis in low birth weight children, underwent a reduction by 17% at 12 months of age after receiving early BCG vaccination in comparison to the delayed vaccinated children [10]. Another randomized trial in the year 2012 compared two groups (vaccine administered and control), and concluded that BCG vaccination may contribute towards reduced mortality because of lesser deaths from respiratory sepsis/pneumonia [27]. In 2015, a placebo-controlled randomized trial suggested that the immunogenicity of H1N1 (2009 influenza A pandemic) vaccine was augmented in healthy adults due to BCG vaccination [28].

4.3.2. Advancing and ongoing clinical trials

At present, there are 3 active clinical trials going on to find out whether the BCG vaccination prevents SARS-CoV-2 infection in healthcare workers involved in the care of COVID-19 patients. A registered study on clinicaltrials.gov, entitled “BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE)” (clinical trial number:NCT04327206) is a two-group, multicentre, phase III randomised controlled trial involving 10,078 healthcare workers to find out whether BCG vaccination reduces the severity and occurrence of COVID-19. Another registered study “Reducing Health Care Workers Absenteeism in COVID-19 Pandemic Through BCG Vaccine (BCG-CORONA)” (clinical trial number: NCT04328441) primarily aims to reduce the absenteeism among healthcare workers with direct patient contacts during COVID-19's epidemic phase and to reduce ICU/hospital admission or death in healthcare workers with direct contacts with patients during COVID-19's epidemic phase. In the third registered study, entitled “BCG Vaccine for Health Care Workers as Defense Against COVID-19 (BADAS)” (clinical trial number: NCT04348370), researchers hypothesize that BCG vaccination can reduce infection and severity of disease in healthcare workers during the epidemic phase of SARS-CoV-2. Their hypothesis was based on the findings of several *in vivo* and *in vitro* studies, according to which, the BCG vaccine was able to prevent several respiratory tract infections and reduced the mortality and morbidity by percentage as high as 70%.

5. BCG vaccination against COVID-19: a presumed hype?

Presently, WHO does not recommend the usage of BCG vaccination to treat COVID-19 because of the absence of any concrete evidence suggesting that the vaccine prevents the SARS-CoV-2 infection. Although, it has been observed in the studies and experiments conducted both on animal and human subjects that the vaccine has off-target or non-specific effects (NSEs), the proper classification and clinical relevance of these effects are yet to be discovered. Epidemiological studies reporting less occurrence of COVID-19 in BCG vaccinated infants are regulated by various influential factors such as demographical differences and burden of disease in the country, pandemic phase in each country, and testing rates for SARS-CoV-2 infection in each country. Thus these epidemiological findings are weak evidences and prone to confounding as they are based on population rather than individual data.

The fact that a BCG vaccine administered decades ago in childhood will alleviate COVID-19 now is also implausible and questionable because the favorable NSEs of the vaccine might get altered by the subsequent infliction of a different vaccine.

One of the main reasons, why it is essential to stick to WHO's recommendation to not use BCG vaccine is that there might be a bare possibility that up-regulation of the immune system by BCG vaccination and its NSEs will aggravate COVID-19 in a minority of patients with severe ailments [29,30].

6. Conclusion

Due to the lack of strong clinical evidence corroborating the fact that BCG vaccine, possessing various NSEs and anti-viral effects enhancing the immunity against viral infection, might be a possible hope to combat COVID-19. Several randomized controlled trials are in progress in order to evaluate whether the BCG vaccine reduces the severity and occurrence of COVID-19 in healthcare workers. Unless a SARS-CoV-2 specific vaccine is not developed, it is crucial to stick to the WHO guidelines. Administration and of BCG vaccine should be done only under scientific supervision and the vaccine to cure COVID-19 should be only in randomized controlled trials [31].

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Disclosure statement

The authors report no conflicts of interest.

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