

BCG Against COVID-19: Old Vaccine for a Novel Virus?

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Article Info

Article Notes

Received: June 3, 2020

Accepted: June 27, 2020

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Keywords:

COVID-19

Pandemic

BCG

Vaccine

Bladder Cancer

Abstract

COVID-19 pandemic caused by SARS-CoV-2 is overwhelming the globe. Epidemiological studies found an association between universal BCG vaccination policies in countries and reduced morbidity and mortality for COVID-19. This review is trying to explain how a 100-year-old vaccine for tuberculosis could help fight the novel coronavirus. Moreover, it highlights possible impact on urology practice.

On 11th March 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic caused by novel coronavirus SARS-CoV-2. While aggressive containment measures have been initiated by many parts of the world, the number of cases is still rising, with Europe and the United States now being the hot spots of the pandemic, but with an increasing number of cases in developing countries. At the time of writing this article, the United States of America (USA) has the highest number of cases reported. Meanwhile, COVID-19 has not yet hit the Middle East and North Africa as hard as the rest of the world^{1,2}.

In an observational study, the impact of COVID-19 is different in different countries. They compared large number of countries' BCG vaccination policies with the morbidity and mortality for COVID-19. They found that countries without universal policies of BCG vaccination e.g. Italy, UK, Netherlands and USA, have been more severely affected compared to countries with universal and long-standing BCG policies. Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality³.

Another epidemiological study, interestingly published by two urological consultants, reported that countries with national program of whole population BCG vaccination appear to have a lower incidence and death rate from COVID-19⁴.

These observations should be interpreted with caution since there can be pitfalls in epidemiological studies that show an association between BCG vaccination and COVID-19 incidence and case fatality rates;

- It can be argued that observation / correlation does not mean causation.
- Authors recognized that these data are observational and based on a single time-point and that there may be several confounding issues such as limited testing and reporting in many countries³.
- Differences in demographic and genetic structure of the populations in different locations.

- Differences in the non-pharmaceutical interventions being adopted in different locations (such as quarantine or social distancing).
- Differences in the positions on the epidemic curve of each location.

BCG vaccine's heterologous beneficial 'off target' effect against non-tuberculosis infections is well known. Children vaccinated with BCG suffer less from other respiratory illnesses^{5,6} and it could protect against asthma and autoimmune diseases such as type 1 diabetes⁶.

Population-based BCG vaccination may have a role in reducing the impact of this disease and is being studied in a prospective trial. Given the safety of the BCG vaccine and its low cost, it is worth considering it as a possible preventive strategy in the interim while other vaccine trials are underway⁶. Trained immunity can be a tool for enhancing population immunity during a pandemic ahead of the availability of a specific vaccine.

BCG vaccine works on the innate immune system and produces a memory like response termed "trained immunity" which helps in faster recognition triggering a quicker inflammatory response.

The general perception in immunology is that innate immunity, as opposed to adaptive immunity, is static and does not adapt to an enhanced functional state. However, it has been challenged with an increasing body of scientific literature indicating enhanced nonspecific protection against infections after previous exposure to certain microbial components. It has been recently proposed that the non-specific effects of BCG are mediated through epigenetic reprogramming of monocytes, a process called *trained immunity*⁶.

Evidence is available to support the occurrence of trained immunity in the context of BCG immunization: monocytes from adults who receive BCG vaccination exhibit increased expression of various surface markers related to activation and produce higher quantities of cytokines, such as IL-1 β , IL-6, IFN γ and TNF, in response to infection with various pathogens compared with monocytes from adults who do not receive BCG vaccination. On one side, this may raise the concern that BCG can increase inflammation through non-specific activation of myeloid cells, which may exacerbate the cytokine storm in COVID-19. Yet on the other side, it was found that this provides protection encompassing a wide range of organisms, including bacteria such as *Staphylococcus aureus*, fungi such as *Candida albicans* and viruses such as the yellow fever virus⁷.

In the case of COVID-19, in addition to infection by the virus itself, some patients have also suffered excessive immune responses, with the uncontrolled production of pro-inflammatory proteins, cytokines in what is now

termed cytokine storm⁸. Therefore, BCG might help to better orchestrate this inflammatory immune response⁶.

Since cytokine storm has been postulated as a mechanism of severe morbidity and mortality in COVID-19 cases, can this boosting of immune response be harmful to patients? We can argue that in healthy individuals vaccinated with BCG, in which innate antimicrobial mechanisms would be boosted by trained immunity, this is most likely to lead to inhibited viral replication, decreased viral loads and subsequently less inflammation and symptoms. This concept is supported by the decrease in viremia seen following yellow fever vaccination of individuals who were previously vaccinated with BCG⁹.

Moreover, an initial defective immune response in some individuals at high risk e.g. elderly people can result in high viral loads, inefficient systemic inflammatory response and severe disease⁹.

On the other hand, few studies explored the impact of BCG vaccination on humoral responses to heterologous antigens e.g. in adults, BCG was shown to boost antibody titres against influenza vaccine. Infants given BCG at birth also had higher antibody levels to HBsAg and to polio antigens than infants whose BCG vaccination was delayed¹⁰.

Another study showed 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 strain. These results may have implications for the design of vaccination strategies and could lead to improvement of vaccination efficacy¹¹.

The humoral immune response in the context of TB has been understudied, but recent evidence suggests that B cells and antibodies may play a more significant role than previously appreciated. There have been several studies measuring the specific antibody response to BCG vaccination. Overall, reported outcomes to date are inconsistent, but indicate that humoral responses are heterogeneous and may play different roles in different species, populations, or individual hosts¹².

Lu et al¹³ discussed the role for antibodies (Abs) in TB which has been unclear yet they presented data to highlight the existence of distinct Ab Fc effector profiles that correlate with different TB disease states and suggest mechanisms by which humoral immunity may modulate pathogenesis. Using a systems serology approach, they showed highly divergent Ab signatures between individuals with latent TB (Ltb) and active TB (Atb). Individuals with Ltb possess Abs able to drive superior NK cell activation. This increased Ltb Ab functionality correlates with increased binding to the activating Fc γ RIII, known to drive Natural Killer (NK) cell activation and Antibody Dependent Cell mediated Cytotoxicity (ADCC). Moreover, the divergent functional

profiles observed between Ltb and Atb are associated with distinct Ab glycan profiles, validated an independent, geographically distinct cohort, highlighting the potential utility of Ab glycosylation profiles as biomarkers of disease state. Finally, these differences were linked to differential activation of innate immunity and Mtb killing within primary macrophages, suggesting that Abs may not only mark disease states but also contribute functionally to infection outcome¹³.

They found that beyond opsonization, Ltb Abs enhanced several macrophage responses against intracellular Mtb including phagolysosomal maturation and inflammasome activation independent of pyroptosis which suggests that Abs could direct inflammasome activation in macrophages, and this may contribute to bacterial control¹³.

In another recent study, Lu et al¹⁴ concluded that differential glycosylation occurs preferentially on the Fc domain, providing significant discriminatory power between different states of *M. tuberculosis* infection and disease.

As mentioned earlier, trained immunity leading to enhanced innate immune responses to different pathogens after a vaccination is mediated by metabolic and epigenetic rewiring in innate immune cells, which leads to increased gene transcription and improved host defense. Since the ongoing research work for a specific vaccine¹⁵ as well as its mass production can take time, BCG as a cheap, licensed and readily available vaccine can be a tool to boost population immunity while waiting for a specific vaccine to come into the light.

Researchers want to test whether the tuberculosis vaccine could have a similar effect against the new coronavirus, either by reducing the risk of being infected, or by limiting the severity of the symptoms. The BCG vaccine does not directly protect against the coronavirus, but provides a boost to the immune system, which may lead to improved protection and a milder infection. If the BCG vaccine or another inducer of trained immunity provides nonspecific protection to bridge the gap before a disease-specific vaccine is developed, this would be an important tool in the response to COVID-19 and future pandemics¹⁶. Several clinical trials have been recently launched to investigate the possible protective of BCG vaccine including; (BRACE) trial¹⁷ in Australia and (BADAS) trial¹⁸ in USA.

The BCG revaccination to Reduce the impact of COVID-19 in Australian healthcare workers following Coronavirus Exposure (BRACE) Trial is a multi-centre randomised controlled clinical trial of the BCG vaccine against COVID-19. The trial aims to enroll 10,000 healthcare workers from across Australia and Europe to investigate whether an existing, commonly-used vaccine can reduce the effects of COVID-19 infection¹⁷.

BADAS trial (BCG As Defense Against SARS-Cov-2) is a randomized double blinded clinical trial with an estimated enrollment of about 1800 participants. Randomization will be done centrally and computer generated with stratification per hospital in random blocks. The BCG vaccine will be administered by research nurses. Participants and investigators will be blinded. The research nurse that administers the BCG vaccine or placebo will not be blinded. This research nurse will not be involved in the collection of outcome data. Primary outcome is incidence of COVID-19 infection while secondary outcome is disease severity. Estimated study primary completion date is May 2021¹⁸.

One major concern regarding the outcome of such clinical trials is its impact on availability of BCG vaccine for its original role against *Mycobacterium tuberculosis*, the etiological agent of tuberculosis (TB) which is a leading cause of human disease and death, particularly in developing countries. In the global context, TB is intimately linked to poverty, and control of TB is ultimately a question of justice and human rights. The BCG vaccine has existed for 80 years and is one of the most widely used of all current vaccines, >80% of neonates and infants in countries where it is part of the national childhood immunization programme. BCG vaccine has a documented protective effect against meningitis and disseminated TB in children¹⁵. Diverting BCG from TB care to a hypothesized and yet unproven application for COVID prevention, raise the concern the huge cost to the world's deadliest infectious disease, which is tuberculosis.

Meanwhile, BCG is one of the therapies most commonly delivered by urologists. Not known to many other specialties in medicine, BCG has been used to treat non-muscle-invasive bladder cancer (NMIBC) for more than 40 years now. Through intra-vesical instillation, It is one of the most successful biotherapies for cancer in use with an initial complete response rates of 55–70% in patients with high-risk stage I bladder cancer¹⁹. Here it is ironic that one of our oldest vaccines / immunotherapies might help against the novel threat facing humans.

COVID-19 pandemic caused a massive reduction on elective surgical service provision as well as outpatient activities including Intra-vesical BCG adjuvant treatment for NMIBC. Intravesical BCG service provision has been a subject of debate and to date there is no standardized protocol about how to provide this adjuvant treatment during the pandemic crisis. British Association of Urological Surgeons (BAUS)²⁰ initially recommended against BCG treatment during the pandemic due to concern about 'potential immunosuppressive effect' yet later recommended considering risk / benefit of giving or continuing intra-vesical instillations. Recommendations for BCG treatment amid COVID-19 pandemic are summarised

Table 1: Summary of recommendations for intra-vesical BCG treatment during COVID-19 pandemic

| | |
|-----------------------------------|--|
| EAU²¹ | Intermediate risk NMIBC = Low priority High risk NMIBC = High priority |
| BAUS²⁰ | Induction= complete if possible then defer further treatment Maintenance= Consider the risk/benefit ratio |
| BCAN²² | Intra-vesical BCG should be continued |
| Ficarra et al²³ | Induction= at least 4 doses then defer Maintenance = skipping dose 3 is acceptable |
| Lenfant et al²⁴ | Defer for 3 weeks if COVID positive (Discharge if on maintenance for > 1 year) |

in Table 1.

These upcoming clinical trials have raised some concerns in urology practice. For long, even before this COVID-19 crisis, there have been concerns about BCG shortage due to an increasing global demand for the product. There are some recommendations about how to overcome such shortage including using one-half or one-third of BCG dosage, skipping maintenance therapy or using a preferable alternative e.g. Mitomycin C²⁵. On the contrary, compared to using one whole vial of BCG e.g. TICE (50 mg) per intravesical instillation per patient, the dose needed for intradermal administration of BCG vaccine in an adult is 0.1 ml meaning that one vial of BCG is enough to vaccinate 10 adults¹⁸ and this can provide reassurance to the impact of such trials on BCG shortage.

Moreover, there is evidence to support the systemic immunologic impact of intra-vesical BCG rather than sole effect on the bladder²⁶⁻²⁸. Through this immunomodulatory effect, regulating immune/cytokine response at some level, could intra-vesical BCG treatment have been protective from cytokine storm syndrome that has been proposed as a pathophysiological mechanism for severe COVID-19 morbidity and mortality?

Whether there is a significant difference in cases of COVID-19 infection between bladder cancer patients treated BCG or not, is currently a question under investigation. Is it possible that urologists have been already immunizing our patients even before the COVID-19 pandemic? This *hypothesis* needs further investigation based on the results of the ongoing trials e.g. BADAS trial, first to prove the protective effect of BCG vaccine against COVID-19.

Conclusion

BCG vaccine has been proposed as a possible prophylaxis against COVID-19. Epigenetic programming is the proposed mechanism for the so known ‘trained immunity’ which is challenging the long accepted concept of ‘static’ innate immunity. This can explain the broad non-specific protective effect of BCG vaccine. Ongoing clinical trials have been launched to validate the possibility of using BCG to protect against SARS-CoV-2. The impact of the

outcome of such trials on BCG availability for its original uses, both against TB and as adjuvant immunotherapy for NMIBC, is concerning. Hence we need to stay vigilant as such trials can have an impact on our practice.

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