Demystifying BCG Vaccine and COVID-19 Relationship

Efforts for developing vaccines for novel coronavirus disease (COVID-19) are ongoing, but it is unlikely to be available in the immediate future [1]. In the absence of specific therapy, the researchers are exploring other potential preventive and therapeutic options. Recently, there has been a buzz about the protective effect of Bacille Calmette-Guérin (BCG) vaccine in COVID-19. Based on epidemiological correlations, many unpublished preprints hypothesized that the BCG vaccine may offer protection against COVID-19. It gained so much popularity that within 20 days three randomized controlled trials (RCTs) got registered, and many more are in the pipeline [2]. To make an informed decision, we must understand the mechanism of action of BCG, and appraise the robustness of the evidence.

The basis of the possible use of the BCG vaccine against COVID-19 lies in its non-specific effects (NSEs) over the immune system [3]. The NSEs of BCG are mainly mediated by potentiating innate immune response through epigenetic mechanisms.These epigenetic changes within the innate cells act as *de novo* enhancers to boost the immune response against a secondary challenge [3-5]. This enhancing response is popularly known as 'trained immunity' and is very characteristic of BCG. This trained immunity also offers protection against a variety of pathogens (Salmonella, Shigella, malaria, respiratory viruses, *etc*.) other than Mycobacterium tuberculosis, and forms the basis of its use in bladder cancer, melanoma etc. However, this non-specific effect is mostly short-lived and wanes soon after the primary BCG stimulus is cleared from the body. By virtue of the NSEs, BCG vaccine has shown to decrease all-cause mortality in children. Though a few observational studies suggest that the NSEs may last till adulthood, but the overall evidence is still inadequate and is of low quality [3,6,7].

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 COVID-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 COVID-19 is striking, it does not prove causal relationship unless tested in well-designed clinical trials. Also, we should not forget that the NSEs of the BCG vaccine has not been well-studied in human beings and their clinical relevance is unknown [2,3]. Therefore, in the absence of evidence, the BCG vaccination for the prevention of COVID-19 cannot be recommended. The result of the ongoing RCTs shall guide us further.

JOGENDER KUMAR[1*] AND JITENDRA MEENA[2]

Departments of Pediatrics, [1]Post Graduate Institute of Medical Education and Research, Chandigarh; and [2]All India Institute of Medical Sciences, New Delhi; India.
*Jogendrayadv@gmail.com

REFERENCES

1. ELLA KM, MOHAN KV. Coronavirus vaccines: Light at the end of the tunnel. Indian Pediatr. 2020 Apr 15 [Epub] Available from: https://www.indianpediatrics.net/ COVID29.03.2020/PERS-00163.pdf. Accessed April 26, 2020.

2. World Health Organization. Bacille Calmette-Guérin (BCG) vaccination and COVID-19. Available from: *https://www.who.int/news-room/commentaries/detail/ bacille-calmette-guérin-(bcg)-vaccination-and-covid-19.*

3. SAGE Working Group on BCG Vaccines and WHO Secretariat. Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections. World Health Organization; 2017. Available from: *https://www.who.int/immunization/sage/ meetings/2017/october/1_BCG_report_revised_version_online.pdf.* Accessed April 14, 2020.

4. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. Clin Microbiol Infect. 2019;25:1473-8.

5. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, *et al*. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host Microbe. 2018;23:89-100.e5.

6. Usher NT, Chang S, Howard RS, Martinez A, Harrison LH, Santosham M, *et al*. Association of BCG vaccination in childhood with subsequent cancer diagnoses: A 60-Year Follow-up of a clinical trial. JAMA Network Open. 2019;2:e1912014.

7. Abbott S, Christensen H, Lalor MK, Zenner D, Campbell C, Ramsay ME, *et al*. Exploring the effects of BCG vaccination in patients diagnosed with tuberculosis: Observational study using the Enhanced Tuberculosis Surveillance system. Vaccine. 2019;37:5067-72.