Volume 2 • Issue 1 • 2020

Editorial

Journal of Biotechnology and Immunology

Does BCG Vaccination give some Partial Immunity Against Covid 19 ?

Rajeev Shah[1]*, Aarjav R Shah[2], Reena Mehta[3] Ashvika Suthar[4] and Katerina Raka[5]

[1]*Professor & Head, Microbiology Department, Pacific Medical College & Hospital, Pacific University, Udaipur. India*

[2]*Shreeji Clinic, Mumbai, India*

[3]*Expert in Genetics & Cancer/Expert in DNA Technology, University of New South Wales, Australia*

[4]*Microbiologist, NAMO Medical College, Silvassa, UT, India.*

[5]*Biopathologist. Yiannoukas medical Laboratory, Samos, Greece*

***Corresponding Author:** Rajeev Shah, Professor & Head, Microbiology Department, Pacific Medical College & Hospital, Pacific University, Udaipur. India.

Received: April 05, 2020; **Published:** April 14, 2020

Unexpectedly Covid 19 has different morbidity and mortality in different countries. There might be many factors responsible for such differences like different climate include temperature and humidity, difference in cultural norms, migration effects and health infrastructure. Here one more eye-catching factor which is implementation of BCG vaccination program and obvious difference in morbidity and mortality in countries where this program has been running since past last many years has been discussed. BCG vaccination has been shown to offer broad spectrum protection to respiratory tract infections. In this article large number of countries with BCG vaccination implementation policies with the morbidity and mortality for COVID-19 has been compared. It has been observed that countries without universal policies of BCG vaccination (Italy, Spain, UK, Nederland, USA) have been found more severely affected compared to countries with implementation of universal and long-standing BCG policies.

Even countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the concept that BCG protects the vaccinated elderly population. It has also been found that BCG vaccination also reduced the number of reported COVID-19 cases in a country. This concept is supported by reduced morbidity and mortality makes BCG vaccination a potential new tool in the protection against COVID-19 to some extend. The spread of Covid 19 like pneumotrophic viruses infection totally depends on certain factors like- viral load of respiratory secretion (VL) or in other words infectious dose. The recipient immune status specifically organ specific local immunity of person at the time of inhaling suspended viral particles plays main leading factor for getting an infection. But post exposure invasion depends upon variable factors like- MID50 (Minimum infective dose), herd immunity and co-morbidity.Thus transmission of COVID-19 from partially immune person to another individual with same immune status due to BCG vaccination policy of the country make COVID-19 strain slowly less and less virulent after each transmission through partial BCG immune individuals, due to some sort of herd immunity, and vice versa slowly exaltation is induced in strainis of Covid-19 in absence of BCG vaccination. So this could be a probable reason how and why even with little bit partial herd immunity, BCG vaccination can lower down significant morbidity and mortality in the countries where it is still in practice.

The COVID-19 pandemic originated in China and it has quickly spread over all continents affecting most countries in the world [1]. However, there are some striking differences on how COVID-19 is behaving in different countries. For instance, in Italy there has

been strong curtailing of social interactions and COVID-19 mortality is still high. In contrast, Japan had some of the earlier cases, but the mortality is low despite not having adopted some the more restrictive social isolation measurements like lockdown. These puzzling differences have been adjudicated to different cultural norms as well as differences in medical care standards. The difference in COVID-19 morbidity and mortality can be partially explained by national policies on Bacillus Calmette-Guérin (BCG) vaccination. BCG is a live attenuated strain derived from an isolate of Mycobacterium bovis used widely across the world as a vaccine for Tuberculosis (TB), with many nations, including Japan, India and China, having a universal BCG vaccination policy in newborns. Other countries such as Spain, France, and Switzerland, have discontinued their universal vaccine policies due to comparatively low risk for developing tuberculosis infections as well as the proven variable effectiveness in preventing adult TB; countries such as the United States, Italy, and the Netherlands, have yet to adopt universal vaccine policies for similar reasons. Several vaccines including the BCG vaccination have been shown to produce positive "heterologous" or non-specific immune effects leading to improved response against other nonmycobacterial pathogens. For instance, BCG vaccinated mice infected with the vaccinia virus were protected by increased IFN-Y production from CD4+ cells [2]. This phenomenon was named trained immunity and is proposed to be caused by metabolic and epigenetic changes leading to promotion of genetic regions encoding for pro-inflammatory cytokines [3]. BCG vaccination significantly increases the secretion of pro-inflammatory cytokines, specifically interlukin 1 beta (IL-1B), which has been shown to play a indispensible role in antiviral immunity [4]. Additionally, a study in Guinea-Bissau found that children vaccinated with BCG were observed to have a 50% reduction in overall mortality, which was attributed to the vaccine's effect on reducing respiratory infections and sepsis [5]. Given our current understanding of the BCG vaccine's nonspecific immunotherapeutic mechanisms and by analyzing current epidemiological data, this investigation aims to identify a possible correlation between the existence of universal BCG vaccine policies and the morbidity and mortality associated to COVID-19 infections all over the world.

The epidemiological evidence indicates that some of the differences in morbidity and mortality produced by COVID-19 across countries might be partially explained by a country's BCG vaccination policy. Italy, where the COVID 19 mortality is very high, never implemented universal BCG vaccination. On the other hand, Japan had one of the early cases of COVID-19 but it has maintained a low mortality rate despite not implementing the most strict forms of social isolation [6]. Japan have been implementing BCG vaccination since 1947. Iran had also been heavily hit by COVID-19 and it started its universal BCG vaccination policy only in 1984 potentially leaving anybody over 36 years old unprotected. Why did COVID-19 spread in China despite having a universal BCG policy since the 1950's? During the Cultural Revolution (1966-1976), tuberculosis prevention and treatment agencies were disbanded and weakened [7]. So it is obvious that could have created a pool of potential hosts that would be affected by and spread COVID-19. Currently, however, the situation in China seems to be improving. So all these suggests that BCG vaccination seem to significantly reduce mortality associated with COVID-19. It had also found that the earlier that a country established a BCG vaccination policy, the stronger the reduction in their number of deaths per million inhabitants, consistent with the concept that protecting the elderly population might be crucial in reducing mortality. However, there is still not proof that BCG inoculation at old age would boost defenses in elderly humans, but it seems to do so in Guinea pigs against M. tuberculosis [8]. BCG vaccination has been shown to produce broad protection against viral infections and sepsis [9], raising the possibility that the protective effect of BCG might be not directly related to actions on COVID-19 but on associated co-occurring infections or sepsis. However, it had been also found that BCG vaccination was correlated with a reduction in the number of COVID-19 reported infections in a country suggesting that BCG might confer some protection specifically against COVID-19. The broad use of the BCG vaccine across a population could reduce the number of carriers, and combined with other measures could act to slow down or stop the spread of COVID-19. Different countries use different BCG vaccination schedules [10], as well as different strains of the bacteria [11]. The correlation between the beginning of universal BCG vaccination and the protection against COVID-19 suggests that BCG might confer long-lasting protection against the current strain of coronavirus. However, randomized controlled trials using BCG are required to determine how fast an immune response develops that protects against COVID-19. BCG is generally innocuous with the main side effect the development of inflammation at the site of injection. However, BCG is contraindicated in immune compromised people as well as pregnant women [12].

BCG is a live attenuated bacterial vaccination, proved to shown some immunity against leprosy and certain forms of cancers. One factor for such nonspecific immunity or protection may be that BCG activates antigen presenting cells (APCs) via PAMPS (Pathogen-associated molecular patterns or PAMPs are molecules shared by groups of related microbes that are essential for the survival

of those organisms and are not found associated with mammalian cells. PAMPs and DAMPs(damage associated molecular pattern) bind to pattern-recognition receptors or PRRs associated with body cells to induce innate immunity. Pathogen-associated molecular patterns or PAMPs are molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells.. PAMPs and DAMPs bind to pattern-recognition receptors or PRRs associated with body cells to induce innate) immunity that interacts with toll like receptor TLRs (13,14), which activate the inflammatory cascade thereby recruiting inflammatory cells to the site of infection and providing maturation signals for neutrophils, macrophages and dendritic cells. Such initation may be crucial for restricting the infection at the initial site. Moreover, activation of the pro-inflammatory cascade also results in expression of adhesion molecules, co-stimulatory molecules as well as MHC class II molecule. MHC class II molecules engage CD4+ cells via the TCR receptor while the adhesion and cost imulatory molecules bind to their respective receptors on CD4+ T cells for additional high affinity binding for T cell activation.

Whether BCG changes local environment for differentiation of T cells or BCG components drive this differentiation is still not clear. For tumor cell killing, expression of FAS ligand and tumor necrosis factor related apoptosis–inducing ligand (TRAIL) on macrophages and neutrophils are also involved in apoptosis of tumor cells [15]. BCG also generates human peripheral blood mononuclear cells into special population of BCG activated killer cells (BAK) [16]. Phenotype of these cells are CD8+, CD56+ and lymphocyte activated killer cells (LAK) for killing target cells 14. Th1 cytokines, such as IL2 and IFNγ are shown to activate BAK cells for cytotoxicity [17].

In past two strains of the virus had caused outbreaks of severe respiratory diseases in humans: SARS-CoV (or SARS-CoV-1), which caused the 2002-2004 outbreak of severe acute respiratory syndrome (SARS), and SARS-CoV-2, which caused the 2019–20 pandemic of coronavirus disease 2019 (COVID-19) [18]. There are hundreds of other strains of SARSr-CoV, all of which are only known to infect non-human species: bats are a major reservoir of many strains of SARS-related coronaviruses, and several strains have been identified in palm civets, which were likely ancestors of SARS-CoV [18,19].

Moreover, there are many other unknown /unraveled factors still to be found out, like difference in genetic make up, herd immunity and many more along with BCG vaccination even other factors like pandemic of SARS and MARS might have given some herd immunity which also even help in lowering morbidity and mortality in some countries where this pandemic had caused herd immunity which may decrease morbidity and mortality in these countries.

At the end we conclude that there are enough of statistical and scientific data supporting the possibilities of BCG vaccination might have improved innate immunity which might have decreased morbidity and mortality in countries where still BCG vaccination policy is still in active mode, further extensive research is required in this regards and if found positive. Even though many researches are going on to develop specific vaccines against Covid 19. For once, we may believe that BCG does not give any protection against Covid 19, at the same time it does not have any contraindication too. So, BCG vaccination polices should be re-implemented at birth to protect their citizens against Covid -19, in countries where it had been discontinued like Italy, Spain, USA, france, UK, etc to protect next generation against such pandemic or epidemic attacks in future, till any specific vaccine against Covid 19 will not be invented.

References

1. Zhou, F. et al. (2020). Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 6736, 1–9.
2. ed Mathurin, K. S., Martens, G. W., Kornfeld, H. & Welsh, R. M. (2009). CD4 T-Cell-Mediated Heterologous Immunity between Mycobacteria and Poxviruses. J. Virol. 83, 3528–3539.
3. Netea, M. G. et al. (2016). Trained immunity: A program of innate immune memory in health and disease. Science (80). 352, aaf1098–aaf 1098.
4. Kleinnijenhuis, J. et al. (2014). Long-lasting effects of bcg vaccination on both heterologous th1/th17 responses and innate trained immunity. J. Innate Immun. 6, 152–158.
5. Kristensen, I., Aaby, P. & Jensen, H. (2000). Routine vaccinations and child survival: Follow up study in Guinea-Bissau, West Africa. Br. Med. J. 321, 1435–1439.
6. Japan was expecting a coronavirus explosion. Where is it? | The Japan Times. Available at: https://www.japantimes.co.jp/news/2020/03/20/national/coronavirus-explosionexpected-japan/#.XnllWahKjIU. (Accessed: 23rd March 2020)
7. Development and expectation of tuberculosis service system in China. Available at: http://www.zgflzz.cn/EN/Y2012/V34/I9/557. (Accessed: 24th March 2020)
8. Komine-Aizawa, S. et al. (2010). Influence of advanced age on Mycobacterium bovis BCG vaccination in guinea pigs aerogenically infected with Mycobacterium tuberculosis. Clin. Vaccine Immunol. 17, 1500–1506.

9. Moorlag, S. J. C. F. M., Arts, R. J. W., van Crevel, R. & Netea, M. G. (2019). Non-specific effects of BCG vaccine on viral infections. Clinical Microbiology and Infection 25, 1473–1478.
10. Zwerling, A. et al. (2011). The BCG world atlas: A database of global BCG vaccination policies and practices. PLoS Med. 8,.
11. Horwitz, M. A., Harth, G., Dillon, B. J. & Masleša-Galić, S. (2009). Commonly administered BCG strains including an evolutionarily early strain and evolutionarily late strains of disparate genealogy induce comparable protective immunity against tuberculosis. Vaccine 27, 441– 445.
12. Fact Sheets | Infection Control & Prevention | Fact Sheet - BCG Vaccine | TB | CDC. Available at: https://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm. (Accessed: 23rd March 2020) It is made available under a CC-BY-ND 4.0 International license. author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: https://doi.org/10.1101/2020.03.24.20042937.
13. P.E. Fine. (1995). Variation in protection by BCG: implications of and for heterologous immunity Lancet, 346, pp. 1339-1345
14. N.E. Aronson, M. Santosham, G.W. Comstock, R.S. Howard, L.H. Moulton, E.R. Rhoades, et al. (2004). Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60-year follow-up study JAMA, 291, pp. 2086-2091
15. T.J. Kemp, A.T. Ludwig, J.K. Earel, J.M. Moore, R.L. Vanoosten, B. Moses, et al. Neutrophil stimulation with Mycobacterium bovis bacillus Calmette-Guerin (BCG) results in the release of functional soluble TRAIL/Apo-2L Blood, 106 (2005), pp. 3474-3482
16. S. Brandau, J. Riemensberger, M. Jacobsen, D. Kemp, W. Zhao, X. Zhao, et al. NK cells are essential for effective BCG immunotherapy Int. J. Cancer, 92 (2001), pp. 697-702
17. J. Riemensberger, A. Bohle, S. Brandau. (2002). IFN-gamma and IL-12 but not IL-10 are required for local tumour surveillance in a syngeneic model of orthotopic bladder cancer. Clin. Exp. Immunol., 127, pp. 20-26
18. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (March 2020). "The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2". Nature Microbiology. 5 (4): 536–544.
19. Lau SK, Li KS, Huang Y, Shek CT, Tse H, Wang M, et al. (March 2010). "Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events". Journal of Virology. 84 (6): 2808–19.