Review Article

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A REVIEW ON CONNECTION BETWEEN BCG VACCINATION AND COVID 19 CASES: FACTS AND FIGURES

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ABSTRACT

Apart from its magnificent effect against the tuberculosis disease, the BCG vaccine has other nonspecific beneficial effects on the immune system that protect against a wide range of other infections. Scientific Community around the globe is linking this non-specific immunity raised by BCG with incidence of the morbidity and mortality associated with Corona Virus infection. Research is going on to find its role in shielding effect towards respiratory infection secondary to COVID-19 infection. Authors are presenting a review of literature available for the same along with possible mechanism of action of BCG against SARS-COVID and reporting the incidence of COVID infections in countries with and without BCG as Standard Immunization.

Keywords: COVID, BCG, Respiratory Infection, Immunity.

INTRODUCTION

The recent outbreak of SARS CoV-2 is becoming a challenge for the world in terms of treatment and finding a vaccine for the same, as the virus is showing multiple mutations and there is no clear picture of how the immune system is responding to this virus.[1] Finding the correlation between the efficacy of the BCG vaccine in already immunized neonates and adults to protect against Covid -19 infection, when compared to the population who is not vaccinated is a major research to be made which will further develop an insight as how to evolve in the fact that mass vaccination of BCG has a shielding effect towards the Respiratory infection.[2,3] In current papers authors have attempted to explain the global occurrence of Covid-19 cases in countries and its correlation with BCG Vaccination protocol. An attempt is also made to explain the possible mode of action of BCG through which it can play a crucial role to develop immunity against SARS CoV-2.

Elucidation

Much speculation is being made about the fact that the populations that are immunized for tuberculosis have a better safety shield towards Covid infections. What comes into play is the B cell mediated immunity which fights against the tubercle bacilli invasion. The vaccinated BCG vaccine is also found to trigger other major immune responses that fight against a spectrum of infections in adults, children and neonates. BCG, can trigger trained immunity, This raises the tantalizing possibility that BCG could train innate cells to improve early control of the SARS-CoV-2 virus, to reduce Covid-19 disease or even prevent infection.[4,5] (Figure 1).

We have enough of epidemiological evidence that suggest non-specific mortality benefits of live, attenuated vaccines. Bacillus Calmette-Guerin (BCG) which induces a 38-45% mortality reduction is one such example[6,7] . What is cardinal here is the fact that the mortality benefit from BCG is due to reduction in respiratory tract infections and neonatal sepsis, and is not TB-specific.[8] Even when vaccinated in geriatric patients, BCG is known to decrease respiratory infections.[9] BCG vaccine acts as a main potent stimulator of the trained immune system which causes nonspecific effects on the immune response which is underexploited in terms of finding a more efficacious vaccine. These nonspecific effects on the body help to fight against various respiratory infections, asthma like symptoms in children and are seen to reduce the viral load in adults.[10]

Considering the fact based on data available that BCG vaccine in itself, is able to prevent the infection caused by Covid- 19 is unclear. As the efficacy of antibiotics used for symptomatic treatment along with the Innate immunity response cannot also come into play. When the vaccine in itself is 50-60% effective in the cases of pulmonary tuberculosis and wanes as we age, it is another factor to understand about the nonspecific immunity which it develops. When compared for the lesser incidences of Covid 19 infection, in the countries where BCG vaccination is given in neonates, the demographic factors like weather, temperature and ecological configuration can't be ruled out.[11]

The humoral response is developed in context of TB vaccine. B cells and antibodies plays a significant role, potential effect of antibody mediated immunity include enhanced phagocytosis, enhanced inflammation activation and enhanced cytotoxic NK cell activity. It has been found that the vaccine may lead to 30 % to 50% improvement in the immune response against a pathogen such as SARS-CoV-2. BCG can alter the body response towards

pathogens. It could rearrange the DNA for the expression of different genes.[12] One evidence suggests that BCG vaccine can prevent neonates from a broad range of infection and can prevent babies dying from sepsis, but exactly how it works is unclear. It has been found that the newborns vaccinated have twice as many immune cells called neutrophils in their blood.[13] Beyond neutrophils there might be some other effects that may prove beneficial in fighting from Covid-19.

When antibodies are concerned which are produced by B cells they are a part of Adaptive immune system which can recognize any molecule that invades the body, while other form of adaptive immunity is cellular immunity by T cells which specifically kills cells invaded by viruses. Here B cells are responsible for killing a wide variety of pathogens, while the T cells have the ability to kill the viruses which are intra-cellular; this is the response which is very similar to what happens in Covid infection.[14] The literature of the risk factors associated with the nature of the illness in critical stages of Covid 19 have now been reported in various clinical data, but the different factors affecting the immune system are not clear. An article says that an increase in the Cellular adenosine triphosphate [c-ATP] can potentially improve the innate and adaptive immune systems to either prevent or fight Covid.[15]

The nonspecific effects mentioned for the BCG vaccines are not known, there is no evidence showing that BGC vaccination works on which physiochemical mechanism which helps in better fighting of the Covid 19. A major physiology being unknown and not been validated rules out the chances of better shield in BCG vaccinated patients. Along with the attempt to understand probable mode of action and scientific utility of BCG Vaccination for management of Covid-19, firstly the data pertaining to status of BCG Vaccination program of whole population across the nations has been retrieved. (Figure 2)

Authors have also looked further into the reported cases of Covid-19 Globally (Figure 3) and have also correlated the occurrence of Covid-19 nation-wise along with their BCG Vaccination policy. (Figure 4) and Mortality rate of Covid-19 in percentage of total infected nation wise (Figure 5).

The BCG Status report demarcates the graph grossly into 3 groups. First are the nations with BCG Vaccination policy for all which includes African countries along with Asian and South American countries. Second group is of nations who had BCG Vaccination policy in the past but does not practice it currently for e.g. almost all European nations and Australia. Last Group is of the set of nations who have BCG Policy for selective age group such as USA and Canada.

If we establish a correlation between Figure 2 and Figure 3, it is very easy to crux out that incidence of Covid-19 is much less in those nations who practice a regular BCG Vaccination policy for whole population. Moving further Figure 4 is clearly suggesting that high income countries such as Italy, Belgium, USA and Lebanon which does not have universal BCG Policy have reported higher number of Covid-19 cases. Figure 5 is another very interesting pictorial displacing distribution of mortality rate in percentage in various nations. It is showing mortality rate of unto 14-18 % in most of European nations, whereas in US it is 6-8 %. Interesting fact to notice is that US is experiencing highest number of Covid cases worldwide and even at a lesser mortality rate, the overall reported deaths are much higher. Figure 6 and 7 are demonstrating age distribution of Covid-19 cases and age distribution of Covid-19 deaths in USA, respectively. These figures clearly show very insignificant number in 0-5 year's age group in which BCG Vaccination is still considered in USA. It also shows that even though the percentage of Cases reported in much higher in younger age group, the mortality rate is high in age group of 50 years and above.

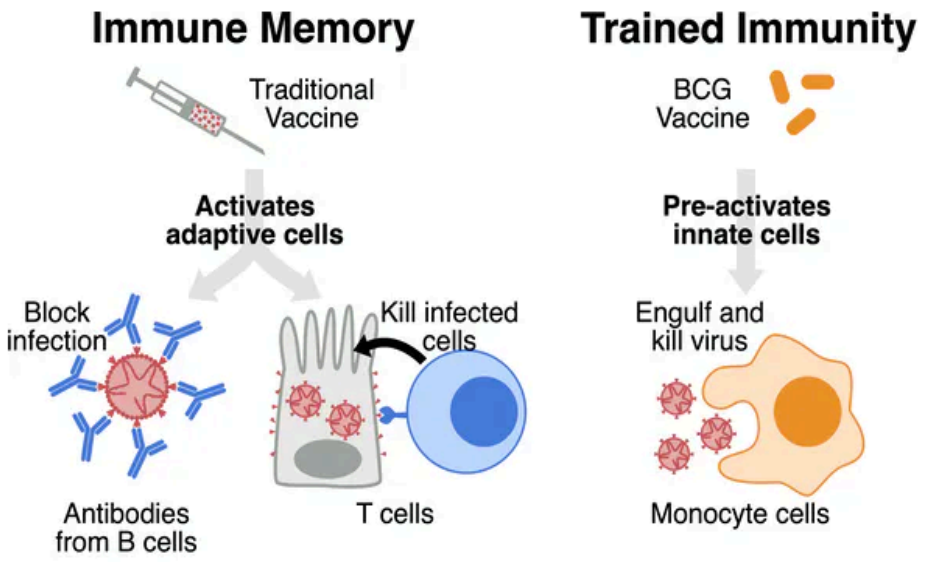

Figure 1: The BCG Vaccine targets trained immunity, whereas most other vaccines target immune memory (Source: Kylie Quinn *et al.*)

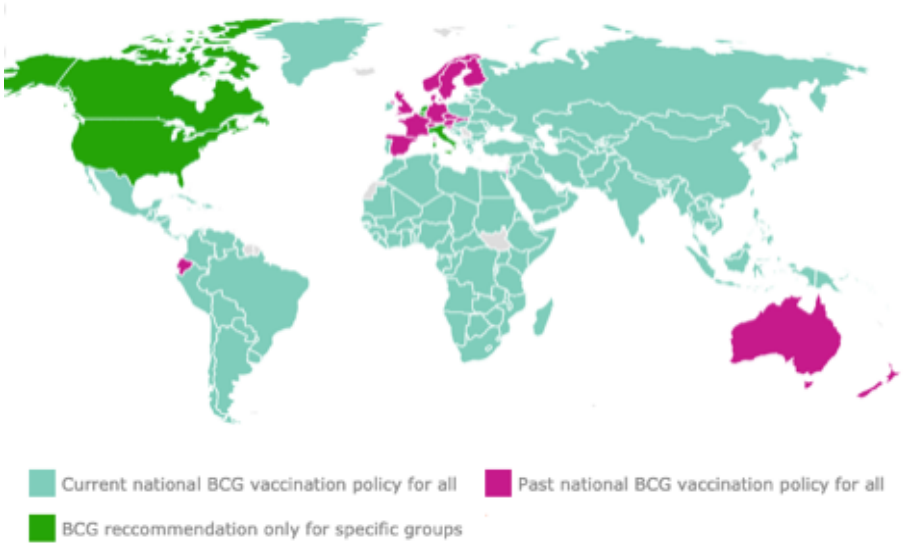

Figure 2: Status of BCG Vaccination worldwide (Source: The BCG World atlas, 2nd Ed. McGill Uni. Health Centre)

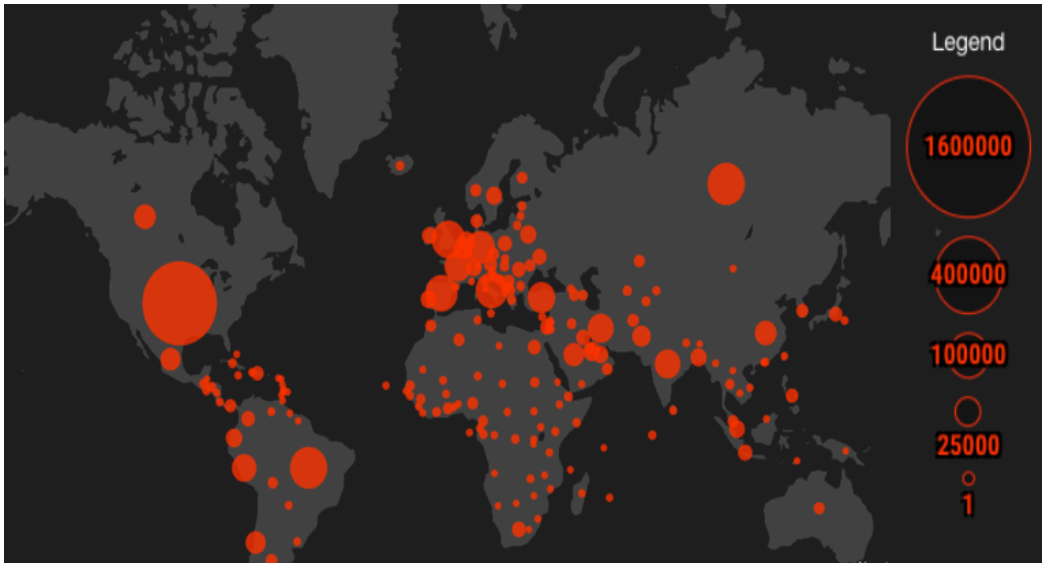

Figure 3: Status of Covid-19 Cases worldwide (Source: Nikkei Asian Review news graphics)

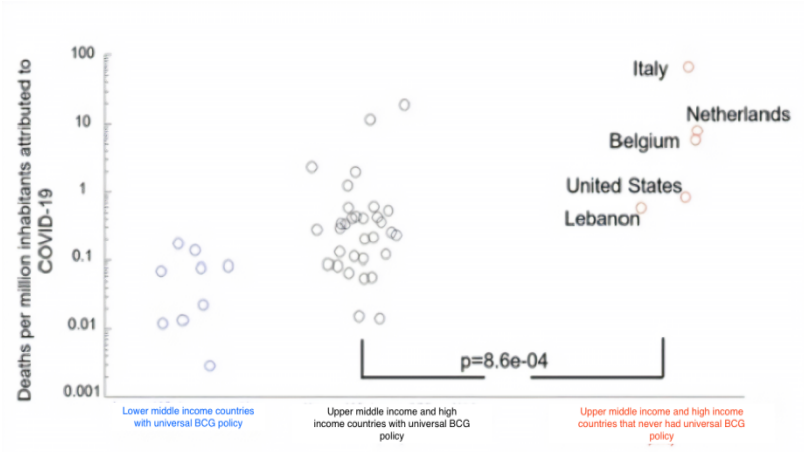

Figure 4: Graphical correlation of Covid Causalities with BCG Vaccination status (Source: The News Minute, April 2020)

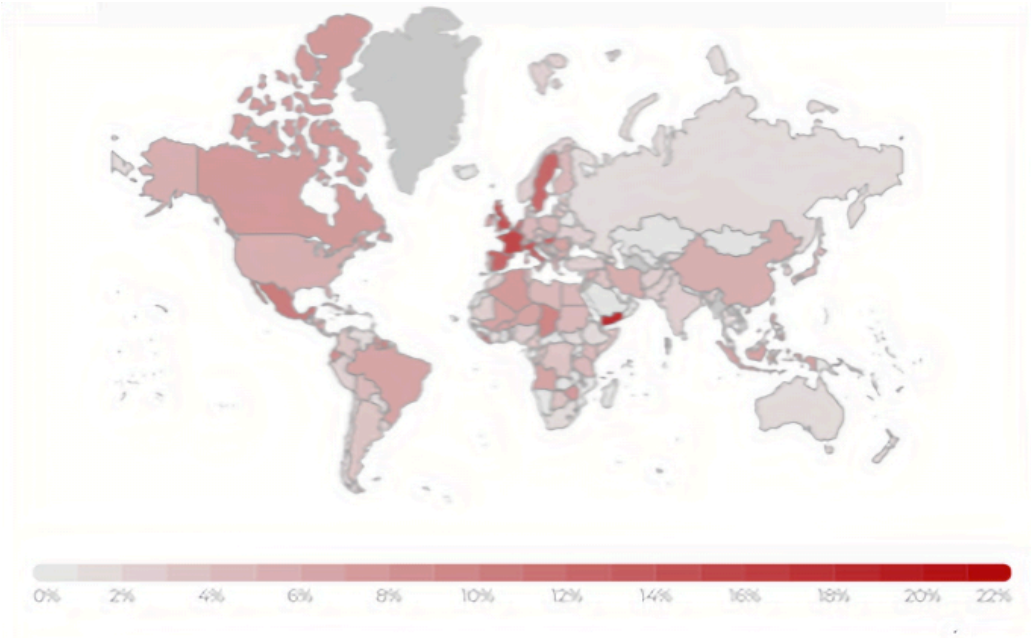

Figure 5: Distribution of Death incidences related to Covid-19 (Source: Al Jazeera/John Hopkins University)

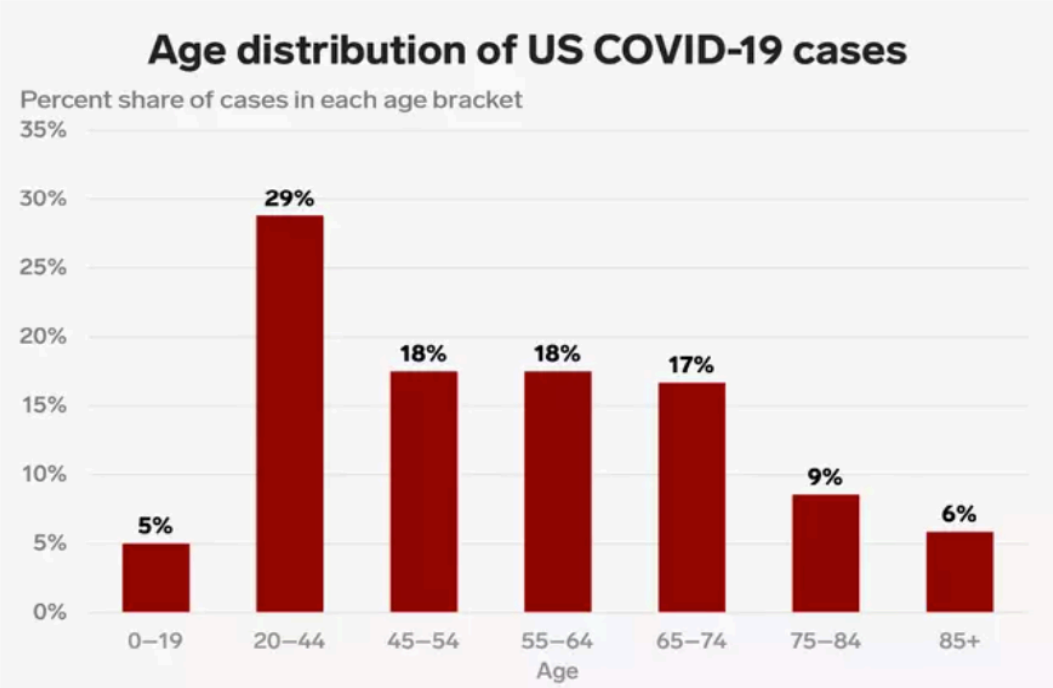

Figure 6: Age distribution of Covid-19 cases in USA (Source: CDCP Covid-19 Response team/ Tyler Sonnemaker)

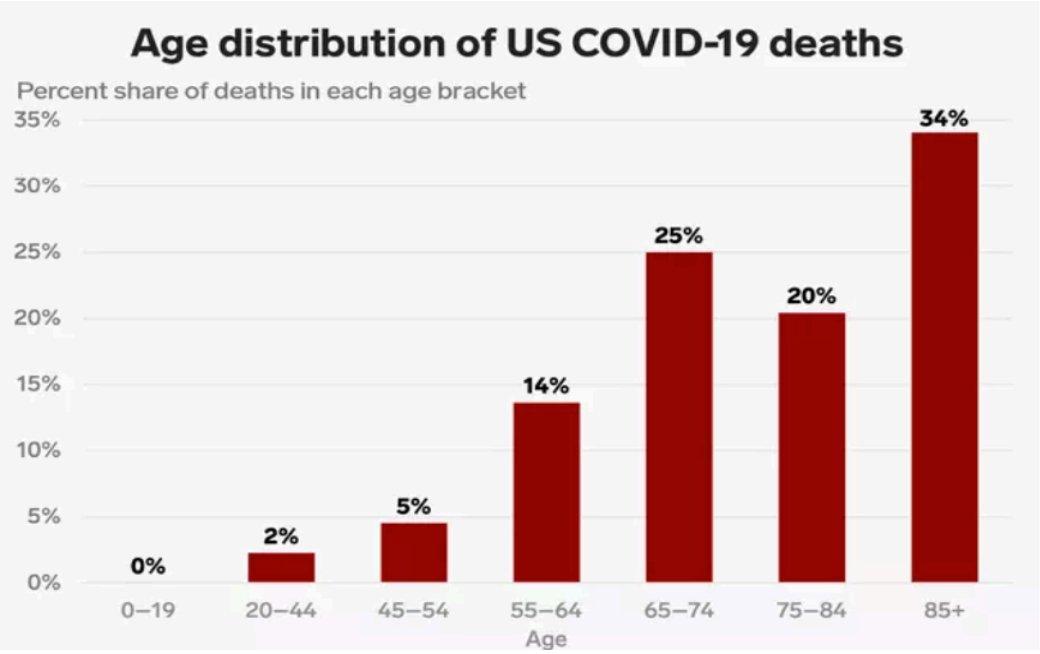

Figure 7: Age distribution of Covid-19 Deaths in USA (Source: CDCP Covid-19 Response team/ Tyler Sonnemaker)

DISCUSSION

The hypothesis as in why Covid 19 has a worst prognosis in elderly patients as compared to the lower risk and a smaller number of complications in children can be attributed to a difference in the cellular energy. Aging is one of the factors that may attenuate the respiratory capacity of the mitochondria, which can be attributed towards mitochondrial DNA mutations and may be the inability of the immune cells to secrete IFN following viral infection .This may be due to ATP depletion in the aging cells, it can be concluded that the gradual decline in the prognosis with the age can be related to depletion in the c-ATP.[15,16] By these mentioned studies it can be said, that till some extent the c-ATP level can be considered important in the infectivity and prognosis in Covid 19. By enhancing the c-ATP levels both the innate and cytotoxic immune systems can be improved. It also concludes that c-ATP may have therapeutic and preventive effects.[16,17]

The treatment strategies which specifically work on the principle of decreasing the heightened activity of immune system components to SARS CoV-2 should be explored extensively. This is an important subject of discussion since one of the prime reasons for life threatening pulmonary damage caused during Covid-19 is a direct sequel of increased influx of neutrophils and macrophages in response to production of exaggerated release of IFN by plasmacytoid dendritic cells as part of activation of host's immune response.[18]

Correlation of status of BCG Vaccination policy among Countries with the number of incidents reported there, is giving a very significant connects between this Vaccination and Covid-19. It is strenuous and demanding at the same time to find a fool proof and clear inter-relationship between the two. The pictorial recreation of data is very strongly indicating that among those nations where BCG Vaccination is practiced for whole of population have reported lesser number of both reported cases as well as mortalities irrespective of their socio-economic or health care standing. Authors suggest further randomized and blinded controlled trials to have a substantial standing over significance and correlation of BCG Vaccination and Covid-19. If it does positively, it is well understood that revaccination of BCG is safe and can be reintroduced with a purpose to give nonspecific immunity to handle SARS CoV-2 related symptoms.

CONCLUSION

If the BCG vaccine or another inducer of trained immunity provides non-specific 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 pandemics. While awaiting a coronavirus- specific vaccine, using an existing, available and safe vaccine such as BCG to boost host immunity may represent an important tool against coronavirus.

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