Australian Journal of Basic and Applied Sciences

2020 November; 14(11): pages 58-63
DOI: 10.22587/ajbas.2020.14.11.6

Original paper AENSI Publications

BCG Vaccine in Preventing COVID-19 Epidemic Had to be Reviewed: Correlation does not Imply causation

Hayder Abdul-Amir Maki Al-Hindy[1*], Mazin Jaafar Mousa [2], Hayder Obayes Hashim [3]

[1]Ph.D. (Medical Physiology), Ass. Prof., University of Babylon, College of pharmacy, Iraq
[2]F.I.B.M.S, (Histopathologist). Ass. Prof., College of Pharmacy, University of Babylon, Iraq
[3]Ph.D. (Biotechnology), Ass. Prof., Department of Clinical Laboratory Sciences, College of Pharmacy, University of Babylon, Iraq

Correspondence Author: Hayder Abdul-Amir Maki Al-Hindy, Department of pharmaceuticals and toxicology, College of Pharmacy, University of Babylon, Babylon, Iraq
Email: makihayder@yahoo.com

Received date: 22 July 2020, Accepted date: 28 November 2020, Online date: 29 November 2020

Abstract

Background: During the last December 2019, a characteristic coronavirus was detected as an etiological agent for an epidemic of potential lethal unusual pneumonia. Miller's et al compared various nations with their severe acute respiratory syndrome-corona virus II (SARS-COV2) morbidity and mortality and found a significant positive correlation between the year when universal BCG vaccination policies were adopted and the country's mortality rate.
Objectives: an attempt to criticize Miller's opinion, shed a light on the impact of BCG from an immunological and clinical point of view, as well as discussing the old and recent role of BCG on immunity.
Methods: The available data has been reviewed about the immunological effects of both BCG vaccine and ACE receptors and their correlations with SARS-COV2 infection.
Results: A lot of points goes with and against Miller's proposal have been discussed. The correlation of BCG vaccine from immunological and clinical points of view to several disorders had been delibrated. The role of ACE receptors and ACE inhibitors in SARS-COV2 infection had been conferred.
Conclusion: the correlation of the BCG vaccine with morbidity and mortality of SARS-COV2 does not imply causation. Additional systematic methodical researches and properly designed trials are desirable to describe this correlation, till the scientists can reach to final decisions

Keywords: Bacillus Calmette-Guérin, BCG, SARS-COV2, COVID-19, Angiotensin-converting enzyme.

INTRODUCTION

The Bacillus Calmette-Guérin (BCG) vaccine was established in the early 20th Century by Albert Calmette and Camille Guérin (Secretariat., 2017). The procedure had included sub-culturing various *Mycobacterium tuberculosis* strains then *M. Bovis* so that the strains manufactured turn out to be progressively less virulent, on every sub-culturing occasion (Fine et al., 1999). The effective use of the BCG inoculation is to defend against tuberculosis (TB), even though it is far-off from perfect in this respect. The preparation is thought to diminish the risk of contracting TB by around 50%, although this dramatically differs by nations; for instance, despite the fact the UK shows a protecting effect of 60-80%, the BCG protecting effect diminishes to near 0% in equatorial countries (Colditz et al., 1994, Secretariat., 2017).

Last December 2019, a characteristic coronavirus II (COV2) was detected as an etiological agent for an epidemic of potential lethal unusual pneumonia, eventually termed as "coronavirus disease-19 (COVID-19)", in Wuhan, China. This novel COV2 defined "severe acute respiratory syndrome" (SARS-COV2) as similar to the COV, which was accounted for the SARS-pandemic that arose in 2002 (Joseph T. Wu, 2020).

Citation: Hayder Abdul-Amir Maki Al-Hindy et al., 2020. BCG Vaccine in Preventing COVID-19 Epidemic Had to be Reviewed: Correlation does not Imply Causation. Australian Journal of Basic and Applied Sciences, 14(11): 58-63.DOI: 10.22587/ajbas.2020.14.11.6

After that, a primary analysis posted by Miller et al. (Aaron Miller, 2020) on medRxiv, reveals a correlation amongst nations that adopted BCG vaccination strategies and mortality by SARS-COV2 depend on deaths/million populations. The authors compared several states with their SARS-COV2 morbidity and mortality and displayed a significant positive correlation between the year when worldwide BCG immunization strategies were implemented and the country's death rate. Thus, the earlier a strategy was introduced, the more likely a significant percentage of the people, particularly the aged, could be protected.

This review article is an attempt to criticize Miller's opinion, shed light on the impact of BCG from an immunological and clinical point of view, discussing the old and recent role of BCG on immunity, as well as focusing on the role of angiotensin-converting enzyme (ACE) receptors and inhibitors, reaching to few final recommendations.

METHODOLOGY

After check through Miller's works (Aaron Miller, 2020), the following reviews had been analyzed. First, the available COVID-19 mortalities in fourty seven countries (Ritchie, 2020). Second, published "WHO and UNICEF" estimations of BCG vaccine recordings (WHO-UNICEF, 2019). Third, a national database of global BCG vaccinations regimen and strategies of each country (Alice Zwerling, 2011). Finally, the authors surveyed the report on BCG vaccine use for protection against mycobacterial infections prepared by the "SAGE Working Group on BCG Vaccines and WHO Secretariat" (Secretariat., 2017)

Critique of the Millers' et al Opinion

Upon revising Miller's et al. analyses, the authors had identified few opinions that approve and others that disprove what Miller's had pronounced. Both opinions will be summarized in the following section.

Arguments support Miller's opinion:

1- the protecting consequence of BCG vaccinations, expected to exhibit virtually ten-fold difference in both occurrence and death of SARS-COV2 among states with and without a BCG policy was pleasingly extraordinary (Aaron Miller, 2020).
2- An accumulating piece of evidence published by well-directed studies in impressive peer-reviewed papers, along with thorough randomized controlled-trials confirms the efficacy of BCG, to deliberate immunity against viruses other than SARS-COV2 (Uthayakumar et al., 2018, Moorlag et al., 2019b).
3- During the childhood period, BCG vaccine administration was correlated with lower mortality from natural reasons during almost 40 years of follow-up (Rieckmann et al., 2016).
4- BCG vaccine has been studied enough, already offered before more than a century (Sharquie, 2020), and has verified safety by more than 3 billion inoculated people. Hence, further effectiveness studies might just necessitate "Phase-III clinical trials" (i.e. bypassing Phases I & II trials) can require years of vaccine processing.
5-

Arguments disprove Miller's opinion:

1- BCG-induced immunization has mostly been shown to last for less than a few years (Secretariat., 2017). As the BCG vaccine is primarily ordered to infants and children, "BCG-induced-immunity" may not be in charge of decreased SARS-COV2 death in adults and the aged.
2- To compare the income nations, however, SARS-COV2 outbreaks may perhaps be at different epidemic phases. Consequently, fewer illness and death cases in developing countries might be due to the early phase of the epidemic in these countries (Ritchie, 2020).
3- Based on a solitary time-point, such observational statistics may be biased by more than a few confounders like imperfect lab-equipment and reportage-systems of many countries (Sruthijith, 2020).
4- Juvenile BCG vaccination does not ensure lasting protection (Secretariat., 2017). The "purified protein derivative (PPD) test could specify whether or not an individual still has induced immunity or needs to be revaccinated again (Sruthijith, 2020).
5- Ultimate optimal results necessitate further randomized trials using various strains, regime, and timing of the BCG inoculation that could have varying degrees of efficacy.
6- Furthermore, as the age factor increases significantly in the severity of SARS-COV2 infection (Joseph T. Wu, 2020), hence, it is essential to study the age distribution of affected individuals in countries that have adopted the BCG vaccine policy late compared to countries never adopt such policy or those that have initiated it early. In such doing, the countries would be alienated into three classes (WHO-UNICEF, 2019, Zwerling A, 2011):
    a) States stopped the BCG vaccine during the earlier twentieth century from their national immunization policy like the USA, Canada, Spain, Italy, and Lebanon.
    b) States adopt BCG policy during the later twentieth century, like Iran (national regime started in 1984).

Citation: Hayder Abdul-Amir Maki Al-Hindy et al., 2020. BCG Vaccine in Preventing COVID-19 Epidemic Had to be Reviewed: Correlation does not Imply Causation. Australian Journal of Basic and Applied Sciences, 14(11): 58-63.DOI: 10.22587/ajbas.2020.14.11.6

Such sorting could reduce any bias created by categorizing nations based on their socioeconomic rank and/or individual yearly salary.

7- Yutaka Akiyama and Takashi Ishida From the Tokyo Institute of Technology presented a statistically significant alteration in the doubling-times for the "Death-toll" between BCG vaccinated and nonvaccinated nations (Ishida, 2020). The relationship might be counterfeit and does not in a straight line imply causation.

8- To finish, it is worthy of evaluating the SARS-COV2 epidemic in nations who still recommend a booster dose of the BCG vaccine at 5-6 years of age. Remarkably, the list may comprise 32 countries with the lowest rate of SARS-COV2 registered patients like Tunisia, Azerbaijan, and Turkmenistan (Zwerling A, 2011).

Another Methodological Critique can be Listed Below:

- Study design: environmental analyses basically cannot in a straight line inform etiology of exposure-disease linkages; instead, they serve us well as firm hypothesis creating inquiries and should not be stretched beyond this goal.
- Timing matters: Miller's et al. compare statistics from several countries with different time-lines for SARS-COV2 with different income statuses. This emphasizes that having premature clinical conclusions from quickly shifting statistics in such a pandemic is challenging.
- Lack of diagnostic testing: the numeral tests performed per capita diverges wildly among countries. Unreliable data-gaining might be in some counties, keeping in mind that the existing number of SARS-COV2 cases is theatrically miscalculated globally due to the lack of diagnostic tests. A precise study depends on precise data (Giri and Rana, 2020).
- Correlation does not indicate causation: An apparent "exposure/outcome" correlation between does not indicate causation.

One can Add an Inquiry:

What is the possible explanation of the high morbidity and mortality of SARS-COV2 in China despite a widespread BCG strategy since the 1950s? China had a declining BCG regimen throughout the Cultural Revolution in the 60s to 70s of the last century, which could have created a pool of possible hosts affected by and spread SARS-COV2.

BCG AND IMMUNITY

BCG-Trained Immunity

There is the well-known phenomenon of "trained-immunity", in which infection with a specific pathogen can induce innate immune system and produces a memory like response against other kinds of pathogens (Moorlag et al., 2019b, Arts and Netea, 2018). Trained immunity aid in fast recognition and triggering a rapid inflammatory reaction (JRJ., 2020). This effect has been mentioned specifically with BCG immunization may render the immune system prepared for other types of contagions (upper respiratory tract viral infection, oral aphthosis, leprosy, viral wart (Sharquie, 2020).

Nonspecific Effects of BCG

Of note, BCG inoculation has a nonspecific immune response in several other conditions including rising anti-influenza immunoglobulins titers if administered before influenza-vaccine, reduction in child mortality and morbidity worldwide, decreased incidence of allergic diseases, treatment of certain malignancies, its effect in typhoid fever, and tuberculous meningitis (Uthayakumar et al., 2018, Moorlag et al., 2019a, Netea and van Crevel, 2014, Gyssens and Netea, 2019, Blok et al., 2020). Current surveys have also proposed that BCG has the potential to defend against infection with a strain of yellow-fever vaccine (JRJ., 2020). An immune-protective outcome of BCG against inflammatory as well as autoimmune disorders has also been reported. For instance, its action on multiple sclerosis insulin-dependent diabetes, and allergic asthma, nonetheless analyses in humans have reached an inconsistent conclusion (Kowalewicz -Kulbat, 2017).

BCG can "retune immune-metabolism" of specific illnesses; it might be through the stimulation of useful regulatory T-cell, the killing of cytotoxic T-lymphocyte, metabolic resetting of cells; explicitly, by enhancing aerophilic glycolysis and reducing phosphorylated oxidation of the immune system. While in T1DM seems to govern and adjust plasma sugars significantly both for HbA1c & continuous 5 years stability (Faustman).

Trained immunity is not Unique for BCG and not a Recent Idea

Inoculations for measles virus and oral-polio are also assumed to have nonspecific advantageous impacts on some other infections. In the past, the BCG vaccine was considered to be protective against SARS, too (Rieckmann et al., 2016; Rajagopal, 2020).

IMMUNITY, BCG AND ANGIOTENSIN-CONVERTING ENZYME RECEPTORS

Angiotensin-converting enzyme (ACE) is a "zinc-dependent-dipeptidase" and can regulate blood pressure by converting angiotensin-I to angiotensin-II. It also brakes down several other peptides, thereby affects diverse physiological functions (Bernstein et al., 2018).

Citation: Hayder Abdul-Amir Maki Al-Hindy et al., 2020. BCG Vaccine in Preventing COVID-19 Epidemic Had to be Reviewed: Correlation does not Imply Causation. Australian Journal of Basic and Applied Sciences, 14(11): 58-63.DOI: 10.22587/ajbas.2020.14.11.6

Historical Review

The first linking of angiotensin-converting enzyme **(**ACE) and immunity was shown in 1975 when 15/17 cases of untreated sarcoidosis were described to have high plasma ACE levels compared to patients with treated cases or persons with the resolved illness (Jung H. 2016).

Angiotensin-Converting Enzyme & Differentiation of Macrophages

ACE impacts innate besides adaptive immunity together by modifying both macrophages and neutrophils activity that is exaggerated when overexpressing ACE (Bernstein et al., 2018). The effects of such ACE-overexpression in humans are unidentified at present. The monocyte can differentiate into macrophage or dendritic cells (through *in-vitro* culture) found to be related to ACE overexpression (Danilov, 2003).

Angiotensin-Converting Enzyme and BCG

Patients on ACE inhibitors (ACEIs) have overexpression of ACE2-receptors reported to be the entry point of SARS-COV2 into cells (Fang L, 2020). Consequently, any medication or inoculation likely to increase the ACE levels may aid under-expression of ACE2-receptors, in that way having some beneficial impact on the host immunity against SARS-COV2. Prior animal studies have exposed that ACE like action augmented after inflammation induced by BCG (Schrier D, 1982).

ANGIOTENSIN CONVERTING ENZYME AND THE IMMUNE SYSTEM

Immune-Effects Induced by Angiotensin-II.

Angiotensin-II (Ang-II) facilitates more than a few proinflammatory reactions by signalling through AT1R. it is well-recognized that the inflammatory response's initial steps can be through the enrollment of inflammatory blood elements to the endothelial and subendothelial compartment (Bernstein et al., 2018). Another chief Ang-II outcome is to upsurge the synthesis of reactive oxygen species by AT1R-mediated activation of NADPH oxidase in both endothelium and subendothelium (Tsi IC., 2016). ROS in line has several-downstream steps that contributed to inflammation, like the inducing of many cellular kinases-pathways besides the activation of factors for "redox-sensitive-transcriptions" like nuclear factor-κB and activator protein-1 (Tsi IC. 2016). Moreover, Ang-II can cause TLR 4 stimulation in several cells, which excites innate immunity (Biancardi et al., 2017). Additionally, Ang-II is shown to enhance dendritic-cell development via the nuclear factor-κB, extracellular signal-regulated-kinases (ERK1 and ERK2) and signal-transducer besides activation of transcription-1 signalling pathways (Meng et al., 2017). Endogenous Ang-II (in T cells) can regulate TNF expression (H.-H, 2017). Additional revisions have stated Ang-II to be involved in autoimmunity-models; perhaps, using an AT1R or ACEI antagonists significantly decreases pathology severity in experimental autoimmune-encephalomyelitis (Tolekova, 2017).

Contributions of this Review to Knowledge:

- Correlation does not imply causation

With additional research, it may appear that the vaccination with BCG does confer defence against SARS-COV2; nevertheless, upon the existing state of knowledge, the authors were unable to state this with any inevitability grade an environmental study does not afford satisfactory indication. Additional straightforward methodical researches and properly designed trials are desirable to describe this correlation.

- Caution urged of the general population

From the latest piece in concurrently published papers, the study's findings are gaining progressively more traction. There is a threat in citing that there are pieces of evidence that BCG as a century-deep-rooted inoculation may improve immunity in individuals, provided that nonspecific defence to other illnesses, and by extension protecting against SARS-COV2 or eliminating severity of its sign and symptoms based on these studies alone. Even if the BCG vaccine is publicized to be effective, that is no satisfactory reason to stockpile. "People should not hoard or attempt to get BCG as they did toilet paper". There is a little chance that the BCG injection could raise the risk of SARS-COV2, but researchers will not identify while waiting for after the clinical-trials. At any rate, the BCG inoculation should not be the first means to fight SARS-COV2. Adopting these conclusions at face value has the prospect of satisfaction in response to the pandemic, mainly in low-income countries. One needs first to guise at how this has been represented in news channels already; the threats of such depictions misleading the public should not be undervalued, for instance, in nations like India, the extensive BCG coverage presented by their widespread immunization strategy may generate a false sense of safety and lead to delay.

- The second version of Miller's study is mandated. An Australian trial is established to start soon or already been started, targeting to investigate whether BCG vaccine defends against SARS-COV2 or reduces its severity in Australian health-providers.

Citation: Hayder Abdul-Amir Maki Al-Hindy et al., 2020. BCG Vaccine in Preventing COVID-19 Epidemic Had to be Reviewed: Correlation does not Imply Causation. Australian Journal of Basic and Applied Sciences, 14(11): 58-63.DOI: 10.22587/ajbas.2020.14.11.6

CONCLUSION

BCG inoculation should not be the first means to fight SARS-COV2, the second version of Miller's study is mandated, we were unable to state with any grade of inevitability that BCG has a sufficient protective effect. Further methodical researches, adequately designed trials are desirable to describe such relations.

ACKNOWLEDGMENT

Great thanks for the librarians and IT technicians of the College of Babylon for their liberal kind help. Our thanksgiving and appreciation for Dr Ahmed Mohammed Ali for his excellent technical support.

REFERENCES

AARON MILLER, M. J. R., KIMBERLY FASCIGLIONE, VIOLETA ROUMENOVA, YAN LI, GONZALO H OTAZU 2020 Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medrxiv.org, 10.1101. doi: 10.1101/2020.03.24.20042937.

ALICE ZWERLING, M. A. B., AMAN VERMA, TIMOTHY F. BREWER, DICK MENZIES, MADHUKAR PAI 2011. The BCG World Atlas: A Database of Global BCG Vaccination Policies and Practices. PLoS Med 8, e1001012. DOI: 10.1371/journal.pmed.1001012.

ARTS, R. J. W. & NETEA, M. G. 2018. Chapter 8 - Epigenetic Rewiring of Monocytes in BCG Vaccination. In: FAUSTMAN, D. L. (ed.) The Value of BCG and TNF in Autoimmunity (Second Edition). Academic Press. doi.org/10.1016/C2017-0-01172-2.

BERNSTEIN, K. E., KHAN, Z., GIANI, J. F., CAO, D.-Y., BERNSTEIN, E. A. & SHEN, X. Z. 2018. Angiotensin-converting enzyme in innate and adaptive immunity. Nature reviews. Nephrology, 14, 325-336. doi.org/10.1038/nrneph.2018.15.

BIANCARDI, V. C., BOMFIM, G. F., REIS, W. L., AL-GASSIMI, S. & NUNES, K. P. 2017. The interplay between Angiotensin II, TLR4 and hypertension. Pharmacol Res, 120, 88-96. DOI: 10.1016/j.phrs.2017.03.017.

BLOK, B. A., ARTS, R. J. W., VAN CREVEL, R., AABY, P., JOOSTEN, L. A. B., BENN, C. S. & NETEA, M. G. 2020. Differential effects of BCG vaccine on immune responses induced by vi polysaccharide typhoid fever vaccination: an explorative randomized trial. European Journal of Clinical Microbiology & Infectious Diseases. 39, 1177–84. doi.org/10.1007/s10096-020-03813-y.

COLDITZ, G., BREWER, T., BERKEY, C., WILSON, M., BURDICK, E., FINEBERG, H. & MOSTELLER, F. 1994. The Efficacy of BCG in the Prevention of Tuberculosis: Meta-analyses of the Published Literature. JAMA : the journal of the American Medical Association, 271, 698-702. Doi:10.1001/jama.271.9.698.

DANILOV, S. M., SADOVNIKOVA, E., SCHARENBORG, N., BALYASNIKOVA, I. V., SVINAREVA, D. A., SEMIKINA, E. L., PAROVICHNIKOVA, E. N., SAVCHENKO, V. G. & ADEMA, G. J. 2003. Angiotensin-converting enzyme (CD143) is abundantly expressed by dendritic cells and discriminates human monocyte-derived dendritic cells from acute myeloid leukemia-derived dendritic cells. Exp Hematol, 31, 9. doi: 10.1016/j.exphem.2003.08.018.

FANG L, K. G., ROTH M. 2020. The Lancet Respiratory Medicine Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? , 8. doi.org/10.1016/S2213-2600(20)30116-8.

FAUSTMAN, D. L., 2020. Benefits of BCG-induced metabolic switch from oxidative phosphorylation to aerobic glycolysis in autoimmune and nervous system diseases. Journal of Internal Medicine;10.1111/joim.13050. doi: 10.1111/joim.

FINE, P. E. M., CARNEIRO, I. A. M., MILSTIEN, J. B., CLEMENTS, C. J. & WORLD HEALTH, O. 1999. Issues relating to the use of BCG in immunization programmes: a discussion document. Geneva: World Health Organization. P. 42. WHO/V&B/99.23. apps.who.int/iris/handle/10665/66120.

GIRI, A. K. & RANA, D. R. S. B. B. 2020. Charting the challenges behind the testing of COVID-19 in developing countries: Nepal as a case study. Biosafety and Health. DOI:10.1016/j.bsheal.2020.05.002.

GYSSENS, I. C. & NETEA, M. G. 2019. Heterologous effects of vaccination and trained immunity. Clin Microbiol Infect, 25, 1457-1458. doi: 10.1016/j.cmi.2019.05.024.

H.-H, M. Y. A. C. C. B. L. Y. C. T. C. A. L. 2017. Angiotensin II Regulates Dendritic Cells through Activation of NF-κB /p65, ERK1/2 and STAT1 Pathways. Cell Physiol Biochem, 42, 9. doi: 10.1159/000479272. Epub 2017 19 July.

ISHIDA, Y. A. A. T. 2020. Relationship between COVID-19 death toll doubling time and national BCG vaccination policy. medRxiv 2020.04.06.20055251. doi.org/10.1101/2020.04.06.20055251.

JOSEPH T. WU, K. L., MARY BUSHMAN ET AL 2020. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nature Medicine, www.nature.com/naturemedicine, 12. 26: 506–510. doi.org/10.1038/s41591-020-0822-7.

JRJ., S. E. A. 2020. Rapid Response: Does BCG bolster one's immunity against COVID-19? The BMJ, 2020;368:m1252. doi.org/10.1136/bmj.m1252.

KOWALEWICZ -KULBAT, M. L., C. 2017. BCG and protection against inflammatory and auto-immune diseases. Expert Rev Vaccines, 16, 10. 16(7):1-10. doi: 10.1080/14760584.2017.1333906.

Citation: Hayder Abdul-Amir Maki Al-Hindy et al., 2020. BCG Vaccine in Preventing COVID-19 Epidemic Had to be Reviewed: Correlation does not Imply Causation. Australian Journal of Basic and Applied Sciences, 14(11): 58-63.DOI: 10.22587/ajbas.2020.14.11.6

MENG, Y., CHEN, C., LIU, Y., TIAN, C. & LI, H. H. 2017. Angiotensin II Regulates Dendritic Cells through Activation of NF-κB /p65, ERK1/2 and STAT1 Pathways. Cell Physiol Biochem, 42(4), 1550-1558. doi: 10.1159/000479272. Epub 2017 19 July.

MOORLAG, S. J. C. F. M., ARTS, R. J. W., VAN CREVEL, R. & NETEA, M. G. 2019. Nonspecific effects of BCG vaccine on viral infections. Clinical Microbiology and Infection, 25, 1473-1478. doi: 10.1016/j.cmi.2019.04.020.

NETEA, M. G. & VAN CREVEL, R. 2014. BCG-induced protection: effects on innate immune memory. Semin Immunol, 26, 512-7. doi: 10.1016/j.smim.2014.09.006. Epub 2014 23 October.

RAJAGOPAL, S. 2020. Opinion: Can BCG Vaccine treat Coronavirus? SIFY.

RIECKMANN, A., VILLUMSEN, M., SøRUP, S., HAUGAARD, L. K., RAVN, H., ROTH, A., BAKER, J. L., BENN, C. S. & AABY, P. 2016. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971–2010. International Journal of Epidemiology, 46 (2), 695-705. doi: 10.1093/ije/dyw120.

Max Roser, Hannah Ritchie, Esteban Ortiz-Ospina and Joe Hasell, 2020. Total deaths, Coronavirus Source Data, Our World in Data. https://ourworldindata.org/coronavirus-source-data.

SCHRIER D, R. L., KATZENSTEIN A, MOORE V. 1982. Role of angiotensin-converting enzyme in Bacille Calmette-Guérin-induced granulomatous inflammation. Increased angiotensin-converting enzyme levels in lung lavage and suppression of inflammation with captopril. Journal of Clinical Investigation, 69(7). 651-57. doi: 10.1172/jci110492.

SECRETARIAT., T. S. W. G. O. B. V. A. W. 2017. Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections. 77. Corpus ID: 34666440.

SHARQUIE, I. K. 2020. BCG is a Good Immunotherapeutic Agent for Viral and Autoimmune Diseases: Is it a New Weapon against Coronavirus (COVID-19)? Electronic Journal of General Medicine 17, 6. Article No: em229. doi.org/10.29333/ejgm/7892.

SRUTHIJITH, K., ET BUREAU 2020. BCG Vaccination Policies Make a Ten Times Difference in Covid-19 Incidence, Mortality: New Study." The Economic Times. https://m.economictimes.com/industry/healthcare/biotech/healthcare/nations-without-bcg-vaccination-saw-higher-cases/articleshow/74956201.cms.

TOLEKOVA, A. 2017. Renin-Angiotensin System: Past, Present and Future. DOI: 10.5772/63179.

UTHAYAKUMAR, D., PARIS, S., CHAPAT, L., FREYBURGER, L., POULET, H. & DE LUCA, K. 2018. Nonspecific Effects of Vaccines Illustrated Through the BCG Example: From Observations to Demonstrations. Frontiers in Immunology, 9: 2869 doi: 10.3389/fimmu.2018.02869.

WHO-UNICEF 2019. Estimates of BCG coverage. https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragebcg.html.