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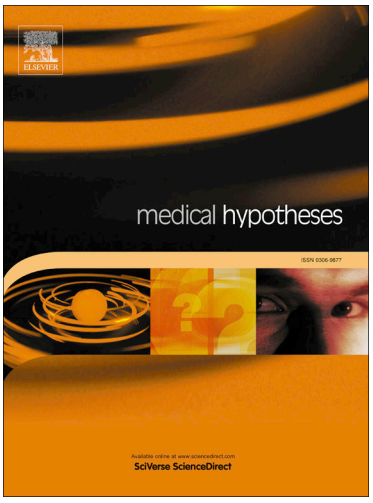

Is Global BCG Vaccination Coverage Relevant To The Progression Of SARS-CoV-2 Pandemic?

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HYPOTHESIS

IS GLOBAL BCG VACCINATION COVERAGE RELEVANT TO THE PROGRESSION OF SARS-CoV-2 PANDEMIC?

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Abstract

The lower than expected number of SARS-CoV-2 cases in countries with fragile health systems is puzzling. Herein, we hypothesize that BCG vaccination policies adopted by different countries might influence the SARS-CoV-2 transmission patterns and/or COVID-19 associated morbidity and mortality through the vaccine's capacity to confer heterologous protection. We also postulate that until a specific vaccine is developed, SARS-CoV-2 vulnerable populations could be immunized with BCG vaccines to attain heterologous nonspecific protection from the new coronavirus.

In January, World Health Organization (WHO) Director General Tedros Adhanom Ghebreyesus said his “greatest concern” was COVID-19 spreading in countries with fragile health systems. Although countries like India, Philippines, Sri Lanka, Cambodia, Thailand, Vietnam and Nepal have reported their first confirmed cases of the SARS-CoV-2 virus in January, widespread examples of community spread have not been reported. In fact, contrary to such justified expectations/predictions, on March 13 2020, WHO declared that “Europe has now become the epicenter of the pandemic, with more reported cases and deaths than the rest of the world combined”. Even though we are still in the midst of this novel coronavirus pandemic and the situation might drastically change in coming days, the disproportionately smaller number of cases reported from disadvantaged/low income countries remains puzzling. We hypothesize that general BCG vaccination policies adopted by different countries might have impacted the transmission patterns and/or COVID-19 associated morbidity and mortality.

Ordinarily, a vaccine provides protection from a particular pathogen, by inducing effector mechanisms directed to that pathogen. However, certain live attenuated vaccines like the Bacillus Calmette–Guerin (BCG), an attenuated strain of Mycobacterium bovis, provide protection not only to a specific pathogen, but also against unrelated pathogens, some of which cause acute respiratory tract infections.[1-7] The underlying mechanism for the BCG vaccination-induced non-specific protection is thought to be mediated via the induction of innate immune memory, or “trained immunity, as was first proposed by Netea and collaborators.[8] Trained-immunity inducing agents reprogramme bone marrow hematopietic stem cells and multipotent progenitors through epigenetic and metabolic changes, resulting in a more robust response in differentiated innate immune cells, following encounter with a pathogen.[8-9] Of interest, in a randomized placebo-controlled human study, BCG vaccination was demonstrated to induce epigenetic reprograming in monocytes, conferring protection against experimental infection with an attenuated yellow fever virus vaccine strain.[10]

Based on these observations, we hypothesized that countries who continue BCG immunization programs would contain the spread of this new coronavirus better than those that did not have or have ceased their national BCG vaccination programs. To

check the validity of this hypothesis, we compared the number of cases and deaths per million people from 40 countries with at least 500 cases according to their BCG vaccination status (Figure 1 and Table 1). Case numbers per million people in countries with a national BCG vaccination programme were statistically significantly lower than those that did not have or have ceased their national BCG vaccination programs ($P<0.0001$). Since case numbers are dependent on SARS-CoV-2 testing capability of each country and might not be representative of the true extent of the regional epidemic, we also compared the number of deaths per million. Results showed that COVID-19 associated deaths relative to the size of the population were statistically significantly lower in countries with a national BCG vaccination programme than those that did not have or have ceased their national BCG vaccination programs ($P<0.0058$). The most affected country with the highest death toll was Italy, which historically never had a national BCG vaccination policy for all. Consistently, Italy also reports higher mortality rates compared to other countries.

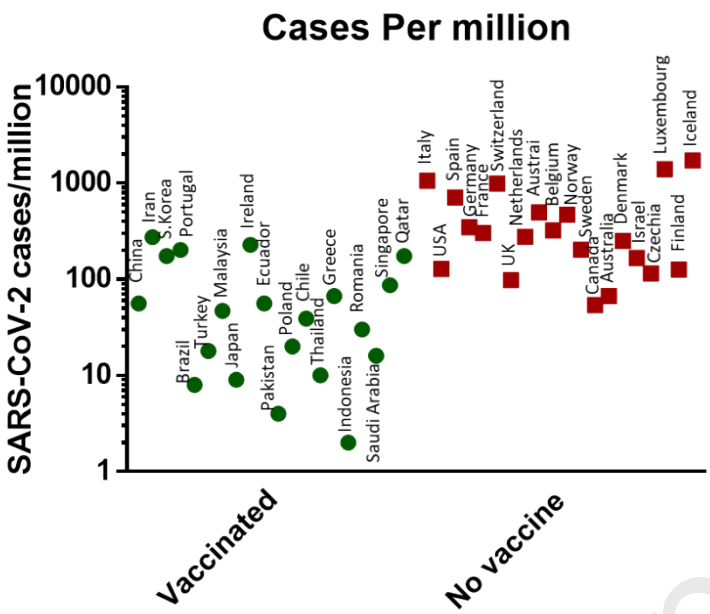

Table Analyzed	Data 1
Column B	No vaccine
vs.	vs.
Column A	Vaccinated
Mann Whitney test	
P value	< 0.0001
Exact or approximate P value?	Exact
P value summary	****
Significantly different? (P < 0.05)	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	253.5 , 566.5
Mann-Whitney U	43.50
Difference between medians	
Median of column A	43.00
Median of column B	290.5
Difference: Actual	247.5
Difference: Hodges-Lehmann	230.0

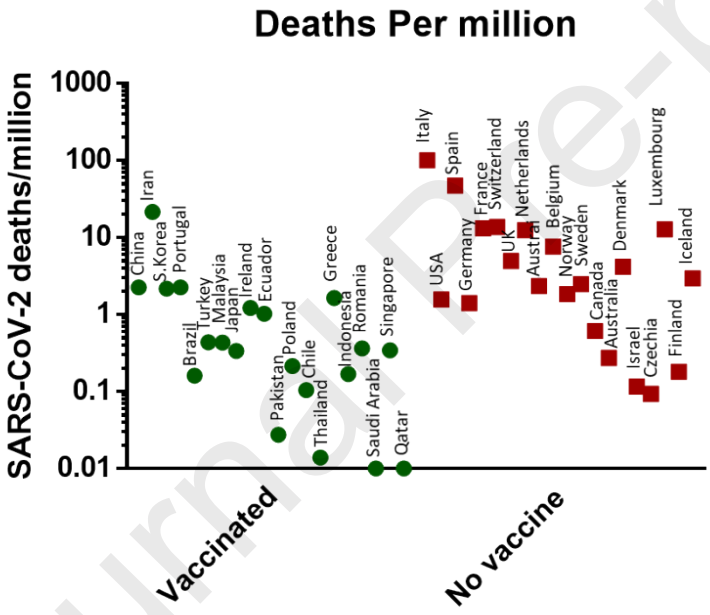

Table Analyzed	Data 1
Column B	No vaccine
vs.	vs.
Column A	Vaccinated
Mann Whitney test	
P value	0.0058
Exact or approximate P value?	Exact
P value summary	**
Significantly different? (P < 0.05)	Yes
One- or two-tailed P value?	Two-tailed
Sum of ranks in column A,B	258.0 , 483.0
Mann-Whitney U	87.00
Difference between medians	
Median of column A	0.3990
Median of column B	2.705
Difference: Actual	2.306
Difference: Hodges-Lehmann	2.021

Figure 1. Comparison of number of cases/million and deaths/million people between countries that follow a national BCG immunization programme and those that did not have or have ceased their national BCG vaccination programmes. Statistical comparison was based on two-tailed Mann Whitney U test. Countries with 500 cases and above were included. Coronavirus related statistics were based on data obtained from https://www.worldometers.info/coronavirus/ (According to the latest update on March 23, 2020, 20:44 GMT).

If BCG vaccination has a general non-specific protective effect against spread of SARS-CoV-2 or COVID-19-associated morbidity and mortality, then would BCG re-vaccination of populations offer a viable alternative of partial protection until a specific vaccine is available? If this strategy is worthwhile, then there is the question of which BCG vaccine strain to chose. The BCG vaccine strains that are employed in the immunization programmes of different countries vary widely. BCG vaccine was first introduced in 1921 and the initial seeds were distributed to various countries. During their serial passage, BCG strains accumulated genomic alterations, including deletions, single-nucleotide polymorphisms and duplications of genomic regions, leading to the emergence of several substrains.[11] Based on their tandem duplication variants (DU-2), BCG vaccines fall into 4 groups (Figure 2). The DU2-I and II group consists of geneologically “early” BCG vaccine strains, including, BCG Japan, BCG Russia and BCG Moreau/Brazil, whereas DU2-III-IV are considered as geneologically more distant “late” vaccines strains (like Pasteur, Denmark , Connaught strains).[11] The vaccine strains differ in terms of their growth characteristics, biochemistry, immunogenicity, and virulence. In contrast to early strains, the late BCG strains are defective in the production of cell wall methoxymycolic acids and possess only the alpha- and ketomycolic acids.[12] Consistent with this difference, early BCG strains persisted up to 6 months in the mesenteric lymph nodes of vaccinated children, whereas no live bacteria could be detected in late strain vacinees.[13] Similarly, methoxymycolate producing early strains were more potent immunostimulating agents than the late strains.[14] Mycolic acids can condition macrophages to produce higher levels of IFN-γ, myeloperoxidase and TNF-α upon renewed exposure to innate triggers.[15] Accordingly, mycolic acids constitute an important group of ligands capable of inducing trained immunity. In this respect, methoxymycolic acids were found to be inflammatory and to activate macrophages, whereas, keto mycolic acids promote anti-inflammatory, alternatively activated macrophages.[16] Therefore, since the persistence and immunostimulatory properties of BCG strains differ, their potential to induce trained immunity in vaccinated individuals could also hypothetically vary.

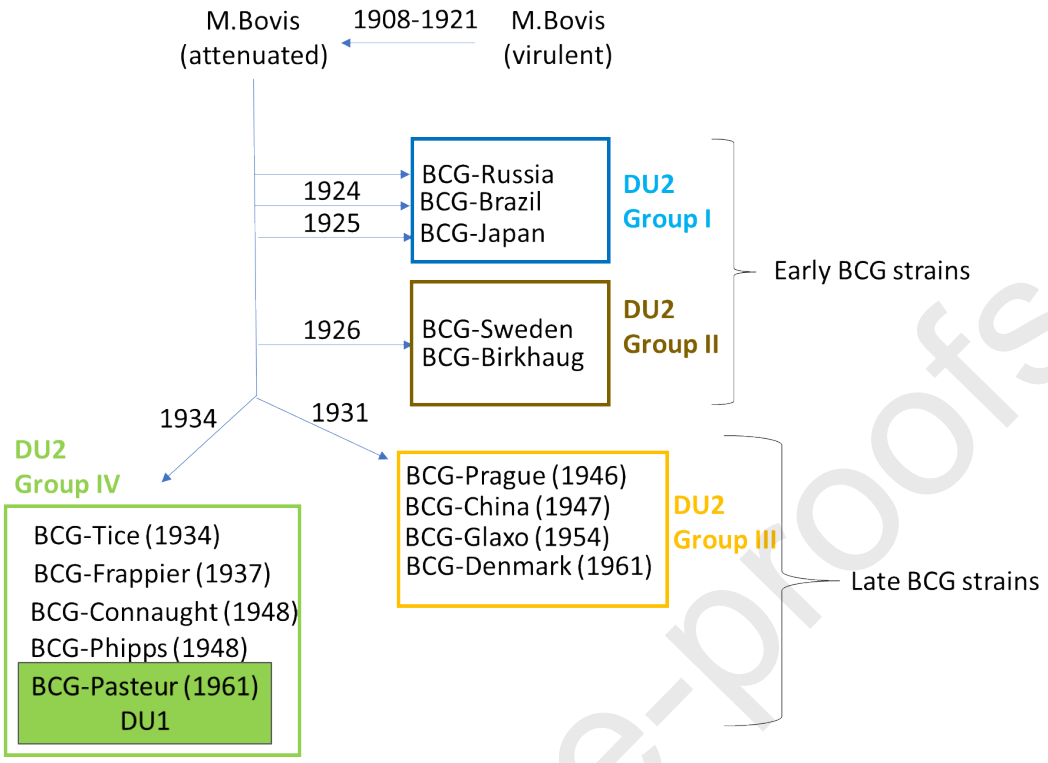

Figure 2. Genealogy of BCG Vaccine Strains. Modified from Brosch et al. (2007).

When we analyzed available data on BCG vaccine strains used in different countries (Figure 3, modified from references 17 and 18), Iran and China, emerged as local producers of their own vaccines. Although the vaccine strains used in these countries are not entirely clear, evidence suggests that the BCG vaccine strain in Iran is BCG-Pasteur 1173p2 and the one in China is a strain derived from Glaxo 1077, representing the most modified and highly attenuated strains deficient of methoxymycolic acids when compared to the Japan and Russia strains.[19-20] It is conceivable that the trained immunity induced by the Iran and China BCG vaccine strains are short-lived compared to those conferred by the widely utilized older strains.

Herein, we hypothesize that, the lower than expected number of cases detected in countries in Asia and Africa with extensive travel and trade links with China might stem from the BCG immunization-induced heterologous protective activity of the vaccine. The only way to test the validity of the hypothesis is to compare the epidemiological data from BCG vaccinated and unvaccinated populations throughout the course of this pandemic. Should this hypothesis hold its ground, then there would be

important repercussions that could save lives. Since BCG vaccination was previously demonstrated to prevent acute respiratory tract infections even in the elderly (5), until a specific vaccine is developed, SARS-CoV-2 vulnerable populations could be immunized with BCG vaccines. Such a strategy would also be suitable for frontline health personnel.

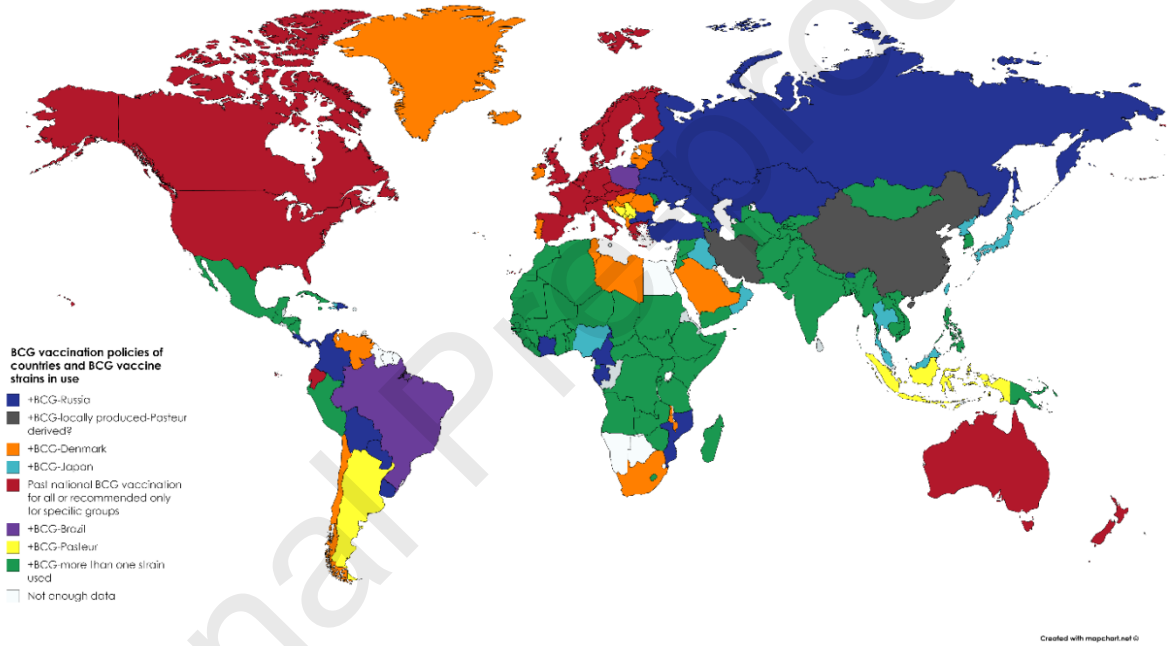

Figure 3. BCG vaccine strains used Worldwide (Modified from data presented in Refererences 17 and 18).

REFERENCES

1. Aaby, P., Kollmann, T. & Benn, C. Nonspecific effects of neonatal and infant vaccination: public-health, immunological and conceptual challenges. Nat Immunol 15, 895–899 (2014). https://doi.org/10.1038/ni.2961)

2. Roth A, Gustafson P, Nhaga A, Djana Q, Poulsen A, Garly ML, Jensen H, Sodemann M, Rodriques A, Aaby P. BCG vaccination scar associated with better childhood survival in Guinea-Bissau. Int J Epidemiol. 2005;34(3):540-7.

3. Hollm-Delgado MG, Stuart EA, Black RE. Acute lower respiratory infection among Bacille Calmette-Guérin (BCG)-vaccinated children. Pediatrics. 2014;133(1):e73-81.

4. de Castro MJ, Pardo-Seco J, Martinón-Torres F. Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis. Clin Infect Dis. 2015;60(11):1611-9.

5. Wardhana, Datau EA, Sultana A, et al. The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. Acta Med Indones 2011;43:185e90.

6. Higgins JPT, Soares-Weiser, K., and Reingold A. (2014). Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines. Available at: http://www.who.int/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf (accessed February 28, 2020).

7. Jensen, K. J., Larsen, N., Biering-Sorensen, S., Andersen, A., Eriksen, H. B., Monteiro, I., et al. (2015). Heterologous immunological effects of early BCG vaccination in low-birth-weight infants in Guinea-Bissau: a randomizedcontrolled trial. J. Infect. Dis. 211, 956–967. doi: 10.1093/infdis/jiu508

8. Netea, M. G., Quintin, J., and van der Meer, J. W. (2011). Trained immunity: a memory for innate host defense. Cell Host Microbe 9, 355–361. doi: 10.1016/j.chom.2011.04.006

9. Non-specific effects of BCG vaccine on viral infections. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Clin Microbiol Infect. 2019 Dec;25(12):1473-1478. doi: 10.1016/j.cmi.2019.04.020. Epub 2019 May 2. Review.

10. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, Kumar V, Xavier RJ, Wijmenga C, Joosten LAB, Reusken CBEM, Benn CS, Aaby P, Koopmans MP, Stunnenberg HG, van Crevel R, Netea MG. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe. 2018 Jan 10;23(1):89-100.e5. doi: 10.1016/j.chom.2017.12.010.

11. Brosch R, Gordon SV, Garnier T, Eiglmeier K, Frigui W, Valenti P, Dos Santos S, Duthoy S, Lacroix C, Garcia-Pelayo C, Inwald JK, Golby P, Garcia JN, Hewinson RG, Behr MA, Quail MA, Churcher C, Barrell BG, Parkhill J, Cole ST. Genome plasticity of BCG and impact on vaccine efficacy. Proc Natl Acad Sci U S A. 2007 Mar 27;104(13):5596-601. Epub 2007 Mar 19.

12. Behr MA1, Schroeder BG, Brinkman JN, Slayden RA, Barry CE 3rd. A point mutation in the mma3 gene is responsible for impaired methoxymycolic acid production in Mycobacterium bovis BCG strains obtained after 1927. J Bacteriol. 2000 Jun;182(12):3394-9.

13. Zeyland, J., and E. Piasecka-Zeyland. 1936. Sur la vitalite´ du BCG dans l'organisme vaccine´. Ann. Inst. Pasteur 56:46–51.

14. Hayashi D, Takii T, Fujiwara N, Fujita Y, Yano I, Yamamoto S, Kondo M, Yasuda E, Inagaki E, Kanai K, Fujiwara A, Kawarazaki A, Chiba T, Onozaki K. Comparable studies of immunostimulating activities in vitro among Mycobacterium bovis bacillus Calmette-Guérin (BCG) substrains. FEMS Immunol Med Microbiol. 2009 Jul;56(2):116-28. doi: 10.1111/j.1574-695X.2009.00559.x. Epub 2009 Apr 27.

15. Korf J, Stoltz A, Verschoor J, De Baetselier P, Grooten J. The Mycobacterium tuberculosis cell wall component mycolic acid elicits pathogen-associated host innate immune responses. Eur J Immunol. 2005 Mar;35(3):890-900.

16. Vander Beken S, Al Dulayymi JR, Naessens T, Koza G, Maza-Iglesias M, Rowles R, Theunissen C, De Medts J, Lanckacker E, Baird MS, Grooten J. Molecular structure of the Mycobacterium tuberculosis virulence factor, mycolic acid, determines the elicited inflammatory pattern. Eur J Immunol. 2011 Feb;41(2):450-60.

17. Ritz N, Curtis N. Mapping the global use of different BCG vaccine strains. Tuberculosis (Edinb). 2009 Jul;89(4):248-51

18. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med. 2011 Mar;8(3):e1001012. http://www.bcgatlas.org/index.php

19. Fallah F, Nasiri MJ, Pormohammad A. Bacillus Calmette-Guerin (BCG) vaccine in Iran. J Clin Tuberc Other Mycobact Dis. 2018 Feb 24;11:22. doi: 10.1016/j.jctube.2018.02.001. eCollection 2018 May. No abstract available.

20. Hu Y, Chen Y, Liang H, Wang Y. An Overview of Coverage of BCG Vaccination and Its Determinants Based on Data from the Coverage Survey in Zhejiang Province. Int J Environ Res Public Health. 2018, 1;15(6). pii: E1155. doi: 10.3390/ijerph15061155.

Conflict of Interest Statement: The authors declare no conflicts of interest

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Countries with National BCG Immunization Coverage						Countries with no National BCG Immunization Coverage					
Country	Total Cases	Total Deaths	Total Cases/ 1M pop	Total Deaths/ 1M pop	Population	Country	Total Cases	Total Deaths	Total Cases/ 1M pop	Total Deaths/ 1M pop	Population
China	81,093	3,270	56	2.258148	1448.089	Italy	63,927	6,077	1,057	100.4801	60.47966
Iran	23,049	1,812	274	21.54054	84.12044	USA	42,434	517	128	1.559504	331.5156
S. Korea	8,961	111	175	2.167727	51.20571	Spain	33,089	2,207	708	47.22282	46.73588
Portugal	2,060	23	202	2.25534	10.19802	Germany	29,056	118	347	1.40921	83.73487
Brazil	1,696	34	8	0.160377	212	France	19,856	860	304	13.1668	65.31579
Turkey	1,529	37	18	0.435579	84.94444	Switzerland	8,547	118	988	13.64034	8.65081
Malaysia	1,518	14	47	0.433465	32.29787	UK	6,650	335	98	4.936842	67.85714
Japan	1,128	42	9	0.335106	125.3333	Netherlands	4,749	213	277	12.42388	17.1444
Ireland	1,125	6	228	1.216	4.934211	Austria	4,468	21	496	2.331244	9.008065
Ecuador	981	18	56	1.027523	17.51786	Belgium	3,743	88	323	7.593909	11.58824
Pakistan	873	6	4	0.027491	218.25	Norway	2,547	10	470	1.845308	5.419149
Poland	749	8	20	0.213618	37.45	Sweden	2,046	25	203	2.48045	10.07882
Chile	746	2	39	0.104558	19.12821	Canada	2,035	23	54	0.610319	37.68519
Thailand	721	1	10	0.01387	72	Australia	1,717	7	67	0.273151	25.62687
Greece	695	17	67	1.638849	10.37313	Denmark	1,450	24	250	4.137931	5.8
Indonesia	579	49	2	0.169257	289.5	Israel	1,442	1	167	0.115811	8.634731
Romania	576	7	30	0.364583	19.2	Czechia	1,236	1	115	0.093042	10.74783
Saudi Arabia	562		16		35.125	Luxembourg	875	8	1,398	12.78171	0.625894
Singapore	509	2	87	0.341847	5.850575	Finland	700	1	126	0.18	5.555556
Qatar	501		174		2.87931	Iceland	588	1	1,723	2.930272	0.341265

Countries with 500 cases and above were included. Coronavirus related statistics were based on data obtained from https://www.worldometers.info/coronavirus/ (According to the latest update on March 23, 2020, 20:44 GMT). BCG vaccination status of each country was deduced from https://www.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf, http://www.bcgatlas.org/ and data presented in Reference 17.

Conflicts of Interest: The Authors declare no conflicts of interest