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Short Communication

BCG Vaccine in Relation To COVID-19 Morbidity and Mortality

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Introduction

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) significantly interrupts daily life activities leading to global social and economic disruption. The infected cases and deaths due to COVID-19 are continuously rising. The lower incidence of COVID-19-cases among countries with Bacillus-Calmette-Guérin (BCG) vaccination background raises the possibility that BCG vaccine could be a protective against COVID-19. Here, we studied the prevalence of COVID-19-cases in relation to population received BCG vaccination. The collected data were compared at two different time points for proper validation and execution of appropriate association. Our investigations showed a correlative association between BCG vaccination and the number of COVID-19-cases. The association obtained can be supported by the fact that BCG vaccination is associated with an increase in trained immunity. This condition has been used previously to establish a protective effect by BCG vaccine against infections due to pathogens other than *Tuberculosis* (TB). The data obtained from this study could encourage the ongoing clinical studies regarding the use of BCG vaccine against COVID-19.

Keywords: COVID-19 pandemic, BCG vaccination, *Tuberculosis* (TB); SARS-CoV-2, Infection Rate, Mortality Rate

Introduction

Coronavirus disease 2019 (COVID-19), a newly emerged global pandemic, caused by SARS-CoV-2 has caused significant fatality. Most patients with COVID-19 exhibit mild to moderate symptoms, while 5% eventually develop acute respiratory distress syndrome (ARDS) and/or multiple organ failure leading to death [1,2]. There's currently no treatment approved for COVID-19, although vaccines and drugs are currently under study. One of the options under trial is the use of Bacille-Calmette-Guérin (BCG) as potential protection against COVID-19.

BCG, a live attenuated Mycobacterium bovis introduced in 1921, is mainly used against tuberculosis, leprosy and other non-tuberculous mycobacteria such as buruli ulcer [3-5]. Several studies have suggested the use of BCG vaccine as an effective treatment for acute respiratory tract infections [6,7]. This suggestion is attributed to the findings that BCG can decrease the level of virus in infected patients. A recent study demonstrated that countries with a mass BCG vaccination policy exhibits less COVID-19 cases than non-BCG vaccinated countries. This has raised the hope that vaccination with BCG may confer protective effects against COVID-19 infection caused by SARS-COV-2. However, the data supporting this hypothesis is still lacking. To test the validity of such hypothesis, a correlation of the epidemiological data from BCG vaccinated versus non-vaccinated populations with the prevalence of SARS-CoV-2

infection and mortality rates is needed. Interestingly, WHO is currently studying this hypothesis including several clinical trials on selected cohorts.

Randomized controlled trials conducted earlier have provided evidence that BCG may protect against respiratory infections [3]. The beneficial effects of the BCG vaccine can include the induction of metabolic and epigenetic changes that enhance the non-specific activation of innate immune cells [8,9]. The mechanism of immune activation induced in response to BCG vaccination can be classified as antigen-dependent and antigen-independent mechanisms. In the case of antigen-dependent mechanism, BCG vaccine enhanced both innate and adaptive immune responses by activating macrophages, dendritic cells, neutrophils, memory B and T cells [9,10]. Since the bacterial antigens are different from viral antigens, this mechanism is unlikely in the case of SARS-CoV-2. In the case of antigen-independent mechanism, the effect of BCG vaccine is due to the non-specific effect on the innate immunity. The bystander B and T cells are activated, and this activation can lead to long-term activation of innate immune cells, termed as trained immunity [9]. The non-specific effect of trained immunity by BCG vaccine is more likely the one with potential role against SARS-CoV-2 infection.

Important features of the trained immunity are that it occurs through epigenetic reprogramming of monocytes at the site of infection. These monocytes undergo histone modification at promoter sites of genes encoding inflammatory cytokines, leading to long-term changes in their ability to respond to novel stimuli and resulting in an increasingly active immune response when they are re-activated [11]. It has been reported that BCG immunized population exhibits an increase in the quantities of cytokines including IL-1β, IL-6, IFNγ and TNF, compared to non-BCG immunized population [12,13].

It has been observed that SARS-CoV-2 infection triggers a local immune response, recruiting macrophages and monocytes, releasing cytokines, and priming adaptive T and B cell immune responses. In most cases, the infection resolves on its own, however, in some cases, a dysfunctional immune reaction occurs [14]. In the case of BCG vaccination, the human body seems to adapt to accept excessive levels of cytokines due to enhanced trained immunity to fight against pathogens, in particular those affecting the respiratory tract such as SARS-CoV-2 [15,16]. Therefore, we assume that an appropriate dose and controlled delivery of BCG vaccine can give some form of protection against COVID-19. To achieve this aim, currently, four clinical trials are ongoing in Australia, Netherland and USA to determine if BCG vaccination can potentially protect healthcare workers during the COVID-19 pandemic [17-19].

Association Between BCG Vaccination and Prevalence Of COVID-19 Infection and Mortality Rates

In this study, we hypothesized that countries which adopted a mass BCG vaccination policy are protected from infection with SARS-CoV-2 contrary to countries that did not adopt the same policy or stopped it. We specifically compared the death rates between the countries that have employed mass BCG vaccination and the countries which stopped or did not employ mass BCG vaccination policy. Data were collected for 71 countries that adopted mass BCG vaccination and 22 countries did not employ or stopped mass BCG vaccination (Table 1,2) using the BCG Atlas published in 2011 [20]. We excluded the African countries from our study due to lack of accurate information about COVID-19 cases. The data regarding the population was obtained from the World Population Clock [21]. The information on the number of COVID-19 cases and deaths was retrieved from the World Population Clock on two different time points, May 12, 2020 and June 24, 2020 and listed in Supplementary (Table 1,2).

Table 1: Comparison of total positive cases for COVID-19 and deaths in population of countries adopted mass BCG vaccination policy and with those that did not adopt or stop mass BCG vaccination policy.

Countries That Currently Recommend BCG Vaccination (N = 71)						Countries Do Not Recommend and Stop BCG Vaccination (N =22)					
Country*	Population**	Total Cases#	%##	Deaths$	%$$	Country*	Population**	Total Cases#	%##	Deaths$	%$$
China	1,439,323,776	82919	0.006	4633	5.587	USA	331,002,651	1406797	0.425	83284	5.92
India	1,380,004,385	74243	0.005	2415	3.253	Germany	83,992,949	173171	0.206	7738	4.468
Indonesia	273,523,615	14749	0.005	1007	6.828	UK	67,886,011	226463	0.334	32692	14.436
Pakistan	220,892,340	32674	0.015	724	2.216	France	65,273,511	140227	0.215	26991	19.248
Brazil	212,559,417	177589	0.084	12400	6.982	Italy	60,461,826	221216	0.366	30911	13.973
Bangladesh	164,689,383	16660	0.01	250	1.501	Spain	46,754,778	269520	0.576	26920	9.988
Russia	145,934,462	232243	0.159	2116	0.911	Canada	37,742,154	71,105	0.188	5167	7.267
Mexico	128,932,753	36327	0.028	3573	9.836	Australia	25,499,884	6964	0.027	97	1.393
Japan	126,476,461	15847	0.013	633	3.994	Ecuador	17,643,054	30419	0.172	2327	7.65
Philippines	109,581,078	11350	0.01	751	6.617	Nether-lands	17,134,872	42984	0.251	5510	12.819

Vietnam	97,338,579	288	0.000	0	0.000	Belgium	11,589,623	53779	0.464	8761	16.291
Turkey	84,339,067	141475	0.168	3894	2.752	Portugal	10,196,709	27913	0.274	1163	4.167
Iran	83,783,942	110767	0.132	6733	6.079	Sweden	10,099,265	27913	0.276	3313	11.869
Thailand	69,799,978	3017	0.004	56	1.856	Austria	9,006,398	15961	0.177	623	3.903
Myanmar	54,409,800	180	0.000	6	3.333	Israel	8,655,535	16529	0.191	260	1.573
S Korea	51,269,185	10936	0.021	258	2.359	Switzer-land	8,654,622	30380	0.351	1867	6.145
Colombia	50,882,891	12272	0.024	493	4.017	Lebanon	6,825,445	870	0.013	26	2.989
Argentina	45,195,774	6278	0.014	317	5.049	Denmark	5,792,202	10591	0.183	527	4.976
Ukraine	43,733,762	16023	0.037	425	2.652	Finland	5,540,720	6003	0.108	275	4.581
Iraq	40,222,493	2913	0.007	112	3.845	Slovakia	5,459,642	1465	0.027	27	1.843
Afghanistan	38,928,346	4963	0.013	127	2.559	New Zea-land	4,822,233	1497	0.031	21	1.403
Poland	37,846,611	16921	0.045	839	4.958	Slovenia	2,078,938	1461	0.07	102	6.982
Saudi Arabia	34,813,871	42925	0.123	264	0.615	**Total**	**842,113,02**	**2783228**	**0.331**	**23862**	**8.573**
Uzbekstan	33,469,203	2519	0.008	10	0.397						
Peru	32,971,854	72059	0.219	2057	2.855						
Malaysia	32,365,999	6742	0.021	109	1.617						
Yemen	29,825,964	65	0.000	10	15.39						
Nepal	29,136,808	217	0.001	0	0.000						
Venezuela	28,435,940	422	0.001	10	2.37						
Taiwan	23,816,775	440	0.002	7	1.591						
Sri Lanka	21,413,249	889	0.004	9	1.012						
Romania	19,237,691	15778	0.082	1002	6.351						
Chile	19,116,201	31721	0.166	335	1.056						
Kazakhstan	18,776,707	5279	0.028	32	0.606						
Guatemala	17,915,568	1114	0.006	26	2.334						
Syria	17,500,658	47	0.000	3	6.383						
Cambodia	16,718,965	122	0.001	0	0.000						
Bolivia	11,673,021	2831	0.024	122	4.309						
Haiti	11,402,528	209	0.002	16	7.656						
Cuba	11,326,616	1804	0.016	78	4.324						
Dominican Republic	10,847,910	10900	0.1	402	3.688						
Czech Republic (Czechia)	10,708,981	8198	0.077	283	3.452						
Greece	10,423,054	2744	0.026	152	5.539						
Jordan	10,203,134	576	0.006	9	1.563						
Azerbaijan	10,139,177	2693	0.027	33	1.225						
Honduras	9,904,607	2100	0.021	116	5.524						
United Arab Emirates	9,890,402	19661	0.199	203	1.033						
Hungary	9,660,351	3313	0.034	425	12.83						
Tajikistan	9,537,645	728	0.008	21	2.885						
Belarus	9,449,323	24873	0.263	142	0.571						

Serbia	8,737,371	10243	0.117	220	2.148						
Bulgaria	6,948,445	2023	0.029	95	4.696						
Singapore	5,850,342	24671	0.422	21	0.085						
Norway	5,421,241	8152	0.15	228	2.797						
Oman	5,106,626	3721	0.073	17	0.457						
Ireland	4,937,786	23242	0.471	1488	6.402						
Panama	4,314,767	8616	0.2	249	2.89						
Kuwait	4,270,571	10227	0.239	75	0.733						
Croatia	4,105,267	2207	0.054	91	4.123						
Moldova	4,033,963	5154	0.128	182	3.531						
Georgia	3,989,167	642	0.016	11	1.713						
Bosnia and Herzegovina	3,280,819	2158	0.066	117	5.422						
Mongolia	3,278,290	42	0.001	0	0.000						
Armenia	2,963,243	3538	0.119	47	1.328						
Jamaica	2,961,167	505	0.017	9	1.782						
Qatar	2,881,053	25149	0.873	14	0.056						
Albania	2,877,797	876	0.03	31	3.539						
Lithuania	2,722,289	1491	0.055	50	3.353						
North Macedonia	2,083,374	1674	0.08	92	5.496						
Latvia	1,886,198	950	0.05	18	1.895						
Bahrain	1,701,575	5513	0.324	9	0.163						
Total	**5,494,701,651**	**1,422,397**	**0.026**	**50,702**	**3.565**						

Data have been collected on May 12, 2020 from https://www.worldometers.info/coronavirus/

*Countries collected from https://www.worldometers.info/world-population/population-by-country/

**Population of each country collected from https://www.worldometers.info/world-population/population-by-country/

Total cases are the COVID-19 positive until May 12, 2020 collected from https://www.worldometers.info/coronavirus/

% are the percentage positive cases of COVID-19 to the total number of populations

$ Death is the total number of deaths infected with COVID-19 until May 12, 2020 collected from https://www.worldometers.info/coronavirus/

$$ % is the percentage of the deaths to the total number of positive COVID-19

@ Countries adopt mass BCG vaccination as single or multiple doses

@@ Countries did not adopt mass BCG vaccination or stop it

BCG vaccine is recommended as single or as multiple doses, http://www.bcgatlas.org/

Table 2: Comparison of total positive cases for COVID-19 and deaths in population of countries adopted mass BCG vaccination policy and with those that did not adopt or stop mass BCG vaccination policy.

Countries that Currently Recommend Bcg Vaccination (N = 71)						Countries Do Not Recommend and Stop Bcg Vaccination (N=22)					
Country*	**Population****	**Total Cases#**	**%##**	**Deaths$**	**%$$**	**Country***	**Population****	**Total Cases#**	**%##**	**Deaths$**	**%$$**
China	1,439,323,776	83,449	0.006	4634	5.553	USA	331,002,651	2,462,554	0.744	124,281	5.047
India	1,380,004,385	472,985	0.034	14,907	3.152	Germany	83,992,949	193,254	0.23	9,003	4.659
Indonesia	273,523,615	49,009	0.018	2,573	5.25	UK	67,886,011	306,862	0.452	43,081	14.039
Pakistan	220,892,340	188,926	0.086	3,755	1.988	France	65,273,511	161,348	0.247	29,731	18.427

Brazil	212,559,417	1,192,474	0.561	53,874	4.518	Italy	60,461,826	239,410	0.396	34,644	14.471
Bangladesh	164,689,383	122,660	0.074	1,582	1.29	Spain	46,754,778	294,166	0.629	28,327	9.63
Russia	145,934,462	606,881	0.416	8,513	1.403	Canada	37,742,154	102,242	0.271	8,484	8.298
Mexico	128,932,753	196,847	0.153	24,324	12.36	Australia	25,499,884	17,449	0.068	693	3.972
Japan	126,476,461	18,024	0.014	963	5.343	Ecuador	17,643,054	51,643	0.293	4,274	8.276
Philippines	109,581,078	32,295	0.029	1,204	3.728	Nether-lands	17,134,872	49,804	0.291	6,097	12.242
Vietnam	97,338,579	352	0.000	0	0.000	Belgium	11,589,623	60,898	0.525	9,722	15.964
Turkey	84,339,067	191,657	0.227	5,025	2.622	Portugal	10,196,709	40,104	0.393	1,543	3.847
Iran	83,783,942	212,501	0.254	9,996	4.704	Sweden	10,099,265	62,324	0.617	5,209	8.358
Thailand	69,799,978	3,157	0.005	58	1.837	Austria	9,006,398	17,449	0.194	693	3.972
Myanmar	54,409,800	293	0.001	6	2.048	Israel	8,655,535	22,044	0.255	308	1.397
S Korea	51,269,185	12,563	0.025	282	2.245	Switzer-land	8,654,622	31,376	0.363	1,958	6.24
Colombia	50,882,891	77,113	0.152	2,491	3.23	Lebanon	6,825,445	1,644	0.024	33	2.007
Argentina	45,195,774	49,851	0.11	1,116	2.239	Denmark	5,792,202	12,615	0.218	603	4.78
Ukraine	43,733,762	39,014	0.089	1,051	2.694	Finland	5,540,720	7,167	0.129	327	4.563
Iraq	40,222,493	36,702	0.091	1,330	3.624	Slovakia	5,459,642	1,607	0.029	28	1.742
Afghani-stan	38,928,346	29,640	0.076	639	2.156	New Zea-land	4,822,233	1,519	0.031	22	1.448
Poland	37,846,611	32,821	0.087	1,396	4.253	Slovenia	2,078,938	1,541	0.074	109	7.073
Saudi Arabia	34,813,871	167,267	0.48	1,387	0.829	**Total**	**842,113,022**	**4139020**	**0.492**	**309170**	**7.47**
Uzbekstan	33,469,203	6,901	0.021	19	0.275						
Peru	32,971,854	264,689	0.803	8,586	3.244						
Malaysia	32,365,999	8,596	0.027	121	1.408						
Yemen	29,825,964	1,015	0.003	274	27						
Nepal	29,136,808	10,728	0.037	24	0.224						
Venezuela	28,435,940	4,366	0.015	38	0.87						
Taiwan	23,816,775	446	0.002	7	1.57						
Sri Lanka	21,413,249	2,001	0.009	11	0.55						
Romania	19,237,691	24,826	0.129	1,555	6.264						
Chile	19,116,201	254,416	1.331	4,731	1.86						
Kazakhstan	18,776,707	18,765	0.1	136	0.725						
Guatemala	17,915,568	14,819	0.083	601	4.056						
Syria	17,500,658	231	0.001	7	3.03						
Cambodia	16,718,965	130	0.001	0	0						
Bolivia	11,673,021	27,487	0.235	876	3.187						
Haiti	11,402,528	5,429	0.048	92	1.695						
Cuba	11,326,616	2,319	0.02	85	3.665						
Dominican Republic	10,847,910	28,631	0.264	691	2.413						
Czech Republic (Czechia)	10,708,981	10,777	0.101	343	3.183						
Greece	10,423,054	3,310	0.032	190	5.74						

Jordan	10,203,134	1,071	0.01	9	0.84						
Azerbaijan	10,139,177	14,305	0.141	174	1.216						
Honduras	9,904,607	14,571	0.147	417	2.862						
United Arab Emirates	9,890,402	46,133	0.466	307	0.665						
Hungary	9,660,351	4,114	0.043	576	14						
Tajikistan	9,537,645	5,630	0.059	52	0.924						
Belarus	9,449,323	59,945	0.634	362	0.604						
Serbia	8,737,371	13,235	0.151	263	1.987						
Bulgaria	6,948,445	4,242	0.061	209	4.927						
Singapore	5,850,342	42,623	0.729	26	0.061						
Norway	5,421,241	8,788	0.162	249	2.833						
Oman	5,106,626	33,536	0.657	142	0.423						
Ireland	4,937,786	25,396	0.514	1,726	6.796						
Panama	4,314,767	28,030	0.65	547	1.951						
Kuwait	4,270,571	41,879	0.981	337	0.805						
Croatia	4,105,267	2,388	0.058	107	4.481						
Moldova	4,033,963	15,078	0.374	495	3.283						
Georgia	3,989,167	914	0.023	14	1.532						
Bosnia and Herzegovina	3,280,819	3,676	0.112	173	4.706						
Mongolia	3,278,290	215	0.007	0	0.000						
Armenia	2,963,243	21,717	0.733	386	1.777						
Jamaica	2,961,167	678	0.023	10	1.475						
Qatar	2,881,053	90,778	3.151	104	0.115						
Albania	2,877,797	90,778	3.154	47	0.052						
Lithuania	2,722,289	1,804	0.066	78	4.324						
North Macedonia	2,083,374	5,445	0.261	259	4.757						
Latvia	1,886,198	1,111	0.059	30	2.7						
Bahrain	1,701,575	23,570	1.385	69	0.293						
Total	**5,494,701,651**	**5,108,013**	**0.093**	**166,661**	**3.263**						

Data have been collected on June 24, 2020 from https://www.worldometers.info/coronavirus/

*Countries collected from https://www.worldometers.info/world-population/population-by-country/

**Population of each country collected from https://www.worldometers.info/world-population/population-by-country/

Total cases are the COVID-19 positive until May 12, 2020 collected from https://www.worldometers.info/coronavirus/

% are the percentage positive cases of COVID-19 to the total number of populations

$ Death is the total number of deaths infected with COVID-19 until May 12, 2020 collected from https://www.worldometers.info/coronavirus/

$$ % is the percentage of the deaths to the total number of positive COVID-19

@ Countries adopt mass BCG vaccination as single or multiple doses

@@ Countries did not adopt mass BCG vaccination or stop it

BCG vaccine is recommended as single or as multiple doses, http://www.bcgatlas.org/

To reveal the efficacy of BCG vaccination in protection against SARS-CoV-2 infection, we analysed the global percentage of BCG vaccinated population and the current COVID-19 death rates. (Figure 1A) showed that approximately 70% of the total population, included in this investigation, were adopted BCG vaccination, whereas ~11% of the total population were not or stopped BCG vaccination. Approximately 19% of the total population remains unidentified and excluded from the analysis due to lack of data or other factors. Interestingly, a correlative association was noticed since 64% of COVID-19 cases were documented in the non-BCG vaccinated population, while only 33% of COVID 19 cases were documented in BCG vaccinated population (Figure 1B). Another stark association was observed when mortality cases in both groups were considered. In the case of non-BCG vaccinated population, the mortality rate was 82%, whereas 17% mortality was observed in BCG-vaccinated population (Figure 1C). Similarly, a comparable trend was observed when the same measures were taken 42 days later on June 24, 2020. Within the same population (Figure 1D), 1.2 (Figure 1E) and 0.5 (Figure 1F) times the COVID 19 infected and dead cases were documented in BCG vaccinated population, respectively.

The infection rate within the countries that did not adopt mass BCG vaccination was ~13-fold those adopted mass BCG vaccination (Figure 2A). Similarly, the death rate in the countries that did not adopt BCG vaccination policy was 2.3 times those adopted mass BCG vaccination (Figure 2A). Data collected on June 24, 2020 showed that the infection and death rates within the countries did not adopt BCG vaccination were 5.3 and 2.3-fold those adopted BCG vaccination, respectively (Figure 2B). Although the infection rate was reduced, the death rate still similar to the data collected on May 12, 2020 and the overall trend indicating a correlative association between the BCG vaccination and reduction in COVID-19 cases.

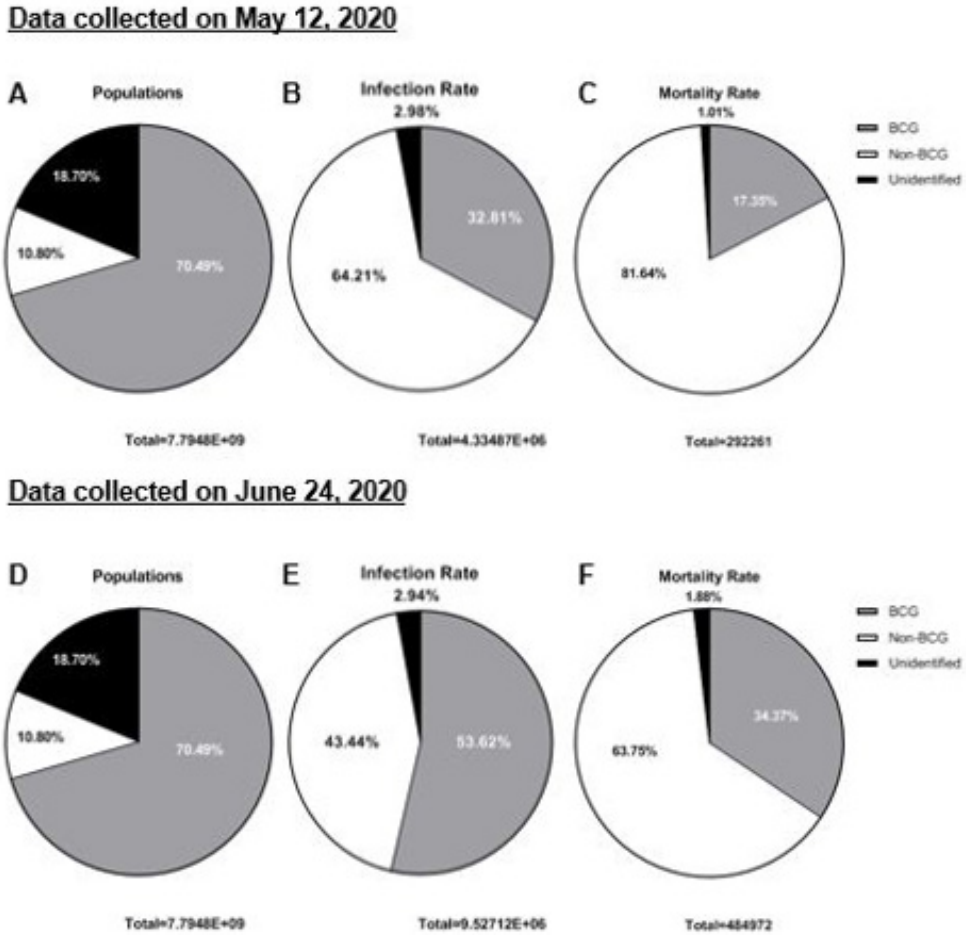

Figure 1: Association between BCG vaccination and prevalence of SARS-CoV-2 infection and death at two different time points. (A-C) Data collected on May 12, 2020 and (D-F) Data collected on June 24, 2020. (A and D) Represnts the percentage of population that adopt mass BCG vaccination (BCG) versus those do not adopt mass vaccination (Non-BCG) in relation to the total population. (B and E) The percentage of the infected population that adopt BCG and not adopt BCG vaccination policy to the total infected number of collected countries. (C and F) The percentage of deaths due to COVID-19 in relation to population adopt BCG versus those not-adopt BCG vaccination. Unidentified is the population for african countries excluded from the study due to the lack of accurate information.

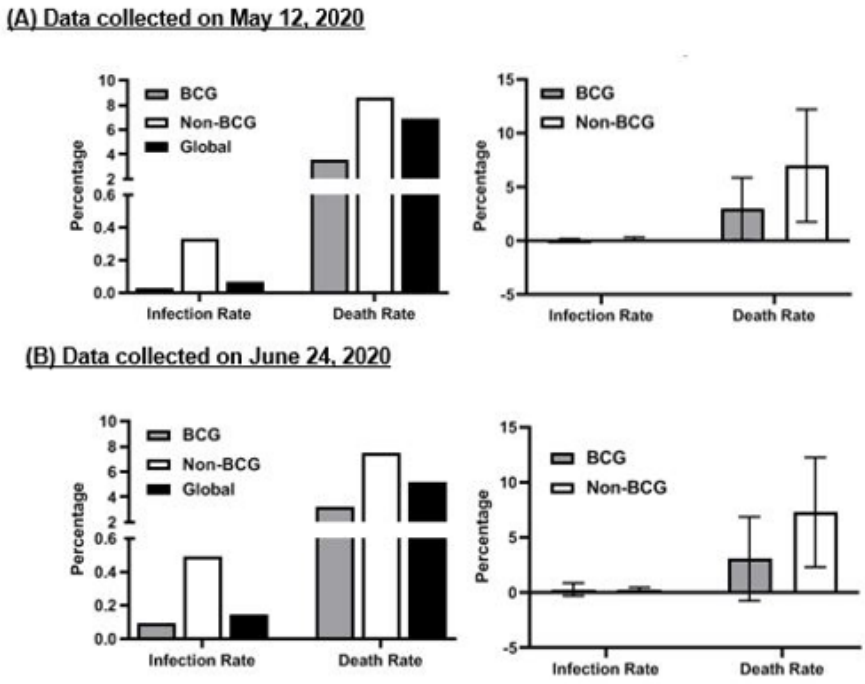

Figure 2: BCG vaccination in relation to COVID-19 infection and death rates at two different time points, (A) May 12, 2020 and (B) June 24, 2020. The percentage of infected population with SARS-CoV-2 that adopt mass BCG vaccination or not in relation to the total number of populations. Global infection is the percentage of the total infected population with SARS-CoV-2 to the total global population. Mortality rate is the rate of death due to the infected numbers in case of mass BCG / non-BCG vaccination. Global death is the portion of deaths to the overall SARS-CoV-2 infections.

BCG Vaccination Shall be an Important Factor In COVID-19 Incidence

During the current COVID-19 pandemic, suspected correlation has emerged between BCG vaccination and the spread of COVID-19. Countries like India, Pakistan, Russia, Japan, Vietnam, and Turkey, which are maintaining a mass BCG immunization program, have shown a lower incidence of COVID-19 cases, while countries like United States, Canada, UK, Spain, France, Netherlands, Belgium and Italy, which are discontinued the use of vaccine, have shown higher COVID-19 cases and mortalities. To support this further, Iran (started BCG vaccination in 1984) has shown a significant higher mortality rate among old-age population than those in China and India, who started this vaccination policy early in 1940s. Although an important factor could be the mass BCG vaccination policy followed by the countries showing lower SARS-CoV-2 infection rate [22], Other factors may be involved in this observation, including the low rate of testing, partial or full lockdown, social distancing and public adherence to these measures.

Other studies indicated similar correlations between BCG vaccinated countries and the reduced spread and severity of COVID-19 cases compared to higher mortality rate in case of countries without vaccination policy were reported [23, 24]. A recent study also noted that countries with a universal vaccination policy, such as Japan and Brazil, seemed to be impacted less by COVID-19 compared to those that did not, such as Italy, USA and Netherlands [25]. Though, this potential association lends a strong support to the notion that BCG vaccination could be a deciding factor in offering protection against SARS-CoV-2 infection. However, at the moment, this data needs to be cautiously endorsed in relation to other deciding factors including age, gender, ethnicity, obesity, and other co-morbidities that can be determinant in the infection outcome. Such data is currently not available and needs further investigations to get a clear picture of the prospective protection of BCG vaccination against SARS-CoV-2 infection. However, keeping in view a clear trend the notion that BCG vaccination affords preotection against SARS-CoV-2 infection demands further study to combat this deadly pandemic in both short and long terms.

Conclusion and Future perspectives

Our data analysis presented here is clearly indicated a potential association between BCG vaccination and COVID-19 prevalence. This pattern was further supported by several studies and the innate immunity mechanisms conferred by BCG vaccination. Despite these promising correlations, it is still early to draw a definitive conclusion and more experiments are required for proper valida-

tion. Furthermore, there are still questions to be addressed to justify the hypothesis supporting the protective action of BCG against COVID-19.

Countries like Australia and Germany which have no mass BCG immunization program showed lower morbidity and mortality rate due to SARS-CoV-2 infections. However, it could be due to imposition of early lockdown restrictions, young age of the infected cases, public adherence to social distancing procedure and most importantly the vigorous testing and contact tracing policies implemented by these countries. The innate immunity of people in low-income countries exposed to the high level of environmental pollutants compared to the developed world. Though not proved, climate and weather conditions could also play a part in the spread of the disease. Geographic location of countries may be a deciding factor too due to climate conditions.

Therefore, it is essential to devise models keeping in mind these variables to investigate the impact of BCG vaccination in relation to protection against COVID-19. It would be interesting to observe if the protection against COVID-19 provided by BCG could be long lasting or will fade away with time and the age for vaccination. These can also help to devise new plans especially for countries who have abandoned BCG vaccination in the last couple of decades. Lastely, immunological and epidemiological studies supporting or opposing these correlations are necessary to be conducted to present a global consensus in the fight against COVID-19.

Authors Contribution

Rauf Bhat, Sameh Soliman, Ahmed Fahmy and Mohamed Husseiny: Conceptualization, Methodology, Data collection and interpretation, Drafting, reviewing and approval of the final version for submission, all authors attest they meet the ICMJE criteria for authorship.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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