BCG vaccination and its possible effects on the acceleration of incidence and mortality by the new coronavirus: second step.

Carlos Eduardo Duarte* https://orcid.org/0000-0001-6671-0820

Guilherme Gaeski Passuello https://orcid.org/0000-0002-5547-3484

Raquel Almeida Lopes Neves https://orcid.org/0000-0003-2619-0036

Fernanda Cappi Santos Duarte https://orcid.org/0000-0001-6671-0820

Hospital Beneficência Portuguesa – Centro Avançado de Ritmologia e Eletrofisiologia – São Paulo/SP - Brazil

*Corresponding author: carlosduarte@ritmologiacare.com.br

ABSTRACT

Introduction: The pandemic caused by the new coronavirus brought difficulties to global health and the economy. The race for an effective therapy to control the disease is launched, and an understanding of the pathophysiology is necessary. The BCG (bacillus Calmette–Guérin) vaccine activates and modulates innate immunity, and its protective effect against the new coronavirus should be investigated. **Objective:** To compare the incidence, mortality, and lethality rates of COVID-19 according to the vaccination program for BCG of the main countries affected by the pandemic. **Methods:** The second of three phases of a data survey was carried out from official sources on the number of cases and number of deaths by COVID-19 between April 11 and May 11, 2020, and the incidence, mortality and lethality rates were calculated and compared among predefined groups according to their BCG vaccination programs. In the same way, the acceleration rate between the groups in the period under analysis was performed. **Results:** Similar to the results found in the first phase in April, the countries without an active BCG vaccine program had, on average, 3.96, 9.34, and 2.35 ($p < 0.001$) higher ratios in the incidence, mortality and lethality rates, respectively. **Conclusion:** There is a protective connection between the presence of active BCG vaccination programs and the number of cases and deaths per inhabitant in the countries studied, showing a possible cross effect of innate immunity against the new coronavirus.

KEYWORDS: COVID-19, Coronavirus, BCG vaccine, Incidence, Lethality.

INTRODUCTION

The first lessons learned, the fruit of epidemiological information, regarding COVID-19, are that the elderly with systemic atrial hypertension (SAH) and diabetes mellitus (DM) is the main risk groups for an unfavorable outcome[1]. Descriptions of severe cases in young people, adolescents, and adults without comorbidities[2] sharpen other hypotheses.

The pandemic progress has been made from East to West, and the different mortality and lethality rates in border regions need to be clarified[3].

The response of the so-called innate immunity composed of macrophages, lymphocytes (CD4+), and natural killers must be able to eliminate the virus[4]. The key to the broad spectrum of different impacts in border countries, as well as among individuals with similar exposures, should be found in how the immune system reacts to infection by SARS-CoV-2. To this end, understanding the quality of the individual or collective innate response is of paramount importance. For this purpose, the authors tried to correlate the epidemic impact of different countries in three consecutive months with their vaccine status of BCG (bacillus Calmette–Guérin), which acts mainly by activating or training innate immunity[5].

HYPOTHESIS

Countries with expanded and continuous BCG vaccination status will have less impact on COVID-19 incidence, mortality, and/or lethality rates compared to countries that have abandoned or never had vaccination programs.

METHODOLOGY

Surveys of case numbers and deaths by COVID-19 were conducted between December 31, 2019, and April 11, 2020, and between April 11 and May 11, 2020. The countries selected for this survey were the same as those published in April 2020[6], this time divided into eight groups for comparisons according to specific characteristics described below:

- Group 1.1: United States, Spain, and the United Kingdom = Countries chosen because of their territorial proximity and vaccine situations different from those in group 1.2.
- Group 1.2: Mexico, Portugal, and Ireland = Countries chosen because of their territorial proximity and vaccine situations different from those in group 1.1.

- Group 2.1: United States, France, Germany, Spain, Italy, United Kingdom, Belgium, Iran, Switzerland, and the Netherlands = Countries that have vaccination programs for specific groups only or have abandoned their programs.
- Group 2.2: Mexico, Ireland, Portugal, Chile, Hungary, Poland, Turkey, South Korea, Japan, Russia, Israel, Brazil, and Austria = Countries with existing BCG vaccination programs.
- Group 3.1: United States, France, Germany, Spain, Italy, United Kingdom, Belgium, Iran, Switzerland and the Netherlands = Same group 2.1, repeated for comparison with the countries in group 3.2.
- Group 3.2: Mexico, Ireland, Portugal, Chile, Hungary, Poland, Turkey, South Korea, Japan, Russia, Israel, Brazil, Austria, India, China = Countries from group 2.2 including China and India.
- Group 4.1: United States, Italy, Belgium, Netherlands = Countries from group 2.1 that never had universal vaccination programs.
- Group 4.2: France, Germany, Spain, United Kingdom, Iran, and Switzerland = Countries from group 2.1 that have had vaccination programs but have discontinued them.

For the description of the profile of each group, the following measures were presented: incidence (Eq. 1), mortality (Eq. 2), and lethality rates (Eq. 3). For each rate, the confidence interval was calculated using the confidence interval method for proportions.

$$Incidence\ rate\ = \frac{Number\ of\ new\ cases\ of\ the\ disease\ in\ a\ population\ throughout\ time}{Number\ of\ people\ at\ risk\ of\ developing\ the\ disease\ over\ the\ period}$$

$$Mortality\ rate\ = \frac{Total\ number\ of\ deaths\ for\ a\ given\ cause\ over\ the\ period}{Estimated\ population\ of\ a\ given\ area}$$

$$Lethality\ rate\ = \frac{Number\ of\ deaths\ from\ the\ disease}{Number\ of\ cases\ of\ the\ disease}$$

The incidents ratio obtained by dividing the incidence rates of the compared groups was presented for the comparison of the interest groups. The mortality and lethality ratios are

also presented. To test the null hypothesis that the rates are equal between groups of interest, the Z-test was used to compare proportions.

For analysis of the acceleration/inhabitant variable, the following descriptive measures are presented: mean, standard deviation, median (q50), and quartiles (q25 and q75). The groups at this stage were compared using the Mann–Whitney test to compare independent groups.

The analyses were performed using the software R version 3.6.3, and a significance level of 5% was considered.

RESULTS

The incidence, mortality, and lethality rates for each group were calculated, as shown in Table 1. To facilitate the interpretation of results, incidence and mortality numbers are presented based on 100,000 inhabitants and lethality numbers based on 100 cases.

Table 1. Descriptive table of groups regarding incidence, mortality, and lethality rates.

Group	Population	Cases	Deaths	Incidence (CI 95%)	Mortality (IC 95%)	Lethality (CI 95%)
1.1	441,473,267	1,807,931	139,182	409.522 (408.927;410.118)	31.527 (31.361;31.693)	7.698 (7.66;7.737)
1.2	141,725,718	85,836	6,076	60.565 (60.161;60.972)	4.287 (4.18;4.397)	7.079 (6.908;7.253)
2.1	771,322,365	2,613,735	227,038	338.864 (338.454;339.275)	29.435 (29.314;29.556)	8.686 (8.652;8.721)
2.2	843,964,174	721,850	26,582	85.531 (85.334;85.728)	3.15 (3.112;3.188)	3.682 (3.639;3.726)
3.1	771,322,365	2,613,735	227,038	338.864 (338.454;339.275)	29.435 (29.314;29.556)	8.686 (8.652;8.721)
3.2	3,582,014,174	876,628	33,513	24.473 (24.422;24.524)	0.936 (0.926;0.946)	3.823 (3.783;3.863)
4.1	417,844,066	1,662,214	125,218	397.807 (397.204;398.411)	29.968 (29.802;30.134)	7.533 (7.493;7.573)
4.2	353,478,299	951,521	101,820	269.188 (268.648;269.729)	28.805 (28.629;28.983)	10.701 (10.639;10.763)

CI: Confidence interval.
*Incidence and mortality calculated based on 100,000 inhabitants.
**Lethality calculated based on 100 cases.

Among the countries analyzed, those with no vaccination program in place had the highest incidence and mortality rates (group 1.1) and the highest lethality (group 4.2). On the other hand, the countries that have their programs in place presented lower incidence, mortality, and lethality rates.

Table 2 presents the incidence, mortality, and lethality ratios for the pairs of groups to be compared, as well as the p-value resulting from the hypothesis test for comparisons of two proportions. Such a result indicates that there is a difference between all pairs of groups compared.

Table 2. Comparative table with incidence, mortality and lethality ratios, and respective p-values for comparisons of proportion.

	Incidence ratio	**p-value**	**Mortality ratio**	**p-value**	**Lethality ratio**	**p-value**
Group 1.1 vs 1.2	6.762	< 0.001	7.354	< 0.001	1.088	< 0.001
Group 2.1 vs 2.2	3.962	< 0.001	9.345	< 0.001	2.359	< 0.001
Group 3.1 vs 3.2	13.846	< 0.001	31.461	< 0.001	2.272	< 0.001
Group 4.1 vs 4.2	1.478	< 0.001	1.040	< 0.001	0.704	< 0.001

The main comparisons between countries in the groups 2.1 and 2.2 or 3.1 and 3.2 support the central hypothesis of this work, generating higher incidence, mortality, and lethality ratios in countries without vaccination programs. When comparing groups 1.1 and 1.2 (Table 3), for example, the incidence ratio indicates that the incidence in group 1.1 is 6.762 times higher than in group 1.2. Also, mortality and lethality are 7.354 and 1.088 times higher in group 1.1 than in group 1.2, respectively. It can be seen that there was no difference between acceleration/inhabitants in this comparison.

Table 3. Detailed measurements for accelerations by groups (group 1.1 vs. group 1.2).

	Group 1.1 (n = 3)					**Group 1.2 (n = 3)**					
	Mean	**SD**	**Q50**	**Q25**	**Q75**	**Mean**	**SD**	**Q50**	**Q25**	**Q75**	**p-value**
Last 30 days											
Cases	0.25352	0.06546	0.28477	0.23153	0.29114	0.16779	0.16145	0.13180	0.07958	0.23800	0.70
Deaths	0.02949	0.00826	0.02535	0.02473	0.03218	0.01250	0.01279	0.00766	0.00525	0.01732	0.40
Apr 11 (G1) vs May 11 (G2)											
Cases	0.03511	0.02564	0.02109	0.02032	0.04290	0.05066	0.04350	0.05489	0.03004	0.07339	1.00
Deaths	0.01176	0.01126	0.00991	0.00573	0.01687	0.00421	0.00362	0.00354	0.00226	0.00583	0.40

Tables 3, 4, and 5 present the descriptive measures for acceleration/inhabitants in the interest groups, as well as the result of the interest groups comparison test. Table 4 shows the results of the comparison between groups 2.1 and 2.2. It can be observed that there is evidence of a statistical difference between accelerations in the last 30 days for both cases (p

= 0.008) and deaths (p = 0.001). Group 2.1 has mean and median acceleration values higher than group 2.2. On the other hand, when comparing the acceleration up to April 11 in group 2.1 with the acceleration up to May 11 in group 2.2, it is observed that there is no evidence of a difference between the accelerations of cases (p = 0.284). However, there is evidence of the difference between the accelerations of deaths (p = 0.001), with the acceleration being higher in group 2.1.

Table 4. Detailed measurements for accelerations by groups (group 2.1 vs. group 2.2).

	Group 2.1 (n = 10)					**Group 2.2 (n = 13)**					
	Mean	**SD**	**Q50**	**Q25**	**Q75**	**Mean**	**SD**	**Q50**	**Q25**	**Q75**	**p-value**
Last 30 days											
Cases	0.19594	0.08755	0.20286	0.13633	0.27523	0.08964	0.09367	0.07536	0.02737	0.13180	**0.008**
Deaths	0.02279	0.01533	0.02217	0.01300	0.02504	0.00474	0.00700	0.00284	0.00150	0.00384	**0.001**
Apr 11 (G1) vs May 11 (G2)											
Cases	0.04299	0.03829	0.03848	0.01993	0.06068	0.02589	0.02607	0.01478	0.00727	0.03305	0.284
Deaths	0.01081	0.00834	0.00961	0.00454	0.01216	0.00169	0.00214	0.00098	0.00065	0.00178	**0.001**

Table 5 presents the results of the comparison between groups 3.1 and 3.2. Similarly to what is observed in Table 4, it is possible to observe that there is evidence of a statistical difference between the accelerations in the last 30 days for both cases (p = 0.003) and deaths (p = 0.001), and the mean and median values of acceleration are higher in group 3.1 in relation to group 3.2. Regarding the comparisons of the acceleration up to April 11 in group 3.1 vs. acceleration up to May 11 in group 3.2, a difference was identified only for the acceleration of deaths (p = 0.001), and the acceleration of group 3.1 is higher than that of group 3.2.

Table 5. Detailed measurements for accelerations by groups (group 3.1 vs. group 3.2).

	Group 3.1 (n = 10)					**Group 3.2 (n = 15)**					
	Mean	**SD**	**Q50**	**Q25**	**Q75**	**Mean**	**SD**	**Q50**	**Q25**	**Q75**	**p-value**
Last 30 days											
Cases	**0.19594**	0.08755	0.20286	0.13633	0.27523	**0.07804**	0.09197	0.02960	0.01552	0.12873	**0.003**
Deaths	**0.02279**	0.01533	0.02217	0.01300	0.02504	**0.00413**	0.00668	0.00201	0.00095	0.00383	**0.001**
Apr 11 (G1) vs May 11 (G2)											
Cases	**0.04299**	0.03829	0.03848	0.01993	0.06068	**0.02250**	0.02575	0.01369	0.00344	0.03204	0.129
Deaths	**0.01081**	0.00834	0.00961	0.00454	0.01216	**0.00147**	0.00207	0.00077	0.00033	0.00161	**0.001**

DISCUSSION

A study was published in which the authors made a cut of the analysis on March 21 and found similar correlations between the importance of BCG vaccination and the incidence and lethality of COVID-19[7]. However, although the source of the data was similar, this work used initial acceleration rates of the number of cases and the number of deaths up to April 11 and subsequent accelerations from April 11 to May 11 (Figs. 1 and 2).

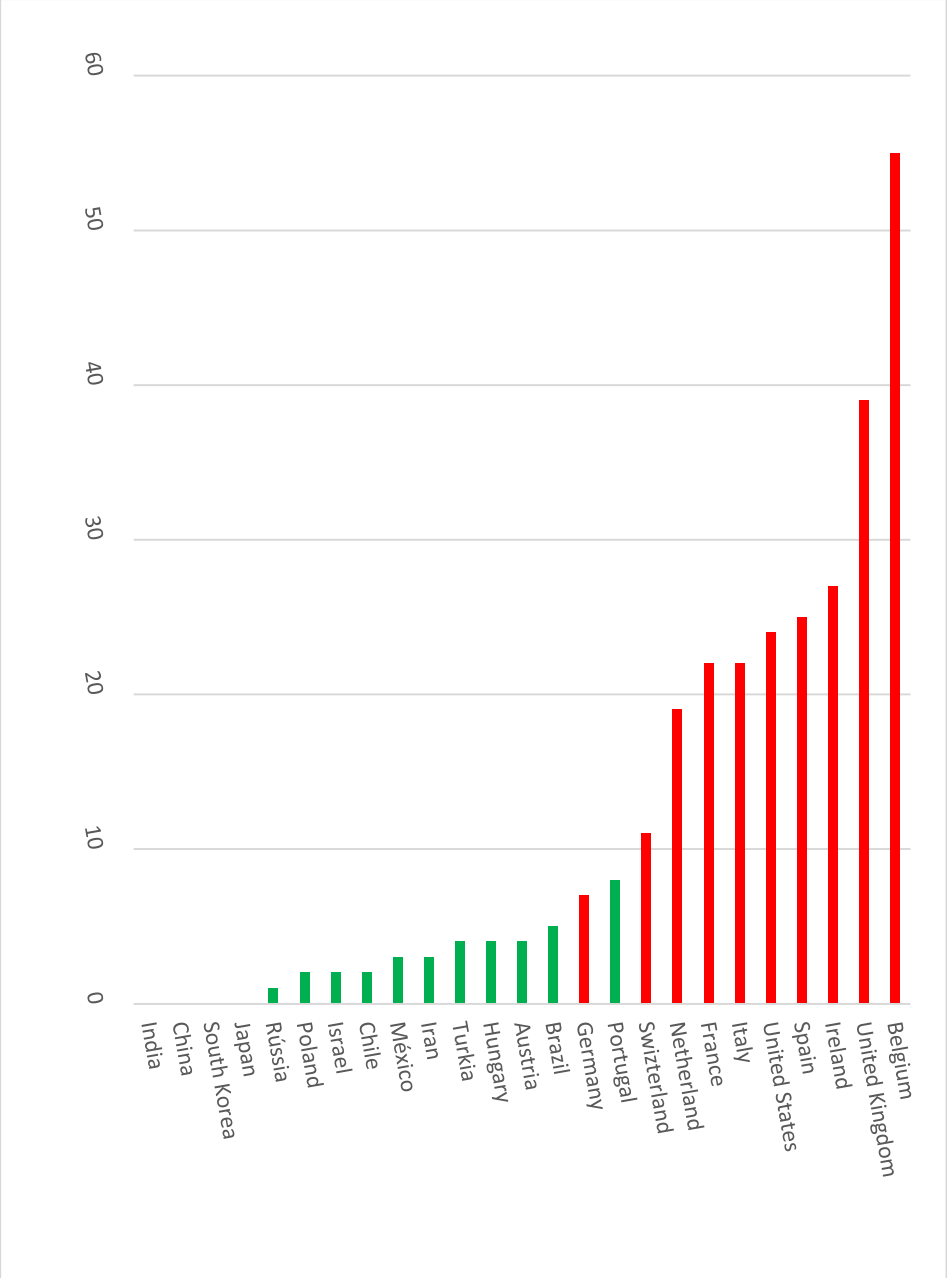

Figure 1. Acceleration of the mortality rate (last 30 days) P/d²/100,000 inhab.

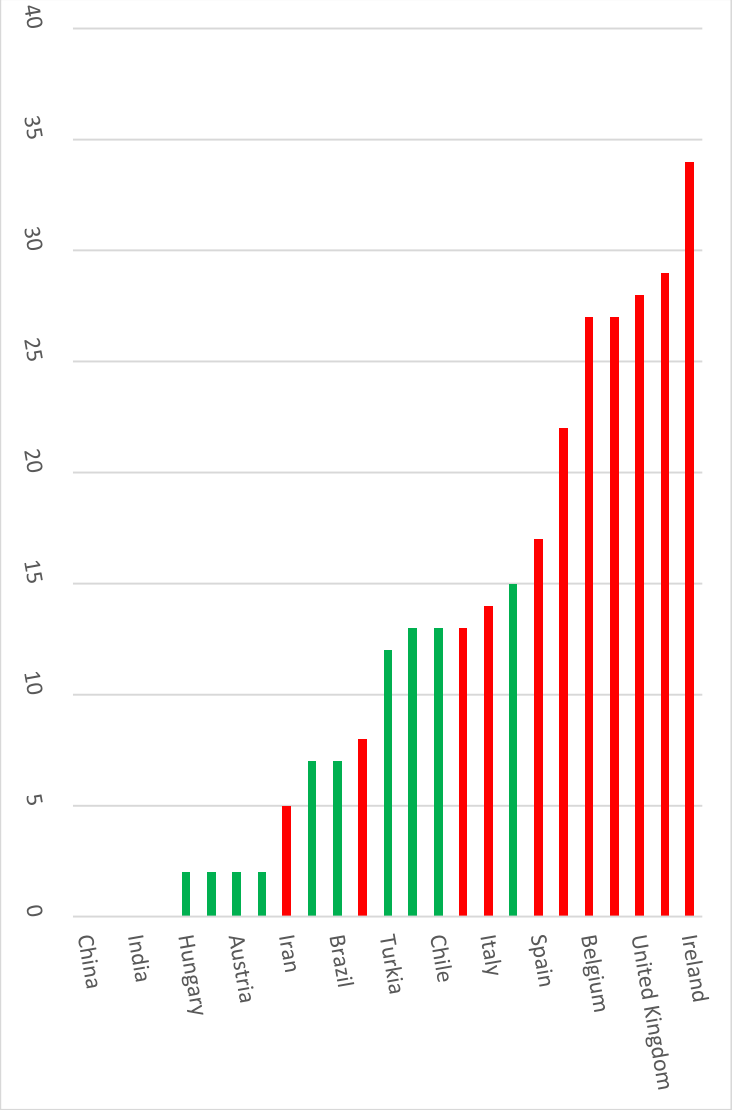

Figure 2. Acceleration of the incidence rate (last 30 days) P/d²/100,000 inhab.

One of the biggest criticisms to the work published by this group regarding the first phase of this work[6] was that, in the analysis of April 11th, the highest incidence, mortality and lethality rates of the groups of countries without an active program would be because these countries were on average ten days ahead of the group of countries with an active program. In this second phase, in order to minimize the time bias, the strategy adopted was to compare the current data, from April 11 to May 11, of countries with active vaccination with the data up to April 11 of countries without active vaccination. As a result, the average is now 20 days ahead of the possible bias of the previous work. Thus, Tables 3, 4, and 5 show that, even though they advance in time, the countries in the active vaccination group remain with

the reasons for the higher rates. Data that refute the idea of temporal correlation and maintenance of the same behavior of severity of the disease impact.

A randomized controlled Israeli study showed that the incidence was not different among young people born three years before and three years after the interruption of their vaccination program. The authors discuss that the results cannot be used to assess the impact or severity of COVID-19. The conclusion of this study only reaffirms the results found here because the accelerations of cases were not different in situations where the mortality and lethality ratios were (Table 2). This fact reinforces the idea that the BCG vaccine does not prevent the spread of the disease, but probably protects from a severe outcome[8].

The new analysis included in the May 2020 evaluation with non-BCGs countries (Fig. 3), where countries such as Belgium, the United States, the Netherlands, and Italy, which have never had vaccination programs, are compared to those that have discontinued their programs. The result was consistent with the same acceleration of cases and deaths (Table 3) but with higher incidence and mortality (Table 2).

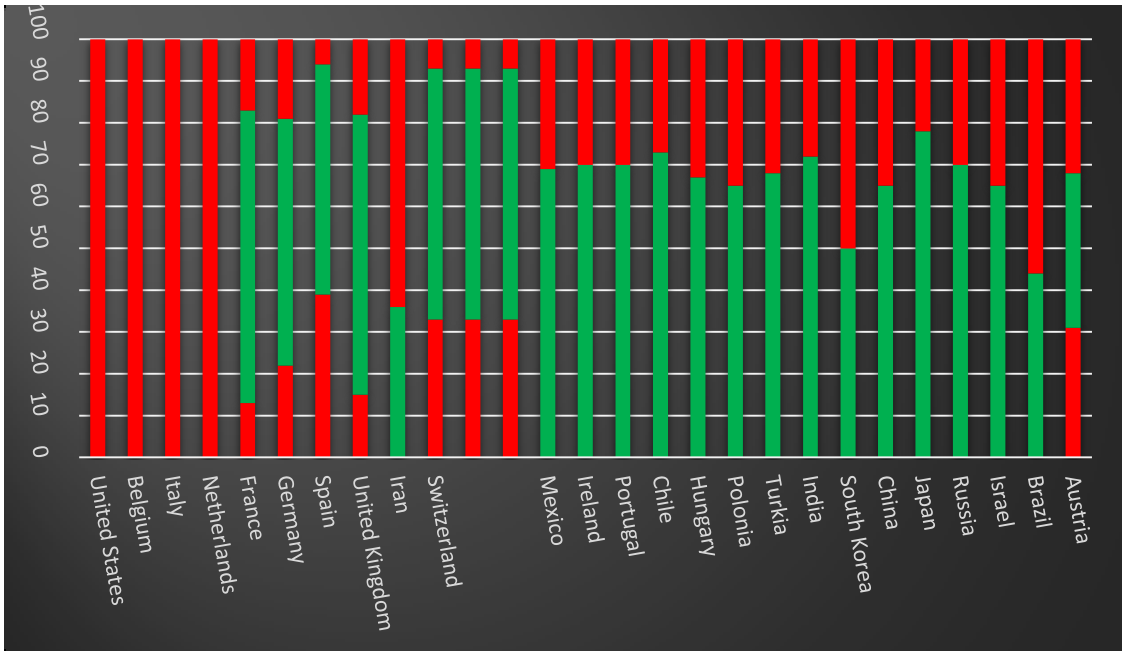

Figure 3. Age range under vaccination by BCG in different groups.

This study reveals that BCG vaccination coverage may have different impacts in different countries and could bring plausibility to some unanswered questions such as the most significant impact on older adults where BCG immune memory is more likely to be lost; people and regions with similar exposure and contamination results with different impacts; as well as highlighting the result of greater lethality in countries with better health

system conditions and without vaccination coverage. A double-blind, randomized trial with tuberculin test (PPD) as a vaccine memory parameter could be proposed for evidence accumulation.

The central bias of the first paper published in April by this group was minimized with the temporal correction in the evolution of the pandemic and, even with temporal correction, a statistically significant difference in favor of countries with active BCG vaccination coverage was evidenced.

CONCLUSION

The lower numbers of cases and deaths by COVID-19 in countries that have a BCG vaccination program in place is instigating and biologically plausible. So far, with pandemic numbers in progress, a correlation has been found between the coverage of such programs and the number of cases and deaths in the countries studied over the two consecutive months. Prospective and controlled studies should be stimulated quickly, as BCG may be the main weapon for severe case prevention until a specific vaccine is developed.

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