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

Carlos Eduardo Duarte[1,*], Raquel Almeida Lopes Neves[1], Fernanda Cappi Santos Duarte[1], Guilherme Gaeski Passuello[1]

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

*Corresponding author: carlosduarte@ritmologiacare.com.br

Duarte CE: https://orcid.org/0000-0001-6671-0820

Neves RAL: https://orcid.org/0000-0003-2619-0036

Duarte FCS: https://orcid.org/0000-0002-7592-0640

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

ABSTRACT

Introduction: BCG vaccine (bacillus Calmette–Guérin) has been developed against tuberculosis and proven to be used for other purposes by activating and/or training innate immunity. The protective effect against the new coronavirus should be investigated and tested while a specific vaccine is not available. **Objective:** To compare the acceleration rates of incidence and lethality of COVID-19 according to the vaccination program for BCG of the main countries affected by the pandemic. **Methods:** Part one of three of the data survey from official sources on the number of cases and number of deaths by COVID-19 between December 31, 2019 and April 11, 2020, being calculated the incidence, mortality and lethality acceleration rates, and compared among predefined groups according to their BCG vaccination programs. **Results**: Countries without a vaccination program in place or that never had one for BCG had incidence and mortality acceleration rates of 21.36 and 53.21 times higher ($p < 0.001$), respectively, than the same rates in countries with a universal vaccination program. In addition, patients with an expanded vaccination program had a 43% lower mortality rate ($p < 0.001$) compared to countries with a vaccination program at birth only. **Conclusion:** There is a correlation between the coverage of BCG vaccination programs and the acceleration in the number of new cases and deaths in countries, showing a possible protective factor in places with existing BCG vaccination programs.

Keywords: COVID-19, Coronavirus, BCG Vaccine, Incidence, Lethality.

INTRODUCTION

A series of pneumonia cases of unknown etiology appeared in the city of Wuhan, in Hubei province, China, in December 2019, where the new coronavirus was identified and named as 2019-nCoV. Since this is a new strain of the virus, and we lost the opportunity to isolate the first cases, direct combat became very difficult. The first epidemiological information was that the elderly with systemic atrial hypertension and diabetes mellitus would be the main risk groups[1].

Descriptions of severe cases in young people, adolescents, and adults without comorbidities[2] question the hypothesis that fragility is paramount for a tough outcome.

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].

Numerous hypotheses are made daily and range from the geographical position, climate, altitude, age pyramid, and the population's capacity to adhere to public policy measures such as social distancing and/or quarantine[4].

The coronavirus infection reaches humans through mucous membranes. It is intuitive that the host's response, whether related to form or intensity, brings out its clinical expression and after the passage through the mucosa, a mechanical barrier, the so-called innate immunity composed by macrophages, lymphocytes (CD4+) and natural killers, must be able to eliminate the virus and/or present antigens to antibody-producing cells, humoral immunity, so that infection is banned and permanent protection is created[5]. The loss of this battle or an exacerbated reaction of the immune system itself can lead to death.

A treatment that improves the innate immune response will increase the efficiency of the immune system as soon as the virus enters the bloodstream. To this end, understanding the quality of the individual or collective innate response is of paramount importance. In order to achieve this, the authors have correlated the epidemiological moment of the

pandemic in different countries with their BCG (bacillus Calmette–Guérin) vaccination status, which mainly acts by activating or training innate immunity[6].

HYPOTHESIS

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

METHODOLOGY

COVID-19 primarily surveyed the number of cases and the number of deaths between December 31, 2019, and April 11, 2020. The same data should be compared on May 11 and June 11.

The data source is official and published by John Hopkins Hospital[3]. Countries were chosen in descending order from the number of cases published on April 11, 2020, and divided into two categories: In the first, countries with no tuberculosis vaccination programs or with low vaccination coverage[7]. In the second, the countries with the highest vaccine coverage either by vaccine applied at birth or two or more life stages. The categories were divided into seven subgroups, which are composed of the countries mentioned above, followed by the reasons for grouping them (Table 1):

- **Group 1:** United States, Spain, Italy, Germany, France, Iran, United Kingdom, Belgium, Switzerland and the Netherlands = Countries that have vaccination programs only for specific groups such as the United States or have abandoned their programs;
- **Group 2:** China, Brazil, Portugal, South Korea, Russia, Israel, Ireland, Chile, Japan, Mexico, Hungary, Turkey, Austria, Poland, and India = Countries that have

vaccination programs in place or have high vaccination coverage above 90% such as Austria.

    - Group 2a: The same countries in Group 2, excluding India and China, due to population size.

- **Group 3:** Hungary, Chile, Russia and Portugal = Countries that conduct an extended vaccination scheme and in two moments of life[7,8];
- **Group 4:** China, Brazil, South Korea, Israel, Ireland, Japan, Mexico, Turkey, Austria, Poland and India = Countries with a vaccination scheme at birth only;
- **Group 5:** the United States and Mexico, Spain and Portugal and the United Kingdom and Ireland = Countries chosen due to their territorial proximity and different vaccination situations, which were subdivided into two groups as follows:
    - Group 5.1: United States, Spain, and the United Kingdom.
    - Group 5.2: Mexico, Portugal, and Ireland.

For the profile description of each group, the following measures are presented: incidence, mortality, and lethality rates. Such measures are calculated as follows[9]:

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

$$Mortality\ rate = \frac{Total\ number\ of\ deaths\ for\ a\ given\ cause}{throughout\ time, the\ estimated\ population\ of\ a\ given\ area}$$

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

For each rate, the confidence interval was calculated using the confidence interval method for proportions[10].

To compare the groups of interest, the ratio of incidences, obtained by the division between the incidence rates of the groups that are being compared, are presented. The reasons for mortality and lethality are also presented.

To test the null hypothesis that the rates are equal between groups of interest, the Z test was used for comparison of proportions[10]. The analyses were performed using R software version 3.6.3[11], and a significance level of 5% was considered.

RESULTS

Table 1 presents descriptive incidence, mortality, and lethality rates for each interest group. Incidence and mortality values are presented based on 100,000 inhabitants and lethality values based on 100 cases.

Table 1. Descriptive table of the groups concerning the incidence, mortality, and lethality rates on April 11, 2020.

Group	Population	Cases	Deaths	Incidence (CI 95%)	Mortality (CI 95%)	Lethality (CI 95%)
1	771,322,365	1,163,501	89,362	150.845 (150.571;151.119)	11.586 (11.51;11.662)	7.68 (7.632;7.729)
2	3,582,014,174	252,993	7,799	7.063 (7.035;7.09)	0.218 (0.213;0.223)	3.083 (3.016;3.151)
2a	843,964,174	162,390	4,207	19.241 (19.148;19.335)	0.498 (0.484;0.514)	2.591 (2.514;2.669)
3	185,962,987	36,867	691	19.825 (19.623;20.029)	0.372 (0.345;0.401)	1.874 (1.739;2.019)
4	3,396,051,187	216,126	7,108	6.364 (6.337;6.391)	0.209 (0.204;0.214)	3.289 (3.214;3.365)
5.1	441,473,267	683,556	43,816	154.835 (154.469;155.203)	9.925 (9.832;10.018)	6.41 (6.352;6.468)
5.2	141,725,718	27,405	955	19.337 (19.109;19.567)	0.674 (0.632;0.718)	3.485 (3.272;3.71)

CI: Confidence interval.

*Incidence and mortality calculated based on 100,000 inhabitants.

**Lethality calculated based on 100 cases.

The countries of group 5.1 (the USA, Spain, and the UK) were selected for comparison with their peers (Mexico, Portugal, and Ireland) and presented higher incidence and mortality rates among the groups studied, with 154.835 cases per 100,000 inhabitants and 9.925 deaths per 100,000 inhabitants. When comparing groups 5.1 and 5.2, it was observed that incidence, mortality, and lethality are higher in group 5.1 than in group 5.2. presenting an incidence of 8.01 times higher, mortality 14.73 times higher, and lethality 1.84 times higher than group 6.2 ($p < 0.001$) (Table 2).

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 vs group 2	21.36	< 0.001	53.21	< 0.001	2.49	< 0.001
Group 1 vs group 2a	7.84	< 0.001	23.24	< 0.001	2.96	< 0.001
Group 1 vs group 3	7.61	< 0.001	31.18	< 0.001	4.10	< 0.001
Group 1 vs group 4	23.70	< 0.001	55.35	< 0.001	2.34	< 0.001
Group 3 vs group 4	3.12	< 0.001	1.78	< 0.001	0.57	< 0.001
Group 5.1 vs group 5.2	8.01	< 0.001	14.73	< 0.001	1.84	< 0.001

Regarding mortality, groups 1 and 5.1 have the highest values, 11.586 and 9.925 deaths per 100,000 inhabitants, respectively. Group 4 is the one that presents the lowest mortality, 0.209 deaths per 100,000 inhabitants, and here the fact that China is included may reflect this result due to its large number of inhabitants, but group 3 (countries with an

expanded vaccine scheme) is the one with the lowest lethality rate, with 1.87 deaths per 100 cases ($p < 0.001$).

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.

Comparing group 1 with group 2, the ratio estimates indicate that the incidence rate in group 1 is 21.36 times higher than the same rate in group 2. Also, group 1 has a mortality rate of 53.21 times higher and a lethality rate 2.49 times higher than group 2. This behavior is likely to be related to the populations of China and India, and the ratio will be reduced to 7.84 in the incidence ratio and 23.24 in the mortality ratio when excluded for calculation purposes; however, the maintenance of the lethality ratio occurs independently of the groups.

Another interesting data is given when comparing groups 3 and 4. Group 3 presents an incidence rate 3.12 times higher and mortality coefficient 43% lower ($p < 0.001$) and may reflect the higher diagnostic capacity of the country but with less severity.

When comparing groups 1 with 2a and 1 with 3, it was found that the incidence ratio is around eight and the mortality ratio 23.24 and 31.18 times, respectively.

The calculations for a better understanding of the speed variations of the incidence and lethality curves in the different countries were made considering the initial acceleration (IA), in cases/d²/100,000 inhab., extracted from the date of case 1 until case 100 and the final acceleration (FA), in cases/d²/100,000 inhab., extracted from the date of the case 101 until the cases of April 11, 2020 (Figs. 1–3). Subsequently, the ratio between the acceleration of current deaths (cases > 101) and the acceleration of initial deaths (cases 0–100) was obtained. This calculation generates a nondimensional value, where countries with values > 1 are in the phase of increasing the speed of cases and values < 1 are the ones that the speed of mortality

per 100,000 inhabitants decreased. Only four countries: Japan, Israel, Chile, and Hungary (Fig. 4) had values < 1; the United States had the highest ratio with an index of 354.

Figure 1. Initial acceleration of diagnosis of the cases 0–100 in different countries with two categories of vaccination coverage.

Figure 2. Diagnostic acceleration of > 101 cases in different countries with two categories of vaccine coverage.

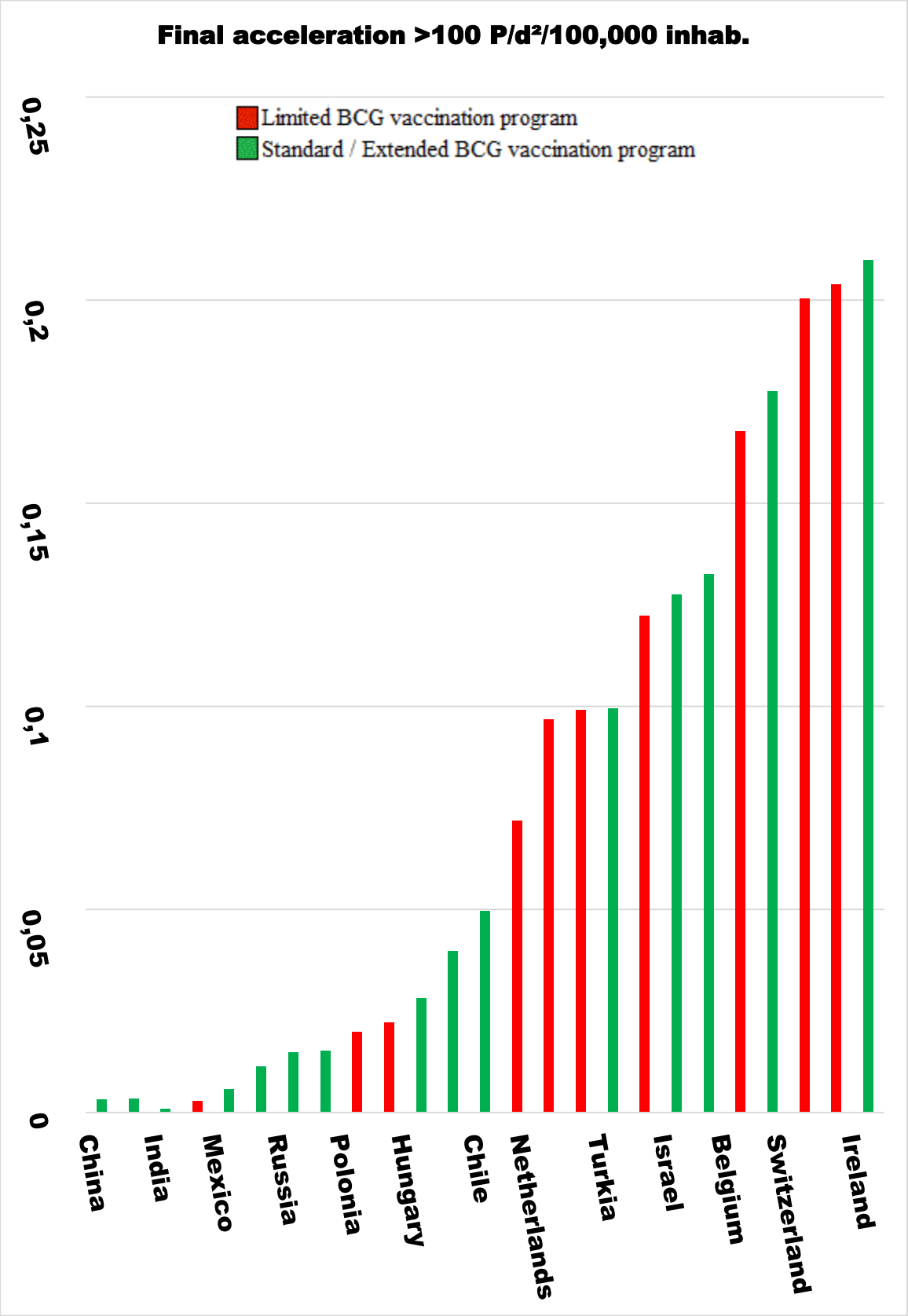
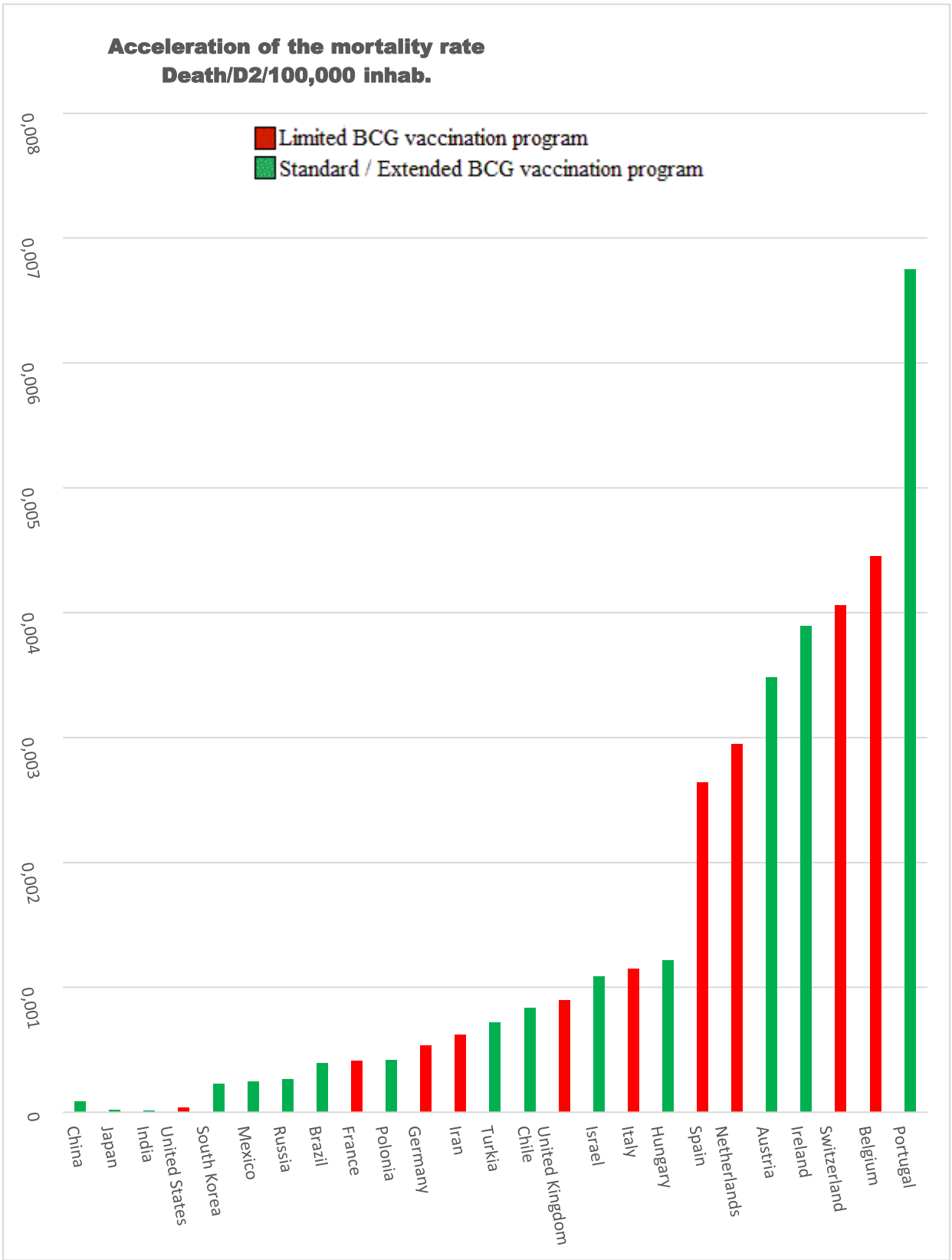


Figure 3. Initial acceleration of deaths from 0–100 in different countries with two categories of vaccination coverage.



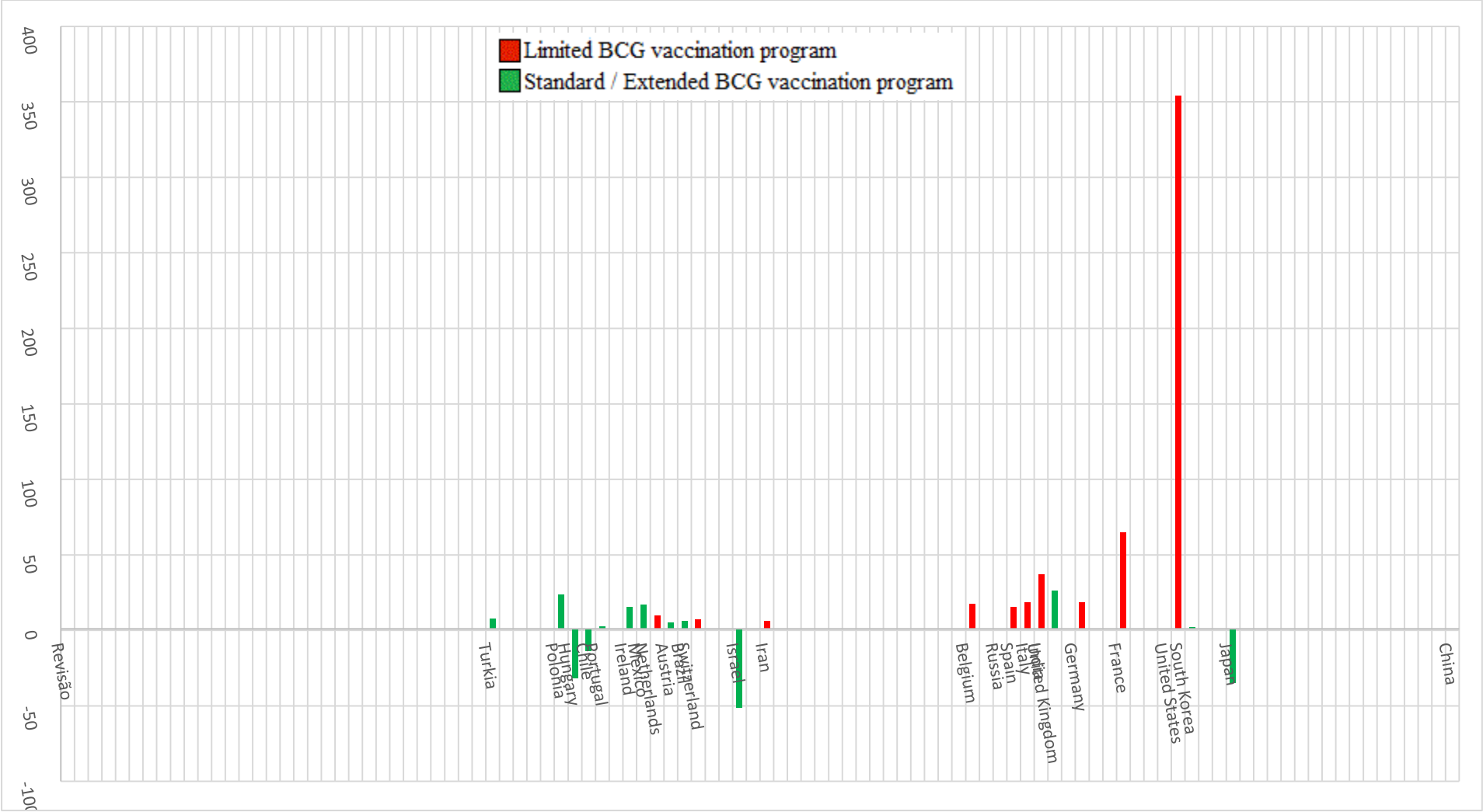


Figure 4. Initial and final acceleration ratios (0 – 100 cases) and (100 – current cases).

DISCUSSION

During the preparation of this article, a paper was published in which the authors made a cut of the analysis on March 21 and found similar correlations of the importance of BCG vaccination with the incidence and lethality of COVID-19[12]. However, although the source of the data was similar, the initial acceleration rates for the number of cases and the number of deaths (0–100) and subsequent accelerations (from 101 to April 11) were used in the present work. Further studies will be done by the authors of this work on the accelerations from April 11 to May 11 and finished with accelerations from May 11 to June 11.

Analyzing Fig. 4, the fact that BCG vaccination promotes a protective effect on the incidence and lethality of COVID-19 in several countries was identified as a major criticism: most countries in group 2 are temporarily behind in the course of the pandemic. To minimize the selection bias, a time equalization of all countries was individually performed in this study from the start date of the pandemic, which will not be necessary for future analyses, since the evolution of the pandemic itself will clarify this issue (Fig. 5).

The acceleration in the number of deaths in the D30 of the countries in group 1 remained four times higher than in group 2 and 2a. It is expected that the fact that this work has been based on the acceleration of the indexes will remain with statistical significance in future analyses on May 21 and June 21. The importance of this future analysis is to reinforce the protective hypothesis of the BCG vaccination program primarily in unvaccinated and high-risk populations for the development of the severe form of COVID-19. At the same time, there is no specific vaccine against the new coronavirus.

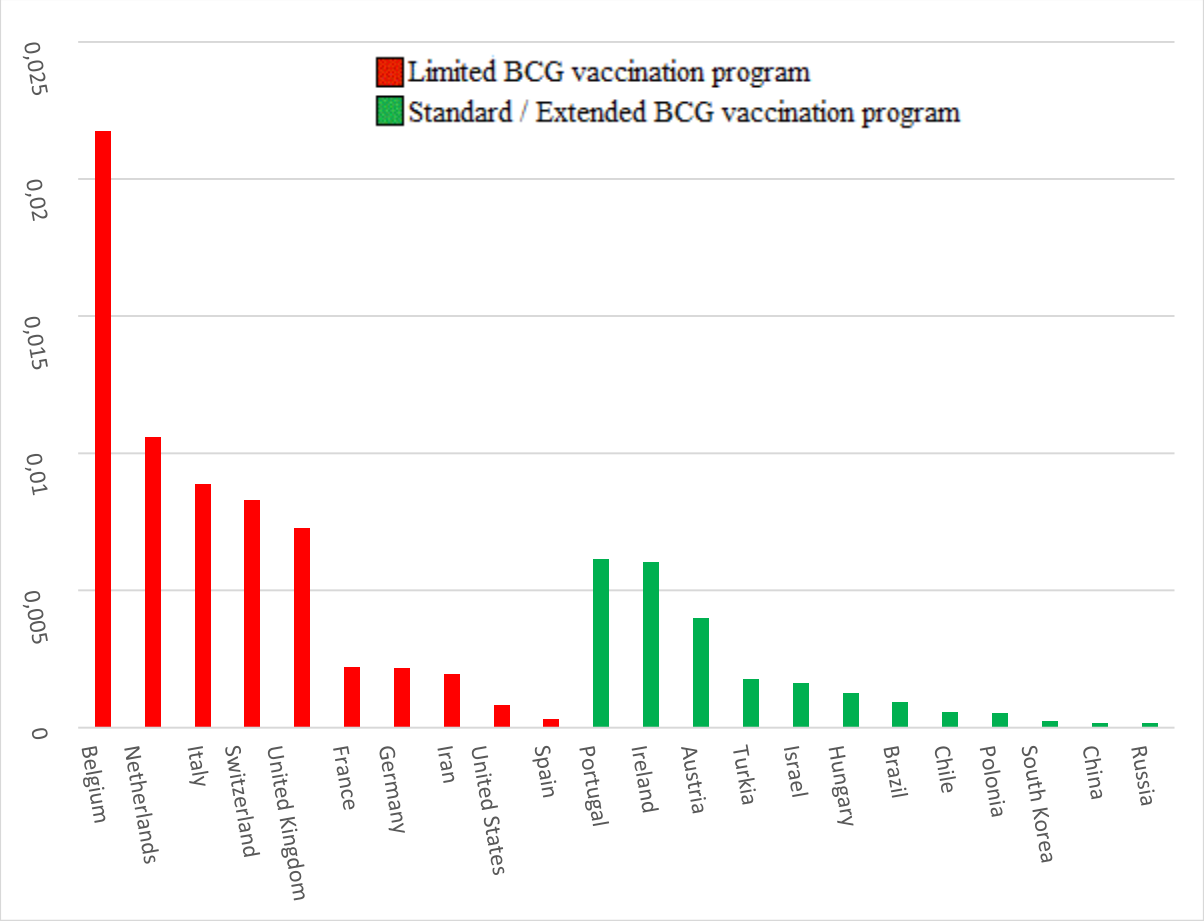


Figure 5. Acceleration of deaths on the 30th day.

CONCLUSION

The lower numbers of cases and deaths by COVID-19 in countries that have a vaccination program in place is instigating and biologically plausible. So far, with the numbers of the pandemic in progress, a correlation between the coverage of such programs and the number of cases and deaths in the countries studied has been found. The new data collection and analysis will be essential to establish or refute this concept. Controlled studies with easy-to-use methodologies should be quickly encouraged and, until a specific vaccine is developed, this may be our primary weapon.

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