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# 1 **Correlation between universal BCG vaccination policy and reduced mortality for COVID-** 2 **19**

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## 8 **Abstract**

9 COVID-19 has spread to most countries in the world. Puzzlingly, the impact of the disease varies  
10 in different countries. This variation is attributed to differences in cultural norms, mitigation efforts,  
11 and health infrastructure. Here, we propose that national differences in COVID-19 impact could  
12 be partially explained by different national policies with respect to Bacillus Calmette-Guérin (BCG)  
13 vaccination. BCG vaccination has been reported to offer broad protection from other respiratory  
14 infections besides tuberculosis. We compared BCG vaccination policies with the morbidity and  
15 mortality for COVID-19 for middle-high and high-income countries. We found that countries  
16 without universal policies of BCG vaccination (Italy, the Netherlands, USA) have been more  
17 severely affected compared to countries with universal and long-standing BCG policies. The  
18 difference cannot be accounted for by differences in disease onset, adoption of early social  
19 distancing policies, state of health services, nor income level. Reduced mortality suggests BCG  
20 vaccination could be a potential new tool in the fight against COVID-19.

## 21 **Introduction**

22 The COVID-19 pandemic originated in China and has quickly spread across the world, affecting  
23 nearly every country. However, there are some striking differences in how COVID-19 is behaving  
24 in different countries. For instance, in Italy there has been strong curtailing of social interactions  
25 but COVID-19 mortality is high (29315 deaths as of May 5<sup>th</sup>, 2020 ). In contrast, Japan had some  
26 of the earlier cases, but the mortality is low (556 deaths as of May 5<sup>th</sup>, 2020) despite not having  
27 adopted some of the more restrictive social isolation measurements (“Japan Was Expecting a  
28 Coronavirus Explosion. Where Is It? | The Japan Times” n.d.). These puzzling differences have  
29 been adjudicated to different cultural norms as well as differences in medical care standards. In  
30 addition, it has been proposed that the reduced mortality in children might be due to recent  
31 vaccination(Cao et al. 2020). Here we propose that the country-by-country difference in COVID-  
32 19 mortality can be partially explained by national policies on Bacillus Calmette-Guérin (BCG)  
33 vaccination.

34 BCG is a live attenuated strain derived from an isolate of *Mycobacterium bovis* used widely across  
35 the world as a vaccine for Tuberculosis (TB), with many nations, including Japan and China,  
36 having a universal BCG vaccination policy in newborns(“WHO | Tuberculosis” n.d.). Other  
37 countries such as Spain, France, and Switzerland, have discontinued their universal vaccine  
38 policies due to comparatively low risk for developing *M. bovis* infections as well as the proven  
39 variable effectiveness in preventing adult TB. Countries such as the United States, Italy, and the  
40 Netherlands, have yet to adopt universal vaccine policies for similar reasons.

41 Several vaccines including the BCG vaccination have been shown to produce positive  
42 “heterologous” or non-specific immune effects leading to improved response against other non-

43 mycobacterial pathogens. For instance, in severe combined immunodeficiency (SCID) mice,  
44 which lack functional B- and T-cells, BCG vaccination protected against a secondary non-  
45 mycobacterial challenge, demonstrating the ability of innate immune cells to mount a non- specific  
46 'memory-like' response(Kleinnijenhuis et al. 2014). This phenomenon was named 'trained  
47 immunity' and is proposed to be caused by metabolic and epigenetic changes leading to the  
48 promotion of genetic regions encoding for pro-inflammatory cytokines(Netea et al. 2016). BCG  
49 vaccination significantly increases the secretion of pro-inflammatory cytokines, specifically IL-1B,  
50 which has been shown to play a vital role in antiviral immunity(Kleinnijenhuis et al. 2014).  
51 Additionally, a study in Guinea-Bissau found that children vaccinated with BCG were observed to  
52 have a 50% reduction in overall mortality, which was attributed to the vaccine's effect on reducing  
53 respiratory infections and sepsis (Kristensen, Aaby, and Jensen 2000) i.

54 Reports on the duration of BCG vaccination protection against TB vary between 10 years(Sterne,  
55 Rodrigues, and Guedes 1998) and 60 years (Aronson et al. 2004). BCG protection for conditions  
56 other than TB has also shown long-lasting protection: a 60-year follow up of a clinical trial  
57 suggested that individuals who received the BCG vaccination during early childhood subsequently  
58 demonstrated a 2.5 fold reduction of lung cancer development (Usher et al. 2019). Whether the  
59 mechanism responsible for the BCG vaccination's long-standing effectiveness against  
60 mycobacterial pathogens carries over as a means of protection against the novel COVID-19  
61 remains unknown, but the potential opens up an interesting area for exploration.

62 Given our current understanding of the BCG vaccine's nonspecific immunotherapeutic  
63 mechanisms and by analyzing current epidemiological data, this investigation aims to identify a  
64 possible correlation between the existence of universal BCG vaccine policies and mortality  
65 associated to COVID-19 infections all over the world.

## 66 **Methods**

67 We collected the BCG vaccination policies across countries from the BCG World Atlas(Zwerling  
68 et al. 2011), available from <http://www.bcgatlas.org/>. We complemented the database with  
69 respect to the dates of initiation of BCG vaccination. The additional references are in the adjunct  
70 table. Data on COVID-19 cases and death per country were obtained from  
71 <https://google.org/crisisresponse/covid19-map> on May 5th, 2020. We included in the analysis  
72 only countries with more than 1 million inhabitants. The mortality rate might be influenced by  
73 multiple factors including a country's economics and the age distribution of the population. To  
74 account for economical differences, we classified countries according to their GNI per capita in  
75 2018 using the World Bank data  
76 ([https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-](https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups)  
77 [lending-groups](https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups)). Countries were divided into three categories: low income (L) with an annual  
78 income of 1,025 dollars or less, lower-middle income with an income between 1,026 and 3,995  
79 dollars, and middle-high and high-income countries, which included countries with annual  
80 incomes over 3,996 dollars.

81 COVID-19 mortality increases steeply with age(Zhou et al. 2020). Universal vaccination policies  
82 are more common in developing countries which tend to have younger populations. A younger  
83 population would show spurious reduced mortality for COVID-19. To control for this variable, we  
84 did not use the total number of inhabitants per country to calculate the mortality rate, but we  
85 considered the susceptible population as the inhabitants over 65 years of age per country(Shet  
86 et al. n.d.). Medians between populations were compared using the Wilcoxon rank sum test.

87 Multivariate linear analyses were done using the function *fitlm* in Matlab (R2017b). The Matlab  
88 script is available as supplementary material.

## 89 Results

90 Initially, we compared countries that never had in place a universal BCG vaccination policy (Italy,  
91 USA, Lebanon, Nederland, and Belgium), with countries that have a current universal BCG  
92 vaccination policy. Low-income countries report a median of 12.6 deaths per million people over  
93 65 years of age. In fact, 23% (4/17) of these countries reported zero deaths attributed to COVID-  
94 19, consistent with the hypothesis for a protective role of BCG vaccination. This effect, however,  
95 could be attributed to significantly lower testing rates in low income countries (Spearman  
96 correlation between median income and tests per million inhabitants,  $\rho=0.8083, p<1e-6, n=101$   
97 countries). Therefore, we will only consider middle-high and high-income countries for our  
98 analysis, which should compare countries with similar levels of medical care standards, sanitation,  
99 and testing levels for COVID-19. Middle high and high income countries with universal policies have a  
100 high BCG coverage, with a median of 97% with the 10 percentile being 87% and the 90 percentile being  
101 99%.

102 Middle-high and high-income countries that have a current universal BCG policy (55 countries)  
103 had a median of 84.5 deaths per million people over 65 years of age (see **Figure 1**). In contrast,  
104 middle-high and high-income countries that never had a universal BCG policy (5 countries) had  
105 a higher mortality rate, with a median of 1583.2 deaths per million people over 65 years of age.  
106 This difference between the median number of deaths was significant ( $p=0.008$ , Wilcoxon rank  
107 sum test).

108 An alternative explanation for the reduced number of deaths in countries with universal BCG  
109 vaccination policies could be that COVID-19 arrived late in these countries and that they are in  
110 the earlier stages of the epidemic. To evaluate for the significance of a possible confounding effect  
111 of epidemic stage, we plotted the number of deaths per million inhabitants over 65 years of age  
112 versus the number of days since the first reported case of COVID-19 per country (see **Figure 2**).  
113 As expected, there is a general increase in the number of reported deaths (as of 05/05/20) as  
114 more days pass since a country's first reported case. Additionally, middle-high and high-income  
115 countries *with* universal BCG vaccination policies that saw larger case volumes relatively early  
116 have a median of 105.1 deaths per million people over 65 years of age. This is significantly lower  
117 ( $p= 0.0059$ , Wilcoxon rank sum test) than the median of 1583.2 for countries in the same  
118 economic category that never implemented a universal policy and were affected at comparable  
119 times or even later (with at least 68 days passing since the first reported case). Therefore, the  
120 increased mortality for countries that never implemented a universal BCG vaccination policy  
121 cannot be explained by an earlier epidemic onset.

122  
123 Although we have stratified the countries and compared only those with middle-high and high-  
124 income levels that should be relatively homogeneous, differences in the strength of the health  
125 system, poverty rates, and quality of public health policy in response to COVID-19 could still be  
126 residual confounders that explain the observed increased death rates in countries that never  
127 implemented a universal BCG vaccination policy. In order to address these confounders directly,  
128 we used a multivariate linear regression analysis (see Table 1) on the middle-high and high-  
129 income countries (55 with BCG policy+6 that never had a policy). We included the days since the  
130 first reported case as covariates to account for differences in the stage of the epidemic in a country.  
131 We included two variables that accounted for the quality of the public health policy with respect  
132 to COVID-19. One was the number of tests performed per million people in a country which would  
133 correlate with the strength of a country's response. The other was the speed of a country's  
134 reaction to the pandemic which we quantified as the number of days between the first detected

135 case and schools closing. We used the median life expectancy in a country as a surrogate for the  
136 strength of the health system. Although the countries that we considered were middle-high and  
137 high-income countries, we also included the median income per country. Although median income  
138 might fail to capture the degree of resources assigned to effective COVID-19 mitigation measures,  
139 it would serve as an indicator of possible measures that could be taken. Finally, we included the  
140 BCG vaccination policy as a binary variable.  
141

	Estimate	Standard Error	T statistic	P value
Intercept	9.4735	3.6302	2.6096	0.016
Number tests per million people	7.2609e-06	6.4418e-06	1.1272	0.27182
Log10(days since first COVID-19 case)	-4.4502	1.8847	-2.3612	0.027487
Log10(days from first case to school closing + 2)	0.39123	0.41023	0.95369	0.3506
Median life expectancy (years)	0.023614	0.029294	0.80611	0.42881
Median income (US dollars)	-6.7105e-06	1.1589e-05	-0.57904	0.56845
BCG policy (1 current, 0 never)	-1.4656	0.35403	-4.1396	0.000429

142  
143 Table 1. Multivariate analysis of log10(deaths per million inhabitants over 65 years of age).  
144 Number of observations: 29, Error degrees of freedom: 22  
145 Root Mean Squared Error: 0.494  
146 R-squared: 0.599, Adjusted R-Squared 0.49  
147 F-statistic vs. constant model: 5.48, p-value = 0.00134  
148

149 Consistent with our previous analysis, we found that the only significant covariate (p=0.000429)  
150 was the presence of universal BCG vaccination policy in reducing the mortality of COVID-19.  
151 None of the other factors reached significance (p>0.01). However, there still might be other factors  
152 (genetic or environmental) that might be producing the correlation between BCG vaccination  
153 policy and reduced deaths due to COVID-19.

154 The number of deaths per million people over the age of 65 years did not correlate with the  
155 number of tests performed (p=0.27182), indicating that the number of deaths was a robust  
156 indicator that did not depend on a country's testing response. Nevertheless, we have used data  
157 from COVID-19 attributed deaths as reported by each country. There still might be systematic  
158 differences across countries on whether a death is attributed to COVID-19. For instance, if  
159 countries with universal BCG vaccination would tend to assign COVID-19 deaths to other causes  
160 (atypical pneumonia), that could create a spurious correlation between BCG vaccination and  
161 reduced mortality. In order to address this concern, we used a smaller dataset of European  
162 countries (<https://www.euromomo.eu/>) that calculated excess deaths in 2020. We extracted the  
163 data from weeks 12 to 17 of the year 2020 (see **Figure 3**) when the epidemic was peaking in

164 Europe. Countries with universal BCG vaccination policy had median excess deaths per week of  
165 0.42 (n=5), whereas countries without universal BCG vaccination policies had significantly higher  
166 median excess deaths of 16.02 per week (n=3, p=0.035, Wilcoxon rank sum test). Albeit a small  
167 sample, this independent measurement supports the idea that the reported correlation between  
168 a country's BCG vaccination and reduced mortality due to COVID-19 is not an artifact of national  
169 differences in COVID-19 death assignment.

170 A possible mechanism for a putative protective effect of BCG in a population might include direct  
171 protection in the elderly population, which is the most affected group(Zhou et al. 2020), as well as  
172 herd immunity acting over the whole population, both young and old. Using data from March 21<sup>st</sup>,  
173 2020(Miller et al. 2020), we reported a negative correlation between the year start of the  
174 vaccination policy and mortality both in middle high and high income countries with current  
175 policies, as well as countries that had stopped their policies. This was consistent with BCG  
176 vaccination producing a long-lasting protection to the elderly population from BCG vaccination  
177 received in childhood. However, using the current data from May 5<sup>th</sup>, there is no significant  
178 correlation between start year of the vaccination and mortality per million people over 65 years of  
179 age (see **Fig. 4**). We do not know if the early reported correlation was spuriously produced by  
180 the evolving nature of the pandemic, or if earlier response to the disease are less affected by a  
181 country's pandemic mitigation responses and depend more on intrinsic immunity in the elderly  
182 population to COVID-19. This would be consistent with a recent pre-print report (Berg et al. 2020)  
183 suggesting that BCG vaccination policy slows down the spread of COVID-19, making it easier to  
184 observe differences in the protective effect of BCG earlier in the epidemic.

185 A second possibility for a putative protective effect of BCG for COVID-19 could be a reduction in  
186 the spread of the disease, acting across the population. This would be reflected as a reduction in  
187 the number of COVID-19 reported cases. Consistent with this hypothesis, the countries with low-  
188 income levels that have a universal policy (16 countries) reported a smaller number of cases of  
189 COVID-19 per million inhabitants with a median of 8.85. However, the issue of underreporting  
190 might be more critical for estimating the number of cases and we have excluded the low-income  
191 countries from further analysis. Middle-high and high-income countries that have a current  
192 universal BCG vaccination policy (55 countries) had a median of 313.6 cases per million  
193 inhabitants (see **Figure 5**). Consistent with the role of BCG in slowing spread of COVID-19;  
194 middle-high and high-income countries that never had a universal BCG policy (5 countries) had  
195 about 10 times the number of cases, with a median of 3522.0 cases per million inhabitants. This  
196 difference in the medians between countries was significant (p=0.0283, Wilcoxon rank sum test),  
197 suggesting that broad BCG vaccination along with other measures could help slow the spread of  
198 COVID-19. However, multivariate analysis of the number of cases (see **Table 2**) revealed that  
199 although the BCG vaccination policy had a negative correlation with the log<sub>10</sub> number of COVID-  
200 19 reported cases, the factor did not reach significance (p=0.12). The most significant factor  
201 (p=0.00599) in determining the number of cases per million inhabitants was the number of tests  
202 performed per million inhabitants. Conclusions based on the number of deaths per million  
203 inhabitants over 65 years of age are more robust than conclusions based on the number of cases  
204 per million inhabitants as they do not depend on the number of tests performed.

205

206

	Estimate	Standard Error	T statistic	P value
Intercept	5.9208	2.7057	2.1883	0.039559
Number tests per million people	1.46e-05	4.8013e-06	3.0408	0.005999
Log10(days since first case)	-2.8594	1.4047	-2.0356	0.054015
Log10(days from first case To school closing + 2)	0.3817	0.30576	1.2484	0.22502
Median life expectancy (years)	0.02121	0.021834	0.97144	0.34189
Median income(US dollars)	1.1029e-05	8.6378e-06	1.2769	0.21497
BCG policy (1 current, 0 never)	-0.42549	0.26387	-1.6125	0.12111

207

208 Table 2. Multivariate analysis of log10(number of cases per million inhabitants). Number of  
209 observations: 29, Error degrees of freedom: 22

210 Root Mean Squared Error: 0.368

211 R-squared: 0.678, Adjusted R-Squared 0.591

212 F-statistic vs. constant model: 7.73, p-value = 0.000148

## 213 Discussion

214 We have shown that differences in mortality produced by COVID-19 across countries are  
215 correlated with a country's BCG vaccination policy. We centered our analysis in middle-high and  
216 high-income countries because they constitute a relatively homogenous group of countries and  
217 under the assumption that reported COVID-19 statistics from these countries would be more  
218 reliable than statistics from less wealthy countries. We performed multivariate analysis on those  
219 countries that controlled for the age distribution of the population, income per capita, stage of the  
220 epidemic of a country, and quality of the medical care. We also included as covariates factors  
221 related to a country's response to COVID-19. These other factors did not explain the lower  
222 mortality in countries with mandatory BCG vaccination. The correlation was confirmed using an  
223 independent measure, excess deaths, from a smaller dataset from Europe.

224 Although these confounders did not explain the observed trend, other unaddressed factors could  
225 be the causal link between BCG vaccination and reduced mortality. This includes complex factors  
226 such as the genetic makeup of the population, as well as environmental factors. Therefore, our  
227 correlational study should not be the basis for changes in clinical practice nor public health policies.  
228 Those changes, if warranted, should be based on the results of well-controlled clinical trials that  
229 could demonstrate a causal relationship between BCG vaccination and COVID-19 outcomes. At  
230 this time, there are currently 14 clinical trials registered at the NIH

231 (<https://clinicaltrials.gov/ct2/results?cond=covid&term=bcg&cntry=&state=&city=&dist=>) exploring  
232 this possibility.

233 We did not find a correlation between early implementation of a universal vaccination policy and  
234 reduced mortality in middle-high and-high income countries. We did not include in our analysis  
235 middle-low or low-income countries because our database might not capture the exact BCG  
236 vaccination policies of former European colonies in Asia and Africa during colonial times. For  
237 instance, BCG Atlas lists for Vietnam a start date of 1985 for universal BCG vaccination, but there  
238 are reports of widespread use of BCG vaccination during the French colonial period (Monnais  
239 2006). Interestingly, Vietnam with a population of 95 million has reported zero fatalities due to  
240 COVID-19.

241 Although COVID-19 deaths are concentrated in the elderly population(Zhou et al. 2020), recent  
242 BCG vaccination in children might play a role in reducing mortality by decreasing the transmission  
243 of the disease to the vulnerable population. Asymptomatic children in Germany(Jones et al., n.d.),  
244 where BCG is not applied to children since 1998, had viral loads that were as high as adults,  
245 which suggests that unvaccinated children may be as infectious as adults. A reduction of the viral  
246 load in children might act as a plausible mechanism by which BCG vaccination in children could  
247 reduce infections and mortality in a country.

248 Looking at an individual's BCG vaccination history offers the possibility to perform better  
249 epidemiological studies than country-wide comparisons to determine vaccination schedules and  
250 strains that might optimize protection against COVID-19 as well as possible mechanisms of BCG  
251 protection. For instance, a recent study determined that BCG vaccination in childhood did not  
252 reduce COVID-19 infection in young adults, a population with reduced mortality due to COVID-19  
253 (Hamiel, Kozer, and Youngster 2020). Patients with bladder cancer that have been treated with  
254 multiple doses of BCG (Alexandroff et al. 1999) constitute a population that is worth studying for  
255 possible protective effects against COVID-19.

256 If BCG were protective for COVID-19, why did COVID-19 spread in China despite having a  
257 universal BCG policy since the 1950s? During the Cultural Revolution (1966-1976), tuberculosis  
258 prevention and treatment agencies were disbanded and weakened("Development and  
259 Expectation of Tuberculosis Service System in China" n.d.). We speculate that this could have  
260 created a pool of potential hosts that would be affected by and spread COVID-19. Currently,  
261 however, the situation in China seems to be improving.

262 Our data suggest that BCG vaccination is correlated with reduced mortality associated with  
263 COVID-19. However, there is still not proof that BCG inoculation at old age would boost defenses  
264 in elderly humans against COVID-19, but it seems to do so in Guinea pigs against *M. tuberculosis*  
265 (Komine-Aizawa et al. 2010).

266 BCG vaccination has been shown to produce broad protection against viral infections and  
267 sepsis(Moorlag et al. 2019), raising the possibility that the protective effect of BCG may not be  
268 directly related to actions on COVID-19 but associated co-occurring infections or sepsis. However,  
269 we also found that BCG vaccination correlated with a reduction in the number of COVID-19  
270 reported infections in a country suggesting that BCG might confer some protection specifically  
271 against COVID-19. The broad use of the BCG vaccine across a population could reduce the  
272 number of carriers, and combined with other measures could act to slow down or stop the spread  
273 of COVID-19. However, an alternative explanation would be that COVID-19 in a person with BCG



274 vaccination would have a milder presentation, reducing the possibility that such a case would be  
275 even detected in the first place.

276 Different countries use different BCG vaccination schedules(Zwerling et al. 2011), as well as  
277 different strains of the bacteria (Horwitz et al. 2009). We have not divided the data depending on  
278 the strain used to determine whether different strains are better at stopping the spread of infection,  
279 as well as reducing mortality in the elderly population, as suggested by Jun Sato("If I Were North  
280 American/West European/Australian, I Would Take BCG Vaccination Now against the Novel  
281 Coronavirus Pandemic." n.d.). As each country might have used the same strain for the whole  
282 population, the difference in strains for different purposes should be gathered in randomized  
283 control trials with different subjects from the same population tested with different strains.

284 Randomized controlled trials using BCG vaccination are required to determine how fast an  
285 immune response develops that protects against COVID-19. BCG is generally innocuous with the  
286 main side effect of inflammation at the site of injection. However, BCG is contraindicated in  
287 immunocompromised people as well as pregnant women("Fact Sheets | Infection Control &  
288 Prevention | Fact Sheet - BCG Vaccine | TB | CDC" n.d.), so care should be taken when applying  
289 this possible intervention for COVID-19.

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296 information.

297

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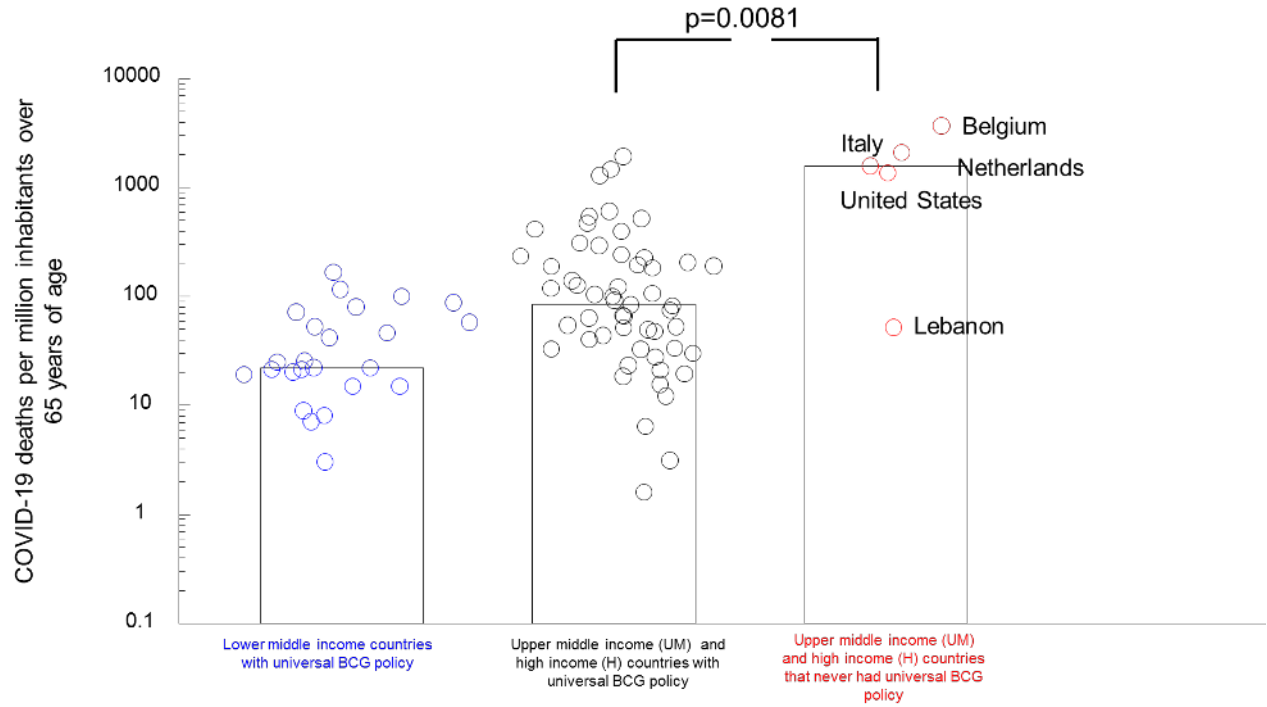
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382 **Figure 1:** Higher death rates were presented in countries that never implemented a universal  
383 BCG vaccination policy. Bars indicate the median value of a given group of countries.

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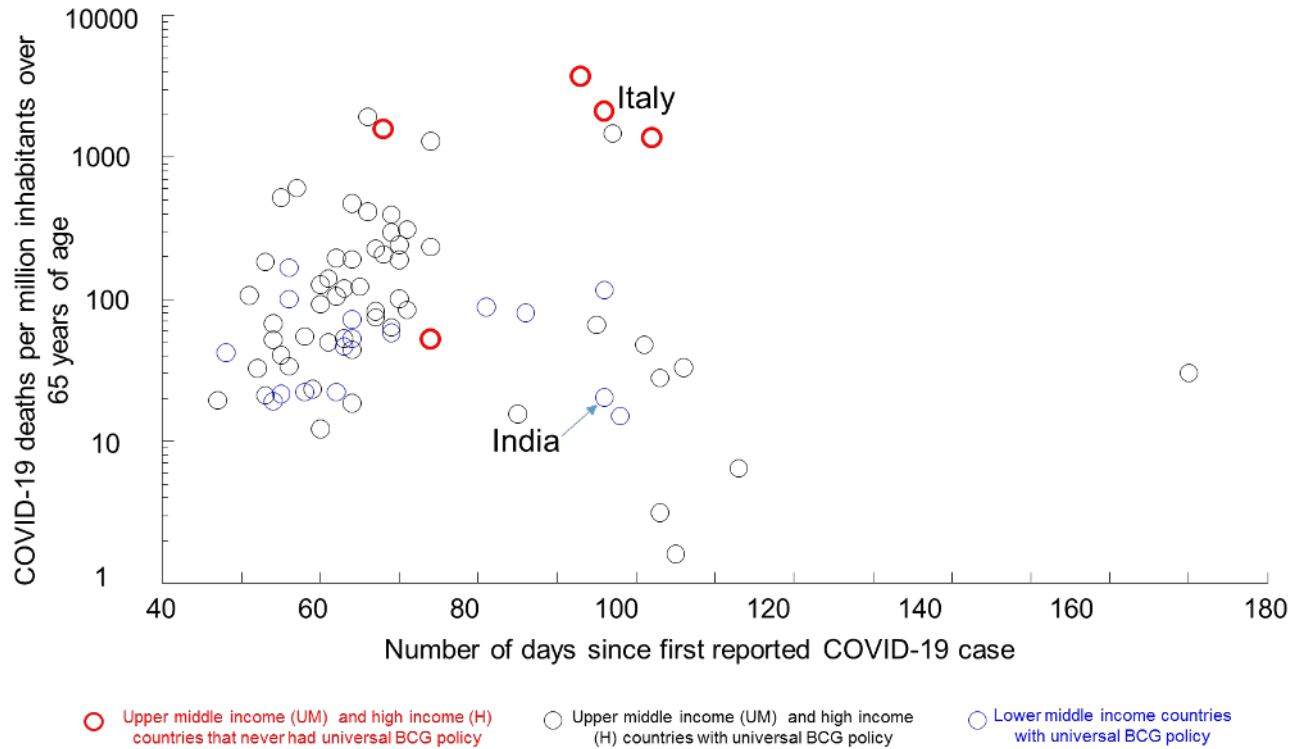
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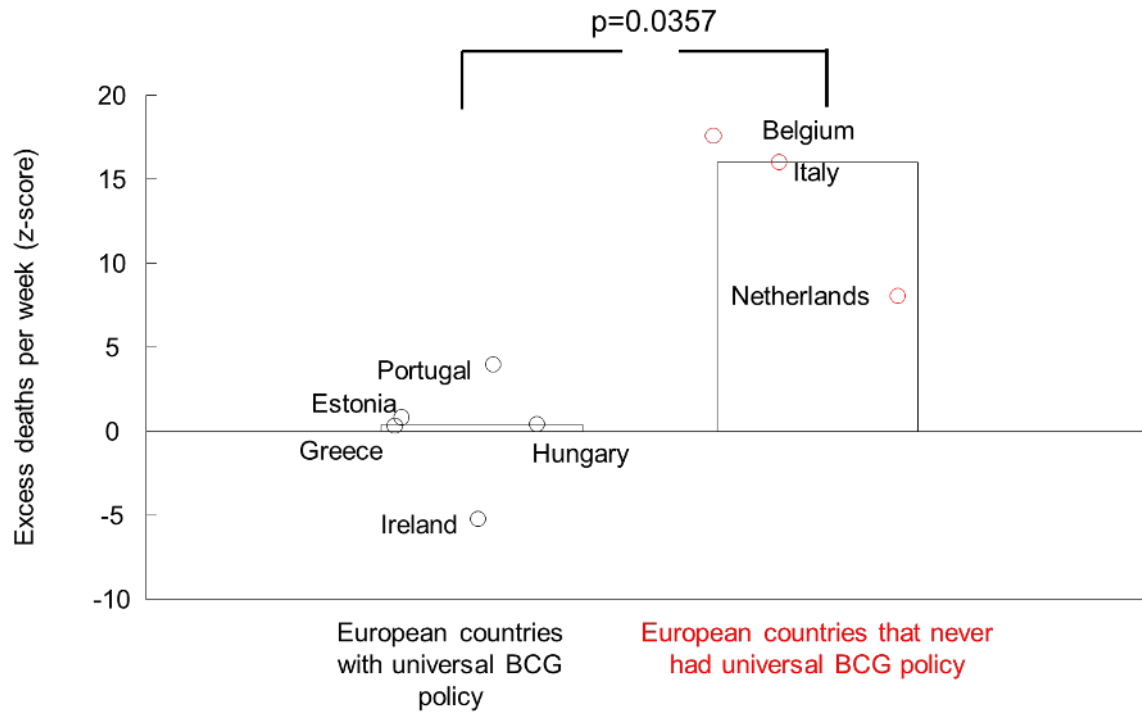
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394 **Figure 2:** Date of onset of the epidemic does not explain higher number of deaths in countries  
395 that did not establish a universal BCG policy.

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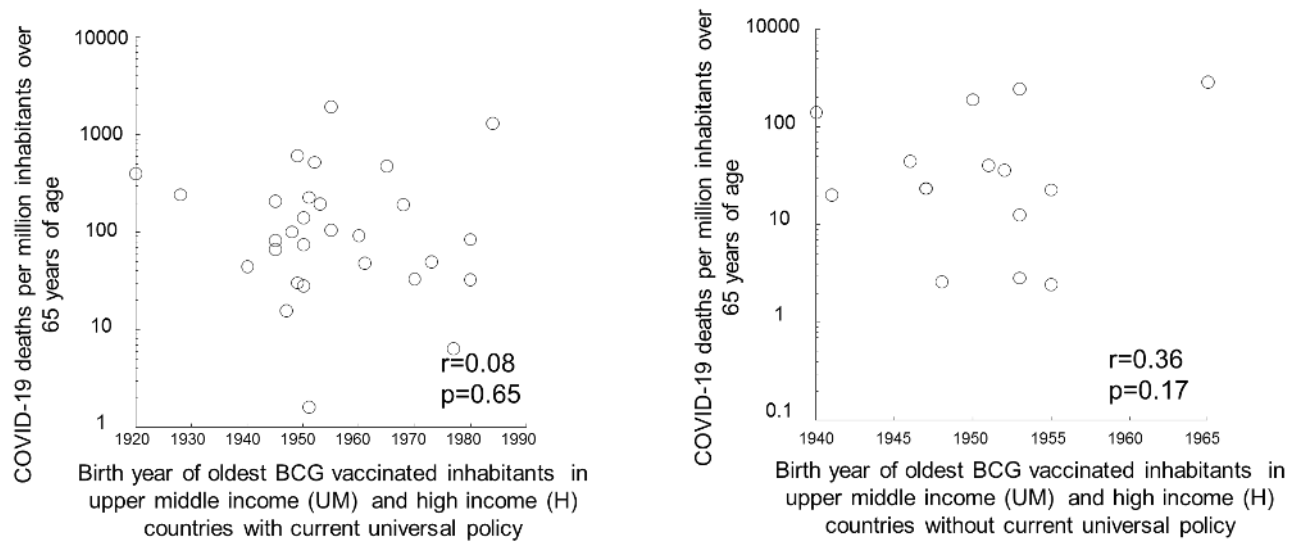
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400 **Figure 3:** Higher excess deaths were presented in European countries that never implemented  
401 a universal BCG vaccination policy. Bars indicate the median value of a given group of countries.

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406 **Figure 4:** Earlier date of the start of vaccination does not correlate with reduced mortality . Left  
407 panel correspond to upper middle income and high income countries with current universal BCG  
408 vaccination policy. The right panel corresponds to countries that do not have a current universal  
409 vaccination policy.

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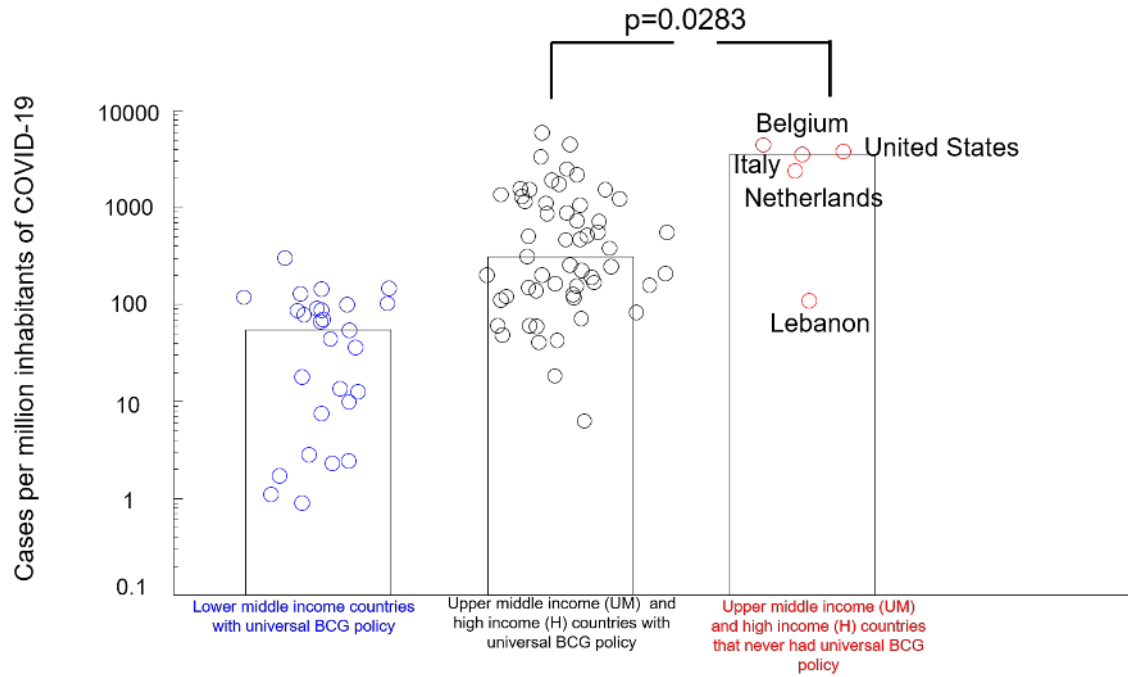
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428 **Figure 5:** Higher number of COVID-19 cases were presented in countries that never  
429 implemented a universal BCG vaccination policy. Bars indicate the median value of a given group  
430 of countries.

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