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BCG Correlation with Latent Tuberculosis Can Lead to Spurious Correlation with Reduced COVID-19 Mortality

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Background: Many factors have been suggested to confound coronavirus disease 2019 (COVID-19) studies, and BCG studies have been criticized for not adjusting for many confounders. We conducted this study to analyze the presumed effectiveness of the Bacillus Calmette–Guérin (BCG) vaccine in decreasing the COVID-19 mortality rate, and to answer the question of whether this is confounded by latent tuberculosis (LTB) prevalence.
Materials and Methods: We chose sixty-nine malaria-free countries with different BCG vaccination policies. TB prevalence was considered as a proxy for LTB. The BCG, TB prevalence, and COVID-19 mortality data are publically available. Contingency coefficients (C.C.) and a Receiver Operating Characteristic (ROC) analysis were used to assess the relationship between TB prevalence and BCG status, and identify cutoff points in each BCG group category. A stem–leaf plot was also used to explore the data's apparent behavior concerning COVID-19 in relation to the BCG groups.
Results: TB prevalence was significantly associated with BCG status. There was a highly significant association according to (C.C.) between TB prevalence and BCG group categories. Countries not implementing BCG vaccinations had low TB prevalence, and vice versa (p value = 0.000). ROC analyses indicating that BCG group is significantly associated with corresponding TB prevalence.
Conclusions: BCG country status has a highly significant relationship with TB prevalence. This can confound BCG and COVID-19 mortality and morbidity studies. In the absence of a correlation ,this can lead to a spurious correlation between BCG and reduced COVID-19 mortality or morbidity.

Keywords: COVID-19 mortality; latent tuberculosis; SARS-CoV-2; BCG; confounder.

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1. INTRODUCTION

The WHO currently recommends that, in countries with a high tuberculosis (TB) burden, a single dose of the Bacillus Calmette–Guérin (BCG) vaccine should be provided to all infants as soon as possible after birth as part of childhood immunization programs. In countries with low TB incidence rates, the provision of the BCG vaccine may be limited to neonates and infants in recognized high-risk groups, or older children who are negative for TB infection according to the tuberculin skin test (TST) [1]. Despite clear evidence and the WHO's recommendations, however, global BCG administration practices appear to be arbitrary [2,3]. Among 180 countries, 154 reported universal BCG vaccination, 20 reported having had a national BCG policy for everyone in the past, and the remaining six reported selective vaccination for persons in high-risk groups. BCG coverage ranged from 53% to 99%; the coverage was <80% in six high-incidence countries [4].

Studies on the BCG vaccine's efficacy against TB have been confounded by the cross-reactivity of antigens and absence of measures for excluding latent infection [5].

Early in the coronavirus disease 2019 (COVID-19) pandemic, Miller *et al.* [6] showed that countries with mandated BCG vaccinations had lower COVID-19 morbidity and mortality rates. Furthermore, Sala et al. [7], Berg et al. [8] Dayal et al. [9] Akiyama et al. [10], Green et al. [11] Hegarty et al. [12] ,Shet et al. [13], Ozdemir et al. [14] and, more recently, Brooks et al. [15] showed significant correlations between BCG and COVID-19 mortality. Early in this pandemic, it was also suggested by a few studies that latent tuberculosis (LTB) could mitigate COVID-19 morbidity and mortality [16-21]. Some tested TB prevalence [16,20,22] as a proxy for LTB, while others considered LTB estimates that might cross-react with BCG and other mycobacteria. Other studies considered positivity in the TST/interferon-gamma release assay (IGRA) as a measure of the potential protective effect of the resident populations' exposure to *Mycobacterium* spp., whether from BCG vaccination or as a result of exposure to environmental mycobacteria [17,18,23]. Raham TF and Al-Momen H. *et al*. shed light on the effectiveness of TB prevalence as a proxy for LTB, according to different BCG groups bypassing the BCG effect [16,20].

BCG studies are likely to be confounded by LTB, since low-TB countries do not implement vaccination, and countries with high TB prevalence implement BCG programs. About one-quarter of the world's population has LTB [24,25],making the latter an important factor to adjust for.

Furthermore, malaria's confounding effect was not adjusted for in most of these studies; this is of special importance because malaria is highly endemic in most high-TB countries.

The study of risk and confounding factors is very important since previous studies have shown hugely disparate case-fatality rates, in spite of some reporting significant findings. For example, disparities exist among both countries with low LTB incidence or BCG coverage and those with high LTB incidence or BCG coverage [23]. Regarding malaria's influence on COVID-19 mortality, it was suggested by a few preliminary studies to reduce it [22,26].

In the context of the conflicting evidence regarding BCG's significant correlations, the growing evidence of a role of LTB and malaria, and a lack of literature defining LTB's confounding effect in malaria-free countries, we suggest that a confounding effect exists, as a background hypothesis for this study. This study is important at this time because several clinical trials are underway to evaluate the efficacy of BCG vaccination for COVID-19.

2. MATERIALS AND METHODS

It was not appropriate or possible to involve patients or the public in this work; we used data summated at the general practice level and related, publicly published morbidity and mortality statistics.

The main objectives of this study were based on the hypothesis that the decreased mortality rate in BCG studies is related to the influence of LTB rather than the BCG effect, and that BCG studies have been confounded by LTB prevalence. We designed this study to look for an association between TB prevalence (reflected as LTB prevalence) and BCG policy status in the absence of a confounding effect from malaria, through restricting the sample to malaria-free countries. Furthermore, the stem-leaf graphical plot method was proposed to illustrate (apparent) BCG group behavior regarding COVID-19 mortality.

We selected countries that have achieved at least three consecutive years of zero indigenous

cases of malaria. The total number of countries was 69, as shown in Appendix A. Countries eligible to apply for WHO certifications of malaria-free statuses were included [27]. Countries and territories with populations of less than 1 million were excluded and are listed in Appendix B.

The data for the TB prevalence, BCG, malaria, and COVID-19 mortality are publicly available (references are listed in Appendix B).

The chosen countries were distributed among the BCG category statuses, as shown in Appendix A, and categorized according to three ordinal scales (low: ≤15, moderate: 16–49, and high: ≥50), according to the highest-available TB prevalence during 2011–2018. The different classifications of countries according to BCG-vaccine policy status are: just a single current BCG with no previous booster (JSC1-BCG), just a single current BCG with a previous booster (JSC2-BCG), multiple current BCGs (MC-BCG), one previous BCG (JP-BCG), and no previous or current BCG (NP/C-BCG or BCG: 0 or the BCG control group) (Appendix A).

Contingency coefficients (C.C.) and Receiver Operating Characteristic (ROC) analysis were used to test the relationship between TB prevalence and BCG status, and to identify the cutoff points in each BCG group category. A stem–leaf plot was also used to explore the data's apparent behavior concerning COVID-19 mortality rate for different BCG groups. All the statistical operations were performed using the statistical package SPSS, ver. 22.

3. RESULTS AND FINDINGS

Table 1 shows the distribution of TB prevalence during 2011–2018 in three categorized BCG groups, as well as a comparison that is significant in terms of the contingency coefficient of the reflected relationship between the preceding factors; they had either a random or constrained distribution. The results show a highly significant relationship at $P<0.01$, indicating that a meaningful constrained distribution is accounted for regarding the studied factors.

Regarding the low- TB-prevalence category the distribution of the NP/C-BCG group was 83.30% (highest), followed by 81.0% of the JP-BCG group, and the lowest was 6.3% of the JSC2-BCG group.

Regarding the moderate-TB-prevalence category, the distributions were 75.0% of the JSC2-BCG group (highest), and both JP-BCG and MC-BCG were 14.3% (lowest).

Regarding the high- TB-prevalence group, the distributions were 71.4% for MC-BCG and 0.00% for NP/C-BCG (BCG: 0, or the BCG control group).

Table 2 and Fig. 1 show estimates of the area of the trade-off between the sensitivity and specificity; sensitivity is plotted against a complementing specificity outcome to examine the trade-off, which is called the ROC curve. The significance level for the testing area was under 50% guideline, with a 95% confidence interval of all the probable combination pairs for the four statuses of the BCG groups under the proposed guideline group (the control) due to NP/C-BCG group status.

The results show that strong and highly significant asymptotic values regarding the area under the curve at $P<0.01$, concerning the different BCG group categories, in just three groups. There was no significant area under the curve at $P>0.05$ for the JP-BCG group. This indicates that the TB prevalence rates are good disseminators for the BCG groups: JSC1-BCG, JSC2-BCG, and MC-BCG. The highest TB cutoff point was within MC-BCG, which was 29.50, followed by JSC1-BCG (20.00) and then JSC2-BCG (15.00). The magnitudes of the areas under the curves followed the same ranking and were 0.964, 0.939, and 0.938, respectively, with highly significant asymptotic values and short 95% C.I intervals of 0.872–1.057, 0.848–1.029, and 0.835–1.040, respectively. A non-significant asymptotic value for JP-BCG signifies that TB prevalence does not categorize this group. The cutoff value was the lowest within this table (Table 2, Fig. 1).

The stem–leaf graphical plots clearly illustrate the apparent behavior of COVID-19 mortality within the BCG groups (Fig. 2); they show that the ranking of mortality rates by BCG group status gives the impression of high mortality within the no-BCG-vaccination groups, and low mortality in countries with BCG vaccination.

4. DISCUSSION

Many BCG studies showing a significant relationship between BCG and a reduction in COVID-19 mortality and/or morbidity have been

criticized for not considering confounding factors, and simply assessing the differences in the incidence/mortality of COVID-19 based on having or not having BCG vaccination policy, as well as sharing the same sources of information with questionable data accuracy [25,28,29,30].These studies were, therefore, considered to represent only weak evidence. On the other hand, other studies have found no statistical evidence for an association between BCG vaccination policy and either SARS-CoV-2 morbidity or mortality, as shown by Chimoyi L *et al.* (study included 97 countries with 73 having a policy of current BCG vaccination) [30], Aksu *et al.* (A retrospective cross-sectional study which involve 123 adults with COVID-19 pneumonia) [31] Fukui M *et al.* (who merged country-age-level case statistics with the start/termination years of BCG vaccination policy) [28], Clément *et al.* (who used regression discontinuity method to measure the effect of BCG vaccine at birth on a large number of patients) [32] Hamiel U *et al.* (a study on a large population-based cohort) [33] Asahara M (found no positive results from the Diamond Princess and cross-national differences) [34] and Hensel J. *et al.* (after correction for confounding variables, most notably testing rates, found there was no association between BCG vaccination policy a nd COVD-19 spread rate or percent mortality) [35].

However, these studies also did not define the possible confounding effects of TB or malaria.

A confounding factor may mask an actual association or falsely demonstrate an apparent association between a study's variables where no real association between them exists [36]. This confounder may lead to the overestimation of the true association between an exposure and outcome [37]. One of limitations of this study is that it did not address whether there is a certain cumulative effect of the BCG on TB effect in reducing COVID-19 mortality , since it focused on the relationship between TB prevalence and BCG status. Furthermore, it is limited by not measuring BCG vaccination coverage rate, stage of epidemic, socio-economic differences, and differences in practicing of preventive measures to contain the disease, etc.

The efficacy and effectiveness of BCG vaccination against TB have been found to differ considerably between studies and populations [38].

The BCG vaccine has a documented protective effect against TB meningitis and disseminated TB in children, but it prevents neither primary infection nor, more importantly, the reactivation of a latent pulmonary infection, which is the principal source of bacillary spread in the community. The impact of BCG vaccination on the transmission of *Mycobacterium* TB is, therefore, limited [39].

Despite BCG being effective in 50% of the target population, much controversy surrounds its effect on mild forms of infection, as well as the duration of its effect [25].

According to the WHO's recommendations, countries with low TB burdens may limit BCG vaccination to infants in high-risk groups (or TST-negative older children) and adults at high risk for occupational TB exposure and who are TST negative [38]. Most people with TB immunoreactivity do not develop active TB upon immunosuppression, suggesting that they have cleared their infections while retaining immunological memory to them [40].
In most European Union (EU) and Western European countries, the tuberculosis (TB) notification rates are lower than 20 cases per 100,000 population. This rate is decreasing by around 4% yearly in the EU, overall. In 2003, it reached 13.8 per 100,000 [41,42].

Table 4 shows a highly significant association between TB prevalence and certain BCG groups: countries not implementing BCG vaccinations had low TB prevalence, and vice versa (p value = 0.000). Table 2 and Fig. 1 show the ROC analyses indicating that BCG group is significantly associated with corresponding TB prevalence. These results confirm an association between TB prevalence and BCG status.

The finding of this study that BCG status is highly associated with TB prevalence leads us to conclude that BCG studies can be easily confounded by LTB. The ranking of mortality rates within BCG group statuses shown in a stem–leaf plot (Fig. 2) follows the rank of association between TB prevalence and BCG status. This gives the impression of high mortality within groups with no BCG vaccination and low mortalities within countries with BCG vaccination.

This could apply to all BCG studies not adjusting for LTB.

In countries that do not undertake vaccination, confounding occurs simply because of a possible low TB prevalence, giving a false impression that

not administering BCG is the cause of high mortality. Another possible confounder is previous TB prevalence, since the immunity generated by TB lasts for a certain period of time. We tried to control for this by considering the highest available TB prevalence during 2011–2018.

For these reasons, BCG studies should be designed properly to avoid bias. Estimation using the TST could also confound the LTB studies since BCG results in a positive TST result. We took the TB prevalence among countries as a proxy reflecting LTB infection to avoid this bias. However, in clinical trials, both TST and IGRA testing seem to be important, since BCG vaccination can cause a positive result for nontuberculous mycobacteria, while IGRA testing does not [43].

The low COVID-19 mortality in some countries cannot be explained by either low TB prevalence or malaria-free status, such as in Cyprus, which has not implemented BCG vaccination, and Slovakia, which previously implemented a BCG program. These findings suggest that other factors play roles in decreasing COVID-19 mortality.

Table 1. "Kendall's-τ Correlation Coefficient" mortality rates marker and highest TB prevalence in 2011-2018

Marker	Correlation Coeff. and P-value	TB prevalence 2018
COVID-19 deaths /M in September ,2 ,2020	Correlation Coefficient	-0.175 *
	Sig. (2-tailed)	0.046
	No.	69

* Correlation is significant at the .05 level (2-tailed).

Table 2. Distribution of different BCG Status due to COVID-19 deaths /M with comparison's significance

BCG Status	No. and %	COVID -19 deaths /M up to August 2, 2020.		Total	C.S. P-value
		< 50 Death / M.	> 50 Death / M.		
JSC1-BCG**	No.	13	6	19	LRT = 9.757
	% No.	68.4%	31.6%	100%	P=0.045
JSC2-BCG***	No.	7	9	16	S(*)
	% No.	43.8%	56.3%	100%	
MC-BCG****	No.	1	6	7	
	% No.	14.3%	68.4%	100%	
JP-BCG*****	No.	6	15	21	
	% No.	28.6%	71.4%	100%	
NP/C-BCG ******	No.	2	4	6	
(Control)	% No.	33.3%	66.7%	100%	
Total	No.	29	40	69	
	% No.	42.0%	58.0%	100%	

** S: Sig. at P<0.05; testing based on a LRT: likelihood ratio test*

*** JSC1-BCG : Just single current BCG- no previous booster. *** (JSC2-BCG): just single current with previous booster. **** (MC-BCG): multiple current BCG. ***** (JP-BCG): just previous BCG. ****** (NP/C-BCG or , BCG : 0 or the BCG controlled group:no previous or current BCG*

Table 3. Descriptive statistics of (COVID -19 deaths /M) and testing of all probable combinations towards countries' BCG status classifications

Statistics	BCG Status				
	I	II	III	IV	V
5% Trimmed Mean	48	89	159	206	310
Median	34	63	119	108	237
Minimum	0	5	10	4	17
Maximum	182	591	297	622	853
Range	182	586	287	618	836
Interquartile Range	63	159	230	370	615

Kruskal-Wallis Test P-value		**Chi-Square = 16.482 P=0.022 (S)**
Mann-Whitney Test C.S. P-value	I X II**	Z = - 1.623; P=0.109 ; (NS)/ (CE)*
	I X III**	Z = - 2.342 ; P=0.018; (S)*
	I X IV**	Z = - 2.804; P=0.004 ; (HS)*
	I X V**	Z = - 1.814; P=0.069 ; (NS)/(CE)*
	II X III**	Z = -1.370; P=0.175 ; (NS)/(CE)*
	II X IV**	Z = -1.364; P=0.175 ; (NS)/(CE)*
	II X V**	Z = - 1.290; P=0.203 ; (NS)*
	III X IV**	Z = - 0.027; P=1.000 ; (NS)*
	III X V**	Z = - 0.714; P=0.534 ; (NS)*
	IV X V**	Z = - 0.437; P=0.670 ; (NS)*

HS: Highly Sig. at P<0.01; S: Sig. at P<0.05; NS: Non Sig. at P>0.05. CE: confounding effect if p<0.2
**I:(JSC1-BCG :Just single current BCG no previous booster); II:(JSC2-BCG :Just single current with previous booster);III:(MC-BCG :Multiple Current BCG); IV:(JP-BCG :Just Previous BCG); V:(NP/C-BCG(Control) BCG : 0 = No Previous or Current BCG)*

Table 4. Distribution of highest TB prevalence 2011- 2018 in three categorized responses by different BCG statuses, as well as comparison significant

BCG Status	**No. and %**	**Highest TB prevalence recurrently in 2011- 2018 .**			**Total**	**CS P-value**
		Low	**Mode.**	**High**		
JSC1-BCG**	No.	2	5	12	19	C.C. = 0.659
	% No.	10.5%	26.3%	63.2%	100%	P=0.000
JSC2-BCG***	No.	1	12	3	16	HS*
	% No.	6.3%	75.0%	18.8%	100%	
MC-BCG****	No.	1	1	5	7	
	% No.	14.3%	14.3%	71.4%	100%	
JP-BCG*****	No.	17	3	1	21	
	% No.	81.0%	14.3%	4.8%	100%	
NP/C-BCG ******	No.	5	1	0	6	
(Control)	% No.	83.30%	16.70%	0.00%	100%	
Total	No.	26.0	22.0	21	69	
	% No.	37.7%	31.9%	30.4%	100%	

HS: Highly Sig. at P<0.01, Testing based on a contingency coefficient – C.C. test
** *JSC1-BCG : Just single current BCG- no previous booster.* *** *(JSC2-BCG): just single current with previous booster.* **** *(MC-BCG): multiple current BCG.* ***** *(JP-BCG): just previous BCG.* ****** *(NP/C-BCG or , BCG : 0 or the BCG controlled group:no previous or current BCG*

Table 5. ROC analyses with higher available TB prevalence in 2011- 2018 accuracy in discriminating for BCG group status

BCG Status	**Cutoff Point**	**Sen.**	**Spec.**	**Area**	**Std. Error**	**Asymp. Sig.***	**Asymp. 95% C.I.**	
							L.b.	**U.b.**
JSC1-BCG**	20.00	0.842	1.000	0.939	0.046	0.001	0.848	1.029
JSC2-BCG***	15.00	0.938	0.833	0.938	0.052	0.002	0.835	1.040
MC-BCG****	29.50	0.857	1.000	0.964	0.047	0.005	0.872	1.057
JP-BCG*****	19.50	0.143	1.000	0.528	0.144	0.838	0.246	0.810

* *HS: Highly Sig. at P<0.01; NS: Non Significant at P> 0.05. Just single current BCG- no previous booster.*
** *JSC1-BCG : Just single current BCG- no previous booster.* *** *(JSC2-BCG): just single current with previous booster.* **** *(MC-BCG): multiple current BCG.* ***** *(JP-BCG): just previous BCG*

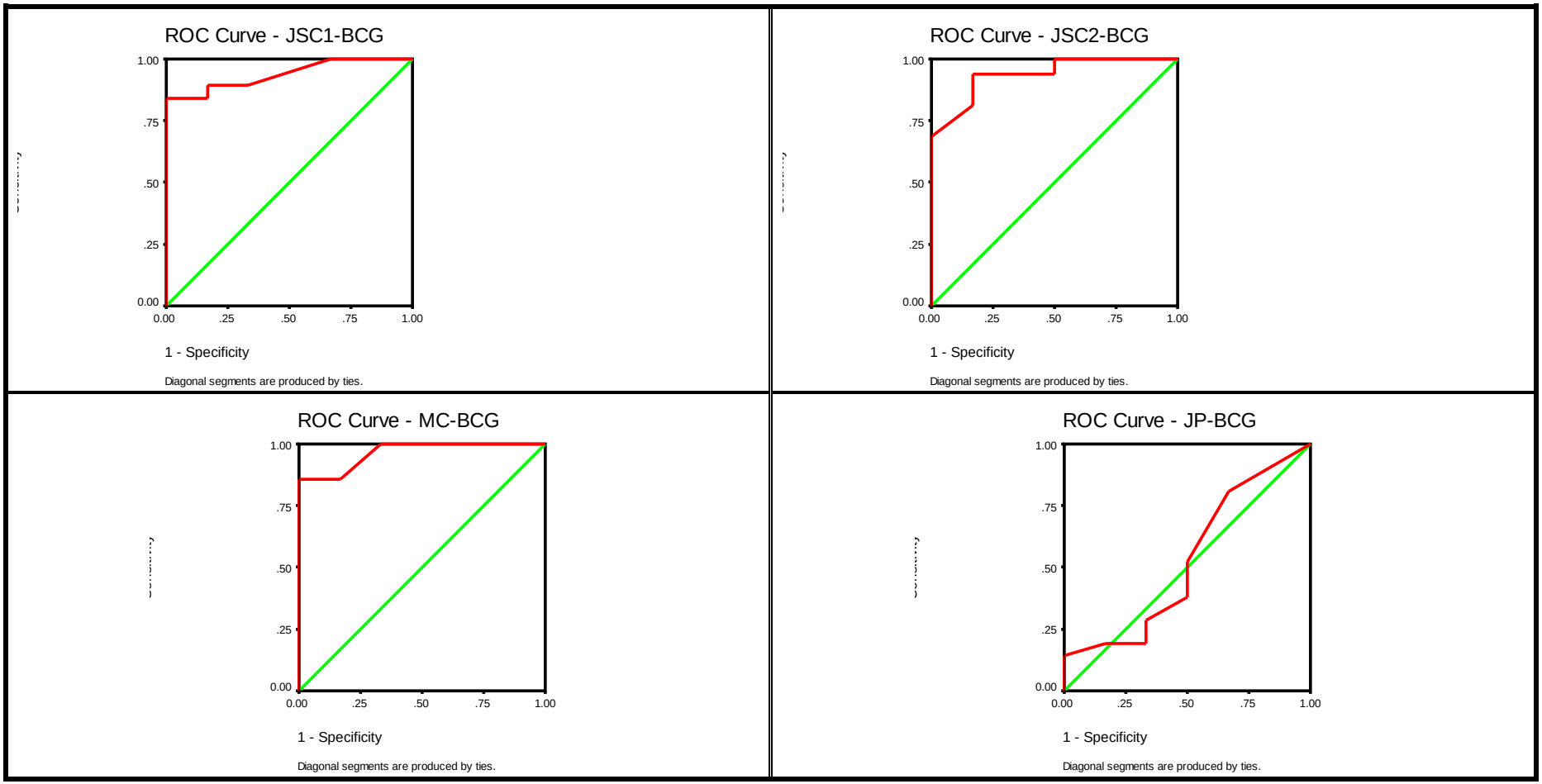

Fig. 1. ROC Curve plots for studied TB prevalence rates in relation with BCG different categorized groups

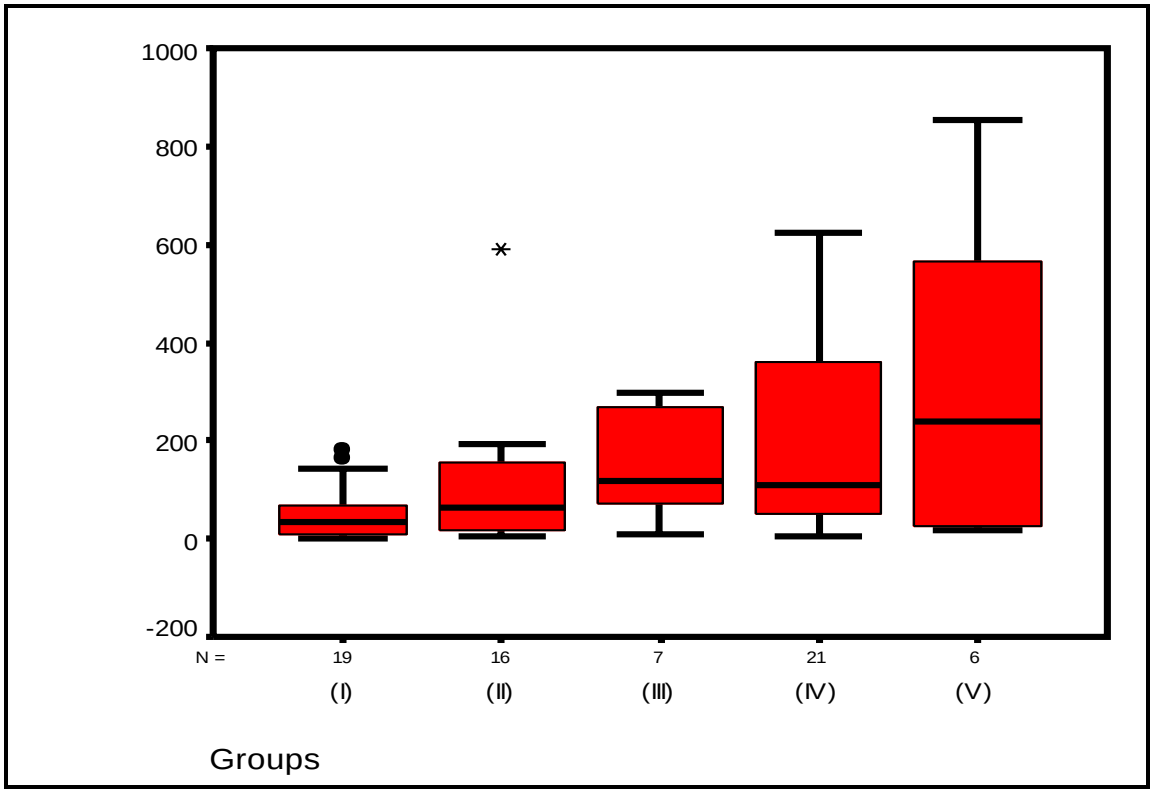

Fig. 2. Stem-Leaf plots of (COVID-19 deaths /M up to August 2, 2020) due to effects of studied marker (BCG status). I:(JSC1-BCG :Just single current BCG no previous booster); II:(JSC2-BCG :Just single current with previous booster);III:(MC-BCG :Multiple Current BCG); IV:(JP-BCG :Just Previous BCG); V:(NP/C-BCG(Control) BCG : 0 = No Previous or Current BCG)

5. CONCLUSIONS

BCG country status has a highly significant relationship with TB prevalence, which could confound BCG and COVID-19 mortality and morbidity studies.

6. RECOMMENDATION

We recommend that TB's potential confounding effect on BCG results should be considered in ongoing and future studies and trials. To over come this confounded effect latent TB should be ruled out in these clinical trials.

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HIGH LIGHTS

- Many studies showed a relation between BCG and COVID-19 mortality reduction
- Influence of latent TB on COVID-19 mortality was also suggested later,
- Sixty-nine malaria-free countries were selected to look for any association between latent TB prevalence and BCG countries' status, and to look for possible confounded LTB effect on BCG studies.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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APPENDIX A. TB PREVALENCE 2011-2018 AND COVID-19 DEATHS/MILLION REPORTED ON SEPTEMBER 2, 2020 IN DIFFERENT CLASSIFICATION ACCORDING TO BCG VACCINATION POLICY

Country	Covid-19 Deaths/M 2/September 2020	TB Prevalence highest available figure in 2011-2018.*
**JSC1-BCG : Just Single Current BCG no Previous Booster		
Algeria	34	**75**
Lesotho	0	**788**
Mauritius	8	**22**
Jordan	1	**530**
Iraq	182	**43**
Libya	35	**40**
Morocco	31	**107**
Qatar	71	**760**
United Arab Emirates	39	**140**
Albania	101	**550**
Greece	26	**490**
Hungary	64	**9**
Lithuania	32	**56**
Kyrgyzstan Kyrgyz Republic	162	**144**
Turkmenistan	0	**70**
Cuba	8	**7**
Jamaica	7	5
Paraguay	46	**43**
Sri Lanka	144	**65**
***JSC1-BCG : Just Single Current with Previous Booster		
Bosnia and Herzegovina	189	**37**
Poland	54	**19**
Japan	10	**17**
Mongolia	111	**428**
Kuwait	125	**23**
Singapore	5	**47**
Argentina	193	**27**
Uruguay	13	**33**
Estonia	48	**18**

Latvia	18	**29**
Romania	192	**84**
Chile	591	**18**
Serbia	82	**17**
Tunisia	7	**35**
Croatia	46	**8**
Belarus	72	**55**
****MC-BCG: Multiple Current BCG		
Armenia	297	41
Kazakhstan	84	89
Republic of Moldova	250	152
Republic of North Macedonia	290	13
Uzbekistan	10	79
Russian Federation	119	80
Ukraine	60	91
*****JP-BCG: Just Previous BCG		
Italy	587	**7**
UK and Northern Ireland	611	**10**
Sweden	575	**9**
Switzerland	232	**7**
Canada	242	**6**
Austria	81	**8**
Spain	622	**12**
Slovakia	6	**7**
Slovenia	64	**7**
Czechia	40	**18**
Denmark	108	**6**
Finland	61	**6**
France (Metropolitan)	469	**9**
Germany	112	**8**
Ireland	359	**7**
Israel	104	**8**
Trinidad and Tobago	18	**21**
Australia	26	**7**
Norway	49	**6**
Portugal	179	**24**

New Zealand	4	**65**
******NP/C-BCG : BCG : 0 = No Previous or Current BCG (The Controlled Group)		
Lebanon	26	13
Bahrain	111	18
Netherlands	363	6
Belgium	853	9
United States of America	567	7
Cyprus	17	6

*TB Prevalent Groups: (Low: ≤ 15), (Moderate: 16-49), and (High: ≥ 50).

** JSC1-BCG : Just single current BCG- no previous booster. *** (JSC2-BCG): just single current with previous booster. **** (MC-BCG): multiple current BCG. ***** (JP-BCG): just previous BCG. ****** (NP/C-BCG or , BCG : 0 or the BCG controlled group:no previous or current BCG

APPENDIX B. REFERENCES FOR DATA

Category	References
Covid-19 deaths/M as it is in September,2,2020	Worldmeter. Coronavirus Accessed: 2/9/2020 https://www.worldometers.info/coronavirus/?
Malaria elimination references	1-https://www.who.int/malaria/areas/elimination/malaria-free-countries/en/ 2CDC Malaria Information and Prophylaxis, by Country [E] https://www.cdc.gov/malaria/travelers/country_table/e.html **3**- World malaria report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. file:///C:/Users/zz/Downloads/9789241565721-eng.pdf **4**- The World Bank. Data. Incidence of Malaria https://data.worldbank.org/indicator/SH.MLR.INCD.P3 **5**-WHO. Global Health Observatory data repository. By Category. Malaria .Cases https://apps.who.int/gho/data/node.main.MALARIAINCIDENCE?lang=en **6**- Roser M , Ritchie H. Our World in Datta. Malaria . last revised in October 2019. https://ourworldindata.org/malaria Accessed: 3/9/202 6-Constantinou K. Anopheles (malaria) eradication in Cyprus. Parassitologia. 1998 Jun;40(1-2):131-5. PMID: 9653740. 7-Bulletin of the World Health Organization • Past issues Volume 86: 2008 • Volume 86, Number 2, February 2008, 81-160 • 8- Chapter 5. Elimination of malaria in: World Malaria Report 2009. P55 9- Countries and territories certified malaria-free by WHO Last update: 22 May 2019
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Exclusion list	(excluded list of Countries and territories with less than 1 million populations) These include: Montenegro, Seychelles, Iceland, La Réunion, Malta, Monaco, San Marino, Antigua and Barbuda, Luxembourg, Bahamas, Barbados, Dominica, Fiji, Nauru, Grenada, Tuvalu, Tonga, Samoa, Palau, Niue, Saint Kitts and Nevis, Saint Lucia, Micronesia (Federated States of), Marshall Islands, Kiribati, Cook Islands, Brunei Darussalam, Andorra and Maldives, Micronesia, Saint Vincent and the Grenadines.

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