Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Role of latent tuberculosis infections in reduced COVID-19 mortality: Evidence from an instrumental variable method analysis

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ABSTRACT

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, there has been significant interest in the potential protective effect of the Bacillus Calmette-Guerin (BCG) vaccine against COVID-19 mortality. This effect has been attributed to innate immune responses induced by BCG vaccination. However, these studies ignore an important fact: according to World Health Organization estimates, about a quarter of the world's population may have latent tuberculosis infection (LTBI), a condition in which there is no evidence of clinically active tuberculosis but persistent immune responses are stimulated by Mycobacterium tuberculosis antigens. Thus, both LTBI and BCG induce lifelong immunity and may provide immunological protection against COVID-19. In this study, the relationship between LTBI and reduced COVID-19 mortality was analyzed using the instrumental variable method. The results showed with robust statistical support that LTBI was also associated with reduced COVID-19 mortality.

Introduction

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, significant attention has been focused on the relationship between Bacillus Calmette-Guerin (BCG) vaccination and COVID-19 mortality. In particular, there is interest in whether BCG vaccination is associated with a reduction in COVID-19-associated mortality. BCG is the most widespread vaccine against tuberculosis (TB) and also elicits non-specific effects and innate immune memory against non-mycobacterial diseases. A survey of key unpublished and published data regarding the association between BCG vaccination and COVID-19 mortality was conducted, and concluded that there was a lack of evidence to support a protective effect of BCG against COVID-19 [1]. However, such studies ignore the important fact that about one-quarter of the world's population may have latent TB infection (LTBI), a condition in which there is no evidence of clinically active TB but persistent immune responses are stimulated by *Mycobacterium tuberculosis* antigens. The regional data shown in Table 1 illustrate that the number of LTBIs far surpasses the number of active TB infections. The number of LBT infections clearly surpasses that of TB infections. LTBI also induces lifelong innate immune immunity [2–4] and may confer an immunological protective effect against COVID-19.

Statement of hypothesis

Many countries with a relatively high incidence of TB infection, including Japan, require BCG vaccination during early childhood. Most citizens of these countries also have LTBI, which is highly immunoprotective because of elicited innate immune responses. In fact, TB infection leads to LTBI in 90%–95% of cases, while 5%–10% of individuals develop active TB disease [5]. Therefore, the number of TB infections per hundred thousand individuals can be used as a proxy for the number of LTBIs. Furthermore, *M. tuberculosis* infection via BCG vaccination can enhance innate immunity. Therefore, citizens of countries with high prevalence of TB infection (high TB burden countries) together with high BCG vaccination rates are considered to have enhanced innate immunity compared with the citizens of lower TB burden countries. This high level of natural immunity is thought to be responsible for the lower COVID-19 mortality rate.

The aim of this study was to test the hypothesis that LTBI is associated with reduced COVID-19 mortality.

Testing the hyposesis

The instrumental variable (IV) method was used to assess causality. All data used in the analysis are publicly available and are described in the appendix. Much discussion has centered around the strong

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Table 1
Numbers (millions) of Regional TB infections (TBIs) and latent TB infections (LTBIs).

WHO Regions	AFR	SEC	EMS	WP	AMR	EUR
TBIs	**23.7**	**22.6**	**11.3**	**9.6**	**2.8**	**3.0**
LTBIs	**216**	**587**	**104**	**514**	**108**	**124**

Note: The estimated number of TBIs according to WHO region was obtained from the WHO Tuberculosis Report 2018, Table 3.3, and the estimated number of LTBIs according to WHO region was obtained from Table 2 in reference [5]. *Abbreviations*: AFR: African Region, SEC: South-East Asia Region, EMS: Eastern Mediterranean Sea Region, WP: Western Pacific Region, AMR: Region of America, EUR: European Region.

correlation between BCG and COVID-19 mortality. However, correlation does not imply causation, and can sometimes instead reflect spurious relationships. Regression analysis, particularly the IV method, is a statistical method that addresses this problem to assess causality.

Care must be taken in using COVID-19 mortality as a dependent variable [6]. This is because COVID-19 mortality is conditionally observed in potentially infected individuals, and can only be detected by testing of symptomatic or asymptomatic individuals. Therefore, the case fatality rate (CFR), defined as the ratio of the number of COVID-19 deaths per million people to the number of COVID-19 infections per million people, is typically used. As explained above, the logarithm of the number of TB infections per 100,000 individuals (lntb10) can be used as a proxy variable for LTBIs. For this regression analysis to be statistically accurate, the explanatory variable X must first be uncorrelated with the error term u (i.e., the covariance of X and u must be zero). This condition clearly does not hold in general: besides LTBI, many other co-occurring factors, such as cultural norms, mitigation efforts, health infrastructure, and urban concentration, may influence this relationship [8]. Therefore, it is possible that X is correlated with such factors excluded in the regression equation, and that X and the error term may be correlated. This would be an example of a "spurious regression".

To overcome such a problem, the IV method can be used. An IV is a variable that is strongly correlated with the explanatory variable X but is not correlated or only weakly correlated with the error term. The IVs used here were as follows.

- **bcgindex**: The number of years a country has included BCG vaccine in its national immunization program. 1: All individuals received mandatory vaccinations; 0 BCG neither previously nor currently mandatory; Values between 0 and 1: BCG previously mandatory but now discontinued. See Data Appendix for details of the construction of the BCG index.
- **region:** The World Health Organization (WHO) regional classification was used here**.** 1: African Region; 2: South-East Asia Region; 3: East-Mediterranean Sea Region; 4: Western-Pacific Asia Region; 5: Region of America; 6: European Region.
- **pop65**: The ratio of the population over 65 years of age.

Four diagnostic tests were performed to assess whether the estimates were statistically relevant. One test was concerned with the explanatory variables and the other three were concerned with the IVs. The Wu-Hausman test assesses the endogeneity of the explanatory variables. If the null hypothesis is rejected, one can simply use the standard ordinary least squares regression instead of using the IV. The first test of an instrument is Sargan's exogenous test, which assesses whether the right number of IVs are selected and confirms that they are sufficiently uncorrelated with the error term. Finally, it is necessary to perform a "weak IV test" to check if the selected IVs are strongly correlated with the explanatory variables.

The instrumental variables used here were **bcgindex**, **region** and **pop65**. Two models were estimated using the IV method: one with three instruments and the other with two instrument (**bcgindex** and **region**). Most of the countries with low income levels (annual per capita income less than $825 USD) reported zero deaths attributed to COVID-19 [7]. To avoid underreporting bias in these countries, they were excluded. The total number of countries analyzed was thus 104.

Conclusion

The results are shown in Table 2. The estimates of the Generalized Moment Method (GMM), which is often used as an alternative to the IV method, are also reported.

For the diagnostic tests of the two estimation models, Sargan's exogenous test indicated that the selected IVs met the exogenous property. The results of the weak IV test indicated that the IVs were sufficiently and strongly correlated with the explanatory variables. Therefore, all the estimation results presented here were statistically robust. All the coefficients of **lntb10** were approximately -0.02, indicating a negative association between LTBI and COVID-19 mortality. Thus, these results lend statistical support to the hypothesis that LTBI can protect against COVID-19 mortality.

Because these estimation models were linear-log type, the estimated coefficient of -0.02 must be carefully interpreted. Every 10% increase in LTBI prevalence would be expected to reduce the CFR of COVID-19 by about a 0.2 percentage point ($-.0019 \approx -.02 \times \ln(1.1)$). The region with the highest LTBI burden is South-East Asia with an estimated LTBI incidence of 587 cases per million inhabitants. The region with the lowest LTBI burden is Europe, with an estimated LTBI incidence of 124 cases per million people. Thus, the incidence of LTBI in Southeast Asia is five times higher than in Europe. According to the estimations presented here, it should lower the CFR of COVID-19 in Southeast Asia by a 3 percentage point. These results may explain why the CFR for COVID-19 is so low in Southeast Asian countries compared with European countries.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

Table 2
IV estimation of the relationship between LTBI and COVID-19 mortality.

Dependent variable: Case fatality rate (CFR)				
Regressor	Model 1 (IV)	Model 1 (GMM)	Model 2 (IV)	Model 2 (GMM)
Ln(tb10)	−0.0198***(0.00365)	−0.0176***(. 0034)	−0.0194***(0.00365)	−0.0172***(0.00336)
Intercept	0.1107***(0.01350)	0.1039***(. 01,348)	0.1092***(0.01,350)	0.1012***(0.01,361)
Instrument variables				
	bcgindex, region, pop 65	bcgindex, region, pop 65	bcgindex, region	bcgindex, region
Wu-Hausman Test	22.8949(p = 0.0000)	25.0373(p = 0.000)		
Sargan Test	3.46284(p = 0.1787)	3.2009(p = 0.0732)		
Weak Instrument Test	33.416**	49.3901**		

Note: Values in parentheses represent standard errors. (***), $p < 0.01$ and (**), $p < 005$.

influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110214.

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