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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Short Communication

Influence of malaria endemicity and tuberculosis prevalence on COVID-19 mortality

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ABSTRACT

Objectives: Regarding severe acute respiratory syndrome coronavirus 2, it is known that a substantial percentage of the adult population does not become infected when exposed to this novel coronavirus. Several studies provide an initial indication of the possible role of pre-existing immunity, whether cross-immunity or not. The possible role of latent tuberculosis (TB) and malaria has been suggested to create innate cross heterogeneous immunity. In this study, we looked for the influence of these factors on coronavirus disease 2019 (COVID-19) mortality in malaria-endemic countries.

Study design: Eighty malaria-endemic countries were enrolled in this cross-sectional study. Data subjected to testing included TB prevalence, Bacillus Calmette-Guérin (BCG) vaccine coverage, malaria incidence, and COVID-19 mortality.

Methods: Hierarchical multiple regression type of analysis was used for data analyses. TB prevalence per 100,000 population standardized to BCG coverage rates was taken as a direct factor in the test. Malaria incidence per 1000 population was considered an intermediate factor. The outcome was COVID-19 mortality per million population.

Results: The results showed with robust statistical support that standardized TB prevalence was significantly associated with reduced COVID-19 mortality. Malaria had an additional effect in reducing COVID-19 mortality, with a highly significant association.

Conclusions: Malaria and standardized TB prevalence are statistically significant factors associated negatively with COVID-19 mortality.

Introduction

In 2011, Netea et al.[1] proposed the term 'trained immunity' to describe the ability of innate immune cells to non-specifically adapt, protect, and remember primary stimulation.

Studies conducted over the past few decades have revealed certain adaptations connected with innate immune cells (i.e., monocyte/macrophages), and natural killer cells are responsible for the non-specific effects of a vaccination beyond its target.[2]

Latent tuberculosis (TB) infection was suggested to create a heterogeneous immune response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection in different patterns and severity based on different Bacillus Calmette-Guérin (BCG) statuses.[3,4] Further studies have consolidated such a role for latent TB.[5–7]

In Italy, it has been suggested that the Black population is less affected by coronavirus disease 2019 (COVID-19) owing to suggested previous exposure to malaria and the presence of anti-glycosylphosphatidylinositol antibodies, which have a possible protective effect against malaria reinfection and may give cross-protection against SARS-CoV-2 infection.[8,9] Furthermore, an epidemiological paradox between COVID-19 and malaria endemicity was noticed during the initial phase of the pandemic.[10]

Adding to this evidence, further study showed that high endemicity of TB and malaria and universal BCG programs were suggested to have a cushioning effect on the proportion of the population affected by COVID-19.[6]

Both BCG implementation and latent TB prevalence, later on, did not fully explain variances in COVID-19 mortalities across different countries. In South Africa, for example, the COVID-19 mortality per million (M) population was 238 per M population at the time of the study, whereas the TB prevalence per 100,000 population was 520, which is very high. Moreover, these studies did not explain the low

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COVID-19 mortality rates in countries that have relatively low TB prevalence per 100,000 population, such as Togo, Benin, and Mali, where the estimated TB prevalence is 36, 56, and 53, whereas COVID-19 mortality per M population is 3, 3, and 6, respectively.

Our study's background hypothesis stands on the possible heterogeneous immunity generated by malaria in addition to possible heterogeneous immunity generated by TB. This study compared COVID-19 mortality in malaria-endemic countries against TB prevalence standardized by BCG coverage. Then, the mortality rate was tested again when the malaria incidence effect was added to the composite sample to look for statistical associations and significances.

This study addressed mortalities instead of morbidities because the real number of affected people was beyond counting, and many confounders affect testing because of the wide distribution of asymptomatic persons. Furthermore, this study considered standardized TB prevalence to BCG coverage instead of non-standardized TB prevalence values.

Results and findings

Eighty malaria-endemic countries were enrolled in this cross-sectional study. Data subjected to testing included TB prevalence, BCG coverage, malaria incidence, and COVID-19 mortalities as it were on August 31, 2020.

Hierarchical regression of a composite multiple linear model was used for data analyses.

According to hierarchical regression analysis, the direct factor reducing mortality rates concerning COVID-19 was the standardized TB/100,000 population by BCG vaccination coverage percentage in 2018 through dividing the factor of TB prevalence/100,000 population rates by the factor of BCG vaccination coverage in 2018. The indirect effect that reduced the mortality rates, named as an intermediate factor, was the malaria incidence for 2018 per 1000 population.

We investigated the validity of the assumptions of the studied model that adopted the results of the quantitative measurements. Table 1 shows the results of the multiple linear model fitness test resulting from the regression analysis of variance.

The effectiveness of the model's fitness was observed in quality when the intermediate factor was present.

The level of significance was greatly reduced compared with the case of the model's quality in the absence of the intermediate factor (Table 1).

Table 2 shows the results from estimating some descriptive statistics accompanying the analysis of the composite linear model. The level of the increase in the value of the multiple correlation coefficient is evidenced by the presence of the intermediate factor in the composite regression analysis.

Table 2
Results of some descriptive statistics accompanying the analysis of the composited linear model of studied functions.

Model	R, Multiple Correction	R square	Adjusted R square	Standard error of the estimate
1	0.301	0.091	0.067	149.0371
2	0.414	0.171	0.139	143.2036

TB = tuberculosis; BCG = Bacillus Calmette-Guérin.
1: predictors: (constant), BCG vaccination coverage 2018 in percentage, TB prevalence per 100,000.
2: predictors: (constant), BCG vaccination coverage 2018 in percentage, TB prevalence per 100,000, malaria incidence for 2018 per 1000.

Discussion

In this study, the prevalence of exposure to *Mycobacterium* spp. (standardized to BCG vaccine coverage) by populations was negatively associated with COVID-19 deaths per M population. This supports the previously mentioned studies.[3–7]

TB prevalence standardization for BCG coverage was an important factor with regard to studying countries currently implementing BCG programs, as long as the coverage was reflecting the degree of benefits added to the factor (latent TB prevalence) that the coverage does. Likewise, the influence of time duration of cessation of the BCG vaccination program was a factor in determining COVID-19 mortality in countries that ceased implementing this vaccine, which we concluded in our previous study.[11]

Malaria can induce an immunological response that is significantly associated with a reduction in COVID-19 mortality. This association needs confirmatory immunological and clinical control studies to establish causation. This finding can explain the variances in COVID-19 mortality among different countries much deeper than latent TB and BCG vaccination. Differences in BCG vaccination policies were of concern earlier than for latent TB, which later became a more prominent concern. Previous studies were conflicting and were criticized because of the possible confounding factors.

In this study, all countries were implementing national BCG programs, but countries with TB prevalence per 100,00 population normalized by BCG coverage rates showed a significant association with the reduction in COVID-19 mortality. The supportive evidence for TB prevalence and malaria incidence in this study was obtained using a robust statistical method—hierarchical multiple regression analysis.

Hierarchical multiple regression analysis is a subset of regression methods that we chose to prove our theory using collected evidence for a proposed role of variables entered in blocks.[12]

Table 1
Fitness test results for the regression analysis of variance with and without effectiveness of an intermediate factor.

Model	SOV*	SS**	Df***	MSS****	F	*P*-value*****
Without intermediate factor	Regression	170266.9	2	85133.45	3.833	0.026, S
	Residuals	1710329.0	77	22212.07		
	Total	1880595.9	79	–		
With intermediate factor	Regression	322044.1	3	107348	5.235	0.002, HS
	Residuals	1558551.8	76	20507.26		
	Total	1880595.9	79	–		

*SOV, source of variation;
**SS, sum of squares;
***Df, degree of freedom;
****MSS, mean sums of squares;
*****HS, highly significant at $P < 0.01$;
S, significant at $P < 0.05$.

Table 3
Estimating parameters of the regression and composite regression models in the presence of the indirect effect of the intermediate factor.

Regression and composite regression models	B	Standard error	Standard Beta	t-value	*P*-value*
(Constant)	126.98	25.87	–	4.908	0.000,HS
	−22.11	8.53	−0.282	−2.593	0.011,S
(Constant)	152.38	26.58	–	5.734	0.000,HS
Standardized of TB/100000 by BCG vaccination coverage percent (2018)	−18.00	8.34	−0.229	−2.16	0.034,S
Malaria incidence for 2018 per 1000	−0.331	0.122	−0.289	−2.717	0.008,HS

TB = tuberculosis; BCG = Bacillus Calmette-Guérin.
* HS: highly significant at $P < 0.01$; S: significant at $P < 0.05$.

TB prevalence was in the 1st block in this study, malaria incidence was in the 2nd block, and reduction of COVID-19 mortality was the effect.

This test allowed us to look at the *R* square change and F-statistic change between the two models, in addition to reporting the level of significance for each predictor variable that was entered into the model in predetermined iterations.

Table 2 shows that the *R* square was 0.091 and increased to 0.171 when the intermediate factor was added to the composite.

Furthermore, these results show that constant parameters constitute a significant proportion causing COVID-19 mortality measured (152.38). TB prevalence, when standardized to a BCG coverage rate, made a −22.11 change, and when malaria incidence was included in the regression model (constants), it made a −0.331 further change. Constants constituted a considerable number not included in the regression model (Table 3).

Based on the benefits of heterogeneous immunity, possibly, two important questions may need to be answered: Does a potent malaria vaccine need to be considered for malaria eradication? Does latent TB management in the future need to be more conservative?

Limitations

Possible confounding variables have not been evaluated, such as population density, ethnicity, life expectancy, comorbidities, lifestyle, the pandemic phase, data accuracy, and health services.

Conclusions

Although confounding variables have not been evaluated, the results of this study suggested that malaria incidence and TB prevalence are possible determining factors for COVID-19 mortality. Further research is needed for exploring such findings.

Author statements

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Ethical approval

Ethical permission is not necessary as this study analyzed publicly published data, and patients were not involved.

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Competing interests

There was no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.02.018.

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