

Association between past tuberculosis epidemic and COVID-19-related mortality through latent infection by natural immunity

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Abstract

The coronavirus disease (COVID-19) pandemic has created a remarkable and varying impact in each region, which calls for broad attention. Recently, the Bacillus Calmette-Guérin (BCG) vaccination has been regarded as a potential candidate to explain this difference. Herein, we hypothesised that past tuberculosis epidemic may act as a latent explanatory factor for the worldwide difference in COVID-19 impact. We compared two indicators of past tuberculosis epidemic, namely, incidence (90 countries for the incidence rate in 1990) and mortality (28 countries for the mortality rate in 1950) with COVID-19 mortality rate. An inverse relationship exists between both past epidemic indicators and COVID-19 mortality. The rate ratio of the cumulative COVID-19 mortality per 1 million was 1.08 (95% confidence interval [CI]: 0.98–1.18) per 1 unit decrease in the incidence rate of tuberculosis per 100,000 people. This association existed even after adjusting for potential confounders (elderly rate, diabetes prevalence, mortality rate from cardiovascular disease, and gross domestic product per capita) [adjusted rate ratio: 1.05, 95% CI: (1.03–1.08)]. After latent infection, *Mycobacterium tuberculosis* survives in the human body and may continue to stimulate trained immunity for lifetime. Our study has revealed one possible mechanism underlying the region-based variation in the COVID-19 impact.

Introduction

The ongoing novel coronavirus disease (COVID-19) pandemic, which is a major concern, remains a mystery that puzzles the world. It has created a remarkable and varying impact in each region. For example, the total number of confirmed deaths due to COVID-19 per million people by country ranged from less than 0.1 to almost 1,000, indicating a four-digit difference (as on 5 April 2020).¹ Non-biomedical factors such as socioeconomic status, cultural, and public health ones may not fully explain this vast divergence.

Currently, the Bacillus Calmette-Guérin (BCG) vaccine has gained increasing attention for its speculated efficacy against COVID-19,²⁻⁴ which is based on the concept of trained natural immunity.⁵ Studies have focused on the different effects of COVID-19 between countries wherein BCG vaccination programmes are currently in place and countries wherein they are not. However, one crucial perspective remains to be discussed before the argument over BCG vaccination.

Since ancient times, tuberculosis continues to pose a major threat to health worldwide.⁶ BCG vaccination in new-borns and infants reduced the risk of tuberculosis by over 50% across populations.⁷ Owing to the heavy disease burden imposed by tuberculosis, BCG vaccination is currently enforced in many countries. This is also the case for Japan, which has been battling against tuberculosis for a long time until now.⁸ People are infected with tuberculosis during youth. In 1950, more than half of the adolescents aged <20 years were infected with tuberculosis in Japan.⁹ The majority (85–90%) of such infected individuals do not develop clinical manifestations of tuberculosis; however, they have latent tuberculosis infection. Even in 2018, about one-quarter of the world's population had latent tuberculosis infection.⁶

In latent infection, the tuberculosis bacterium persists and continues to activate the immune system. Notably, the immunity acquired naturally due to active infection always outstrips the immunity acquired artificially from immunisation. If the 'trained immunity' by BCG vaccination exists,⁵ then the immunity acquired by natural infection with *Mycobacterium tuberculosis* would be more powerful and long-lasting than the immunity acquired artificially from BCG vaccination. Noteworthy, in the early twentieth century, tuberculosis was on the rampage of prevalence in East Asian countries including Taiwan, Thailand, Vietnam, and Japan, wherein the cumulative mortality rates for COVID-19 were remarkably lower than those in other countries such as Spain, Italy, United Kingdom, and the United States of America (USA). In the latter countries, the tuberculosis burden, regardless of whether infection rate or mortality rate, was much lower than that in the former countries.

Thus, we have noticed the following hypothesis (Figure 1). "In countries wherein BCG vaccination is currently in place, the impact of COVID-19 may be limited because the high-risk elderly population was infected with tuberculosis in younger days to get powerful trained natural immunity. Accordingly, current BCG vaccination would indicate a spurious relationship to reflect the past tuberculosis epidemic and an epiphenomenon to produce a spurious relationship with fewer between mortalities of COVID-19, which is seen in some countries including Japan." Then, we tested this hypothesis by comparing the cumulative mortality rates between COVID-19 and past tuberculosis epidemic (incidence rate of 90 countries in 1990 and the mortality rate of 28 countries in 1950).

Results

Figure 2 shows the incidence rate of tuberculosis in 90 countries in the year 1990 (a) and the mortality rate of tuberculosis in 28 countries in the year 1950 (b) according to the status of the BCG vaccination group in 2015. Each country was classified into three groups according to the BCG vaccination status in 2011:¹⁰ The group A: the country currently has a universal BCG vaccination programme, group B: the country did recommend BCG vaccination for everyone, but currently, it does not, and group C: the country never had universal BCG vaccination programmes. As shown, both the incidence and mortality rates of tuberculosis increased in group A than in groups B and C. These reflect that the country in group A is the past epidemic area of tuberculosis. The Spearman's correlation coefficients between the incidence rate in 1990 and the mortality rate in 1950 were 0.73 ($p < 0.001$), which indicate a strong correlation.¹¹

Figure 3 shows the scatterplot of the log-transformed incidence rate of tuberculosis in 1990 against the log-transformed cumulative mortality rate of COVID-19 on 5 April 2020 in 90 countries (group A: 68, group B: 17 and group C: 5). The annual incidence rate of tuberculosis in 1990 (X-axis) ranged from 5.2 per 100,000 persons in Cyprus to 453.0 per 100,000 persons in Indonesia to indicate two-digit variations. The cumulative mortality rate of COVID-19 (Y-axis) ranged from 0.05 per one million persons in India to 943 per one million persons in San Marino to indicate over four-digit variations.

The scatterplot shows an inverse relationship between the incidence rate of tuberculosis in 1990 and COVID-19 (Spearman correlation coefficient = -0.49, $p < 0.0001$). Virtually, all Asian countries that belonged

to group A were located in the lower right to indicate a high incidence rate of tuberculosis and a few mortality rates of COVID-19. In contrast, most European and American countries were located in the upper left to indicate the vice versa. Here, group B (used BCG in the past) and group C (never used BCG) mixed up, with no clear difference in configuration.

Figure 4 shows the scatterplot of the mortality rates of tuberculosis per 100,000 people in 1950 against the mortality rate of COVID-19 on 5 April 2020 per 1 million people in the 28 countries (group A: 12, group B: 11, and group C: 5). The annual mortality rate of tuberculosis in 1950 (X-axis) ranged from 13.8 per 100,000 persons in Denmark to 350.0 per 100,000 persons in South Korea to indicate one-digit variations. The cumulative mortality rate of COVID-19 (Y-axis) ranged from 0.2 per one million persons in New Zealand to 254 per one million persons in Italy to indicate three-digit variations.

Same as the relationship between the incidence rate of tuberculosis in 1990 and mortality rate of COVID-19, an inverse relationship was observed between the mortality rate of tuberculosis in 1950 and mortality rate of COVID-19 (Spearman correlation coefficient = -0.40, $p = 0.035$). Again, most Asian countries that belonged to group A were located in the lower right to indicate a high mortality rate of tuberculosis and a few mortality rates of COVID-19. In contrast, all the European and American countries were located in the upper left to indicate the vice versa. Groups B (used BCG in the past) and C (never used BCG) mixed up, as shown in Figure 3.

Table 1 shows the association of a decrease in the incidence rate of tuberculosis in 1990 and the mortality rate of tuberculosis in 1950 on the cumulative mortality rate of COVID-19. The rate ratio of the cumulative mortality rate of COVID-19 per 1 million was 1.08 (95% confidence interval (CI): 0.98–1.18) per 1 unit decrease in the incidence rate of tuberculosis per 100,000 in 1990. This association was observed even after adjusting the rate of elders aged 65 older, country-level chronic disease prevalence, and gross domestic product (GDP) per capita [rate ratio in the adjusted model 3: 1.05, 95% CI: (1.03–1.08)]. Similar trends were also observed in the association between the tuberculosis mortality rate in 1950 and the cumulative mortality rate of COVID-19.

Table 1 Association of decrease in the incidence rate of tuberculosis per 100,000 in 1990 and the mortality rate of tuberculosis per 100,000 in 1950 on the cumulative mortality rate of COVID-19 on 5 April, 2020 per 1 million people.

	TB incidence in 1990		TB mortality in 1950	
	rate ratio	95% CI	rate ratio	95% CI
Crude model	2.70	(1.09–6.68)	1.39	(0.82–2.38)
Adjusted model 1	2.52	(1.58–4.00)	1.40	(0.82–2.40)
Adjusted model 2	2.65	(1.46–4.81)	9.39	(0.93–95.02)
Adjusted model 3	2.44	(1.32–4.52)	9.32	(0.18–493.74)

CI, confidence interval

The adjusted model 1 was adjusted by the rate of aged 65 older.

The adjusted model 2 was adjusted by the rate of aged 65 older and the prevalence of chronic disease (diabetes and cardiovascular disease).

The adjusted model 3 was adjusted by the rate of aged 65 older, the prevalence of chronic disease (diabetes and cardiovascular disease), and the GDP per capita.

In the supplementary analysis, we evaluated the association of the incidence rate of tuberculosis per 100,000 in 1990 and the mortality rate of tuberculosis per 100,000 in 1950 on the cumulative mortality rate of COVID-19 per 1 million people on 5 August. A scatterplot of the incidence rate of tuberculosis in 1990 against the cumulative mortality rate of COVID-19 on 5 August in the 90 countries is shown in Supplementary Fig. S1, and a scatterplot of the mortality rate of tuberculosis per 100,000 in 1950 is shown in Supplementary Fig. S2. The rate ratios are shown in Supplementary Table S1. Comparing with the results of the main analysis, although the Spearman correlation coefficient was decreased in the analysis with the incidence rate of tuberculosis in 1990 (Spearman correlation = -0.28, $p = 0.008$), a similar correlation was observed in the analysis with the mortality rate of tuberculosis in 1950 (Spearman correlation = -0.43, $p = 0.023$). A positive increase in rate ratios of mortality of COVID-19 on 5 August were also observed with decreasing the incidence of tuberculosis in 1990 and the mortality rate of tuberculosis in 1950. The Spearman correlation coefficients between cumulative mortality of COVID-19 on 4 April and 5 August were 0.58 ($p < 0.0001$) in the dataset of the incidence rate of tuberculosis in 1990 and 0.73 ($p < 0.0001$) in the dataset of the mortality rate of tuberculosis in 1950, respectively.

Discussion

In this study, high mortality rates of COVID-19 were observed in countries that had lower experiences of the past tuberculosis epidemic at 30 and 70 years ago. The past tuberculosis epidemic is the strong determinant that precedes preventive policy for tuberculosis, including vaccination. Thus, the finding supports our hypothesis that the natural trained immunity due to latent persistent infection of tuberculosis has potentially contributed to low mortality rates of COVID-19 rather than the current BCG vaccination status, as seen in Asian countries and contrary to American and European countries. Accordingly, this may explain the reason for the remarkable and varied differences in COVID-19 impact among these countries.

There are studies discussing the possible therapeutic effect of the BCG vaccine on COVID-19.²⁻⁴ However, thus far, previous studies have not been discussed the immunity acquired from natural infection by *M. tuberculosis*, which we assumed to be a real factor against the impact of COVID-19. The results from the statistical analysis supported our hypothesis, which proposes that latent tuberculosis infection may be the real contributor for natural trained immunity, and BCG vaccination could be spuriously associated with the low impact of COVID-19 (Figure 1). Asian countries that were remarked for quite a low mortality

rate of COVID-19 had high levels of the past tuberculosis epidemic. In contrast, European and North American countries, which had a high COVID-19-related mortality rate, had low levels of the past tuberculosis epidemic. In the USA, about 60%-90% of hospitalised infected patients have comorbidities such as high blood pressure, diabetes, and heart disease or other chronic diseases, and about 80% of in-hospital mortality due to COVID-19 occurred in elderly people (≥ 65 years).¹⁹ Although the prevalence rate of these factors may be diverse across countries, associations between high levels of past tuberculosis infection and low mortality rate of COVID-19 were observed even after adjusting for indicators for country levels of elderly rate, chronic medical conditions, and national economic status.

Low mortality rate of COVID-19 was observed in countries receiving current BCG vaccination (group A), while high mortality rate was observed in those not receiving it (groups B and C). Among the latter, however, there was no clear difference in the mortality of COVID-19 between group B (previously used, but discontinued BCG) and group C (never used BCG) countries. If trained immunity induced by BCG lasts until old age, then there should be a clear difference in mortality in countries between groups B and C, which was in contrast to our finding. In addition, even specific acquired immunity from BCG vaccination against the incidence of tuberculosis would last only for 15 years.^{20,21} Trained natural immunity after BCG vaccination would last for some decades, which is far longer than that of specific acquired immunity.

Both group B and C countries had a relatively low impact of past tuberculosis epidemic, where maintenance of BCG vaccination has been differed by a political decision. For example, Norway terminated universal BCG vaccination in 2009, mainly due to a very low incidence of tuberculosis.¹⁷ Therefore, although Norway had been classified as group A in 'the BCG World Atlas' in 2011¹⁰, the group is virtually moved from groups A to B in the analysis. It is obvious that the past tuberculosis epidemic is the strong determinant that precedes preventive policy for tuberculosis including vaccination. Therefore, it appears that BCG vaccination is spuriously associated with COVID-19 impact as indicated in Figure 1.

There are several limitations to this study. First, owing to the ecological study design, caution is needed to apply this finding to individual levels. Ideally, further investigation is desirable to compare the progression of COVID-19 symptoms between people who had a latent infection of tuberculosis and those who do not. Second, the worldwide burden of COVID-19 has changed moment by moment, and it was rapidly expanded through the African and South American regions. These countries have situations in the health care system different from those in high-income countries. In this study, we selected the country for which it was feasible to obtain the data of the past tuberculosis epidemic. Eight African countries and seven South American countries were evaluated. Although we observed positive associations between the mortality rate of COVID-19 and the past tuberculosis epidemic in data on 5 August, the associations were being attenuated when comparing the result in data on 5 April. The effects of the current health care system should also be evaluated in further study. Moreover, our hypothesis needs to be tested continuously and, in the future, examined in different stages and settings of the COVID-19 pandemic.

The high mortality rates of COVID-19 were observed in countries that had lower experiences of the past tuberculosis epidemic. The natural trained immunity due to the tuberculosis infection in the past has potentially contributed to low mortality rates of COVID-19 in Asian countries and high mortality rates of COVID-19 in European and American countries. Natural immunity may play a crucial role in preventing exposed individuals from exacerbation and death due to COVID-19. Given it be true, risk stratification and preventive measures from this viewpoint could be explored. Thus, our findings warrant further investigation.

Methods

Indicators for the impact of COVID-19

The mortality rate of COVID-19 would be more reliable than the infection rate that was considerably influenced by a variety of laboratory tests in these countries. Additionally, the health care level in each country might be associated with the mortality rate of COVID-19. The COVID-19 outbreak rapidly expanded from April through the African continent, wherein many countries have lack of health care equipment and staff.²² Thus, for reducing these bias, we examined the cumulative mortality rate of COVID-19 (total number of deaths per 1,000,000 population) on 5 April, that is, before the spread of the COVID-19 outbreak in the African continent. We obtained data for the 98 countries that had confirmed cases of more than 200 and the death number was more than 1, on 5 April, from the Our World in Data website.¹ As a supplementary analysis, we collected data of the cumulative mortality rate of COVID-19 (total number of deaths per 1,000,000 population) on 5 August for evaluating the current situation.

Information of the indicators of past tuberculosis epidemic for latent tuberculosis infection

We selected two indicators for the past tuberculosis epidemic. First, we calculated the incidence rate of tuberculosis in 1990 for 90 among the 98 countries (91.8%) from the website of Global Note as the oldest record of the incidence rate of tuberculosis.¹² Because the new-born in 1990 became 30 years old in 2020, we assumed that the rate might indicate the past epidemic context of tuberculosis that the young and middle-aged experienced. Second, we determined the mortality rate of tuberculosis in 1950 for 28 among the 98 countries (29.2%) from four references.¹³⁻¹⁶ Because a person born in that year is now (in 2020) 70 years old, we assumed that the mortality rate might indicate the past epidemic context of tuberculosis that the older aged experienced. The mortality data of China in 1950 were substituted by those of Taiwan. Data of South Korea during 1950-1953 had been estimated based on data in 1945 due to the Korean War,¹⁸ and the median of estimated death rates range '300 to 400 per 1,000,000 populations' was utilised for the analysis.

Categorisation by BCG vaccination status.

We classified the targeted countries into three groups according to the status of BCG vaccination in 2011, using the BCG World Atlas;¹⁰ group A: The country, currently, has a universal BCG vaccination

programme, group B: The country used to recommend BCG vaccination for everyone, but currently, it does not, and group C: The country never had universal BCG vaccination programmes. Because Norway stopped universal BCG vaccination in 2009,¹⁷ the group was moved from groups A to B in this analysis.

Statistical analysis

First, for describing the association between BCG vaccination groups and the past history of incidence and mortality of tuberculosis, we calculated the boxplot of the incidence rate of tuberculosis per 100,000 in 1990 and the mortality rate of tuberculosis per 100,000 in 1950 classified by the each BCG vaccination group. Second, we created the scatter plots to compare two indicators of past epidemic statuses of tuberculosis against the mortality rate of COVID-19 on 5 April. Finally, for evaluating the association between the past tuberculosis epidemic status and the mortality of the COVID-19, we calculated the rate ratios of the mortality of COVID-19 and their 95% CI per 1 unit decrease in the incidence rate in 1990 and mortality rate of tuberculosis per 100,000 people in 1950 using the generalised log-linear regression model. We transformed the incidence and mortality rates to inverse and inputted the value into the model. In this analysis, we first calculated the crude rate ratios of COVID-19 mortality. The deaths due to COVID-19 particularly occurred in people who are older and have chronic disease symptoms, and the elderly rate and prevalence of those chronic diseases were diverse across countries.¹⁹ Then, we adjusted the rate of people aged 65 over the most recent year available as adjusted model 1 and additionally adjusted the prevalence rate of diabetes in 2017 and the rate of death due to cardiovascular disease in 2017 (annual number of deaths per 100,000 people) as the adjusted model 2. Finally, we additionally adjusted the GDP per capita as the adjusted model 3. These potential confounders were also obtained from the Our World in Data website.¹ As a supplementary analysis, for evaluating the current situation in COVID-19 outbreaks, we evaluated the association between both indicators of past tuberculosis epidemic statuses and the mortality rate of COVID-19 on 5 August in the same manner as that of the main analysis.

Statistical analyses were carried out using R, version 4.0.2 (R Core Team, The R Foundation for Statistical Computing, Vienna, Austria).

Declarations

Author contributions

K.I initiated the research. K.I and S.K designed the research, corrected the data, carried out the analysis, interpreted the data, prepared a draft of the manuscript, discussed the results, and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Data availability

All data generated or analysed during this study are available at the website and all sources of data indicated in this published article.

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Figures

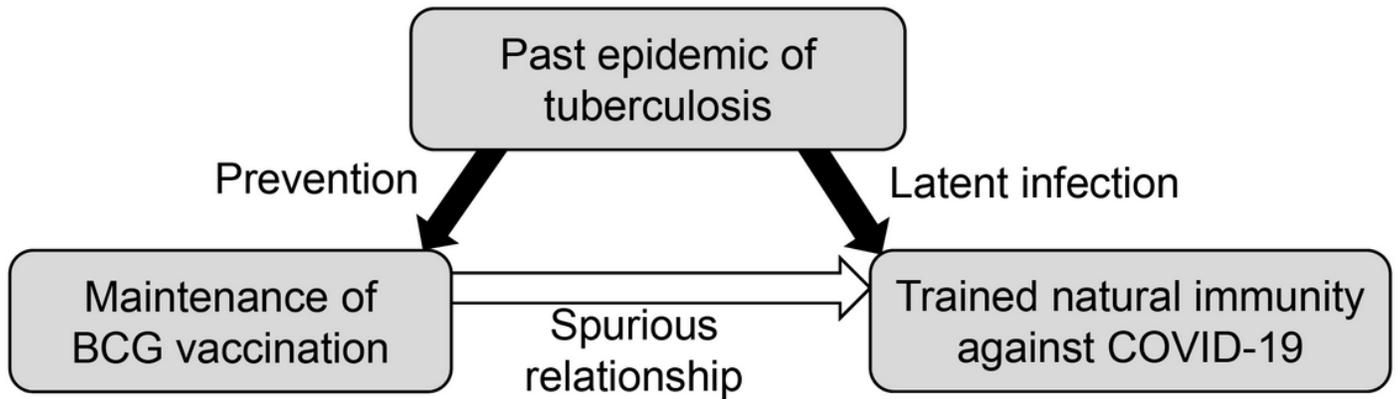


Figure 1

Hypothesis of trained natural immunity in latent tuberculosis infection

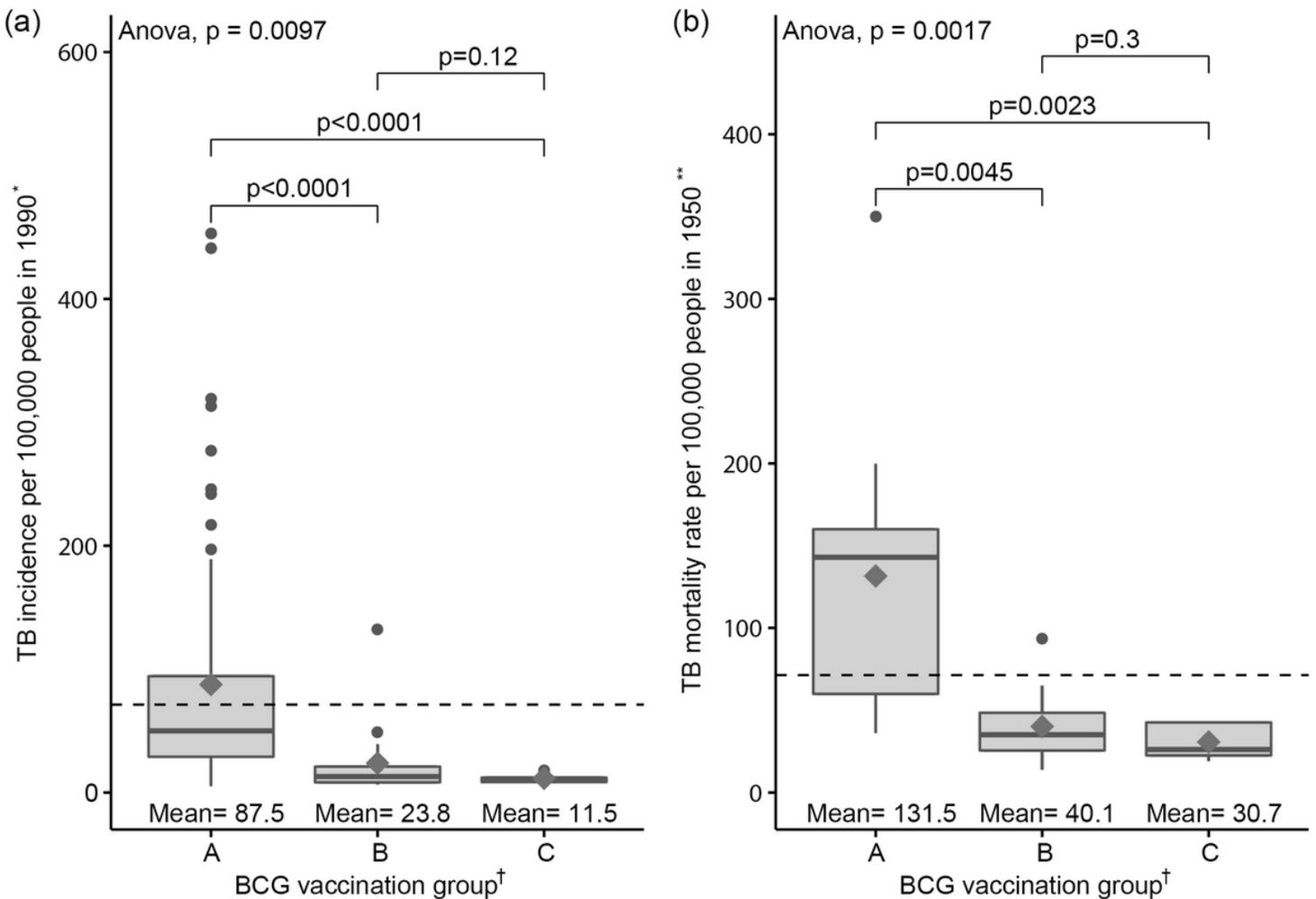


Figure 2

Incidence rate per 100,000 people at 90 countries in 1990 (a) and mortality rate per 100,000 people at 28 countries in 1950 (b) according to the BCG vaccination status in 2015. The dark grey diamond represents the mean value of the corresponding Y-axis values. The bottom and top of the box represent the 25th and 75th percentiles.

75th percentiles, respectively, and the band near the middle of the box is the 50th percentile (median). 'Whiskers' represent the maximum and minimum that extend 1.5 times the interquartile range from the box edges. The vertical dash line represents the mean of Y values across all participants in 1990 and 1950. * Information was obtained from reference (Global Note).¹² ** Information was obtained from References 13–16. The mortality rate of tuberculosis in China was substituted by that of Taiwan. Data of South Korea were estimated based on data collected in 1945. † Information was obtained from the BCG World Atlas.¹⁰ Norway was moved from groups A to B.¹⁷ The P-values shown above the bar were calculated using Bonferroni adjusted t-test. TB, tuberculosis.

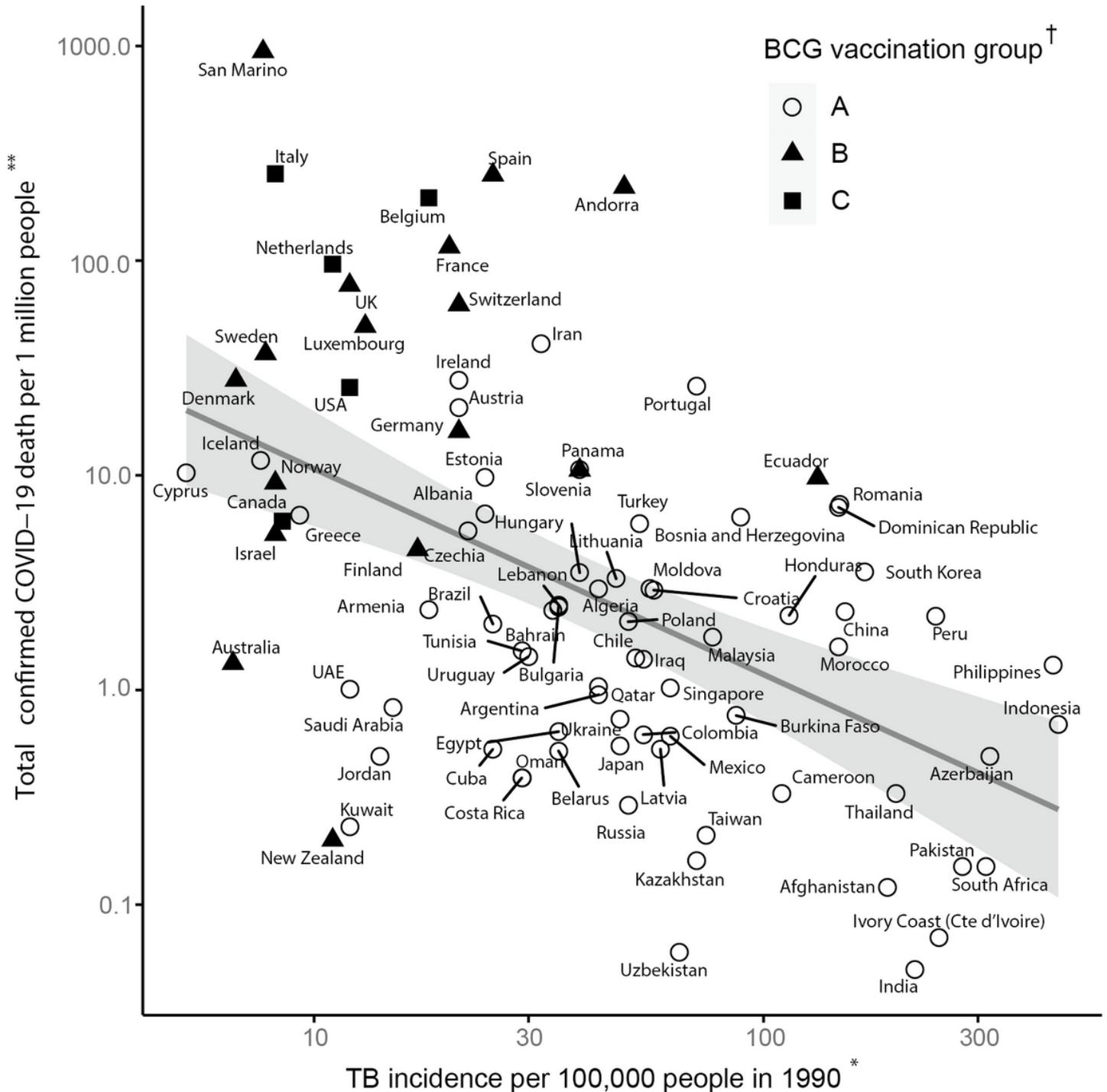


Figure 3

Scatterplot of the incidence rate of tuberculosis (TB) in 1990 versus the cumulative mortality rate of COVID-19 on 5 April, 2020 according to BCG vaccination status among 90 countries *Information was obtained from reference (Global Note) 12. **On 5 April 2020. Information was obtained from Our World in Data.1 † Information was obtained from the BCG World Atlas.10 A: The country currently has a universal BCG vaccination programme. B: The country used to recommend BCG vaccination for everyone, but currently, it does not. C: The country never had universal BCG vaccination programmes. Norway was moved from groups A to B.17 TB, tuberculosis.

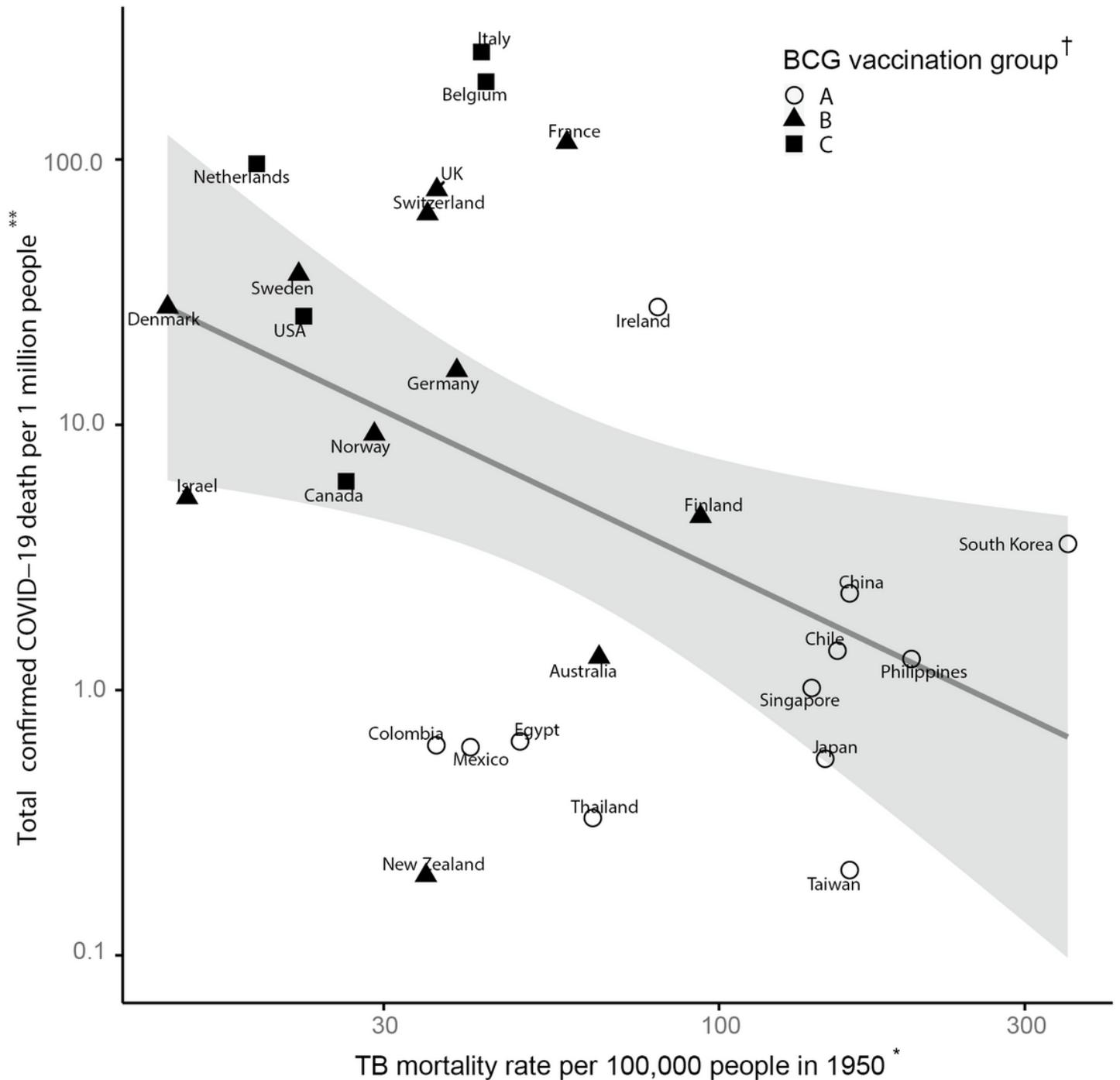


Figure 4

Scatterplot of the mortality rate of tuberculosis (TB) in 1950 versus cumulative mortality rate of COVID-19 on 5 April, 2020 according to BCG vaccination status among 28 countries * On 5 April 2020. Information was obtained from "Our World in Data".¹ ** Information was obtained from References 13-16 The mortality rate of tuberculosis in China was substituted by that of Taiwan. Data of South Korea were estimated based on data collected in 1945.¹⁸ † Information was obtained from "the BCG World Atlas".¹⁰ A: The country currently has a universal BCG vaccination programme. B: The country used to recommend BCG vaccination for everyone, but currently, it does not. C: The country never had universal BCG vaccination programmes. Norway was moved from groups A to B.¹⁷ TB, tuberculosis.

Supplementary Files

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