Current national policies for infant universal bacille Calmette-Guérin vaccination were associated with lower mortality from coronavirus disease 2019

An exciting debate has emerged whether bacille Calmette-Guérin (BCG) vaccination is effective for the coronavirus disease 2019 (COVID-19) pandemic. Some advocated that BCG-vaccinated people are less suffered from the virus because BCG vaccination is recommended in COVID-19 high burden countries. However, the others objected because this seemingly attractive relationship is explainable with confounding factors. In a multiple regression with 171 countries adjusting socioeconomical and climatic covariates, countries with current universal pediatric BCG policy were associated with 30-fold (95% confidence interval, 17–52) decrease of COVID-19 mortality per population compared to countries without the policy.

Keywords: Vaccine, Viruses, Pneumonia, Epidemiology

As of April 10th, 2020, 1.7 million population has been diagnosed with coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 100 thousand died from it [1]. Both numbers of infected cases and death cases are still increasing exponentially though many cities around the world were locked down to prevent further disaster. An exciting debate has emerged whether bacille Calmette-Guérin (BCG) vaccination is effective for the pandemic. Some advocated that BCG-vaccinated people are less suffered from the virus because BCG vaccination is recommended in COVID-19 high burden countries. However, the others objected because this seemingly attractive relationship is explainable with confounding factors such as aged society, resource rich medical system to detect COVID-19, lower temperature, and advanced reporting system of COVID-19 high-burden tuberculosis (TB) low-burden countries [5,6]. We assessed if country-level universal BCG vaccination policy was associated with decreased mortality from COVID-19 after adjusting multiple possible confounding factors.

We selected the COVID-19 mortality per population as a dependent variable because COVID-19 mortality per infected cases and numbers of infected and death cases are easily affected by a number of polymerase chain reaction test conducted and a population size of each country. Gross national income per capita, life expectancy at birth, and infant mortality during the first year after the live birth were selected as independent variables because these parameters reflect how each society is developed, which indirectly explains stature of medical system. Life expectancy at birth was mean-
ingful also because higher mortality from COVID-19 were observed for the elderly. Population density was adopted because this may associate with social distance. Annual average temperature was included as an explanatory variable because confirmed cases and death cases were rare in tropical countries near the equator.

Countries and regions were divided into currently recommended countries (CRC) and currently not recommended countries (CNRC) based on the national policy for the vaccination.

Following data sources were used: (1) number of death cases as of April 10, 2020 from each countries and region: Worldometer “COVID-19 Coronavirus Pandemic” [1]; population size and population density: United Nations “World Population Prospects 2019” [7]; national BCG vaccination policy: “The BCG World Atlas” [6]; gross national income per capita and life expectancy at birth: United Nations Development Programme “Human Development Report 2019” [8]; gross national income per capita and life expectancy at birth: United Nations Development Programme “Human Development Report 2019” [8]; and infant mortality out of live births and annual average temperature: the World Bank “Data Catalog” [9].

Mann-Whitney test was used to compare continuous variables in two groups. Multiple regression analysis was used to adjust covariables. COVID-19 mortality per population, gross national income per capita, infant mortality, and population density were log_{10} transformed before the regression analysis because these variables were long tailed. A half of the minimal mortality next to null was substituted instead of null mortality before log_{10} transformation. BellCurve 2015 (SSRI, Tokyo, Japan) and GraphPad PRISM ver. 7.0 (GraphPad Software, San Diego, CA, USA) were used.

Out of 189 countries and regions presented on Human Development Report 2019, 18 countries were excluded from our analysis due to lack of description of national policy on the BCG World Atlas. One hundred and seventy-one analyzable countries consisted of 146 CRC, most of which recommend the vaccine for infant, and 25 CNRC. Median country level mortalities from COVID-19 per 106 population were 0.42 (interquartile range [IQR], 0–2.02) for CRC and 35.4 (IQR, 11.1–132.0) for CNRC (Fig. 1). This great discrepancy was compatible with previous reports [2-4]. However, CNRC was also significantly associated with higher gross national income per capita (8 [IQR, 4–16] versus 44 [IQR, 35–49] 1,000 US dollar [USD]; p<0.001), longer life expectancy at birth (72 [IQR, 66–76] versus 82 [81–83] years; p<0.001), lower infant mortality (19.2 [IQR, 8.8–37.4] versus 3.1 [IQR, 2.6–3.7] per 1,000 live births; p<0.001), and lower annual average temperature (24 [IQR, 15–26] versus 9 [IQR, 7–11] °C; p<0.001) (Fig. 1).

In a multiple regression analysis using the six parameters as independent variables, CNRC was still related to log_{10} mortality from COVID-19 (partial regression coefficient, 1.48; 95%
confidence interval [CI], 1.24 to 1.72; p<0.001), which is equivalent to 30-fold (95% CI, 17–52) increase of COVID-19 associated mortality per population in CNRC compared to CRC (Table 1). Annual average temperature was another covariate with significant association (p=0.009) (Table 1). Ten degrees Celsius increment of annual average temperature could explain 0.64-fold (95% CI, 0.46 to 0.90) decrease of COVID-19 associated mortality per population (Table 1).

CNRC was further divided into countries that had previously recommended the vaccination and that had never recommended the vaccination [6]. The mortality from COVID-19 did not significantly differ (p=0.400) between countries where BCG had previously recommended (N=19; median, 32.7; IQR, 11.1–101.0; per 10^6 population) and those wherein BCG had never been recommended (N=6; median, 101.6; IQR, 25.5–232.0).

Possible cross-immunization between BCG vaccination and SARS-CoV-2 is a serious concern around the world because it is far from easy to develop a novel vaccine that specifically targets SARS-CoV-2. Biological rationale of this hypothesis is trained immunity by non-specific cross-protection against non-TB pathogens. The large social, economic, and climatic inconsistency between CRC and CNRC made it difficult to derive the conclusion from a cross-sectional study. To date, no peer-reviewed report has presented data that were adjusted for multiple possible confounders. Insufficient adjustment of covariable factors may lead to biased result. Based on our data, infant universal BCG vaccination prevents death from COVID-19.

We need to comment a few limitations. First, our data is preliminary until confirmed by randomized trial because unknown confounders including biological, medical, and social factor may exist. Second, we do not recommend BCG vaccination for adult and children of school age because our data is based on the current policy that recommends the vaccination mainly for infant. Development of novel vaccination for adult is still anticipated. We would like people not to rush for BCG vaccination because this may lead to a supply shortage for infants, increasing their chances of TB meningitis and miliary TB [10].

In conclusion, population based COVID-19 mortality was lower in countries with universal infant BCG vaccination policy. However, a univariable analysis for this topic introduces a strong bias because COVID-19 high-burden countries are TB low-burden developed countries. Based on our analysis of 171 countries and regions, the vaccination policy linked to 30-fold lower mortality after adjusting five socioeconomical covariates.

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