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Article

Significantly Improved COVID-19 Outcomes in Countries with Higher BCG Vaccination Coverage: A Multivariable Analysis

Danielle Klinger [1], Ido Blass [2], Nadav Rappoport [3,*] and Michal Linial [1,*]

[1] Department of Biological Chemistry, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel; danielle.klinger@mail.huji.ac.il; michall@cc.huji.ac.il
[2] The Rachel and Selim Benin School of Computer Science and Engineering, The Hebrew University of Jerusalem, Israel; ido.blass@mail.huji.ac.il
[3] Department of Software and Information Systems Engineering, Faculty of Engineering Sciences, Ben Gurion University of the Negev, Israel; nadavrap@bgu.ac.il

* Correspondence: michall@cc.huji.ac.il; Tel.: +972-54-8820035 (M.L); nadavrap@bgu.ac.il (N.R)

Abstract: COVID-19 pandemic that started in China has spread within 3 months to the entire globe. We tested the hypothesis that the vaccination against tuberculosis by BCG correlates with a better outcome for COVID-19 patients. Our analysis covers 55 countries complying with predetermined thresholds on the population size and number of deaths per million (DPM). We found a strong negative correlation between the years of BCG administration and the DPM along with the progress of the pandemic, corroborated by permutation tests. The results from multivariable regression tests with 23 economic, demographic, health-related, and pandemic restriction quantitative properties, substantiate the dominant contribution of BCG years to the COVID-19 outcomes. The analysis of countries according to an age-group partition reveals that the strongest correlation is attributed to the coverage in BCG vaccination of the young population (0-24 years). Furthermore, a strong correlation and statistical significance are associated with the degree of BCG coverage for the most recent 15 years, but no association was observed in these years for other broadly used vaccination protocols for measles and rubella. We propose that BCG immunization coverage, especially among the most recently vaccinated contributes to attenuation of the spread and severity of the COVID-19 pandemic.

Keywords: Epidemiology; SARS-CoV-2; Multivariable regression; Tuberculosis; Demography; Coronavirus; MMR vaccine.

1. Introduction

COVID-19 spread within 3 months to 213 countries across the globe. The country-specific reports that are compiled daily by the World Health Organization (WHO) and publicly available, provide statistical information on the number of tests performed, the number of confirmed cases, deaths and the cumulative state of patients hospitalized in serious and critical conditions [1]. Along with the spread of the pandemic, most countries imposed a policy of social distancing and other regulation to mitigate COVID-19 [2,3]. Despite the intense effort, key epidemiological parameters are still missing [4-9]. With 400,000 reported deaths and a world average of 51 deaths per million (DPM, June 6th, 2020), the death toll remains the most reliable measure for monitoring the spread and progression of the disease across countries [10]. While some European countries such as Belgium and the UK the DPM is >500, other infected countries (e.g. Hungary, Norway) are closer to the world average. The large differences in COVID-19 outcomes, even among neighboring countries (e.g. Spain and Portugal)

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are not likely to solely reflect differences in the regulations imposed by each country at the initial phase of the pandemic [11,12].

In this study, we tested the possibility that the extent and spreading of COVID-19 cases are associated with the status of tuberculosis (TB) immunization across the world. The Bacille Calmette-Guérin vaccine (BCG) contains a live attenuated strain of *Mycobacterium bovis*, is widely used to eradicate TB and was among the most broadly used vaccination throughout the 20th century in neonatal and young children [13,14]. Currently, the BCG vaccine is provided to the entire population in most countries with high TB incidence [15]. Over the last two decades, numerous countries changed their policy and restricted BCG immunization policy to non-native born migrants from high TB burden countries [16]. Notably, numerous epidemiological and immunological studies demonstrate that BCG vaccination results in reduced morbidity and mortality to subsequent infections, presumably by its effect on the immune response [17]. Specifically, we questioned whether BCG vaccination regimens in different countries are linked with COVID-19 outcome. Our analysis considered a broad range of variables covering demography, economy, medical status, health system strength, and dynamics of the lockdown policy. We found that the BCG admission coverage of the young population is inversely correlated with COVID-19 outcomes. The implication of these observations on national policy for immunization is discussed.

2. Experimental Section

2.1. Data extraction

Information regarding COVID-19 outcomes was extracted daily between January 29th and May 21th, 2020, from the Worldometers website [18]. Demographic measures of countries were extracted from the Worldometers website on April 17th, 2020 [19]. Information regarding the share of population >65 years and economic development indicators were extracted from the World Bank data [20]. Information on educational management and school closure, as a measure of the quarantine statue of the country, was extracted from the UNESCO institute of statistics dataset [21]. Prevalence of chronic diseases (e.g. obesity, type 2 diabetes) and the death rate from cardiovascular disorders were extracted from Our World In Data website. Supplemental **Table S1** provides the source for each of this country-related information.

Information regarding past and present BCG administration practices in every country were extracted from the BCG world atlas [19]. Two vaccination status groups were considered: (i) countries that had either a current or past national mandatory vaccination policy (49 in total), (ii) countries that have only administered BCG vaccinations to specific groups at risk (6 in total)- in these countries, only a negligible fraction of the population is BCG vaccinated [19]. In addition, the estimates for BCG, measles and rubella vaccination coverage between years 1980-2018 were extracted from the annual WHO reports [1]. For additional resources used to establish the years of mandatory BCG administration see supplemental **Table S2**.

2.2. Data analysis and statistical tests

Countries were normalized by accounting for their population size (per 1M, PM). The normalized COVID-19 outcomes that were considered are death (DPM), positively validated cases (CPM), hospitalization with serious and critical conditions (SPM) and recovered (RPM). Accounting for the varying stages of the pandemic in each country, we define a unified aligned key date of a country as the first date when DPM reached for the first time the DPM value 0.5 or higher. The following analysis was conducted across changing dates following the key aligned date (10-50 days). In binary or categorized tests, we applied the ranked Wilcoxon test. For the continuous data, we applied linear regression. The regression fit and the calculated statistical significance (p-value) for the COVID-19 outcomes are reported. We tested the correlations between outcomes and years of BCG administration using Pearson's correlation, and reported p-values as well as permutation tests' p-values. A correlation between the BCG by age groups was determined by partitioning the population of each country into three groups: (i) 24 years and younger; (ii) 25 to 64 years; (iii) 65 years and older.

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From the age partition and the BCG coverage within each age group, a value that measures the *percentage of the population weighted by the share of the age group with BCG* is calculated. Further details on the statistical approach and the data processing are available in supplemental **Text S1.**

3. Results

3.1. BCG administration years are negatively correlated with COVID-19 outcomes

In order to increase the robustness of the analysis, countries were included in the selected cohort if their population is >3M, and they met the criteria of >=3 deaths per 1M population on April 17th 2020. Altogether, there are 134 countries with population size >3M. Among them 55 complied with both thresholds, covering 62.9% of the world population. A regional partition of these countries is shown in **Figure 1**. For detailed information on the countries included in the analyses, see supplemental **Table S3**.

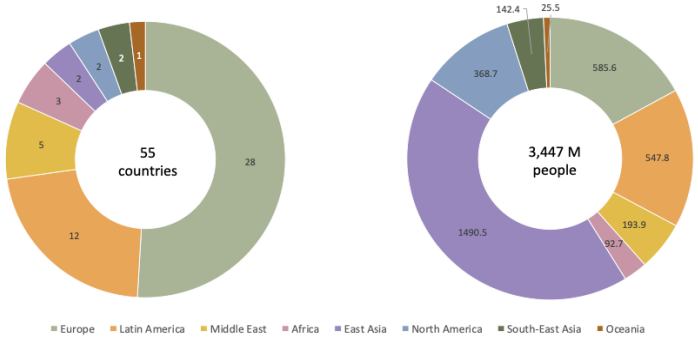

Figure 1. Countries analyzed in this study by geographical regions. Countries that comply with the predetermined thresholds for the population size and a minimum DPM at the analysis date are included. These countries (55 total) are partitioned by their geographical regions (left) and the cumulative population within each region (right).

First, we analyze COVID-19 outcomes as the difference in deaths or cases per million (DPM and CPM, respectively). Thus, the analysis was performed 20 days following 2 different alignment key dates (defined by DPM >= 0.5 and DPM >= 2). **Figure 2** shows strong and significant correlations between COVID-19 outcomes and the number of years of BCG administration. We observed a strong negative correlation with DPM outcome with R = -0.48 (p-value = 0.00056) and -0.47 (p-value = 0.00084) when aligned at DPM threshold of 0.5 and 2, respectively (**Figures 2a, 2b**). Similarly, for the CPM as COVID-19 outcome, we observed a similar trend with R = -0.38 (p-value = 0.0091) and -0.35 (p-value = 0.017) when aligned at DPM of >= 0.5 and DPM >= 2, respectively (**Figures 2c, 2d**).

To test the generality of our observations we repeated the analysis at a broad range of time points along with the progress of the disease, starting from the 10th-day post alignment and showing the trends in 10 days intervals (10 to 50 days, **Figure 3**). For this analysis, we tested the outcomes of COVID-19 confirmed serious/critical cases (SPM) and the number of recovered (RPM), in addition to the DPM and CPM. The results of the DPM and SPM show a highly significant association for all time points, corroborated by the robust results obtained from performing 2000 permutation tests for each time interval for all tested outcomes (supplemental **Table S4**).

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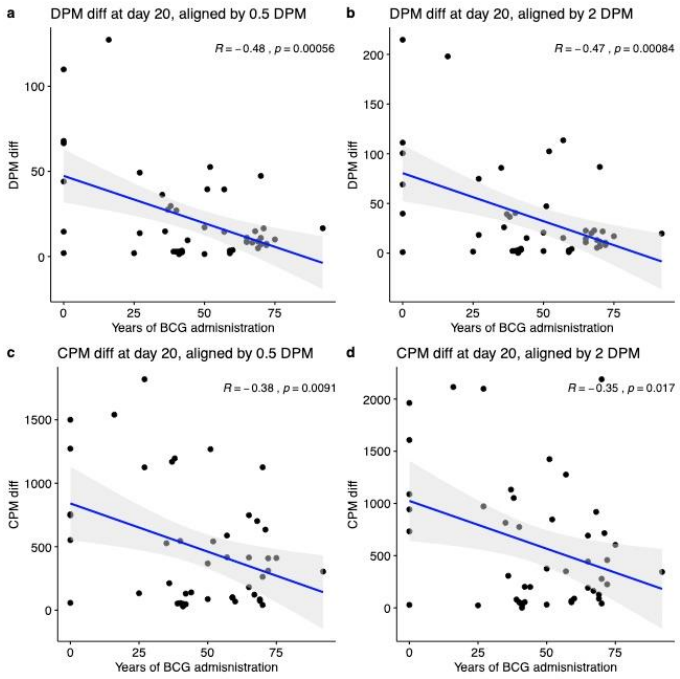

Figure 2. Statistical analysis of COVID-19 outcomes and years of BCG administration. All correlations were measured at 20 days following the alignment key date. Correlations of years of BCG administration with DPM = 0.5 **(a)** and DPM = 2 **(b)**. Correlation with CPM diff. at 20 days when the key date was defined as CPM = 0.5 **(c)** and CPM = 2 **(d)**. DPM diff. and CPM diff. are calculated by the differences in the numbers from the measured date to alignment date. Shaded areas represent the 95% confidence intervals.

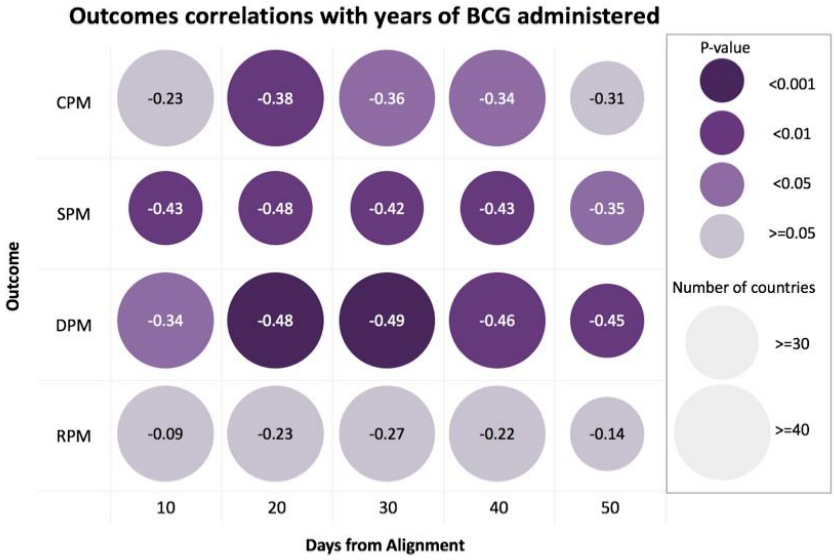

Figure 3. COVID-19 outcomes' correlations with years of BCG administered. Each row represents a different outcome. Each column represents the time interval of the outcome from the alignment date. Circle size depicts the number of countries, and color represents the statistical significance of the correlation with darker purple color indicating a higher significance. Values in circles are the correlation estimates where all the correlations have negative values. Note that while all countries reached 20 days post alignment of DPM >= 0.5, at 50 days post alignment, some countries (5) that were at an earlier phase of the pandemic failed to provide information. DPM, CPM, SPM and RPM stand

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for the number per million for death, validated cases, serious and critical conditions and recovered, respectively.

3.2. Multivariable analysis reveals a strong contribution of BCG administration to the COVID-19 outcome statistics

Countries differ in many quantitative measurements like population size, Gross Domestic Product (GDP), lifespan, median age and more. To control for some of the potential confounding factors, we included numerous demographic values for a multivariable linear regression. The analysis included 23 demographic, economical, pandemic restriction-related and health-related country-based variables. The results show that the number of BCG administration years ranks consistently within the top two most significant coefficients and is within the top coefficients with the larger effect (as measured by the normalized beta coefficient, out of 23 coefficients) (**Figure 4**). The results are consistent among the different times observed (for further analysis see supplemental **Table S5**). Notably, strong positive beta coefficient values are associated with the median age. Cancer percentage is also significant, and may reflect a confounding factor for lifespan and the rarity of cancer occurrence in the young population. The combined contribution of gender, chronic disease prevalence, and economy in the multivariable analysis will not be further discussed.

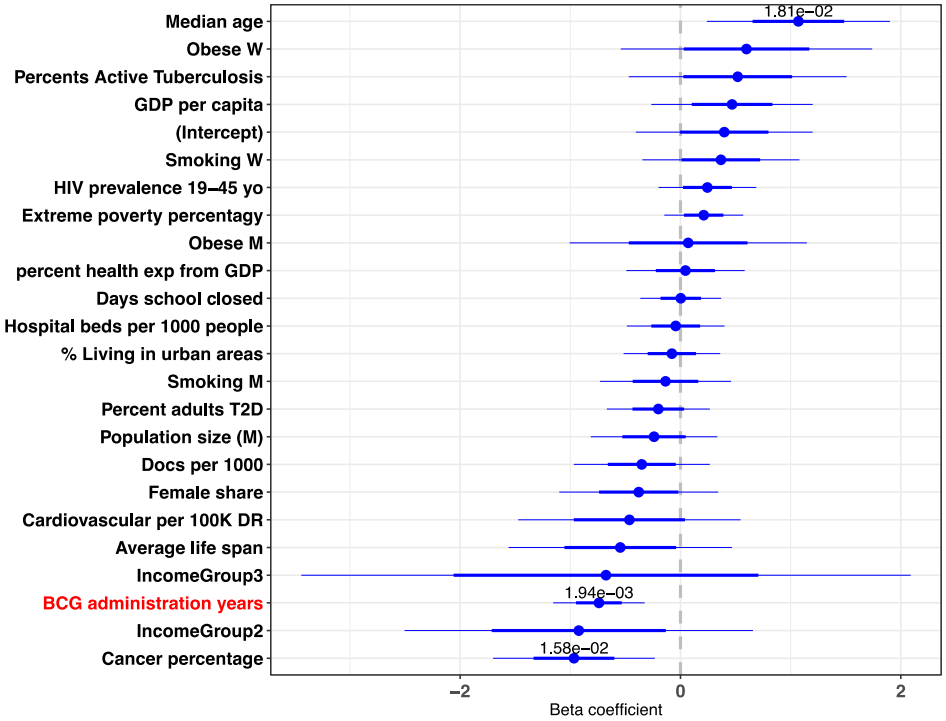

Figure 4. Multivariable analysis of country-centric quantitative data. Beta coefficients of the normalized multivariable linear regression for DPM at day 20 are shown. Blue lines represent the coefficients' 95% confidence intervals. P-values are shown for all variables with p-value < 0.1.

3.3. Highest correlation with BCG age coverage applies to the most recently vaccinated

We next investigated the relevance of age groups to the observation showing that years of BCG administration are strongly correlated with better COVID-19 outcomes. **Figure 5** shows the correlation of total years of BCG administration with DPM difference according to the country-based age composition. The population in each country was partitioned to young (<24 years of age), working-class (25-64 years) and old (>65 years). The correlation with the young age group (testing at 20 days post-alignment key dates) shows the highest significance with R = -0.54, p-value = 7.6E-05 (**Figure 5a**), and the correlation with the age group of 25-64 years (at 20 days) is also significant with

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R = -0.32, with a weaker significance, p-value = 0.028 (**Figure 5b**). Both correlations remain significant throughout 50-day post alignment. Remarkably, for the old age group (>65 years) at all the time-frame tested, the correlation is negligible and insignificant (**Figure 5c**).

Notably, the age composition varies across countries. For testing the robustness of the results, we performed the same correlation analysis while not accounting for the fraction occupied by each of the age groups. The results (20 days post alignment date) are very similar to those obtained by weighting the fraction of the different age groups. Specifically, the correlation for the young age group is R = -0.58, p-value = 2E-05; middle age group is R = -0.35, p-value = 0.016 and the old age group is R = -0.14, p-value = 0.34. We further tested the statistical significance for the other outcomes (SPM, CPM and RPM), by age group according to population share, along different time points. **Figures 5d-5f** show the dominant contribution of the young age group to the negative correlation at 10-50 days post-alignment. Notably, the outcome of recovered per million (RPM) has a significant negative correlation only among the young group. The drop in RPM significance from 30 to 50 days is consistent with the epidemiological survey reporting on the long-time gap till recovery [22]. The middle age group (**Figures 5b, 5e**) is mostly insignificant and shows a borderline significance for the DPM and SPM as outcomes. All observations regarding the elderly (**Figures 5c, 5f**) are insignificant. We conclude that the elderly group does not contribute to the strong correlation with BCG administration.

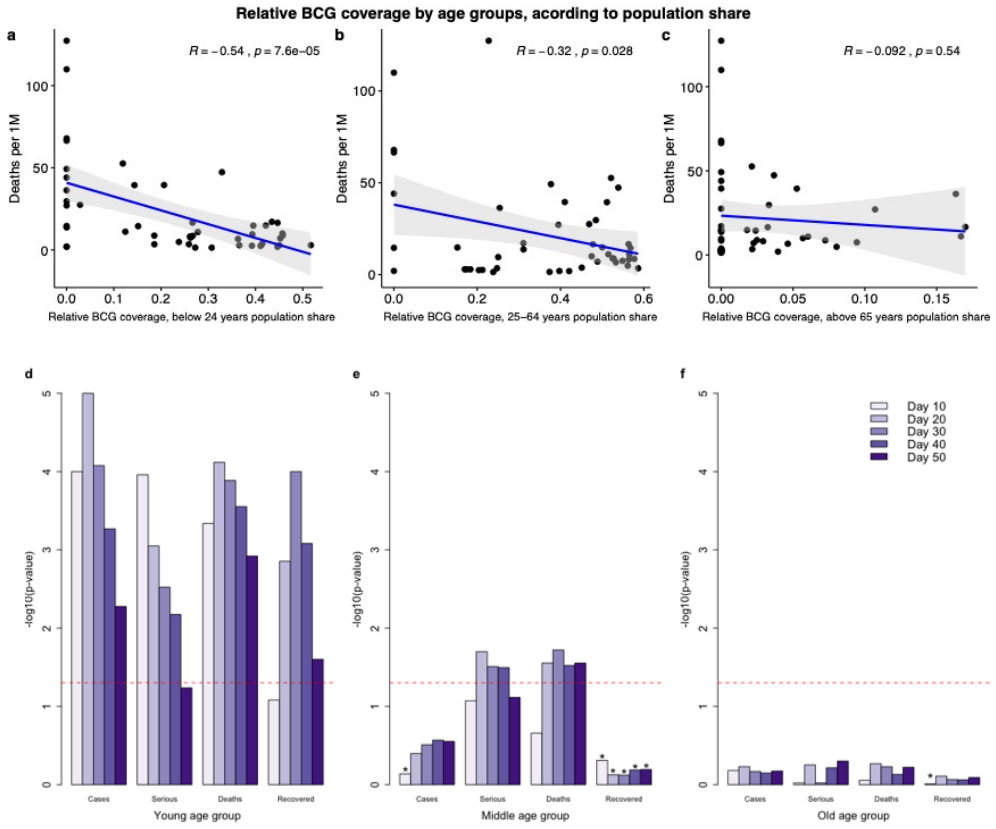

Figure 5. BCG coverage with respect to the DPM difference among three age groups. All correlations (a-c) and statistical significance (d-f) were measured following the DPM>= 0.5 alignment key date. Relative BCG coverage is partitioned to three age groups, weighted by population share: (a) young (0-24 years), (b) middle age (25-64) and (c), old age group (>65 years). The histogram (d-f) shows the statistical significance of the correlation of BCG years of administration and the 4 different COVID-19 outcomes according to the 3 age groups marked as: young (d) middle age (e) and elderly (f). Days from the key alignment date are colored from light to dark purple (10 to 50 days). The statistical significance is shown as -log10(p-value), the dashed red line indicates p-value of 0.05. Asterisk represents the outcome with a positive correlation. All results with a positive correlation (marked by asterisks) are insignificant.

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The pronounced signal in the young age group led us to investigate whether recent immunization may have a positive effect on the outcome. We divided the countries into 3 disjoined groups representing their vaccination policies over the past 15 years, disregarding the population share of the 0-15 age group in each country: (i) countries with mandatory immunization policies over the past 15 years; (ii) countries with mandatory immunization policies, which was applied for less than 7.5 years within the past 15 years; (iii) countries with no mandatory immunization policies over the past 15 years (**Figure 6a**). Applying a test with DPM outcome, yielded highly significant results across all tested post-alignment (10-50 days) dates, establishing that countries with BCG immunization policies over the past 15 years have a significantly lower rate of DPM with respect with countries in group (iii).

The significant result in the young age group raised the question whether others immunizations might have significant effect. To this end we tested COVID-19 outcome and the globally used immunization against measles and rubella. We divided the countries into 2 groups representing their vaccination coverage over the past 15 years (as provided by the WHO): (i) countries with above median coverage; (ii) countries with below median coverage. While the world overall coverage of MCV1 (measles containing vaccine) is high in recent years, with an average of 88% in 2017, as provided by the WHO, the MCV1 coverage from 1990 shows substantial variation (e.g., 73.8% in India, 80.2% in Italy, 85.7% in Algeria, 89.2% in Belgium) [1]. Applying the Wilcoxon test, yielded insignificant results at all tested dates (10-50 days post alignment). Opposite to the BCG results, we found no correlation between the degree of Measles and Rubella vaccination coverage and COVID-19 outcomes (Figures 6b, 6c).

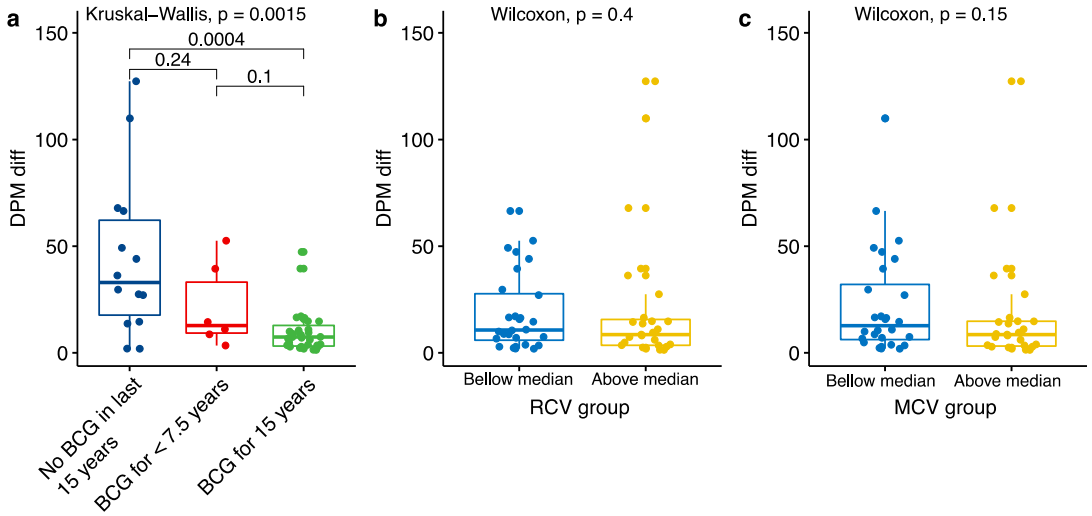

Figure 6. Immunization coverage for 15 recent years. **(a)** The DPM diff. (difference in DPM from the value at alignment key date) in countries that have (green), partially have (red), or have not (blue) rolled immunization BCG programs over the past 15 years. The statistical significance values are shown for each pair. **(b)** The statistics of RCV (rubella) and **(c)** MCV (measles) vaccines and COVID-19 DPM diff. according to the vaccination coverage. The partition of the countries is according to those above (yellow) and below (blue) median % coverage for each of these tested vaccines. Data covering of the past 15 years (2004-2018) was extracted from WHO reports. The statistical significance values are listed.

3.4. Data and materials availability

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All data needed to evaluate the conclusions in the paper are present in the paper and in the Supplement. An online tool for displaying the analytical results is available at: https://covi.shinyapps.io/COVID19/. It is a useful analytical webtool for single variant statistics, correlations, multivariable analyses and more. The user-friendly platform allows to change parameters by setting a threshold on population size, the time along the pandemic progression, selecting predetermined outcomes as a reference date for the alignment and changing the thresholds for alignment date. The code and data are available at: https://github.com/nadavrap/COVID19. Additional data and support related to this study may be requested from the authors.

4. Discussion

The significant strong correlation between the BCG vaccination and better outcomes for COVID-19 is shown across many countries, covering the majority of the world population (**Figure 1** and supplementary **Table S1**). The findings are based on an unbiased view of all countries that comply with predetermined thresholds for DPM and population size (see Methods).

The strong negative correlation between the BCG administration years and DPM was sustained at a range of time-points from the aligned date (**Figure 3**). For testing the stability of the DPM correlation, we repeated the analysis for additional COVID-19 outcomes. We consider the number of hospitalized people (at a specific date) which were indicated by a serious or critical condition (SPM). Obviously, this measurement is strongly dependent on the health care capacity and the actual phase of the pandemic. Using the SPM rather than the DPM as a measure shows that the BCG administration years trend remains stable and significant (**Figure 3**). As expected, the negative correlation to COVID-19 validated positive cases (CPM) is weaker relative to DPM. CPM is likely to reflect the capacity of different countries to carry out reliable molecular tests (PCR-based) or clinical tests (lung CT pathology) [23], and the national policy for targeted testing [24]. We observed no significant correlation for the country-level number of recovered (RPM). We attribute it to the non-standardized definition for COVID-19 recovery [25], the time delay for confirmed recovery [26]. Altogether, RPM is the least reliable outcome as the pandemic peak ranges greatly among countries.

Our multivariable analysis highlights the strength of combining a broad range of country-based quantitative observations. Among the analyzed variables are the economic measures [27], health system capacity (e.g. doctors per 1000 people), population composition, exposure to infection diseases (prevalence of TB), pandemic restriction-related (school closure dates), major comorbidities (e.g. cancer, diabetes) and habits (e.g. smoking by sex). Many of these measures are correlated and may reflect confounding factors. Most importantly, the multivariable analysis validated the importance and statistical significance of BCG immunization years given all other variables (**Figure 4**). Policy toward quarantine, enforcement of isolation regulation (e.g. closure of culture events, public transportation) were implemented at a country-based time point. Including the number of days of closing the educational facilities relative to country alignment date as a variable in the analysis. It was used as a proxy for the level of the constraints imposed along the pandemic progression. While it is expected to have a strong impact of COVID-19 spread[26,28], this variable did not contribute to rejecting the hypothesis, and had a minimal impact on the multivariable analysis (**Figure 4**).

The exact date of BCG administration within each country, combined with the actual immunization coverage (provided by the WHO) and the population structure, allows to explicitly test the effect over time of the BCG immunization. Specifically, partitioning the population to young-, middle- and elderly groups confirmed that the strongest signal towards COVID-19 outcome is associated with young (<24 years, **Figure 5**) and slightly to the middle age group (25-64 years). However, the elderly (>65 years) that are at the highest risk for COVID-19 mortality do not correlate with BCG higher coverage. The implication of this observation for COVID-19 epidemiology is evident.

Our results suggest that in countries where the young population are BCG vaccinated, a maximal protection is provided. Universally, the DPM among young people is very low (0.04% for <17 years) [18]. Therefore, the main contribution of the young age is with regards to the impact on the chain of infection. The middle-age group (25-64 years) overlaps with the group that is specified by an extensive cross-generation social interaction [29]. Thus, the higher BCG coverage of the young and

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middle-aged groups is associated with the attenuation of infection. The lack of correlation between BCG coverage for the elderly (>65 years) and COVID-19 outcomes is in accord with the negligible impact of this population on viral transmission to the community.

Several reports proposed that BCG vaccinated populations are resistant against viruses, and in particular toward SARS-CoV-2 [30]. Despite the broad usage of BCG for almost a century, and the underlying mode of action, the indirect long-term effect of BCG on the immune system remains enigmatic [31-33]. We postulate that the positive effects of BCG immunization on COVID-19 outcomes are achieved by an improved systemic immunity which applies to the most recently vaccinated group. We found no correlation between the degree of measles and rubella vaccination coverage and COVID-19 outcomes- other types of immunizations that were proposed to reduce susceptibility to viral infection (**Figure 6**) [34].

There are several limitations that need to be addressed for fully supporting our main findings and the conclusions from this study. The first difficulty stems from the fact that countries vary greatly by their area, population density and age structure that can mask the apparent BCG protective effect when high resolution analysis is sought [35]. Moreover, difference in culture and habits (e.g. religious gathering, social distancing, smoking), economy, demography and the capacity of the health system often cannot be easily generalized. COVID-19 spread in a large country is dependent on inter-regional mobility, distribution and connectivity of economical hubs (e.g., Lombardy in Italy) and the time-line the pandemic wave. To address some of these inherent difficulties, we duplicated the analyses for countries that were bounded by population size (>3M and <100M). We observed no effect on the main findings as shown in supplemental **Figure S1** and **Figure S2**. (ii) The dynamics of the pandemic limiting the usability of static data [36,37]. By altering the threshold for the alignment date, we confirmed the robustness of the results (**Figure 3**).

The underlying mechanism by which BCG exerts its beneficial effect is not fully resolved. However, the efficacy of BCG against TB is expected to cover approximately 15 years [38]. Thus, the strong statistical significance value for BCG being most effective for recently immunized population argues that the active immunization phase rather than a residual protection from early-life event is associated with a better COVID-19 outcome [39,40]. Importantly, the vulnerability of the immune response of newborns was studied with the goal of developing age-specific vaccination approach. In this view, the BCG induced a robust response [41]. An important factor that needs to be taken into consideration in the admission of different BCG vaccine formulations. It was shown in several in-vitro assays that different source of BCG are likely to yield a range of clinical efficacy [42].

Our results cannot exclude the possibility that a “pre-trained” state of immunity by BCG immunization exerts its positive effect, thus improving COVID-19 outcome at a population level. The finding that shows a strong and robust association of BCG coverage in the young age group with improved COVID-19 outcomes remains suggestive and calls for ongoing monitoring the evolvement of the pandemic world-wide. To this end, we developed a user-friendly platform with the capacity to change any of the dynamic parameters along the pandemic progression.

5. Conclusions

We conclude that the inverse correlation with BCG administration years, the impact of a recent vaccination, and the validated role of the young population in the spread of COVID-19 calls for revisiting the global and national BCG immunization policy. While the WHO does not recommend BCG vaccination for prevention of COVID-19, several clinical trials with BCG are undertaken [43,44].

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Supplementary Materials: The following are available online. Figure S1: correlation of BCG years of admission and COVID-19 outcomes for countries bounded by a population size of >100M; Figure S2: results from a multivariable analysis for countries bounded by a population size of >100M. Table S1: variable resources across countries and populations. Table S2: additional resources on BCG administration years by country. Table S3:

country cohort of 55 countries used in the study. Table S4: correlations and p-values of regression of years of BCG administrations and different outcomes including permutation tests. Table S5: multivariable results at numerous time points for BCG years of admission.

Author Contributions: D.K. coordinated the project. Conceptualization: D.K., N.R and M.L. Methodology: contributed equally by all co-authors. Data extraction: I.B. and D.K. Data design and software: I.B., D. K. and N. R. Interactive website: N.R. Code: I.B., D.H and N.R. Writing of the manuscript, reviewing and editing: D.K., N.R and M.L. Supervision, M.L. and N.R. All authors had full access to all of the data in the study and took responsibility for the integrity of the data and its accuracy. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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