Protective roles of flu infections and BCG vaccination in lowering Covid-19 mortality

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Abstract

The recent Covid-19 pandemic has caused a great loss of lives as well as affected economies in several countries. The loss of Covid-19 deaths is far greater in some countries compared to others. This observation led us to perform epidemiological analysis using disease and vaccination data in the public domain with respect to measles, hepatitis B virus, polio, tuberculosis and flu from twenty five countries across the globe. There is no correlation between Covid-19 incidences or deaths, as well as vaccination coverage, with respect to diseases such as measles, hepatitis B virus and polio. However, countries with lower cases of tuberculosis and higher cases of flu have a significant correlation with respect to Covid-19 deaths. In fact, countries with high BCG vaccination coverage show a significant negative correlation with Covid-19 deaths. Surprisingly, countries such as the USA, Italy, France and Spain which have flu vaccination, but not BCG vaccination, show maximum number of Covid-19 deaths. It appears that high numbers of flu infections are protective and can decrease the number of Covid-19 deaths. Importantly, countries with high flu cases and BCG vaccination, such as India, Egypt, South Africa etc, show relatively lower Covid-19 deaths, reinforcing the protective roles of BCG vaccination. Notably, these general trends are statistically significant for Covid-19 deaths but not Covid-19 incidences. The implications of our results are discussed with respect to the roles of microbial infections in the respiratory tract, vaccinations and other factors in lowering Covid-19 deaths.

Introduction

Coronaviruses belong to a family of enveloped RNA viruses that are known to cause respiratory tract infections in animals and humans: Severe acute respiratory syndrome (SARS), Middle east respiratory syndrome (MERS) and SARS-corona virus 2 (SARS-CoV2). The global pandemic caused by a virus known as SARS-CoV–2 is known as Coronavirus disease 2019 (Covid–19) (Lai et.al., 2020). The virus originated from China in December 2019 and is causing major health issues, widespread death and disrupting economies across a number of countries. SARS-CoV2 infects the upper respiratory tract, causing mild symptoms, or in severe cases causes damage to the lungs (Rubin et.al., 2020). Also, SARS mainly infects the airway and alveolar epithelial cells but, at later stages, viral particles have been detected in blood cells, e.g. monocytes and lymphocytes (Gu et.al., 2005). The SARS family of viruses have a similar mechanism of entry in cells in which the spike protein interacts with the receptor angiotensin converting enzyme (ACE–2) (Zhou et.al., 2020). Polymorphisms in host genes encoding Ccl2 & Mbl (Tu et al., 2005) and Ace2 (Cao et al., 2020) are known to affect susceptibility to coronavirus and SARS-CoV2 respectively. The loss of life and economic damage caused due to Covid–19 is immense in a short span of time and, thus, there is a dire need for potential drugs and vaccines to combat this infection.

The absolute number of death across nations due to Covid–19 is variable (Wikipedia and European center for Disease Prevention and Control; https://en.wikipedia.org/wiki/Template:COVID–19_pandemic_data). Some countries such as the US, Italy, Spain etc have high mortality due to Covid–19;

on the other hand, countries such as China, India etc have a relatively lower mortality due to Covid–19. The reasons for this heterogeneity in different countries are unclear but may be due to multiple factors: population age, immune responses, co-infections, temperature, co-morbidities such as hypertension, diabetes, obesity, cultural norms, health infrastructure, use of masks, early responses by countries to lower the entry of the virus, efficient contact tracing & isolation of Covid–19 patients to prevent spread of infection. Reports suggest that countries with a younger population are more capable of resisting the infection and very few cases of severe symptoms and disease occur (Zhao et.al., 2011). Immune responses along with co-infections are also a major factor. For e.g., the efficacy of flu vaccine is lower when there is a helminth coinfection which induces IL–10 production and suppresses the immune system (Hartmann et.al., 2019). Alternatively, prior immunity against infections such as Flaviviruses are known to generate protection against non-related pathogens, a phenomenon known as cross immunity (Rathore et.al., 2020). In addition, areas with high incidences of malaria demonstrate lower Covid–19 incidences (Ahmed, 2020). Co-morbidities such as hypertension and diabetes have also been suggested to make the host more susceptible to Covid–19 infections (Guan et.al., 2020). Environmental factors such as temperature also have a major effect on Covid–19 transmission and infection as they play an antagonistic role with respect to transmission of Covid–19 especially in tropical countries (Prata et.al., 2020). Another study encompassing thirty provinces in China suggested that both temperature and humidity have a negative association with respect to Covid–19 infections (Qi et.al., 2020). One of the more popular factors that have come into limelight, suggests vaccination policies to have a profound effect on Covid–19 induced infections and mortality. It is well established that vaccination has been most useful as a life saving procedure which has greatly improved our quality of life. Vaccination strategies can have a protective role against a broad class of pathogens, a phenomenon is often termed as trained immunity (Kleinnijenhuis et al., 2014; Arts et.al., 2018). Alternatively, vaccination could also make the host susceptible to other viral infections by different mechanisms such as antibody-dependent enhancement of viral entry which has been reported for dengue and Japanese encephalitis virus (Huisman et.al., 2009). Clearly, a better understanding of the roles of various factors is required to understand the better resistance or susceptibility of different populations across and within countries.

The vast differences in the number of Covid–19 deaths in various countries led us to investigate the correlation between Covid–19 incidences or deaths with the prevalence of various diseases: polio, measles, HBV, tuberculosis and flu from a sample set of twenty five countries. Using existing data available in the public domain, we analyzed the relationship between disease prevalence and vaccination strategies on Covid–19 mediated infections and deaths in each country. Finally, we grouped the countries based on flu prevalence and BCG vaccination and correlated these to incidences and deaths due to Covid–19. Overall, this study demonstrates that Covid–19 deaths are much lower in countries with high flu infections and BCG vaccinations. However, countries with flu vaccinations in the absence of BCG vaccinations demonstrate high Covid–19 deaths.

Materials And Methods

A sample set of 25 countries were analyzed in random firstly with respect to Covid–19 incidences and deaths in which the data was collected from: https://en.wikipedia.org/wiki/Template:COVID–19_pandemic_data. The data regarding T. B. incidences and BCG coverage was collected from: http://www.bcgatlas.org/. Flu incidences and Flu vaccination data was mainly collected from WHO, OECD, Australian department of Health, Human Vaccines and Immunotherapeutics Journal (Mereckiene et.al., 2014; Rosano et.al., 2019). Flu death and T. B. death rates for all the 25 countries were collected from: https://www.worldlifeexpectancy.com/world-health-rankings. Data regarding Measles, HBV and Polio incidences and vaccination was collected from WHO databases, World Journal of Clinical Cases. Graphs were constructed using Microsoft Excel and Pearson's correlation was applied for all the data in which the correlation coefficient value was designated for each graph. Correlation was considered significant if $p<0.1$. p value was calculated using an online calculator specific for Pearson's correlation: www.socscistatistics.com/pvalues/pearsondistribution.aspx. Bar graphs were constructed using Graph Pad Prism 8.0.

Results

Measles, HBV and Polio vaccinations do not correlate with Covid–19 incidences and death: Initially,we arranged a set of twenty five countries based on Covid–19 incidences and deaths in a descending order (*Table 1)*.. Subsequently, these countries were compared with respect to incidences of measles, polio and HBV (*Supplementary Table 1)*.. This data was collected from various databases such as WHO, CDC etc which gave an in-depth comparison with respect to other infections and the Pearson correlation coefficient (*R)* was calculated with respect to Covid–19 incidences and deaths. There was no significant correlation with Covid–19 incidences and deaths and the three diseases studied here. Next, we investigated the roles of specific vaccinations and Covid–19 incidences and deaths. As seen in *Supplementary Table 1,* all countries listed have high vaccination coverage for measles resulting in lower incidences of the disease. We observed that none of the three vaccination strategies had a significant positive or negative correlation with Covid–19 incidences or deaths which suggested that these viral vaccination policies had no protective or deleterious effect on the host with respect to Covid–19 infections (*Supplementary Figure 1)*..

Both Flu exposure and Flu vaccination coverage have a significant correlation with Covid–19 deaths: Next we performed a correlation study with respect to Covid–19 incidences/deaths and percentage Flu positive samples. We observed a negative correlation with Covid–19 incidences as well as deaths; however, there was a significant negative correlation with only Covid–19 deaths (*Figure 1)*.. This possibly meant that high exposure to Flu in countries such as India, Pakistan, Australia etc. had a protective effect against Covid–19. On the other hand, countries such as USA, Italy, France and Spain which have less incidences of flu have higher number of Covid–19 deaths (*Figure 1)*.. As seen in Table 1, high flu vaccination coverage in people over 65 years leads to reduced incidences of flu. Surprisingly, Flu vaccination coverage showed a significant positive correlation value of *0.42* with Covid–19 induced mortality (*Figure 2)*.. This suggested that Flu vaccinations reduced the extent of Flu exposure but had a detrimental effect, leading to higher Covid–19 mortality.

Lower tuberculosis incidences and BCG coverage have a significant association with Covid–19 deaths: We next investigated the effects of Tuberculosis (TB) exposure on the host with respect to Covid–19. We first studied the correlation between TB incidences with Covid–19 incidences or deaths. Countries with high TB incidences (n>100,000) had no significant relationship with Covid–19 incidences or deaths (*Figure 3)*.. Surprisingly, countries such as USA, Italy, Spain etc. where TB incidences are fairly less (n≤10,000) had a significantly positive correlation with both Covid–19 incidences as well as deaths. This suggests that TB exposure could possibly play a role in determining the rate of infection and severity of this disease in a particular population (*Figure 3)*.. As we observed a significant correlation with TB, we compared Covid–19 incidences and deaths with respect to BCG vaccination coverage. We observed that BCG vaccination had a significant negative correlation with respect to deaths (*$R = -0.43$)* from Covid–19 demonstrating a protective role for BCG (*Figure 4)*..

We next segregated the list of twenty five countries based on BCG and seasonal flu vaccinations. We observed that countries which have high BCG vaccination coverage have the best protection against Covid–19 mortalities (*Figure 5)*.. However, countries with only a well-established Flu vaccination program, in the absence of BCG vaccination, were the most susceptible towards Covid–19 mortality. Importantly, countries with both BCG and Flu vaccinations had relative less mortality as compared to those with Flu vaccination alone. This study clearly demonstrated the dominant roles of BCG in lowering Covid–19 deaths.

Discussion

The reasons as to why mortality is higher in some countries but not others due to Covid–19 led us to initiate this study. The main highlights of the study are as follows: First, countries with low TB and high flu incidences have a significant correlation with Covid–19 deaths. Second, BCG coverage has a significant negative correlation with Covid–19 deaths. Third, flu vaccination coverage positively correlates with Covid–19 deaths. Fourth, BCG plays a dominant role over flu vaccination and protects the population from Covid–19 induced mortality. Fifth, Covid–19 deaths correlate with only BCG and flu vaccination but not with measles, polio and HBV vaccinations.

The two main aspects of our study are discussed in light of our findings. There are different types of flu vaccinations (inactivated as well as live) and these are recommended for everyone above 6 months of age. However, the majority of flu related deaths are in the elderly who have a weakened immune system due to senescence. This has led to the development of more potent flu vaccines containing higher antigen or adjuvants which boost the immune system (Smetana et al., 2018). As seen in *Table I,* flu vaccination is effective in lowering the number of flu infections. However, countries with high flu infections show low Covid–19 incidences and deaths but only the latter is statistically significant (*Figure 1)*.. There are several possibilities for the effects of flu infections in lowering Covid–19 infections. First, it is possible that Flu infections may lower the surface expression of the ACE2 receptors and/or lower the entry of the virus into cells. In fact, if influenza vaccination is shown to increase ACE2 expression, it may explain the higher infectivity of the SARS-CoV2 virus in the elderly population leading to greater Covid–19 mortality. Second, it is possible that non-specific immunity is increased upon flu infections, as is known for several viral infections (Benn et al., 2013; Kumar et al., 2018; Rathore et al., 2020). Third is the possibility of viral interference. In reality, there are different microbes present on surfaces and tissues and their interactions affect each other. This aspect is very true for the respiratory tract where several microbes thrive. Viral interference is the phenomenon when one virus inhibits the replication of another virus, virulence properties and damage to the host (Kumar et al., 2018). Several reports have shown roles of flu vaccinations in increasing infections caused by respiratory viruses. A Canadian study has shown that prior vaccination by the trivalent inactivated influenza vaccine is associated with an increased severity of infections by H1N1 (Skowronski et al., 2010). Another study conducted on children from Hong Kong has found the trivalent inactivated influenza vaccination increased non-influenza viral acute respiratory infections (Cowling et al., 2012). A recent study on defence personnel from the US demonstrated that the odds of having coronavirus and metapneumoniae virus infection in personnel vaccinated with flu shots was higher compared to the unvaccinated control (Wolff, 2020). Finally, a long term study involving individuals for over nine years found that infection with Influenza A prevented subsequent rhinovirus infections. Interestingly, the presence of coronavirus negatively affected respiratory synctitial virus, adenovirus and human respirovirus infections (Nickbakhsh et al., 2019). Clearly, these studies demonstrate the complex roles of virus-virus interactions in the respiratory tract. One will need to study the effects on different viruses and infections once a specific SARS-CoV2 vaccine is launched.

Various factors such as genetics, sex, age, adjuvants and scheduling are involved in determining the efficacy of vaccination (Zimmerman and Curtis 2017). Cytokine responses to BCG vaccination are known to vary up to ten fold (Finan C et al., 2008). Also, immune response regulatory variants are known to play roles in the diverse response to immune stimuli in different groups of people (Quach et al., 2016). BCG vaccination leaves a scar at the site of injection. Also, there are different strains of BCG used for vaccination (Horwitz et al., 2009). Since it is a live vaccine, it may create complication in immuno-compromised people—a disease known as BCGosis (Fortin et al., 2007). BCG is a live attenuated vaccine which has been shown to protect new born kids from tuberculosis and it is an efficient paediatric vaccine. However, its efficacy in adults in variable and it is possible that the presence of environmental mycobacteria and high amounts of tubercular mycobacteria especially present in developing nations may modulate immune responses in different countries (Primm et al., 2004). In fact, mycobacteria has also shown to reduce incidences of cancer (Rakshit et al. 2012; Podder et al. 2016).

One of the highlights of BCG vaccination is its long term effects and in some reports protections is observed even after forty to sixty years (Aronson et al., 2004; Nguipdop-Djomo et al., 2016). Remarkably, BCG has been shown to increase the non-specific immunity to several pathogens including respiratory ones (Mukherjee et al., 2017; Moorlag et al., 2019) and lowers mortality in children in low income countries due to fewer deaths from pneumonia and sepsis (Hollm-Delgado et al., 2014; de Castro et al, 2015; Cruz et al., 2017). BCG vaccination before influenza shots leads to higher antibody responses against influenza A or H1N1 virus (Leentjens et al, 2015). How is BCG able to mediate such remarkable effects? BCG vaccination leads to epigenetic reprogramming leading to quicker and higher amounts of pro-inflammatory cytokines especially IL1▯, known as trained immunity (Kleinnijenhuis et al., 2014; Arts et al, 2018). In a study involving reports from European counties that have BCG vaccination versus those without BCG vaccination, both Covid–19 incidences as well Covid–19 deaths were lower in the group with BCG vaccination (Ozdemir et al., 2020). However, in a study of BCG-vaccinated versus unvaccinated individuals in Israel, no role for BCG in affecting Covid–19 incidences was found (Hamiel et al., 2020). This study BCG highlights the protective roles of this vaccine in increasing host immunity leading to lower Covid–19 deaths (*Figure 4)*..

Although the general trends in our study are robust, there are some exceptions which need to be addressed (*Table 1)*.. Let us consider the two extreme points with either high or low Covid–19 deaths. First is the case with Australia which despite having no BCG vaccination programs but an active flu vaccination program has less Covid–19 incidences as well as deaths. On the other extreme is UK which has high BCG and flu vaccination coverage. Despite BCG vaccination, UK has a large number of Covid–19 deaths. Next there are other countries such as Germany, Canada and Sweden which show moderate Covid–19 deaths and have no/less BCG & flu vaccinations. It is possible that there are threshold levels of virus entry which play important roles in its spread. Therefore, cities with lots of international traffic and high population density, e.g. New York & Mumbai, have seen a greater rise in the number of Covid–19 incidences. With respect to Australia, it is possible that the entry of the virus was restricted and higher flu incidences in the population may also have played some roles in lowering the spread of the virus. With respect to the UK, there was an initial policy that allowed the virus to enter the population and spread. By the time, this initial policy was reversed, the virus had possibly spread resulting in great number of deaths, especially in old age homes. Overall, there are multiple factors involved in the spread of the virus.

Despite the heterogeneous issues and confounding factors involved in sampling data for this study, e.g. population density, reports in the data available to the public domain, variations in the climate & light exposure, cultural and diet aspects etc., it is remarkable that we are able to get significant correlations between Covid–19 incidences & deaths and flu incidences and BCG vaccinations in this diverse sample set of twenty five countries. We understand that multiple factors are often involved in governing the number of Covid–19 incidences as well as deaths in a country, but our results reveal a consistent trend, nonetheless. The novel aspect of this study is the interplay of flu infections and BCG vaccination in affecting Covid–19 deaths. Overall, our results highlight the importance of infections and live bacterial immunization in boosting our immunity to unknown pathogens. The results of our study should prompt more detailed clinical studies on the efficacy of BCG in reducing Covid–19 incidences and deaths in the absence and presence of flu vaccinations, especially in the senior age group population. Given the observation that microbes in the respiratory tract greatly influence each other, our results will strongly suggest a study to evaluate the efficacy of BCG in the presence and absence of a vaccine against SARS-CoV2 once it is developed.

Declarations

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Competing interests

The authors declare no competing interests.

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Table

Due to technical limitations, table 1 is only available as a download in the supplemental files section.

Figures

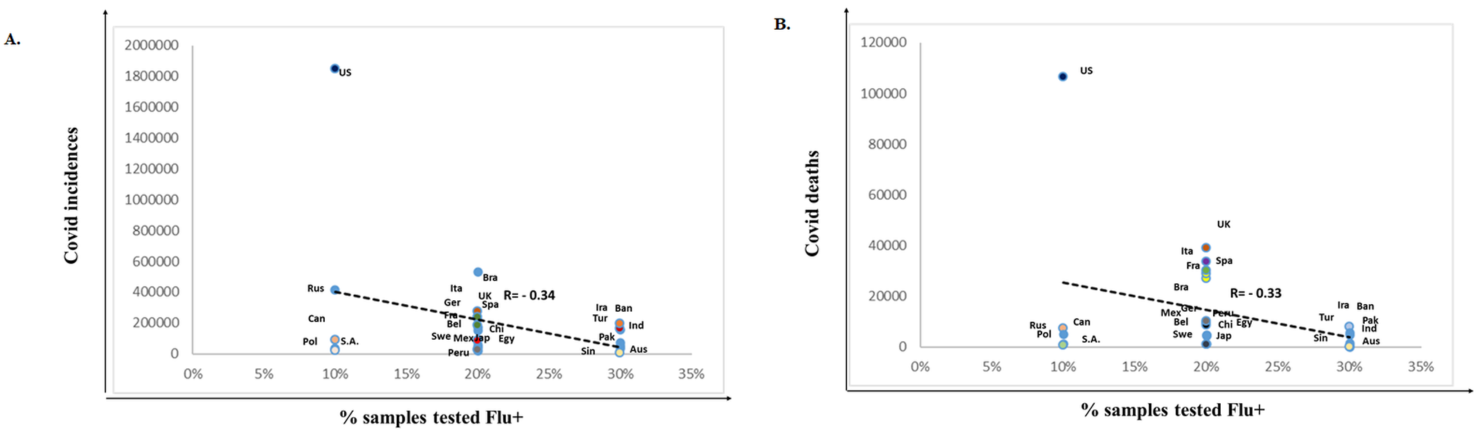

Figure 1

Incidences of Flu negatively correlated with Covid-19 induced deaths: The graph depicting percentage of samples tested positive for Flu and the respective A. incidences (R = -0.34 and p = 0.10) and B. deaths (R = -0.33 and p= 0.08) due to Covid-19. Countries have been grouped based on the percentage of samples that have been tested positive for Flu. The Pearson correlation coefficient value (R) is considered statistically significant if p<0.1.

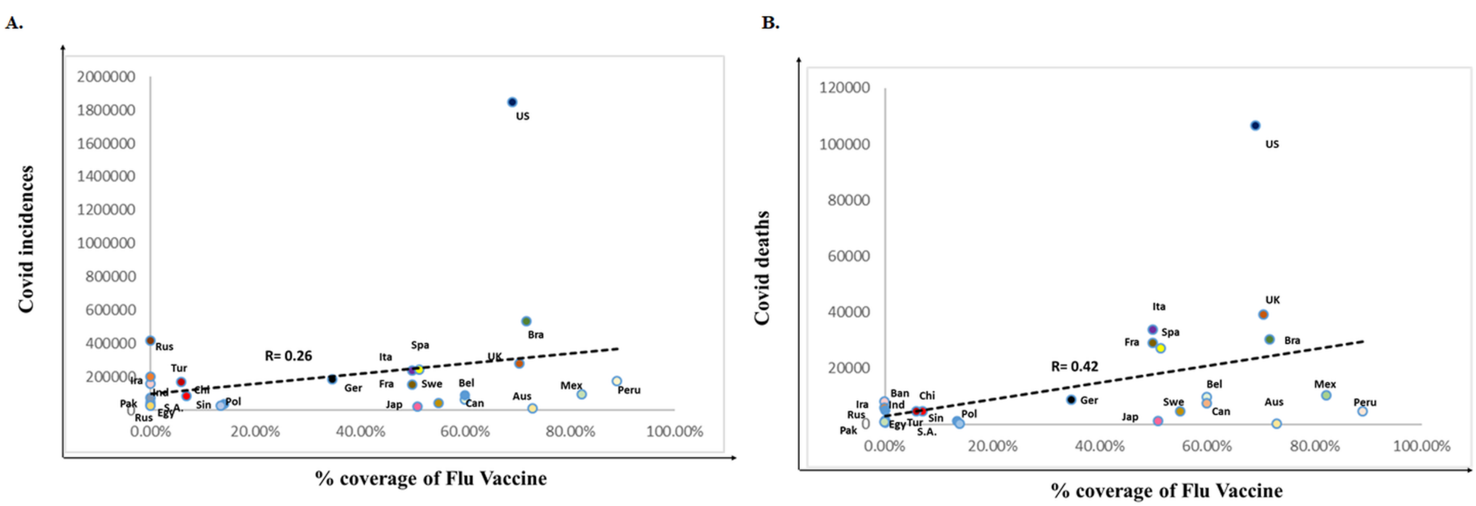

Figure 2

Covid-19 induced deaths positively correlates with Flu vaccination coverage: Graphs were constructed based on % Flu vaccination coverage and was correlated with A. Covid-19 incidences (R= 0.26 and p= 0.20) and B. Covid-19 deaths (R= 0.42 and p = 0.03). Pearson's correlation coefficient value (R) was considered statistically significant when p<0.1.

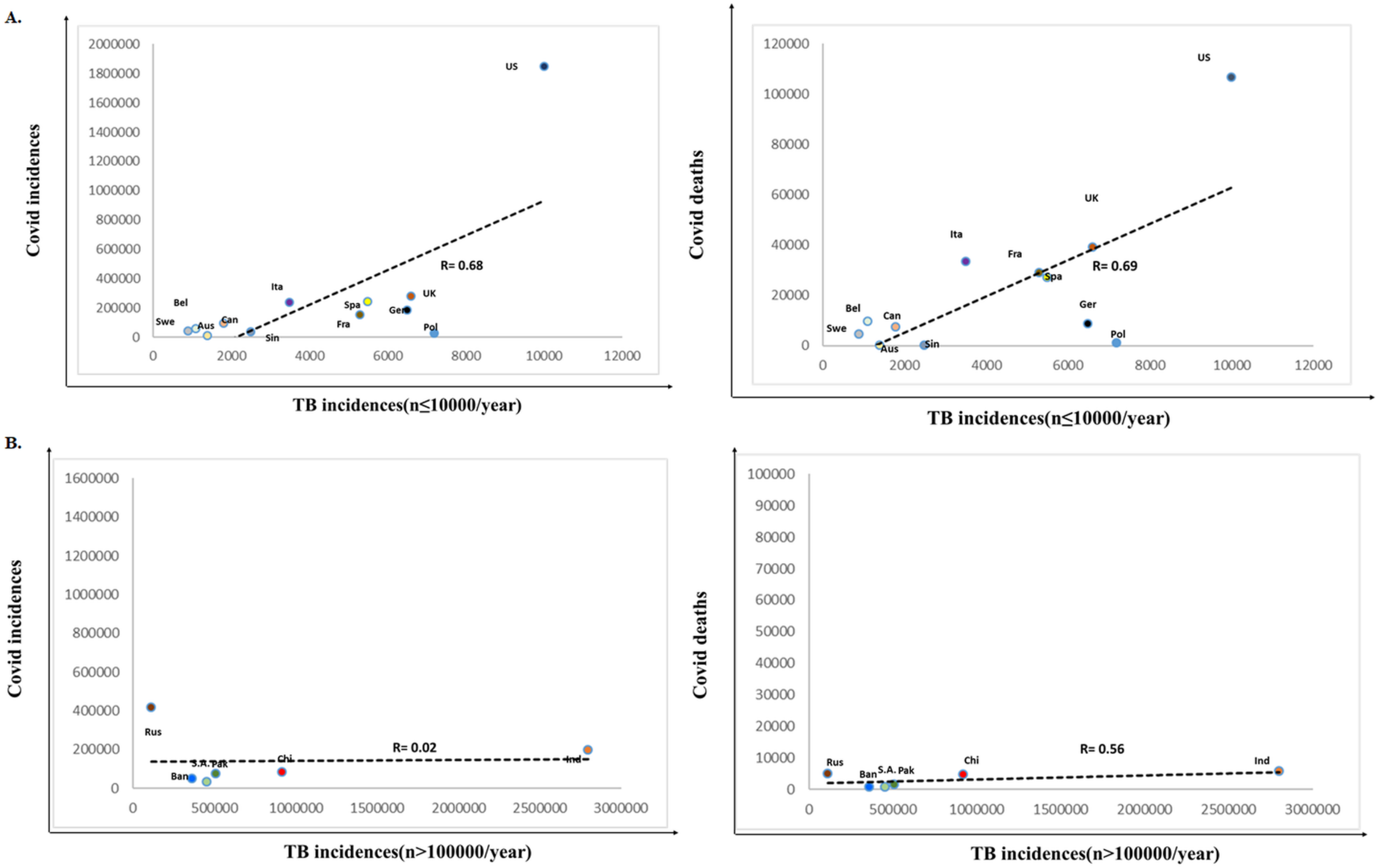

Figure 3

Lower TB incidences positively correlates with Covid-19 incidences and deaths: Scatter graphs were plotted using Table 1 to understand the correlation between TB incidences and Covid-19 incidences/deaths. A. Countries with TB incidences ≤10,000 and the respective incidences (R = 0.68 and p = 0.01) and deaths (R = 0.69 and p = 0.01) due to Covid-19. B. Countries with T.B. incidences >1,00,000 and the respective incidences (R = 0.02 and p= 0.96) and deaths (R = 0.56 and p= 0.23) due to Covid-19. Pearson's correlation coefficient value (R) was calculated for all the four graphs. Correlation between conditions was considered significant for p<0.1.

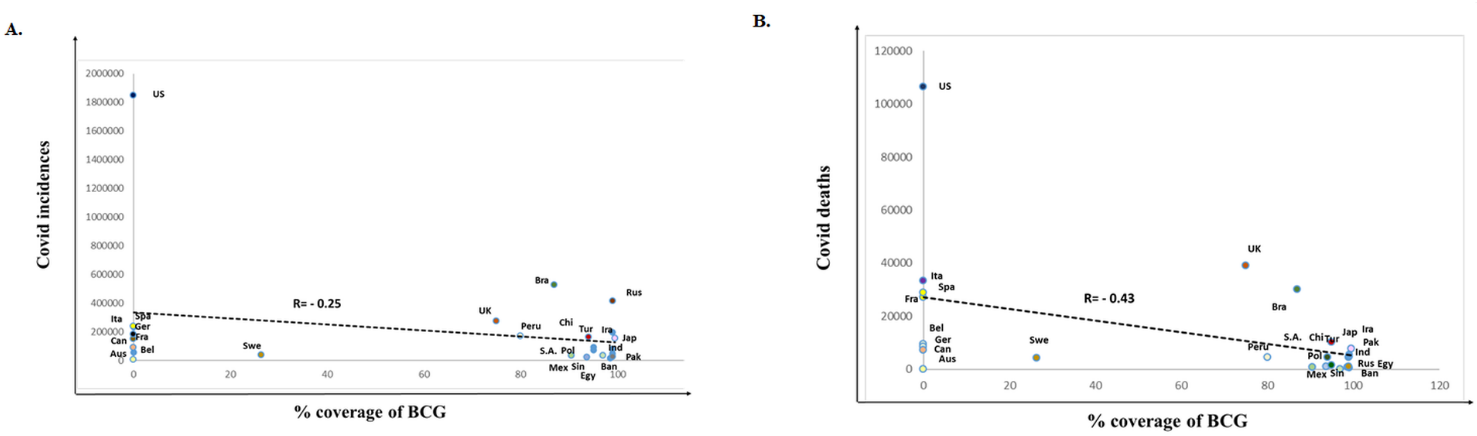

Figure 4

Covid-19 induced deaths negatively correlates with BCG vaccination coverage: The graphs were constructed based on percentage of BCG vaccination coverage and compared against A. Covid-19 incidences (R = -0.25 and p = 0.21) and B. Covid-19 deaths (R = -0.43 and p = 0.02). Pearson correlation coefficient value was considered statistically significant if p<0.1.

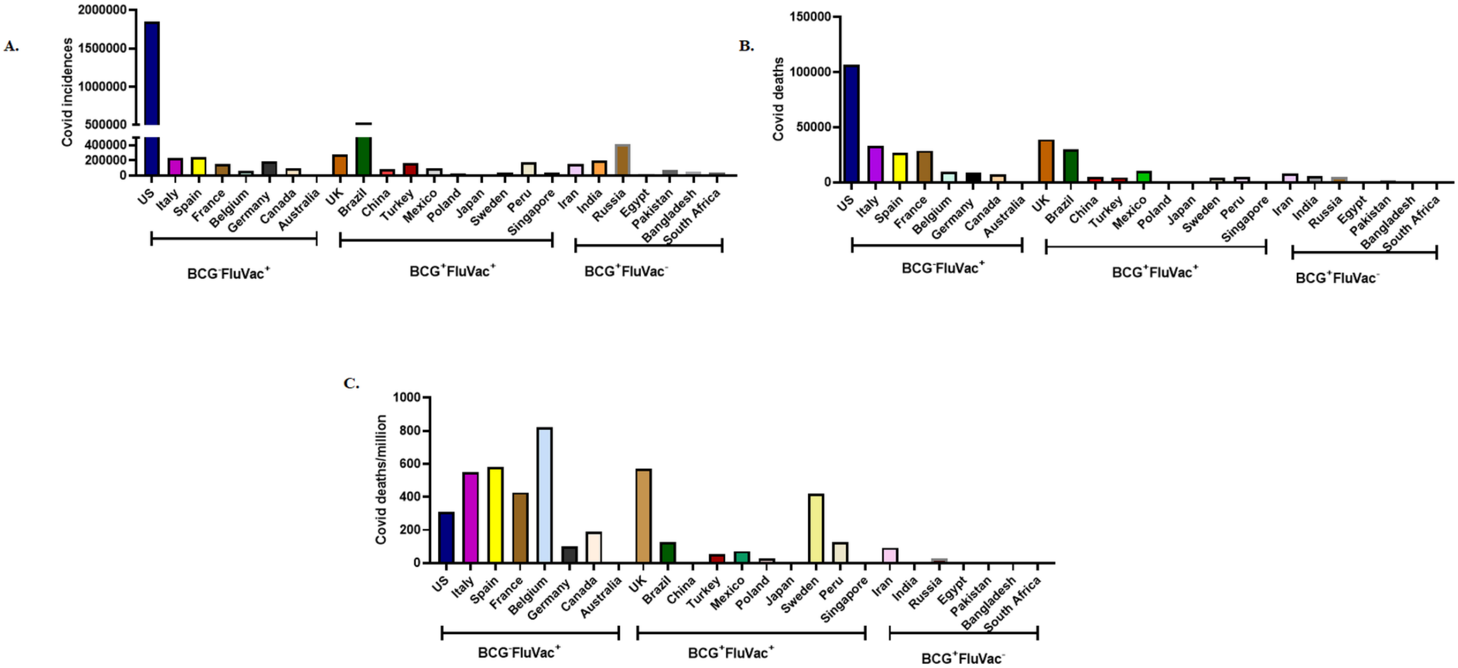

Figure 5

BCG plays a dominant factor in determining Covid-19 induced deaths: Countries were grouped based on BCG and Flu vaccination policies (available or not available) and plotted based on A. Covid-19 incidences B. Covid-19 deaths and C. Covid-19 deaths/million. BCG- and BCG+ & FluVac- and FluVac+ denotes BCG and Flu vaccination that are absent or present respectively for a particular country.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarydata3June2020.pdf
- Table1.docx