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ABSTRACT

Background Covid-19 virus has infected over 300,000 people and led to over 13,000 deaths in its first 3 months; yet the pattern of development is not uniform.. Mechanistic evidence exists to suggest that vaccination with Bacillus Calmette-Guérin (BCG), can have protective effects against viral infection. Herein we examine whether national programs which use BCG vaccination with the aim of reducing tuberculosis infections could account for the differential incidence and mortality observed in Covid-19 between various countries.

Methods We accessed and collated data from three sources - accessed on March 24th 2020 - for the analysis: The European Centre for Disease Prevention and Control for the number of cases and deaths attributed to Covid-19; The World Atlas of BCG for list of countries describing programs of BCG vaccination; and Worldometer.info for the population of all countries.

Findings 178 countries had data from all three sources and formed the basis of our analysis. Current national programs of BCG vaccination exist in 131 countries; 21 countries have no current program of national BCG vaccination; and for 26 countries status is unknown. Over preceding 15 days, incidence of Covid-19 was 38.4 per million in countries with BCG vaccination compared to 358.4 per million in the absence of such a program. The death rate was 4.28/million in countries with BCG programs compared to 40/million in countries without such a program.

Interpretation Countries with national program of whole population BCG vaccination appear to have a lower incidence and death rate from Covid-19. This may be due to the known immunological benefits of BCG vaccination. In the absence of a specific vaccination against Covid-19, population-based BCG vaccination may have a role in reducing the impact of this disease and is being studied in a prospective trial.

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To date, in 3 months, coronavirus pandemic has infected more than 480,000 individuals and caused over 13,000 deaths. Based on transmission in China and initial transmission in Europe, the pandemic is expected to peak in June or July[1, 2]. To try and limit its spread, stringent public health measures are being implemented to slow the spread and protect those most vulnerable. Governments and communities are implementing social distancing and quarantining those with disease to minimize spread.. A coronavirus vaccine is expected to take a minimum of 12 to 18 months to develop. In the meantime, repurposing existing and safe vaccines that induce non-specific immune benefits may be an additional tool[3].

There is strong epidemiologic evidence that live, attenuated vaccines induce non-specific mortality benefits. For example, Bacillus Calmette-Guérin (BCG), a live attenuated strain of Mycobacterium bovis, the most commonly administered vaccine worldwide, induces an ~38-45% mortality reduction[4, 5]. Developed to combat tuberculosis (TB), the mortality benefit from BCG is not TB-specific, but due to a decrease in neonatal sepsis and respiratory tract infections[6]. Not limited to neonates and children, BCG vaccinated elderly (age 60-75) individuals experience decreased respiratory infections[7]. For bladder cancer, intravesicular BCG boosts host immunity, reduces tumor recurrence progression and decreases mortality and has been approved for use in bladder cancer since the 1990s[8].

The non-specific immune benefits of BCG have been known since the 1970s when BCG was shown to improve immunity against listeria and influenza in murine models[9, 10]. More recently, studies have demonstrated that the molecular mechanisms of the non-specific benefits of BCG are due to NOD2 and mTOR mediated changes in the epigenetic landscape of immune cells[11-14]. When medical students were vaccinated with BCG, 3 months later they demonstrated improved immunity to *Staphylococcus aureus* and *Candida*[12]. The BCG priming induces persistent chromatin conformational changes in innate and adaptive immune cells that improves anti-mycobacterial, bacterial, fungal and viral immunity[11, 12, 14-18]. BCG vaccinated healthy controls re-challenged with yellow fever virus demonstrated improved anti-viral immunity and decreased viral loads. After BCG vaccination, the epigenetic-mediated non-specific immune benefits last at least a year[14]. Therefore, while a coronavirus-specific vaccine is being developed , there exists sufficient data to support evaluating BCG vaccination as a means to prime host immunity and mitigate the current crisis[3].

To identify whether BCG vaccination does confer some natural protection, we decided to evaluate the incidence and mortality patterns from Covid-19 with BCG vaccination programs. When we looked at Europe, the current epicentre of the outbreak, we found that the map of countries most affected in Europe bears striking resemblance to the map of countries that do not have national programs of BCG vaccination (Fig 1).

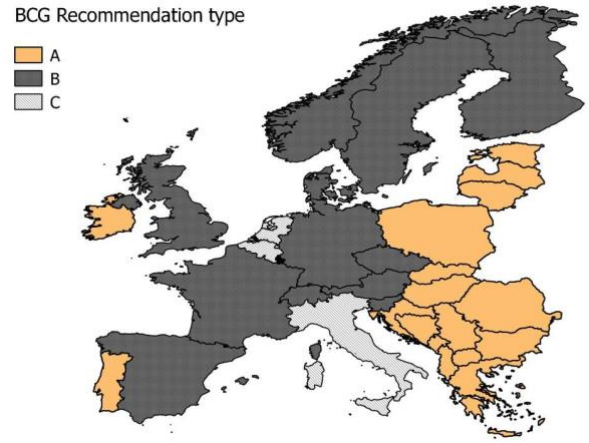

Figure 1a, A - Country with current universal BCG program of vaccination; B – Country no longer has BCG vaccination program; C – Country never had BCG vaccination program. Data courtesy of the BCG World Atlas[4].

Figure 1b. Screenshot of heatmap of SARS-CoV-2 cases in Europe ECDC website[2] , accessed March 24 2020.

To look at this further we collated all reported cases and fatalities of Covid-19 world-wide from the European Centre for Disease Prevention and Control on the previous 15 days, on March 24nd 2020[17]. The per million incidence and fatality was then calculated using the population numbers in 2020 as recorded on Worldometers.info[18]. Finally we collated the countries that have programs of whole population vaccination still in place, as reported on the World Atlas of BCG[19].

Over the 15 day period from 9 March to 24 March 2020, the incidence of Covid-19 was 80 per million population, with a fatality of 0.55 per million. A total of 178 countries were in the database: current national programs of BCG vaccination exist in 131 countries; 21 countries have no current program of national BCG vaccination; and for 26 countries status is unknown. When we dichotomised the data according to those countries with and without BCG programs, the incidence of Covid-19 was 38.4 per million in countries with BCG vaccination whereas the incidence of Covid-19 was 358.4 per million in the absence of such

a program. Likewise, the fatality recorded in countries with BCG programs was 4.28/million, compared to 40/million in countries without a national program. Calculating a crude case fatality rate (CFR) by dividing deaths by cases, countries with a BCG program the CFR was 0.13% and 0.33% in countries without a BCG program. Countries that have a booster injection of BCG 7 to 14 years later had no better outcomes than those with a single inoculation only.

We recognize that these data are observational and based on a single time-point and that there may be are several confounding issues such as limited testing and reporting in many countries. However as these data are derived from 178 countries the trend is striking and supports the mechanistic data that exists for BCG as a protective agent not only for viral and other infections but also against cancer.

There are currently efforts under way to initiate a randomised, blinded, placebo-controlled trial[3]. This would offer a low risk, high benefit proposition. BCG has been used for close to a century and three billion doses have since been administered since it was developed in 1922[19] with a remarkable long-standing safety record. For individuals previously vaccinated, recent studies have demonstrated revaccination is safe, well-tolerated and not associated with an increased frequency or severity of local or systemic reactions than the primary BCG vaccination[20-24]. While awaiting a coronavirus-specific vaccine, using an existing, available and safe vaccine such as BCG to boost host immunity may represent an important tool against coronavirus.

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