COVID-19: A model correlating BCG vaccination to protection from mortality implicates trained immunity

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Summary

- We use a data quality model to demonstrate that BCG vaccination is correlated with protection from death from COVID19
- From a mechanistic perspective, BCG is well described to elicit its protective non-specific effects through the process of trained immunity.
- Therapeutically enhancing trained immunity may therefore be an important mechanism in protection from the lethal effects of COVID19

Introduction:

Several lines of evidence have suggested the Bacille Calmette-Guérin (BCG) vaccine exerts non-specific effects, especially in offering protection from non-mycobacterial respiratory tract infections (Nemes 2019 NEJM, Moorlag et al., 2019). This motivated us to more deeply investigate whether BCG provides protection from disease or death in individuals infected with SARS-Cov2, the causal virus of COVID-19 disease. Indeed, what is unanswered is *how* BCG would confer such non-specific protection from death from COVID-19. Furthermore, if BCG does confer protection, how durable is this effect and can it be quantified? However, prior to being able to attribute and further investigate a protective role to BCG vaccination, a *bona fide* correlation between vaccination and protection from death from COVID-19 must first be established.

Seen differently, the global COVID-19 pandemic is essentially a large-scale, uncontrolled experiment on the non-specific effects of a widely used vaccine, which can be highly heterogeneous in its manufacture and potency. Thus, we sought to interrogate the ecology in which the COVID-19 pandemic is occurring. Importantly, and differing from the prior art, we modeled the available data from the point of view of data quality and data science and less that of epidemiology. Epidemiology requires a longer duration of a pandemic to collect useful and robust data amenable to modeling with epidemiological tools (Bukhari & Jameel 2020). Clearly the complete tool kit for the epidemiological approach is unavailable at this early stage.

A significant challenge early in the COVID-19 pandemic has been identifying available “clean” data (Coronavirus Source Data). Multiple lines of evidence underline the poor quality of the majority of available COVID-19 data, and in particular the poor quality of comparable “case data” which is highly influenced by a country’s testing at this stage (COVID-19 Coronavirus Pandemic, Worldometers). This significantly influences the ability to accurately calculate case fatality rate (CFR) (Leung et al., 2020) and as a consequence CFR estimations are unreliable for the purposes of establishing *bona fide* correlations. Importantly, exponential growth, particularly in the early stages of this rapidly changing event, compounds these errors due to poor quality data over time.

The absence of usable tools and a paucity of trustworthy data for COVID-19 are in stark contrast to those available for SARS and MERS, for example. With *hindsight* those epidemics can be well studied and dissected using the state-of-the-art tools. However, in a fast moving and exponentially expanding disease such as COVID-19, data quality enabled data science may contribute beneficially *early-on* with *foresight* to public health policy and scientific approaches.

In the present study we use mortality data from the COVID-19 pandemic as the most robust data available at this point in time. In correcting for the temporal nature of the pandemic, with deaths initiating at different times in different countries, we used continuous rolling snapshots of deaths per million over time. This analysis was conducted for the top 100 countries ranked by mortality per capita, and normalized in time at 0.1 deaths per million for each country. Using this as a point of departure to construct bona fide correlations, we proceed to develop a high confidence model for a group of the approximately two dozen countries with the largest range of higher quality mortality data. This analysis clearly demonstrated *whether* BCG vaccination is correlated with protection from death from COVID-19. We then linked this correlation to new and existing studies and data suggesting causal protective mechanisms that have been previously and rigorously demonstrated to be mediated by BCG vaccination. These mechanisms converge on “trained immunity,” suggesting that therapeutically enhancing trained immunity may be an important mechanism in individuals demonstrating protection from the lethal effects of COVID-19.

RESULTS:

Establishing a robust correlation between BCG Vaccination & Protection from death from COVID-19

Science currently suffers from an undersupply of quality data and an oversupply of models at this early stage in the pandemic. To "see around corners", requires multiple *trustworthy* observational points that can be used to analyze and develop robust correlations. These data should be sufficient in quantity and quality to plot a *bona fide* function. To understand the "ecology" of BCG vaccination in general, multiple temporal data points must be taken in places where BCG vaccination is routine and then compared to geographies where this does not occur.

To do so we surmised that "mortality data" was the most robust data available today. We arrived at this conclusion through several routes. Firstly, and perhaps most significantly, is the general inconsistency in how the case data is collected and reported across time within nations themselves as priorities and resources change from week to week. For example, before sufficient test resources were available in many European countries, the early priority was to test the very ill only, followed by medical workers and then suspected cases. Contrastingly, in Asia the testing early on was focused on containment and thus testing was prioritized for contacts of confirmed cases, before rapidly being moved to the wider population. Secondly, the sheer number of tests completed to date varies from country to country. Countries that are motivated and have the means to efficiently conduct high numbers of tests per day influence the case numbers heavily in one direction while several large countries still have low testing volumes, making comparisons between countries highly uneven. Thirdly, there is a large amount of inconsistent reporting of the confirmed case data itself, for example asymptomatic individuals were not reported in some countries and this further weakens the reliability of the number of positive cases for comparison. Fourthly, in the early stages of a pandemic testing is neither free of charge, nor widely available except (with important exceptions) in the highest income countries biasing comparisons of testing data across countries in time while resources lag. Lastly and perhaps a hard to resolve problem with testing data is that it remains highly political as a metric, influencing its transparent reporting in many places.

Consequently, case-fatality rates (CFR), the ratio of deaths to confirmed cases, remain unreliable for comparisons as the denominators are highly dependent on test penetration per country.

In summary, test and case data is highly useful in other contexts, however, for the aforementioned reasons it is fundamentally unreliable in developing a robust correlative relationship between BCG vaccination countries and protection from death from COVID19.

"Mortality data" also has its flaws. Countries have had varying definitions for COVID-19 mortality. In some cases, a death with obvious symptoms was considered in scope, while for others a positive test had to be produced. Some countries in Europe initially did not include any deaths outside hospitals but these were subsequently incorporated. Countries have varying healthcare death certification protocols and timings, so some data compresses in days but is normally resolved well in time for total deaths. Also, there is concern that some deaths go unreported as health systems become saturated, however in countries in the midst of the pandemic, abnormal spikes in numbers of deaths are noticeable and usually well reported in the press where post-hoc attribution to COVID-19 can be made.

Taking the above into account, to construct our model we followed mortality data, reversing in time to early in the beginning of the COVID-19 outbreak in each country. Starting at the point that each country reached 0.1 deaths per million inhabitants (Supplemental Table 1), we plotted cumulative deaths per million against time in days (Figure 1 & Supplemental Table 2). The long-term asymptote on this function

reflected deaths per million population for the current wave. Examining this data for countries which started their epidemic earlier, for example China, Japan and South Korea, resulted in sufficient numbers of data points plotted to present day to be able to derive an approximate function from which we could deduce longer term COVID-19 severity per country for comparison. However, for many countries there were simply too few data points in time after the data point when 0.1 deaths per million inhabitants occurs to derive a suitable progression curve. For example, for Brazil there are only 14 such points of data because we are early in their outbreak, and obtaining a longer-term function on so few points of data is not generally predictive, yielding low confidence (Table 1). However, by choosing an initiation point of the crisis amenable to the generation of an approximate progression curve for as many countries as possible, and basing our plots and temporal snapshots only on the higher quality deaths per capita, we were able to distill interesting empirical results (Figure 1).

Noise in the per capita data can occur if countries below a million inhabitants are included. Therefore, for the purposes of this analysis, small nation states, that is nations with populations below a million people, are excluded. As previously mentioned, when this analysis is conducted, only for a small number of countries can multiple snapshots in time be obtained for up to 21 data points (Figure 1 & Table 1 high confidence column). This number of data points affords us a comparable semi-log graph of deaths per million data for a reasonable number of countries. Also, after preparing the table data in this way and studying the relative placement of each country per time snapshot, the model partitions well, BCG vaccination countries from those where no BCG vaccination is occurring or has been halted (Figure 1, Table 1). Thus, our model is robustly predictive of the expanding separation in mortality per capita between BCG and non-BCG vaccinating countries over time.

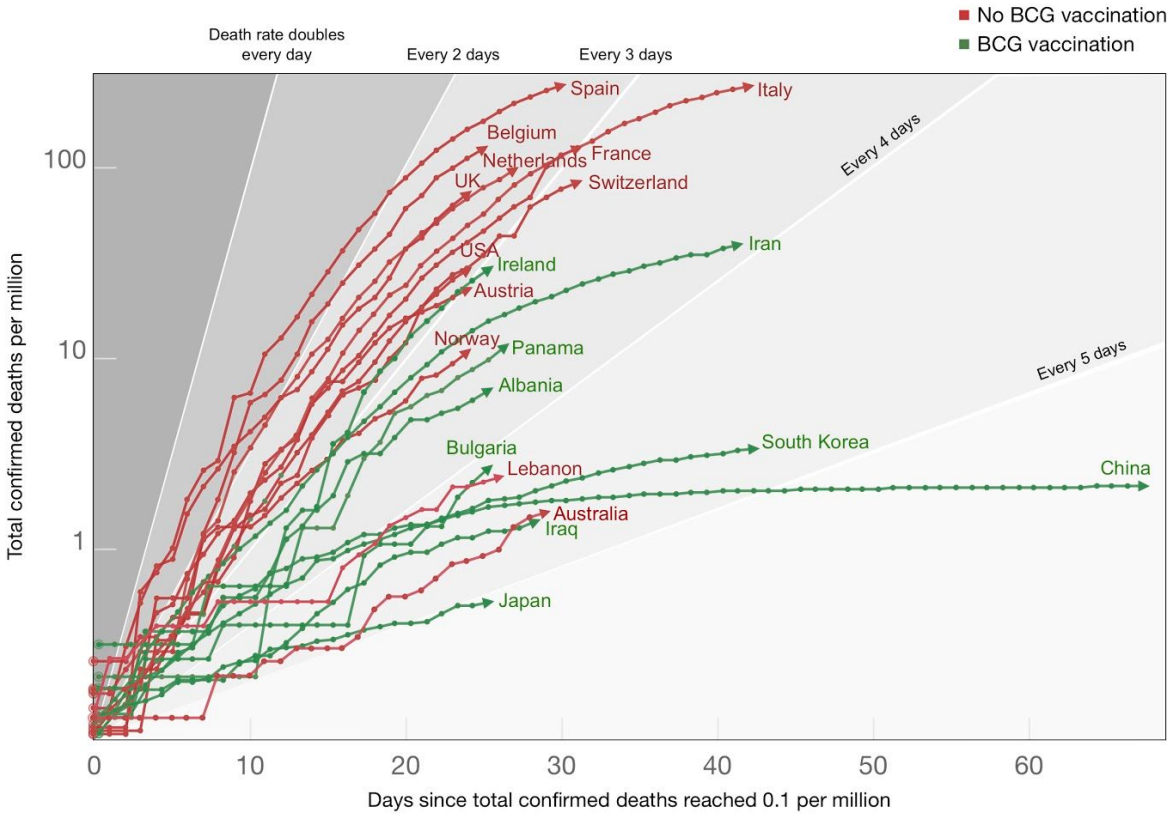

Figure 1. In general, countries with an ongoing BCG vaccination program exhibit reduced COVID-19-associated mortality rates. Data represents days since the total confirmed deaths of COVID-19 per million people reached 0.1. The 20 countries represented here were selected as they have available data for > 21 days after 0.1 deaths per million. The variable time span is from 31 December 2019 to 6 April 2020. Potential explanations for outliers (such as Ireland and Lebanon) are explained in supplemental data. Raw data from OurWorldInData.org.

7 days (low confidence)

	Country	7th day after 0.1 deaths per million	Deaths	BCG
1	Portugal	26-Mar-20	4,2	
2	Czech Republic	1-Apr-20	2,9	
3	Spain	14-Mar-20	2,6	
4	Denmark	23-Mar-20	2,2	
5	UK	20-Mar-20	2,1	
6	Sweden	23-Mar-20	2,1	
7	Romania	30-Mar-20	2,1	
8	Dominican Republic	28-Mar-20	1,8	
9	Finland	29-Mar-20	1,6	
10	Mauritius	29-Mar-20	1,6	
11	Bosnia and Herzegovina	29-Mar-20	1,5	
12	Croatia	1-Apr-20	1,5	
13	Slovenia	25-Mar-20	1,4	
14	Italy	4-Mar-20	1,3	
15	Greece	22-Mar-20	1,2	
16	Belgium	19-Mar-20	1,2	
17	Netherlands	16-Mar-20	1,2	
18	Israel	28-Mar-20	1,2	
19	Germany	23-Mar-20	1,1	
20	Norway	20-Mar-20	1,1	
21	Turkey	28-Mar-20	1,1	
22	France	13-Mar-20	0,9	
23	Serbia	28-Mar-20	0,9	
24	Malaysia	29-Mar-20	0,8	
25	Iran	3-Mar-20	0,8	
26	Hungary	23-Mar-20	0,7	
27	Morocco	30-Mar-20	0,7	
28	Albania	19-Mar-20	0,7	
29	Tunisia	30-Mar-20	0,7	
30	Austria	20-Mar-20	0,7	
31	Brazil	30-Mar-20	0,6	
32	Canada	24-Mar-20	0,6	
33	Argentina	1-Apr-20	0,5	
34	Singapore	29-Mar-20	0,5	
35	Peru	29-Mar-20	0,5	
36	Switzerland	13-Mar-20	0,5	
37	United States	20-Mar-20	0,5	
38	Gabon	28-Mar-20	0,4	
39	Lebanon	18-Mar-20	0,4	
40	Burkina Faso	29-Mar-20	0,4	

14 days (moderate confidence)

	Country	14th day after 0.1 deaths per million	Deaths	BCG
1	Spain	21-Mar-20	21,4	
2	Portugal	2-Apr-20	18,3	
3	Belgium	26-Mar-20	15,4	
4	Denmark	30-Mar-20	12,4	
5	Iceland	3-Apr-20	11,7	
6	Sweden	30-Mar-20	10,9	
7	Netherlands	23-Mar-20	10,4	
8	Italy	11-Mar-20	10,4	
9	UK	27-Mar-20	8,5	
10	Slovenia	1-Apr-20	6,3	
11	Austria	27-Mar-20	5,8	
12	Serbia	4-Apr-20	5,7	
13	France	20-Mar-20	5,7	
14	Germany	30-Mar-20	5,4	
15	Turkey	4-Apr-20	5,0	
16	Israel	4-Apr-20	4,5	
17	United States	27-Mar-20	3,9	
18	Switzerland	20-Mar-20	3,8	
19	Greece	29-Mar-20	3,1	
20	Iran	10-Mar-20	2,8	
21	Ecuador	29-Mar-20	2,7	
22	Norway	27-Mar-20	2,6	
23	Canada	31-Mar-20	2,4	
24	Bahrain	31-Mar-20	2,4	
25	Ireland	26-Mar-20	1,8	
26	Albania	26-Mar-20	1,7	
27	Hungary	30-Mar-20	1,6	
28	Panama	25-Mar-20	1,4	
29	Moldova	2-Apr-20	1,2	
30	South Korea	9-Mar-20	1,0	
31	China	13-Feb-20	1,0	
32	Poland	31-Mar-20	0,8	
33	Algeria	1-Apr-20	0,8	
34	Philippines	30-Mar-20	0,6	
35	Lebanon	25-Mar-20	0,59	
36	Iraq	23-Mar-20	0,5	
37	Gabon	4-Apr-20	0,4	
38	Bulgaria	26-Mar-20	0,4	
39	Paraguay	4-Apr-20	0,4	
40	Costa Rica	2-Apr-20	0,4	

21 days (high confidence)

	Country	21st day after 0.1 deaths per million	Deaths	BCG
1	Spain	28-Mar-20	103,9	
2	Belgium	2-Apr-20	71,4	
3	Netherlands	30-Mar-20	45,0	
4	UK	3-Apr-20	43,0	
5	Italy	18-Mar-20	41,4	
6	France	27-Mar-20	26,0	
7	Switzerland	27-Mar-20	18,6	
8	United States	3-Apr-20	18,3	
9	Austria	3-Apr-20	17,5	
10	Ireland	2-Apr-20	17,2	
11	Iran	17-Mar-20	10,2	
12	Norway	3-Apr-20	7,7	
13	Panama	1-Apr-20	7,0	
14	Albania	2-Apr-20	5,2	
15	Lebanon	1-Apr-20	1,8	
16	China	20-Feb-20	1,5	
17	South Korea	16-Mar-20	1,5	
18	Bulgaria	2-Apr-20	1,4	
19	Iraq	30-Mar-20	1,0	
20	Australia	29-Mar-20	0,5	
21	Japan	30-Mar-20	0,5	

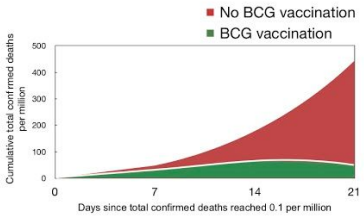

Table 1. Mortality rankings per country at 7 days, 14 days and 21 days since total confirmed deaths reached 0.1 per million. Increasing confidence in correlations is observed over 3 weeks, with a greater number of countries without current BCG vaccine programs entering the higher ranks over time. Inset represents a graphical summary of the data.

Confounding factors

A number of additional outliers and confounding factors exist, known and unknown (See Supplemental Notes). While we ensure that our analysis is subject to rigorous empiricism using noise-free higher quality data, it is impossible to know all the confounding possibilities, for which clinical trials and more high-quality temporal case and mortality data should provide more insight in the future. Important confounding factors in our study included the variabilities in detection of cases, the temporal nature of the virus spread, the influence of dynamic populations, age stratification demographics, variable death certification and reporting times and some differences between the planned and actual BCG execution within countries. However, many of these confounding factors were not exhaustively analyzed and should be explored in greater detail, and in particular *quantified,* in further work. Strain type, which is often dynamic over time was collected in some cases but not yet modelled.

Correlation not causation: *whether* vs *how much*?

Importantly, this analysis at this early stage can show predictive correlations, but alone cannot assign causation. These variables and the sheer paucity of data preclude our analytical approach from indicating "*how much*" of an influence BCG could play in a quantitative manner at this time, though possibly with more data that could change soon. Contrastingly, our early analysis could indicate "*whether*" BCG has an influence. In time and with more data points, stronger empirical evidence will emerge that can bring more quantitative information. Notwithstanding, clear strong signals have emerged especially in the dynamic mortality per capita data as to "*whether*" BCG is influential and given our current situation, this is worth discussing expediently.

Observations of non-specific effects of BCG

The BCG vaccine is primarily used against tuberculosis (TB) (Zwerling et al., 2011). *Mycobacterium tuberculosis* (Mtb), the bacteria that causes TB, currently infects approximately one quarter of the world's population. TB is associated with high morbidity and mortality, particularly in Sub-Saharan Africa. In 2018, 10 million cases of tuberculosis (TB) and over 1.5 million TB-associated deaths were recorded (Global Tuberculosis Report 2019, WHO), which makes it the deadliest infectious disease on the planet. Numerous studies have investigated whether BCG vaccination reduces TB disease burden and associated mortality. Neonatal BCG vaccination has been shown to be associated with lower mortality rates among both TB-exposed and TB-unexposed children (Thysen et al., 2020). Three randomized controlled trials of early BCG vaccination in Guinea-Bissau found a 38% reduction in all-cause neonatal mortality (Jensen et al., 2020). These effects do not only benefit infants, as a recent clinical trial revealed that revaccinating at-risk teenagers with the BCG vaccine they first got as infants could significantly reduce the threat of these patients becoming carriers of TB infection (Nemes et al., NEJM 2018). This latter study has also demonstrated a 73% decrease in non-mycobacterial respiratory tract infections induced by BCG vaccination (data collected within the safety monitoring plan, as the main endpoint of the study was tuberculosis infection). Collectively, these studies provide evidence that the BCG vaccine provides broad immune protective properties against non-related infections and disease. Several studies strongly support this hypothesis. For example, a randomized placebo-controlled study showed that BCG vaccination lowers yellow fever vaccine viremia (Arts et al., 2018). In addition, BCG has been shown to offer protection against bladder cancer (Buffen et al., 2014) and malaria (Berendsen et al., 2019). Overall these studies indicate that the strong protective role of the BCG vaccine is not only limited to TB and indicate that interventions to increase timely BCG vaccination are urgently warranted.

What is the mechanism by which BCG can confer this non-specific immunity?

The heterologous effects of BCG vaccination also served as the basis for the discovery of 'trained immunity', the *de facto* immune memory of the innate immune system (Kleinnijenhuis et al., 2012). Innate immune cells (such as monocytes) exposed to BCG or other stimuli (e.g. β-glucan) prior to exposure to certain infectious agents (e.g. TB), develop enhanced resistance upon reinfection with a second infectious agent, a response referred to as 'trained immunity' (Kleinnijenhuis et al., 2012, Quintin et al., 2012). The enhanced responsiveness observed in trained monocytes is accompanied by durable metabolic changes and the stable accumulation of epigenetic marks on dozens of innate immune responsive genes and enhancer elements (Quintin et al., 2012, Cheng et al., 2014, Saeed et al., 2014, Arts et al., 2016). As a consequence of epigenetic reprogramming, trained genes are more strongly and robustly transcribed. Critically, quantitative correlates of trained immunity beyond increases in deposition of epigenetic marks that can be rapidly and easily interrogated are lacking.

Epigenetic modifications are catalyzed by a large family of chromatin remodelers (Längst et al., 2015). However, the precise mechanism describing how epigenetic marks are directed to specific regions of the genome has been lacking. Accumulating evidence reveals the 'non coding' portion of the genome has a significant role in gene regulation (Mattick, 2004, Amaral et al., 2008, Sanjana et al., 2016). Recently, it has been shown that the non coding genome is extensively transcribed into long non-coding RNA (lncRNA) (Iyer et al., 2015, Hon et al., 2017). LncRNAs can use the folding of DNA in 3D to bring chromatin remodelers proximal to target genes to regulate the epigenetic activation of genes (Wang et al., 2011). A new class of lncRNAs, called Immune Priming LncRNAs (IPLs) have been shown to regulate the "writing" of innate immune memory at "trained" immune genes (Fanucchi et al., 2019). ChIP-seq approaches for assaying the levels of epigenetic modifications at innate immune genes are an approach to assess the degree of "trained" immune activation in BCG vaccinated individuals. The ability to routinely assay such levels in patients post-vaccination (Moorlag et al, in revision) would have significant benefits in assessing vaccine efficacy and nonspecific benefits, such as the reduction of respiratory infections unrelated to Mtb.

Until recently, it has been unclear how this vaccine is able to generate long-term innate immune memory. Recently, Kaufmann et al., used a mouse model to show that BCG reprograms hematopoietic stem cells (HSC) and multipotent progenitors (MPPs) in the bone marrow (Figure 2). Notably, this leads to the expansion and polarisation of MPPs towards myelopoiesis. Further, the macrophages that arise from BCG-reprogrammed HSCs are epigenetically reprogrammed and greatly enhanced in their ability to offer protection to Mtb infection (Kaufmann et al. 2018). This infers that the BCG vaccination-induced epigenetic changes in HSCs and/or MPPs can be transferred to circulating monocytes, and subsequently macrophages. This process enables myeloid cells to preserve a memory of exposure to pathogens, leading to long-lasting enhanced protection against infectious agents, such as Mtb. Similar processes have been described in the bone marrow of human volunteers vaccinated with BCG, in which transcriptional and epigenetic reprogramming of HSCs has been documented three months after the vaccination (Cirovic et al, in revision). Interestingly, in humans it has been demonstrated that not only monocytes/macrophages, but also the neutrophils display a long-term functional boost after BCG vaccination (Moorlag et al, in revision).

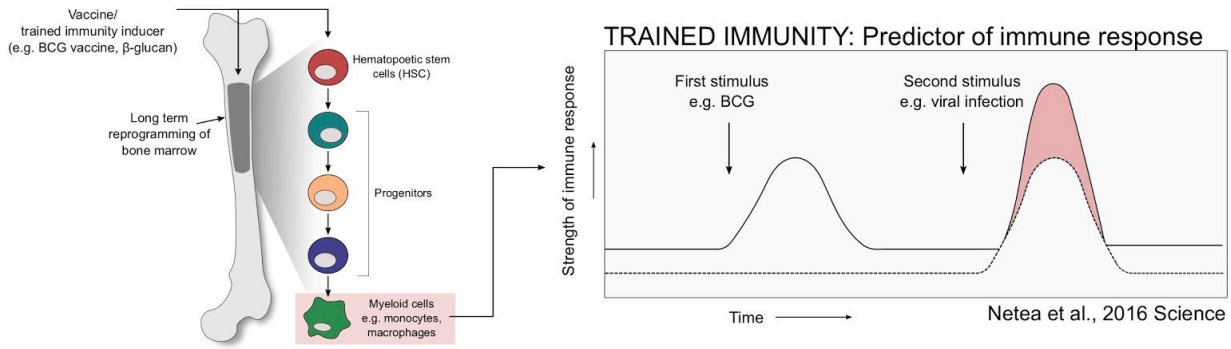

Figure 2: Stimuli that induce trained immunity (e.g. BCG) reprogram the bone marrow niche to induce long term immune memory. As a consequence, myeloid cells that arise from the bone marrow are enhanced in their capability to clear infection.

The exact duration of protection from TB and other diseases by BCG remains unknown. A study conducted in American Indians and Alaska Natives revealed that BCG vaccine efficacy against tuberculosis persisted for 50 - 60 years (Aronson et al., 2004). Interestingly, this study revealed a

moderate reduction in the efficacy of the vaccine over time, the effect of which was more pronounced in men. A retrospective cohort study in Norwegian-born individuals vaccinated with BCG showed an average vaccine effectiveness against all forms of tuberculosis of 49% in a 40-year follow-up (Nguipdop-Djomo et al., 2016). Overall this indicates that a single dose of BCG vaccine can have a long duration of protection against TB. The induction of non-specific protection against heterologous infections is however likely to be shorter-lived, although this remains to be demonstrated.

With the rapid spread of SARS-CoV-2 around the world, an outstanding question is whether BCG vaccination will combat the symptoms and reduce the overall mortality rate of the respiratory disease caused by this virus. Validating the suggested effect of BCG vaccination on COVID-19 in randomized clinical trials is a crucial step before being able to conclude that this approach should be expanded as a tool in this pandemic. Currently, there are several prospective trials being conducted or being prepared worldwide (including ongoing studies in The Netherlands, Australia and Greece) to investigate whether the BCG vaccine would be effective against COVID-19. While we will only know the outcome of these trials in several months, the ongoing COVID-19 pandemic represents a global 'uncontrolled clinical trial' of BCG vaccinated versus unvaccinated populations coupled to vaccine strain. Clearly, the role of trained immunity in mediating the protective effects of the BCG vaccine warrants further investigation. Several avenues of enhancing trained immune responses have been identified (reviewed in Mulder et al., 2019). These novel approaches could serve as a simple and effective measure in reducing COVID-19 associated mortality. Critically, these approaches can be implemented prior to the generation of a SARS-CoV2 vaccine, a development that at its earliest is over a year away.

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Coronavirus Source Data Daily deaths, Coronavirus Source Data, Our World in Data

COVID-19 Coronavirus Pandemic, Worldometers

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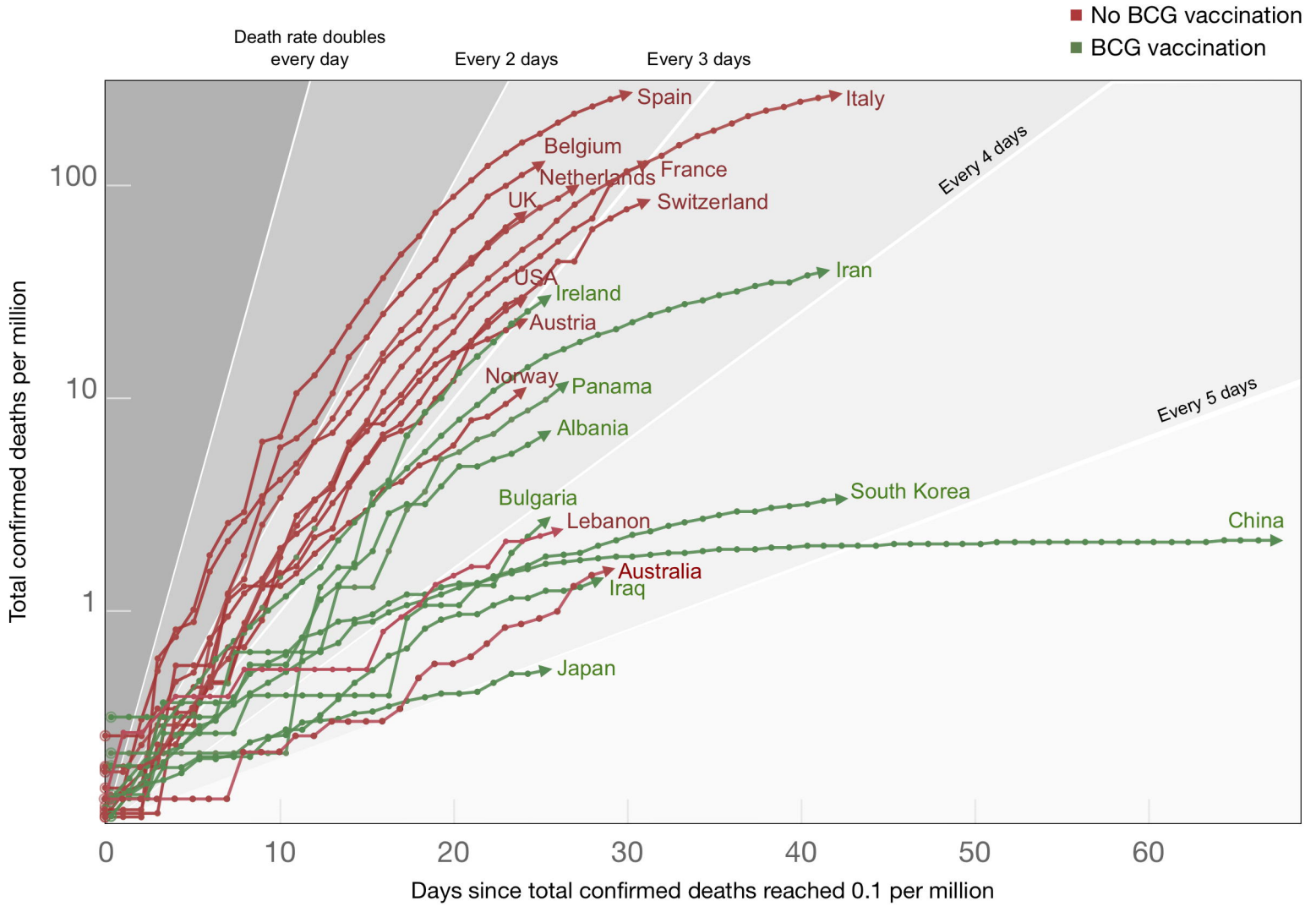
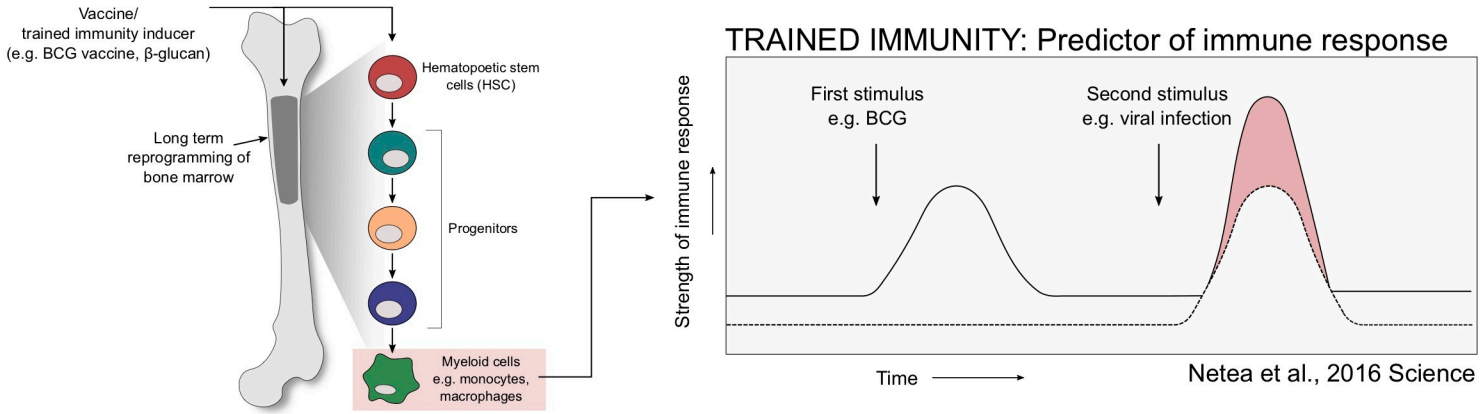

No BCG vaccination
BCG vaccination
Death rate doubles every day
Every 2 days
Every 3 days
Every 4 days
Every 5 days
Spain
Italy
Belgium
Netherlands
France
UK
Switzerland
USA
Iran
Ireland
Austria
Norway
Panama
Albania
Bulgaria
South Korea
Lebanon
China
Australia
Iraq
Japan
100
10
1
0
10
20
30
40
50
60
Total confirmed deaths per million
Days since total confirmed deaths reached 0.1 per million



7 days (low confidence)

	Country	7th day after 0.1 deaths per million	Deaths	BCG
1	Portugal	26-Mar-20	4,2	
2	Czech Republic	1-Apr-20	2,9	
3	Spain	14-Mar-20	2,6	
4	Denmark	23-Mar-20	2,2	
5	UK	20-Mar-20	2,1	
6	Sweden	23-Mar-20	2,1	
7	Romania	30-Mar-20	2,1	
8	Dominican Republic	28-Mar-20	1,8	
9	Finland	29-Mar-20	1,6	
10	Mauritius	29-Mar-20	1,6	
11	Bosnia and Herzegovina	29-Mar-20	1,5	
12	Croatia	1-Apr-20	1,5	
13	Slovenia	25-Mar-20	1,4	
14	Italy	4-Mar-20	1,3	
15	Greece	22-Mar-20	1,2	
16	Belgium	19-Mar-20	1,2	
17	Netherlands	16-Mar-20	1,2	
18	Israel	28-Mar-20	1,2	
19	Germany	23-Mar-20	1,1	
20	Norway	20-Mar-20	1,1	
21	Turkey	28-Mar-20	1,1	
22	France	13-Mar-20	0,9	
23	Serbia	28-Mar-20	0,9	
24	Malaysia	29-Mar-20	0,8	
25	Iran	3-Mar-20	0,8	
26	Hungary	23-Mar-20	0,7	
27	Morocco	30-Mar-20	0,7	
28	Albania	19-Mar-20	0,7	
29	Tunisia	30-Mar-20	0,7	
30	Austria	20-Mar-20	0,7	
31	Brazil	30-Mar-20	0,6	
32	Canada	24-Mar-20	0,6	
33	Argentina	1-Apr-20	0,5	
34	Singapore	29-Mar-20	0,5	
35	Peru	29-Mar-20	0,5	
36	Switzerland	13-Mar-20	0,5	
37	United States	20-Mar-20	0,5	
38	Gabon	28-Mar-20	0,4	
39	Lebanon	18-Mar-20	0,4	
40	Burkina Faso	29-Mar-20	0,4	

14 days (moderate confidence)

	Country	14th day after 0.1 deaths per million	Deaths	BCG
1	Spain	21-Mar-20	21,4	
2	Portugal	2-Apr-20	18,3	
3	Belgium	26-Mar-20	15,4	
4	Denmark	30-Mar-20	12,4	
5	Iceland	3-Apr-20	11,7	
6	Sweden	30-Mar-20	10,9	
7	Netherlands	23-Mar-20	10,4	
8	Italy	11-Mar-20	10,4	
9	UK	27-Mar-20	8,5	
10	Slovenia	1-Apr-20	6,3	
11	Austria	27-Mar-20	5,8	
12	Serbia	4-Apr-20	5,7	
13	France	20-Mar-20	5,7	
14	Germany	30-Mar-20	5,4	
15	Turkey	4-Apr-20	5,0	
16	Israel	4-Apr-20	4,5	
17	United States	27-Mar-20	3,9	
18	Switzerland	20-Mar-20	3,8	
19	Greece	29-Mar-20	3,1	
20	Iran	10-Mar-20	2,8	
21	Ecuador	29-Mar-20	2,7	
22	Norway	27-Mar-20	2,6	
23	Canada	31-Mar-20	2,4	
24	Bahrain	31-Mar-20	2,4	
25	Ireland	26-Mar-20	1,8	
26	Albania	26-Mar-20	1,7	
27	Hungary	30-Mar-20	1,6	
28	Panama	25-Mar-20	1,4	
29	Moldova	2-Apr-20	1,2	
30	South Korea	9-Mar-20	1,0	
31	China	13-Feb-20	1,0	
32	Poland	31-Mar-20	0,8	
33	Algeria	1-Apr-20	0,8	
34	Philippines	30-Mar-20	0,6	
35	Lebanon	25-Mar-20	0,59	
36	Iraq	23-Mar-20	0,5	
37	Gabon	4-Apr-20	0,4	
38	Bulgaria	26-Mar-20	0,4	
39	Paraguay	4-Apr-20	0,4	
40	Costa Rica	2-Apr-20	0,4	

21 days (high confidence)

	Country	21st day after 0.1 deaths per million	Deaths	BCG
1	Spain	28-Mar-20	103,9	
2	Belgium	2-Apr-20	71,4	
3	Netherlands	30-Mar-20	45,0	
4	UK	3-Apr-20	43,0	
5	Italy	18-Mar-20	41,4	
6	France	27-Mar-20	26,0	
7	Switzerland	27-Mar-20	18,6	
8	United States	3-Apr-20	18,3	
9	Austria	3-Apr-20	17,5	
10	Ireland	2-Apr-20	17,2	
11	Iran	17-Mar-20	10,2	
12	Norway	3-Apr-20	7,7	
13	Panama	1-Apr-20	7,0	
14	Albania	2-Apr-20	5,2	
15	Lebanon	1-Apr-20	1,8	
16	China	20-Feb-20	1,5	
17	South Korea	16-Mar-20	1,5	
18	Bulgaria	2-Apr-20	1,4	
19	Iraq	30-Mar-20	1,0	
20	Australia	29-Mar-20	0,5	
21	Japan	30-Mar-20	0,5