

BCG and COVID-19: Correlation or Causality or neither?

CASE

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ABSTRACT

Learning outcomes

The learning outcome is to understand the difference between correlation and causation.

Case overview/synopsis

The case is set during the period of the COVID-19 pandemic, globally a search for effective treatments were underway. An initial forerunner that was being considered was Bacille Calmette-Guerin (BCG), given its effectiveness in the treatment of tuberculosis and other pulmonary-related infections. While there were a lack of randomised controlled trials, initial data from publicly related secondary data sources indicated that, in countries with BCG inoculation policies, the severity of the spread and mortality of COVID-19 was muted. The case is centered around the available information on BCG and COVID-19.

Complexity academic level

Post-graduate students learning statistics as part of a degree programme. The case assumes no prior statistics knowledge and therefore is aimed at teaching the difference between correlation and causation.

Keywords: Management science/operations research; Management/executive education; Management theory

INTRODUCTION

On 23 April 2020, GlobalData Healthcare¹ released an article titled “BCG vaccination may induce heterologous immunity and protect against Covid-19.” Amidst the search for a vaccination to combat COVID-19, Bacille Calmette-Guerin (BCG) was being considered given its immune boosting powers² and evidence of effectiveness against respiratory tract infections³. A comparative study⁴ had indicated that the immune cells of those individual inoculated with BCG were more alert to react to a threat to the immune system than those not inoculated. However, the global vaccination policy for BCG inoculation varied from country to country, and in specific relation to Covid-19, countries such as Italy and the United States of America with no policy for BCG vaccinations had experienced higher Covid-

19 related mortality than countries such as South Korea and Japan which have a universal policy⁵.

As the pandemic continued to claim the lives of individuals globally, a clear understanding of the results of the multiple studies was required. If countries that had BCG vaccination policy showed decreased COVID-19 related mortality, was this indicative of effectiveness of the vaccination? Was the BCG vaccination the cause of decreased mortality of COVID-19 deaths?

BACKGROUND: COVID-19, BCG, MORTALITY

The nature of COVID-19 as a global pandemic was pronounced by the World Health Organisation (WHO) on 11 March 2020, after initially being detected in Wuhan, China. The rapid spread of the virus meant that most individuals were affected to some degree, either directly or indirectly. However, as individuals became increasingly aware, and began tracking the spread at a country and global level, numerous interpretations of what the number of positive cases reported, the number of deaths, and the number of recoveries came about. In South Africa, the National Department of Health provided a daily update on the number of tests conducted, positive cases identified, total recoveries, total deaths and number of new daily cases. A number of individuals were also consumed in the near real-time dashboards, an information management tool that visually tracks and displays key performance indicators, (exhibits 1 and 2).

In addition to tracking various indicators of COVID-19, implications of the virus was on everyone's mind to some extent, and with numerous reports on economic growth prospects, job losses, share-price fluctuations, government regulations, and business survival, the correct interpretation of the information presented was central. As BCG provided a glimmer of hope against Covid-19, understanding if inoculating with BCG reduced the risk of Covid-19 morbidity and mortality was required. Could there be veracity in the glimmer of hope, specifically as Covid-19 was related to pneumonia, a lung infection³? Afterall, BCG is used to prevent tuberculosis (TB) primarily, an infectious disease affecting the lungs⁴.

BCG had been given to individuals since at least 1973 in South Africa⁶, and while many countries globally had adopted a similar regime, not all countries had similar policies for BCG inoculation (exhibit 3). Over and above the inoculation policies, data from the WHO indicates that there were six strains in use globally (exhibit 4), with countries such as India using more than one specific strain, and South Africa a single strain, namely BCG-Denmark. Was the low spread and mortality in South Africa and other countries a consequence of the

BCG inoculation, independent of the strain (exhibit 5)? Was this the reason or was it due to the actions of the South African government or a combination of various other factors? Even if BCG was a significant contributor, there was a potential for over-interpretation, specifically causality between BCG and severity of COVID-19?

The mortality rate of COVID-19 was a major factor in managing the spread of the disease at the time. Mortality is commonly linked directly to death – destined to die⁷, and the mortality rate which is commonly defined as the number of deaths in a particular population, scaled to the size of the population⁸. There were subtle differences between mortality due to COVID-19 and underlying medical conditions that may be exasperated by COVID-19 that lead to death⁹.

There were nuances, which may indicate that mortality due to COVID-19 may be exaggerated. Despite this nuance – and the importance of understanding these nuances, they are more pertinent to interpretation of mortality and mortality rates, rather than effectiveness of BCG inoculation. Government measures such as lock-downs for many countries globally were primarily aimed at gearing-up the healthcare systems to deal with potential increases in the number of individuals needing medical care, minimising the rate of spread among other reasons, in the absence of a cure against Covid-19.

Timing:

Evidence suggesting that BCG had any positive effect on mortality of Covid-19 would require having to control for a host of variables such as socio-economic demographics, the rate at which tests were being conducted, density of individuals per square kilometre, or even seasonality. These would be a minimum set of criteria to satisfy should there be any veracity in BCG and COVID-19 linkages. Was it too early? After all it was only 6-weeks after Covid-19 was declared a pandemic.

Despite this short time span, there were a host of academic articles that were published and a systemic review completed of these were published¹⁰, and while there may be some veracity – the results were tenuous, and mostly conflicting in their outcomes. There was grave uncertainty in all the data and the analysis that was being put forward as well as how individuals interpreted BCG vaccination and policies

THE WORLD OF RAPID INFORMATION, INTERPRETATION:

Academic journal articles^{11,12,13,14,15,16} reporting on BCG and Covid-19 were being rapidly published, yet none providing conclusive evidence that BCG provided protection from Covid-

19. At best, plausible relationships, all the articles results were positive: there were certainly correlations between countries that had BCG vaccine policies for all citizens, in comparison to countries with prior policies for BCG vaccines for all citizens and those for specified groups only. There were some indication that BCG had a positive effect across many of the attributes. But were these results reliable? Some of the studies had control variables, while some did not. If it was to be proven that BCG had any effect on COVID-19, surely controlling for a host of variables was necessary? Furthermore, the existence of a correlation did not indicate that it was true either.

CONCLUSION

Results from a number of sources were mixed and tenuous at best. If countries that had BCG vaccination policy showed decreased COVID-19 related mortality, was this indicative of effectiveness of the vaccination? Was the BCG vaccination the cause of decreased mortality and Covid-19 deaths?

Exhibit 1: Logarithmic graphs Dashboard as at end October 2020 (Source: Authors)

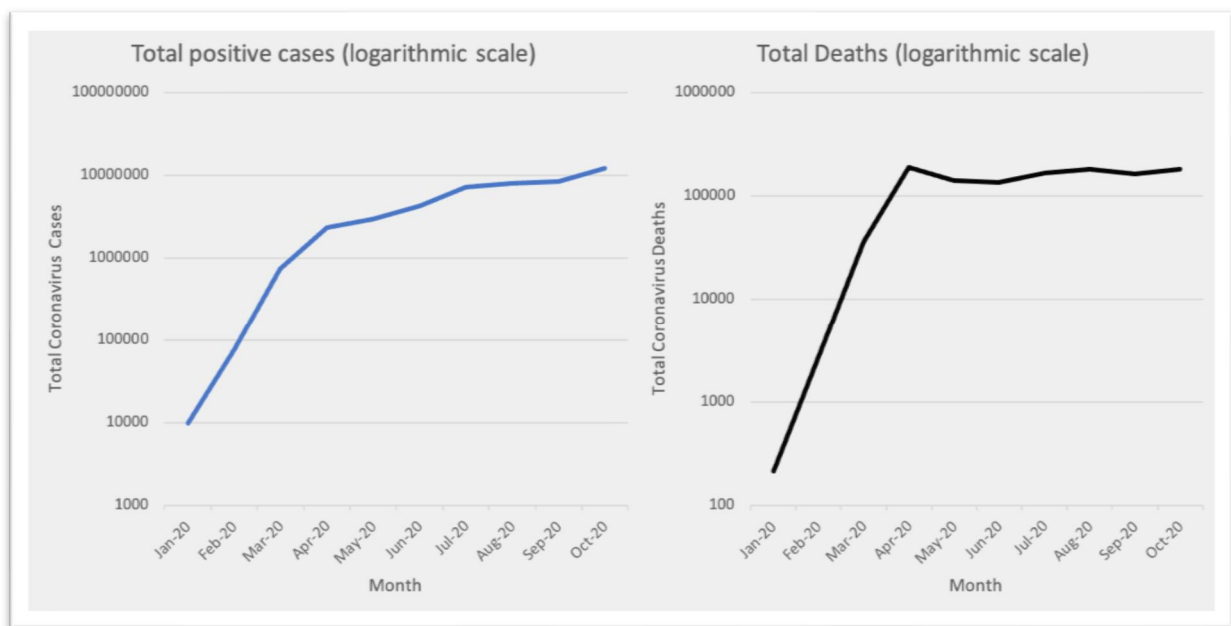


Exhibit 2: Dashboard as at end October 2020 (Source: Authors)



Exhibit 3: BCG World Atlas (source: <http://www.bcgatlas.org/index.php>) accessed 25 May 2020

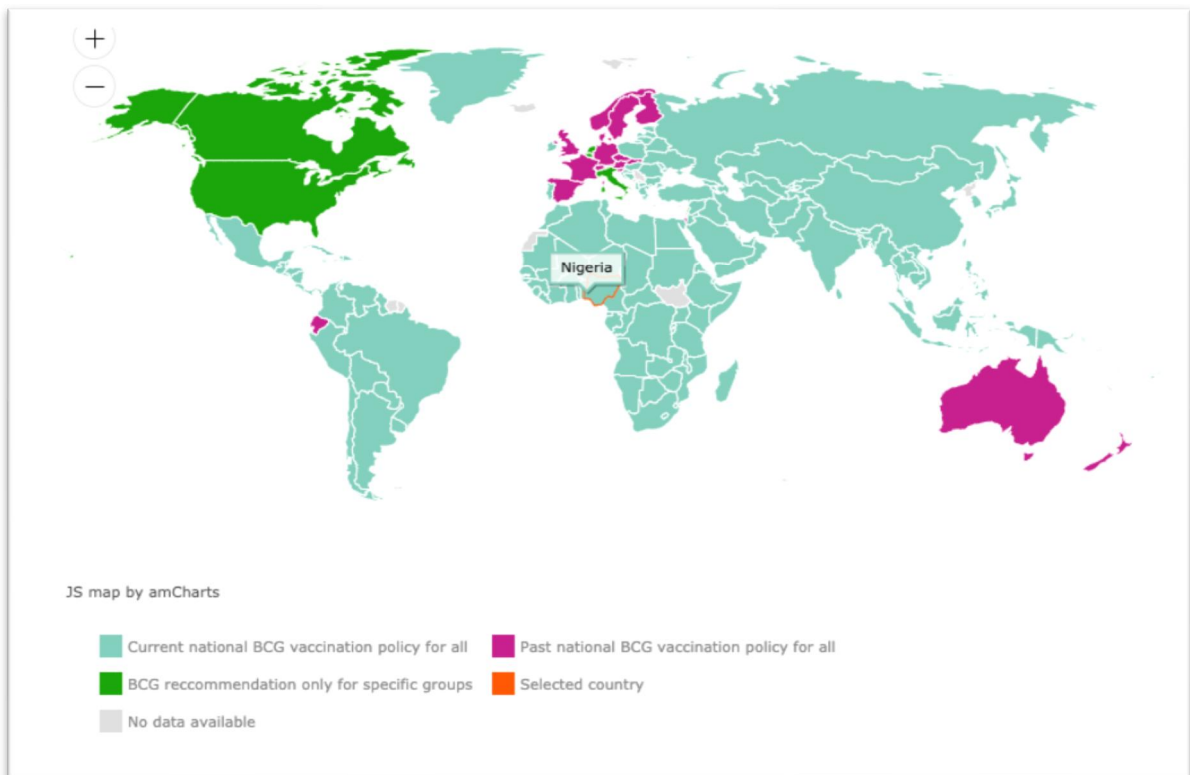


Exhibit 4: BCG vaccine strains used between 2003 and 2007 worldwide. Adapted from Ritz and Curtis (2009).

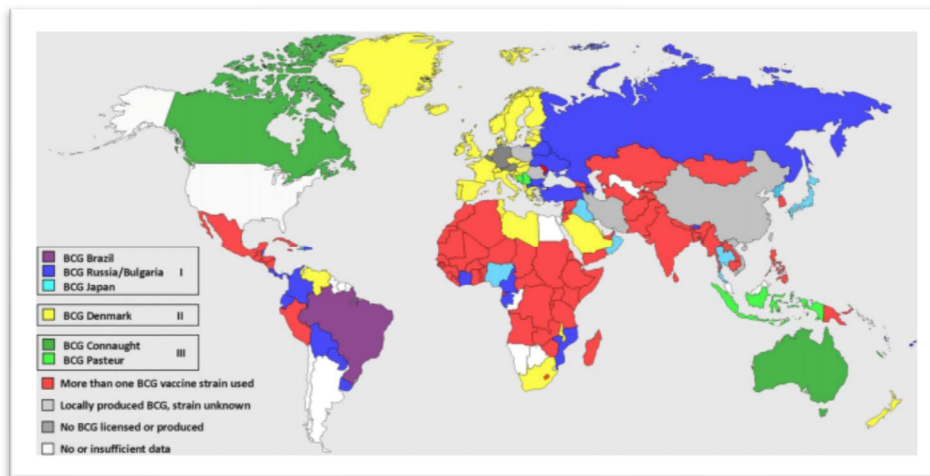
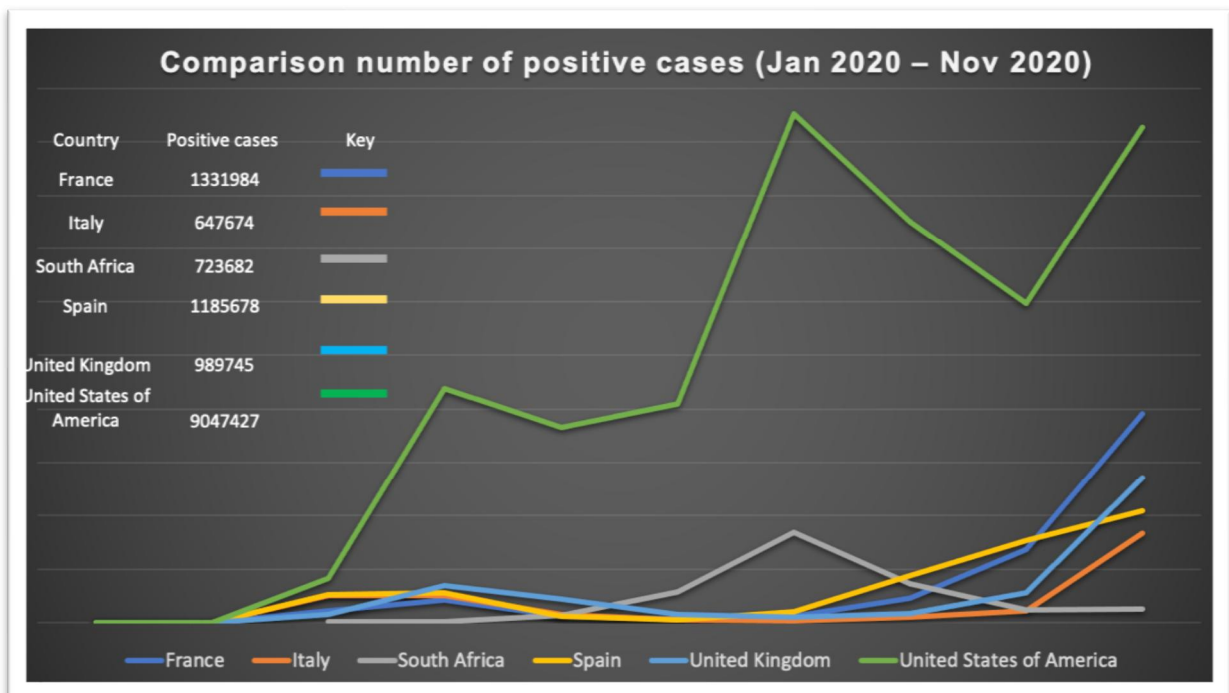


Exhibit 5: Number of positive COVID-19 cases, South Africa vs other countries as at end October 2020 (Source: Authors own)



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