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REVIEW ARTICLE: CORRELATION BETWEEN UNIVERSAL BCG VACCINATION POLICY AND REDUCED MORBIDITY AND MORTALITY FOR COVID-19: AN EPIDEMIOLOGICAL STUDY[1]

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ABSTRACT: *Genome of eukaryotic cells contains up to 69% of the transposable elements and repetitive sequences. To a large extent it is a result of billions of years of evolution through which eukaryotes were encountering gazillions of viruses and storing the footprints of those encounters in its genome. This time Mankind deals with a novel virus belonging to the coronavirus family, which albeit being widely spread in the wildlife is new to humans. Once infected, 80% of humans experience a flu-like symptoms and eventually recover. However, the real menace is posed to those whose vulnerability is determined by old age and underlying medical conditions. Akin to the scenario of alien invasion, this pandemic will leave a notable imprint on social, economic and biological aspects of human existence. How did it happen, or rather, why did we allow this to happen? Let's ponder over the biological, medical and philosophical domains of COVID-19 pandemic.*

KEYWORDS: COVID-19, Coronavirus, Pandemic, Epidemic, Viral Infection, Mortality, Cytokine Storm, Regenerative Medicine, Disease Prevention

INTRODUCTION

The authors of the article deserve appreciation for their scientific work because of - firstly, addressing the global COVID-19 pandemic, a kind of one-sided world war against an unseen enemy; secondly, opening up an opportunity of critically criticising the topic relating to diverse behaviours and patterns of either the COVOD-19 itself or global to local societal culture / structure or both, and thirdly, many established scientific theories today were started with implicit philosophical thoughts rather than with scientific evidence; the authors have handled with scientific methods to initiate future researches. However, I have my observations and reservations regarding the findings.

[1] Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study
Aaron Miller, Mac Josh Reandelar, Kimberly Fasciglione, Violeta Roumenova, Yan Li, Gonzalo H Otazu
medRxiv 2020.03.24.20042937; doi: https://doi.org/10.1101/2020.03.24.20042937

The authors have conducted a kind of 'ecological study design' which is appropriate in this particular context. However, no potential confounding factors (e.g., socio-cultural, biological) have been taken into account. Although investigating such confounders in this design often challenging, any remarks on such factors can be addressed.

The authors' analysis on country-specific BCG vaccination policy with year of coverage does not clearly explain the 'age and sex' distribution of infection and deaths. Italy has never implemented BCG vaccination, so the question of BCG-related immunity in general population of Italy is irrelevant. It means that Italians irrespective of age and sex has no BCG-related non-specific protection against any virus (if there is any; this point is addressed later); thus, all are equally at risk. However, a recent study shows that in Italy, by 17 March 2020, there was no single case in age group 0 – 29 years and both cases and deaths were increasing with increase of age (of total deaths - 0.3% in 29-39 years versus 52% in ≥80 years age group with case fatality rates of - 0.3% and 20.2% respectively. Death rate is markedly higher in males (70%) than in females. These patterns are visibly comparable to the case of China (Onder, Rezza and Brusaferro, 2020). On the other hand, the case of Thailand clearly contradicts the age distribution in Italy and China. According to the report of WHO, majority cases are also male but in age group 20 - 49 years. Notably, Thailand has been implementing BCG vaccination policy since 1967[2]. Thus, the authors' BCG vaccination hypothesis does not explain why this population group is not protected from COVID-19.

The possible confounders which may explain this contrast: in Thailand, there is a clear link between the epidemic outbreak in those relatively young population group and large-scale gatherings in boxing stadiums and Dakwah pilgrimage[3]. How it can be explained in case of Italy and surrounding western European countries?

In Italy (and western European countries; e.g., France, Germany, Belgium, Netherlands), the outbreak follows the same pattern with a steep rise started from 6 March. This fits well with the Carnival, a Catholic Christian festival[4], that was celebrated with huge gatherings from 21 – 23 February, exactly coincides with the Corona incubation period of two weeks (Figure 1).

[2] https://www.ncbi.nlm.nih.gov/pubmed/8160047.
[3] https://reliefweb.int/sites/reliefweb.int/files/resources/2020_03_28_THA%20Sitrep%2035%20COVID19%20FINAL-2.pdf.
[4] This analysis is nothing about religion but to logically explain the possible links between Corona pandemic and broader socio-cultural factors.

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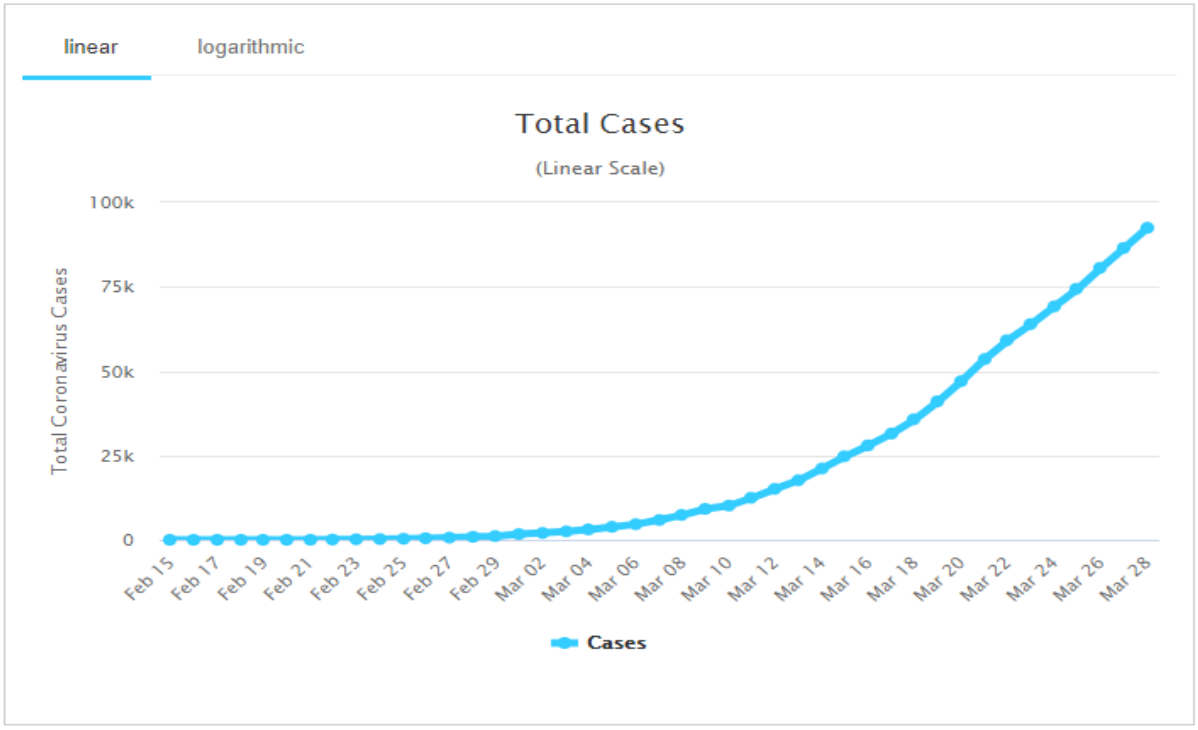

Figure 1: The Daily Trends of Corona Cases in Italy (source: Worldometer[5]).

Notably, in the Netherlands, most of the cases are in the south-eastern Catholic dominant provinces (Noord-Brabant; Limburg). The well-known Bible-belt with majority protestant Christians adjacent to north-west of the affected region have comparatively few cases (Figure 2 and Figure 3 show the geographic comparison between the Bible-belt and COVID-19 distribution in the Netherlands). The protestant inhabitants in the Bible-belt abstain from any vaccination including BCG because of their faith and also do not celebrate carnival. This explains the link of the measles outbreak in 2013 in this population (Bier and Brak, 2015). However, why absence of BCG immunization has not caused COVID-19 outbreak in them is not understandable, taking into account the authors' claim. On the other hand, of the total Christian population in Denmark, the majority nearly 63% are protestant and only 1.3% is Catholic; hence, carnival gathering was limited which may explain the low cases and death rate in Denmark rather than BCG linkage.

I quote the authors: "our data suggests that BCG vaccination seem to significantly reduce mortality associated with COVID-19" – it is a quite strong interpretation since an ecological study design of this type is nearly at the bottom of the validity hierarchy among all designs and mostly generates hypothesis for future research. Scientists have to wait for such a comment after documenting empirical evidence from systematic review of multicentric RCTs in future.

[5] https://www.worldometers.info/coronavirus/country/italy/

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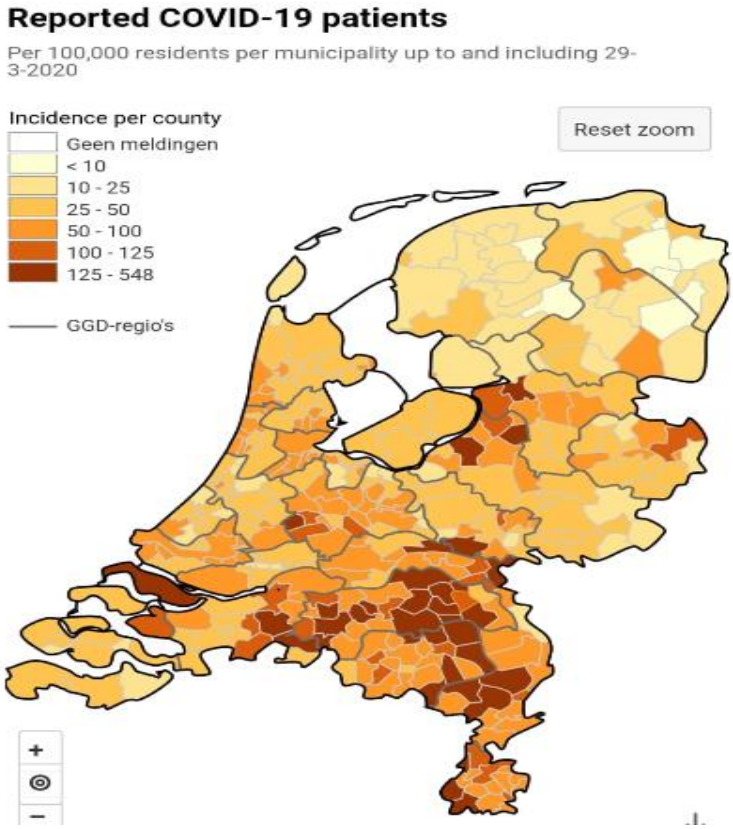

Figure 2: Geographic Distribution of COVID-19 in the Netherlands

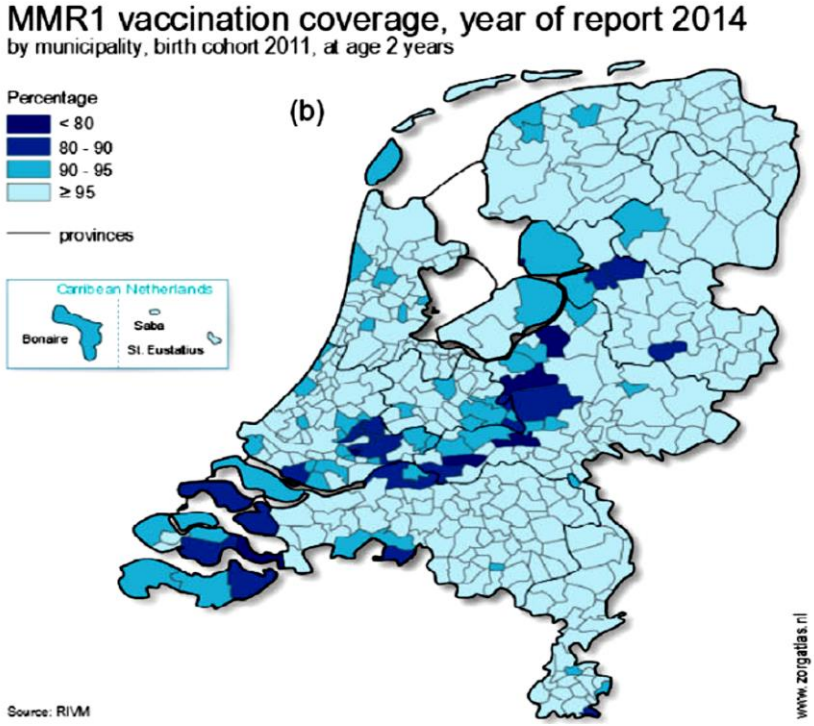

Figure 3: The Protestant Christian Dominant Bible-belt in the Netherlands

I quote the authors again – "BCG vaccination has been shown to produce broad protection against viral infections and sepsis" [6]- this finding is based on animal model and the authors of the source are quite restrictive on this point and suggested for future research to conclude.

A number of developing countries (such as Bangladesh) have global rewarding success on under-5 immunization covering BCG, measles, polio, tetanus, rubella, HBV, diphtheria vaccinations. However, respiratory infections, most often viral, are still the commonest cause of under-5 mortality in those countries; so, the concrete conclusion on the effects of BCG on viral infections including COVID-19 still deserves lot of efforts.

Spread of COVID-19 and mortality: it has been reported that Corona viral load in body fluids (specifically in saliva) at the onset of the disease is much higher than SARS affected cases. The salivary viral load in COVID-19 infected subjects throughout incubation period can be enough to infect. The underlying modes of transmission, in this context, could be risky behaviours (e.g., sharing wine/beer glasses, bottles, canes etc.) might have influenced by the socio-cultural event (i.e., carnival). A subgroup analysis in Italy shows that case fatality rate increases with increase in the number of comorbidities (e.g., diabetes, ischemic heart disease, cancer, atrial fibrillation, stroke, dementia). Of course, outcome of COVID-19 infection ultimately depends on immunological response; however, how BCG plays role/s is too early or conclude.

Overall, the authors' observation is interesting, although not such convincing. It is because in a study on this topic, socio-structural and cultural confounders play crucial roles, which become more complicated with additional biological and biomolecular confounders since a novel virus is behind the scene.

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[6] Source reference 11 of the article - (Moorlag, S. J. C. F. M., Arts, R. J. W., van Crevel, R. & Netea, M. G. Non-specific effects of BCG vaccine on viral infections. Clinical Microbiology and Infection 25, 1473–1478 (2019)).