BCG & COVID-19

Disclaimer: This article is a summary of Research article by Miller et al., Pre-print published on medRxiv. This research article at the time of writing this summary has not been peer-reviewed.

Bacillus Calmette-Guérin (BCG) vaccine is the only licensed vaccine against TB. Besides its effects on TB, BCG also induces heterologous (non-specific) immunity against other infections including viral infections (Moorlag et al., 2019). A recent study by Miller et al., 2020 (medRxiv pre-print) suggest a correlation between BCG vaccination policy and COVID-19 morbidity and mortality. They suggest that high rates of COVID-19 in countries such as Italy, Netherlands and the USA, could be related to non-universal BCG vaccination. However, a randomised clinical trial (RCT) is required to determine this. In line with this RCTs in healthcare workers are on-going in the Netherlands and Australia.

Though results by Miller et al., suggest less severe COVID-19 in countries that do have universal BCG vaccination, there are some caveats to the study (read Universal BCG vaccination and protection against COVID-19: critique of an ecological study for more details*). Firstly heterologous immunity induced by BCG has predominantly been shown to last for < 2 years. Since BCG vaccination is predominantly administered to infants and children, BCG-associated heterologous immunity may not be responsible for reduced COVID-19 morbidity in adults and the elderly. Secondly, COVID-19 epidemics compared between low-, middle- and high-income countries could be at different stages

of the epidemic. Therefore, fewer morbidity and mortality cases in low-income countries could be because these countries are in the early phase of the epidemic. Despite these caveats, RCTs taking place in Netherlands and Australia will determine if BCG confers heterologous immunity against COVID-19. Further epidemiological results presented by Miller et al., can be "confirmed" by testing the hypothesis when the epidemic "matures" in low-income countries, however results from this will be confounded by the different epidemic control strategies implemented by each country.

Journal Article: Miller *et al.,* 2020. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv pre-print

*Main points of Universal BCG vaccination and protection against COVID-19: critique of an ecological study

- **Study Design**: "Ecological studies conflate population level exposures, such as country-wide policies, with exposures at the individual level, such as the effect of the BCG vaccine on a human body…Ecological analysis techniques simply cannot directly inform etiology of exposure/disease relationships; rather, they serve us well as strictly hypothesis-generating queries and should not be stretched beyond this purpose."
- **Timing Matters**: data for Millet et al., were downloaded on 21st March when cases in LMIC were low. " cases in India have increased from 195 on March 21 to 1071 on March 31. In South Africa, cases have increased from 205 on March 21 to 1326 on March 31″
- **Lack of testing**: "Accurate analysis is dependent on accurate data and we know that the current number of coronavirus cases is dramatically underestimated around the world due to shortages of diagnostic tests."
- **Correlation is not causation**: "A critical flaw in the methodology of this study is apparent in the fact that a

perceived relationship between an exposure and an outcome does not mean one causes the other – a concept often expressed through the well-known adage "correlation does not imply causation."

- **Biological plausibility**: "The important take-away is that BCG's protective effect fades over time. So it is not clear how a vaccine that offers protection early in an individual's life would protect individuals against COVID-19 once they are of an advanced age."

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