BCG Vaccination Policy and Protection Against COVID-19: Correspondence

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To the Editor: Meena and colleagues [1] have opined about the recent study [2] which failed to show the protective effect of Bacillus Calmette-Guérin (BCG) vaccine. The quoted study showed no difference in the rate of infection between BCG vaccinated and non-vaccinated young adults, also did not find difference in severity of COVID-19 among above two groups [2]. We discuss the available important scientific evidences those are in favour of BCG's protective efficacy in severity reduction of COVID-19.

Recent analysis has shown proportionately less cases, milder illness and a lower death rate due to COVID-19 in BCG vaccinated population as compared to BCG non-vaccinated across countries and hemispheres [3].

Two separate multi-centre placebo-controlled parallel group randomized trials are ongoing in response to COVID-19 in the Netherlands and Australia to assess whether BCG-Danish vaccine reduces healthcare workers' absenteeism and hospital admission among the elderly during the COVID-19 pandemic [4]. These trials are 'BCG vaccination to protect healthcare workers against COVID-19' (BRACE) and, 'Reducing healthcare workers absenteeism in COVID-19 pandemic through BCG vaccine (BCG-CORONA)' [4]. The above ongoing trials are based on the concept of protection from COVID-19 due to immunity induced by BCG vaccination.

BCG vaccination alters a secondary innate immune response upon viral infection resulting in improved antiviral responses and lowering viremia [5].

The BCG vaccine has shown to reduce the severity of infections caused by structurally similar single-stranded positive-sense RNA virus like SARS-CoV-2 is, in controlled trials. For example, in healthy human volunteers, the BCG vaccine has reduced Yellow fever vaccine induced viremia by 71% (95% CI: 6–91) which was induced by live attenuated Yellow fever vaccine, in the study performed in Netherlands [5].

The people of the TB endemic countries like India seem to have some protection in terms of severity and deaths in comparison to TB non-endemic countries (like Europe and USA) etc. where BCG vaccination is not given. It appears that the immunity might be unable to stop COVID-19 infection, but is likely to diminish its virulence on selective individuals.

Better understanding of the molecular mechanisms is still evolving. Identifying the factors that impact the non-specific effects of BCG, could be a clue towards novel therapeutic options for reduction of severe morbidity and mortality associated with COVID-19.

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Authors' Reply

To the Editor: We appreciate the interest and valuable comments of Mohapatra and Mishra on our article published in IJP [1]. We utilize this opportunity to respond in the best possible way.

The analysis by Ozdemir et al. [2] is based on almost three months old data and has all the limitations highlighted by us [1]. The division of countries into two groups based upon the

current (2018) BCG vaccination status is inappropriate. Many countries have discontinued BCG vaccination in the last decade itself, and residents of those countries who are more than 10 y of age have been vaccinated in the past but are falsely considered non-vaccinated. Children might be the only population sub-group that did not receive the vaccination in those countries where it has been recently stopped but, they comprise less than 5% of total COVID-19 cases and had very few deaths. The majority of the affected individuals (> 40 y old) in artificially classified non-vaccinated nations, actually received the BCG vaccine in childhood. Therefore, such an analysis based on one-year vaccination coverage is technically wrong. Secondly, the relationship of BCG and COVID-19 in most studies including Ozdemir et al. is oversimplified without adjusting for potential confounders like the difference in population demographics, the prevalence of co-morbidities, number of tests done, different stages of the pandemic in various countries, and variation in health infrastructure [1, 3].

We are aware of ongoing trials of the BCG vaccine in COVID-19 and agree that these trials are based upon the non-specific effects of the BCG vaccine [3]. However, it is inappropriate to equate the recent vaccination within a trial to the childhood vaccination received many decades ago. The existing evidence does not support the persistence of non-specific immunological effects of the BCG vaccine beyond childhood. In fact, due to the same reason, we should not equate the childhood vaccination policy of a country with the recent vaccination given in the clinical trial.

We differ from the authors' comment of Indians having inherent protection from the COVID-19 by the routine childhood BCG vaccination policy. As of now, we stand fourth in the countries with the highest number of cases and probably will ascend in the list with the current case rate. Moreover, among the top four countries with maximum COVID-19 cases, three countries (India, Brazil, and Russia) have more than 90% coverage of the BCG vaccine.

We are also aware of the homology between the SARS-CoV-2 and Yellow fever virus, and the effect of trained immunity of the BCG vaccine over many other viruses. However, it's too early to conclude.

These epidemiological associations are prone to biases, and in this rapidly evolving pandemic with frequent changes in data, the conclusions of today may not hold for tomorrow. Therefore, we strongly endorse what World Health Organization states that as of now, there is no evidence of the protective effect of BCG vaccine over COVID-19, and we should wait for the results of the ongoing trials [4].

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