Complex Relationship between COVID-19 and BCG Vaccination Policy

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Dear Editor,

We read the article on BCG vaccination policy and COVID-19 spread by Ozdemir et al. with interest and found it very thoughtful.[1] Our few concerns are as follows.

Firstly, the authors have classified the countries in two groups according to the presence or absence of recent routine childhood BCG vaccination policy. The countries having universal BCG coverage above 90% previously and stopped routine vaccination practice in the last one or two decades only (Czechia, Finland, France, Ireland, Norway, Slovakia, United Kingdom) were classified into the countries with "no BCG-vaccination policy". On the contrary, some of the countries with routine BCG vaccination policy but poor coverage (Nigeria, Somalia, South Sudan) were included in the category of countries following "routine BCG-vaccination policy". Do the authors mean to confer that the protection offered by BCG (by its non-specific effects on immunity) is sustained for one to two decades only post vaccination and the actual immunization coverage of a country does not play a role? In that scenario, BCG vaccination shall be protective for children only (the least-affected age-group with COVID-19), whereas the adults and geriatric population (most-affected) will not be benefitted by it against COVID-19. Such classification (according to recent BCG vaccination status) that completely ignores the previous vaccination status, actual BCG-vaccination coverage, and generalizes the results across all age-groups is scientifically wrong and leads to false conclusions. Therefore, an age-specific comparison of COVID-19 and BCG immunization coverage might be more meaningful.[2]

Secondly, the authors did not adjust for any confounding factors like the number of tests done at that time, population demographics, co-morbidities, health infrastructure, reporting bias, etc. (though they mentioned it in limitations) that can significantly alter the results.[3] A recent study observed positive correlation (opposite to what we think) between the COVID-19 related parameters (cases, death-rate, and case-fatality rate) and BCG vaccination coverage of various countries across the span of four decades. However, with adjustment of confounders, there was actually no correlation between COVID-19 and BCG coverage.[4]

Thirdly, at the time of analysis (April 16, 2020) the pandemic was limited to the northern hemisphere which now has rapidly evolved. For now, four (India, Brazil, Russia, Peru) out of the five most affected countries have routine BCG vaccination policy with more than 90% coverage.[5,6] Therefore, the analysis favouring BCG vaccination in the initial stages of pandemic was too early to predict and was affected by the limited spread of COVID-19. To test this hypothesis, we analyzed the correlation between BCG coverage (2010-2018) and COVID-19 related parameters (Cases per million, and deaths per million) of various countries at two different time-points (March 01, 2020, and June 29, 2020) using various datasets.[5,6] We observed a weak but significant positive correlation (spearmen rho= +0.2-0.4, $p < 0.05$) between the BCG vaccination coverage and COVID-19 cases and deaths(as of March 01, 2020). However, this correlation was not seen on

June 29, 2020 (Table 1).

Based upon the above facts and observations, we conclude that as of now there is no correlation between recent BCG vaccination coverage of a country and COVID-19. As the protective efficacy may not last beyond childhood, we should not equate the childhood vaccination policy of a country with the recent vaccination being done in ongoing trials. Until we have the results of ongoing randomized clinical trials, routine use of BCG vaccine in COVID-19 management should be discouraged and restricted to research purpose only.

References

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Table 1. Correlation between BCG vaccine coverage (2010-2018) of countries with the COVID-19 Cases and Deaths

Time Points	**COVID-19 Parameters** (per million population)	**Years**	**Years**	**Years**	**Years**	**Years**	**Years**
		2018	**2017**	**2016**	**2015**	**2014**	**2013**
June 29, 2020	Total Cases	0.12	0.10	0.06	0.09	0.13	0.12
	Deaths	0.01	-0.03	-0.05	-0.19	0.03	0.04
	No. of Countries (n)	140	140	141	142	142	142
March 01, 2020	Total Cases	0.42*	0.38*	0.35*	0.34*	0.34*	0.37*
	Deaths	0.21**	0.18**	0.15**	0.17**	0.20**	0.22**
	No. of Countries (n)	133	133	134	135	135	135

*Correlation is significant at p-0.01 level

**Correlation is significant at p-0.05 level

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