Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,
Alergología y Asma Pediátrica

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LETTER TO EDITOR

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BCG immunization and COVID-19 disease association

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Dear Editor,

I read the article written by Sharma et al. with great interest.[1] As mentioned in their article, could BCG vaccine really be a game changer solely to protect against SARS-CoV2 respiratory infection? I differ from their viewpoint and have several questions regarding the suggestions discussed in the stated article.[1]

The authors have mentioned that universal BCG immunization provides protection against viral respiratory infections, for example, respiratory syncytial virus (RSV) and human papillomavirus as well as the SARS-CoV2.[1] However, this does not mean that the BCG vaccine might also boost the immune system's ability to fight other pathogens, including the deadly SARS-CoV2 infection.

Earlier studies have mentioned about presumed theory of "trained immunity" and/or nonspecific effects (NSEs) of BCG and other live vaccines.[2] The nonspecific effects of BCG vaccination have not been studied in humans, and even their clinical importance in animal models is also not definite. For instance, a meaningful rate of difference between BCG-vaccinated and non-vaccinated groups for SARS-CoV-2 infection has not been demonstrated in a population-based investigation of 72,060 individuals.[3] Although BCG was also found to induce a trained immune response against avian influenza A in a mouse model, this effect was not associated with clinical and survival improvement.[2]

The authors have pointed in their article that literature and surveys exhibiting spread and severity of COVID-19 are much higher in those countries which did not have any BCG immunization.[1] Findings from these epidemiological studies in literature showing less COVID-19 in countries with routine BCG vaccination are thought to be a weak proof, because these epidemiological results could be dependent on population rather than on individual data, other cofactors, and are likely to be confusing. For example, when the epidemiological data computed the correlation by adjusting for covariates, for example, GDP per capita, hospital bed capacity per thousand individuals, and the number of performed SARS-CoV2 tests per million individuals, the investigators did not detect any meaningful association between the rate of BCG vaccination and the COVID-19 disease.[4] Since different countries implement different policies for BCG immunization, such as route of administration, doses of the vaccine, and universal versus high-risk community vaccination due to undefined BCG efficacy, it is difficult to have a global comparison. Nevertheless, some countries, such as Iran and Latin American countries, in spite of maintaining >90% BCG vaccination rates have high morbidity/mortality from COVID-19. As mentioned in the article,[1] although Italy implemented BCG vaccination, it is one of the countries that has the highest prevalence of and mortality from COVID-19. Similarly, BCG vaccine is used all over the world, except the United States, Germany, Spain, etc., to prevent tuberculosis infection.[1] Germany has relatively low but USA and Spain have high morbidity and mortality from COVID-19. Other possible cofactors for acquiring SARS-CoV2 infection, such as *ACE2* and human leukocyte antigen

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(HLA) expressions in population, should be considered as well. Earlier literature has shown links between HLA-B*4601 and greater risk of having SARS infection.[5]

Does BCG vaccine-induced cellular immunity provide long-term protection? How long does the trained immunity caused by BCG continue after vaccination? If BCG is a protective measure, when should it be administered or read-ministered, especially in the elderly? The authors supposed that BCG vaccine provides protection for up to 60 years of immunization.[1] Earlier researchers have demonstrated that the nonspecific effects of BCG vaccine on monocytes of innate immune system persist for several months, but certain effects, such as the amplified ability of monocytes to produce cytokines, gradually weaken afterwards.[6] Accordingly, how do the authors associate the morbidity/mortality of COVID-19 in adults and the elderly with BCG vaccine given at the age of less than three months?

Certain researchers have implied that one of the explanations for BCG-vaccinated children resistant to different viral respiratory infections is their repeated exposure to other childhood live vaccines. Therefore, it is hard to relate just BCG with COVID-19, since several other live vaccines (polio, rotavirus, measles, mumps, and rubella [MMR], and chickenpox) are given at the age of less than one year. Could there be a cumulative effect of repetitive administration of all these live vaccines during childhood?

In conclusion, further randomized controlled clinical studies are necessary to detect the real association between BCG vaccination and COVID-19 morbidity and mortality.

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