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Commentary

BCG vaccine: Worrying proposal for COVID-19

Emanuel Sarinho^a, Ekaterini Goudouris^{b,*}, Dirceu Solé^c^a Federal University of Pernambuco (UFPE), Avenida Parnamirim n° 327 ap 1303, ZC 52060-000 Recife, Pernambuco, Brazil^b Federal University of Rio de Janeiro (UFRJ), Rua Professor Luis Cantanhede n° 77 ap 101, ZC 22245-040 Rio de Janeiro, RJ, Brazil^c Federal University of São Paulo State (UNIFESP), Rua Mirassol n° 236 ap72, ZC 04044-010 São Paulo, SP, Brazil

ARTICLE INFO

Article history:

Received 13 September 2020

Received in revised form 27 November 2020

Accepted 8 December 2020

Available online 13 December 2020

Keywords:

BCG vaccine

Immunity

Innate

COVID-19

ABSTRACT

Bacille Calmette-Guérin (BCG) vaccine is proven to be effective in protecting against severe tuberculosis. It has been suggested to be able to exert a non-specific beneficial effect as protection against other infectious diseases. The duration of protection against tuberculosis is estimated to be from 10 to 15 years, but the duration of the protection against other infections is not known, maybe up to 20 years, maybe much shorter than that. We don't know it for sure. BCG induced trained immunity paradigm is based on experimental models, cohort studies with low number of individuals, and some epidemiological data in which other possible interfering factors are not controlled. The titles and scopes of scientific articles should be cautiously considered as they can promote indications of getting vaccinated or revaccinated with BCG, before its effectiveness is confirmed and recommendations are published. Besides, revaccination with BCG can put at serious risk patients with primary or secondary immunodeficiency. Maybe BCG vaccine is effective in preventing COVID-19 deaths or reducing its severity, but may the effect of this vaccine be relevant even with poor health politics and assistance? It is very difficult to compare the epidemiologic data about COVID-19 in different countries. There are countless factors, mainly social and related to the healthcare system, which can be more decisive than the hypothesis of trained immunity induced by BCG. Until now, we can say that BCG's protective role is, at least, insufficient, given many other factors that corroborate SARS-CoV-2 infection and/or its severity.

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Bacille Calmette-Guérin (BCG) vaccine is proven to be effective in protecting against severe tuberculosis. It has been suggested to be able to exert a non-specific beneficial effect as protection against other infectious diseases [1]. This increase in the immunogenicity against other microorganisms is considered to be mediated by heterologous effects on adaptive immunity, like T cell-mediated cross-reactivity as well as mediated by trained immunity, a nonspecific metabolic and epigenetic reprogramming, facilitating the subsequent effector response to the first contact with other antigens [2].

Trained immunity is a *de facto* innate immune system memory. The concept involves a biological process in which enhanced inflammatory and antimicrobial properties of innate immune cells triggers an increased non-specific response to subsequent endogenous or exogenous stimuli. This process would be mediated by epigenetic programming of transcriptional pathways rather than genetic recombination as with adaptive immunity. Some authors have identified that BCG immunization can be very advantageous

when it comes to host defense to infectious agents, especially respiratory tract infections [3], but this was not confirmed by other authors [4]. On the other hand, trained immunity induced by BCG could be detrimental when it comes to chronic inflammatory and immune-mediated diseases [5]. This has been proposed as a mechanism for subsequent pulmonary disease in children with severe respiratory syncytial virus (RSV) infections in early life [6] or a mechanism why other infections can determine susceptibility to unrelated diseases [7]. The duration of protection against tuberculosis is estimated to be from 10 to 15 years [8], but the duration of the protection against other infections is not known, maybe up to 20 years [9], maybe much shorter than that [10]. We just don't know it for sure.

Covián et al. [11] analyzed the number of cases and deaths of COVID-19 in different countries and correlated them with their national vaccination programs and concluded that those countries where BCG vaccination is widely given at birth have shown a lower contagion rate and fewer COVID-19-related deaths. The same proposal was published by Gursel & Gursel [9]. Many other non-peer reviewed manuscripts became available online presenting similar data. It is important to note that an epidemiological association

* Corresponding author.

E-mail address: egoudouris@ufrj.br (E. Goudouris).

does not prove the existence of a causal relationship [10]. In addition, most of these papers were available at the beginning of the pandemic (April 2020) or compared countries where the pandemic had started at different times.

An ecological study with careful methodology was published online at the end of July 2020, demonstrating that the rate of increase in confirmed cases and deaths in the first 30 days of the epidemic in each country was significantly lower in countries where there was ample vaccination by BCG until the year 2000 [12]. The authors considered that differences between countries in terms of quality the information provided by the authorities and / or availability of tests would have remained stable during this period, which would eliminate this bias. However, this cannot be taken for granted. In addition, there were significant unexplained differences between the rate of increase in cases and deaths among countries with wide BCG vaccination. The authors mention some relevant points: that previous studies had methodological weaknesses and that it is not known whether BCG would be effective also in adults or for how long BCG would be effective against SARS-CoV-2 [12].

Escobar et al [13] published a study in which they refined the epidemiological analysis and showed that, by mitigating the confounding factors, there is a strong correlation between BCG index and COVID-19 mortality in different socially similar European countries. However, this is not the real life.

On the other hand, a recent systematic review presented a serious warning: “Stop playing with data: there is no sound evidence that Bacille Calmette-Guérin vaccine may avoid SARS-CoV-2 infection” based mainly on low quality of the studies and no inclusion of confounding factors [14].

A cohort study conducted in Israel, with reliable data on almost 600,000 people, found that BCG vaccine had no protective effect on COVID-19 [15]. Meena et al [16] didn't find a significant or consistent relationship between BCG immunization rates and COVID-19 burden. Aksu et al [17] conducted a retrospective cross-sectional study in patients diagnosed with COVID-19 pneumonia, comparing severity in groups of BCG vaccinated and non-vaccinated individuals. They found that BCG vaccination is not associated with pneumonia severity and that age and low income are the main determinants of severe COVID-19 pneumonia [17]. Nonetheless, all these studies were done in adults, with median age of above 35 y.o., long after BCG immunization. Even if we consider a duration of action through trained immunity of 20 years, one cannot be surprised at the lack of benefit of BCG.

Since 1927, Brazil has administered the oral BCG vaccine and since 1974, the intradermic one. It has been mandatory in the first few months after being born since 1976, which places us among countries that have had above 90% vaccination coverage for several decades.

November 2020, Brazil recorded a frightening number of confirmed cases, more than 6 million, and more than 170,000 deaths, predominantly affecting elderly individuals. Nonetheless, people below 20 years of age have not been spared (0,66% of deaths) [18].

We are aware of the reports' limitations involved, in part because of the absence of confirmatory tests, particularly in non-hospitalized cases in many countries. Despite that, we want to draw attention to epidemiological data of the other two epicenters of COVID-19 pandemic and in United Kingdom (UK). In the United States of America (USA), where there is no BCG vaccination, on November 2020 CDC report, 0,2% of deaths occurred in under 18 y.o. group [19]. In India, where BCG vaccination has been taking place since the 1980 s, the mortality rate is lower than in Brazil (more than 9 million cases and almost 135,000 deaths) and 2% of deaths occurred in persons under 26 years of age [20]. In UK, BCG vaccination began in 1953, but universal immunization with BCG was stopped in 2005, so individuals less than 15 y.o. did not

received BCG. The percentage of deaths in the less than 19 y.o. group in U.K. is 0,06% [21].

The argument that countries with high BCG vaccine coverage would present a more favorable situation in relation to COVID-19 is not supported by these epidemiological data. In fact, a careful look at this data could even suggest that the BCG vaccination may have a detrimental effect, perhaps increasing the inflammation caused by SARS-CoV-2 infection.

A booster dose of the BCG vaccine to be given to individuals aged 6 to 14 years was implemented by the Ministry of Health in Brazil in 1994. Adverse reactions to the BCG vaccine are not common, but increased frequency of adverse effects compared to the first dose of the vaccine was observed in Brazil [22]. In view of the lack of evidence in international and Brazilian studies of increased protection against tuberculosis by the use of this second dose, its application was suspended in 2006 in our country. Revaccination with BCG can put at serious risk patients with primary or secondary immunodeficiency [23]. It can bring significant risks also for unidentified HIV positive patients.

We are experiencing nowadays a true “infodemic” associated to COVID-19 pandemic and we need to deal with it by sharpening our critical analysis. The titles and scopes of scientific articles should be cautiously considered as they can promote indications of getting vaccinated or revaccinated with BCG, before its effectiveness is confirmed and recommendations are published.

It is important to note that the BCG trained immunity paradigm is based on experimental models, cohort studies with low number of individuals, and some epidemiological data in which other possible interfering factors are not controlled. The possibility that BCG vaccination could facilitate the long-term immune response to other pathogens is fascinating. Experimental models transferred from the lab to the bed can be useful. However, this hypothesis needs to be verified in real-life through robust clinical and epidemiological studies. Besides that, it may be real, but it can be a transient phenomenon, of short duration or weak effect.

Maybe BCG vaccine is effective in preventing COVID-19 deaths or reducing its severity, but may the effect of this vaccine be relevant even with poor health politics and assistance? It is very difficult to compare the epidemiologic data about COVID-19 in such different countries. There are differences in demographic and genetic structure of populations as well as many differences in the non-pharmaceutical interventions adopted. There are countless other factors, mainly social and related to the healthcare system, which can be more decisive than the hypothesis of trained immunity induced by BCG. Until now, we can say that BCG's protective role is, at least, insufficient, given many other factors that corroborate SARS-CoV-2 infection and/or its severity. Randomized clinical trials with appropriate methodology are needed before the use of BCG on a large scale is recommended.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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