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European Association of Urology

Editorial

COVID-19 and Bacillus Calmette-Guérin: What is the Link?

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Article info

Article history:
Received 28 March 2020

The outbreak of coronavirus disease 2019 (COVID-19) has rapidly led to a worldwide public health threat with devastating consequences not only in terms of the availability of resources for health care systems and providers but also because of the effects on social and economic stability. Similar to past viral pandemics and other emerging infectious diseases, COVID-19 has stimulated intense debate on current (and future) preventative measures, among which vaccination is one of the most prominent.

A topic of intense debate and a matter of scientific interest for future research is the role of bacillus Calmette-Guérin (BCG) vaccination in this emerging scenario. Since BCG is one of the therapies most commonly delivered by urologists, here we highlight some points that we think will be of interest to and guidance for practicing urologists.

Historically, BCG, a weakened strain of *Mycobacterium bovis*, has been used as a vaccine against tuberculosis. The vaccination is given to children in their first year of life in most countries across the world. The protection against active tuberculosis is variable among different countries and studies, but is estimated to be approximately 60% [1]. Vaccinations have been considered to function mechanistically by imitating pathogens, leading to an expansion of "memory" T lymphocytes and B lymphocytes that can combat future exposures. It has been thought that the innate immune system, compromising macrophages, natural killer cells, neutrophils, and other white blood cells, had no such memory to help combat future attacks. This hypothesis has been put to the test using BCG vaccination. Although nonspecific effects of BCG were suspected back in the 1970s [2], more recent work by Netea and colleagues [3–5] using BCG have shown that the innate immune system can develop "memory", which is termed *trained immunity*, through epigenetic reprogramming of different innate immune cell types. In both human and murine models they have shown that BCG vaccination can lead to trained immunity, which helps eliminate various non-mycobacterium infections including staphylococci, candidiasis, yellow fever, and influenza.

The innate immune system and trained immunity can be considered in the fight against bladder cancer, but more importantly in the fight against viruses including COVID-19 [6]. A small randomized study by Leentjens et al [7] showed that BCG vaccination before influenza vaccination in healthy individuals resulted in a significantly more pronounced antibody response against influenza A (H1N1) compared to placebo. These findings are the basis for the initiation of BCG vaccination trials to fight infections such as COVID-19. There are trials under way studying the effect of BCG vaccination to increase resistance to infections in the elderly population and to try and help prevent severe COVID-19 infection in health care workers.

At the time of writing, Europe is considered the epicenter of the COVID-19 pandemic. A map of the countries most affected in Europe shows considerable overlap with the map of countries without a national program of BCG

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https://doi.org/10.1016/j.euo.2020.04.001

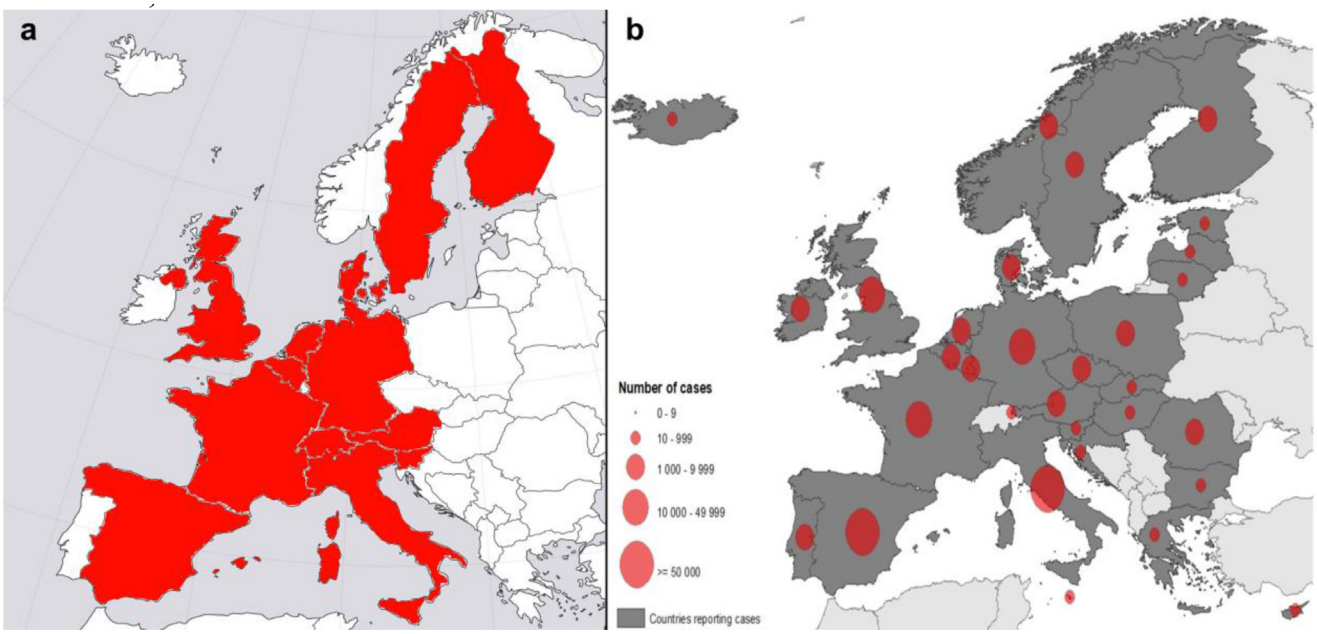

Fig. 1 – (A) Map of bacillus Calmette-Guérin (BCG) vaccination policy in Europe by country. Red denotes countries without a current BCG vaccination program. Data courtesy of the BCG World Atlas [10]. (B) Screenshot of a heat map of COVID-19 cases in Europe from the European Centre for Disease Prevention Control website [8] on March 22, 2020.

vaccination (Fig. 1). We used the European Centre for Disease Prevention and Control list of the number of cases and fatalities of COVID-19 in 179 countries on March 22, 2020 [8]. The population of each country in 2020 on *Worldometers* was used to calculate per million incidence and mortality data [9]. The crude case fatality rate was calculated by dividing the reported death rate by incidence. We examined these data by countries with a current program of whole-population vaccination according to the *World Atlas of BCG* [10].

On March 22, 2020, the daily incidence of COVID-19 was 4.5 per million population, with a fatality rate of 0.22 per million. Twenty-six of the 179 countries had unknown status regarding BCG vaccination, while 132 have current BCG vaccination programs and 21 have no national BCG program. We pooled the data into two groups according to countries with and without BCG programs. The daily incidence of COVID-19 was 0.8 per million in countries with BCG vaccination compared to 34.8 per million in countries without such a program. The mortality was 0.08 per million in countries with a BCG vaccination program and 34.8 per million in countries without a program. The crude case fatality rate was 4.1% in countries with BCG vaccination and 5.1% in countries without BCG vaccination.

These data are based on a report for a single day, March 22, 2020, and should be interpreted as hypothesis-generating in view of a number of confounding issues, such as differing stages of the pandemic and variations in testing and reporting across countries and likely underestimation of asymptomatic cases. Moreover, as the pandemic wave is now moving to the USA, where a stratified BCG vaccination program is under way, new important data will become available. Clinical trials have just been initiated and are likely to shed some light on the issue within a reasonable time.

As suggested by panels of experts [11,12], intravesical BCG should be continued during the COVID-19 pandemic because it remains the gold-standard adjuvant treatment for patients with high-risk non–muscle-invasive bladder cancer to prevent recurrence and progression [13]. To date, there are no reports that patients receiving intravesical BCG have a higher risk of contracting COVID-19. For induction therapy, US experts suggested that if a patient has had four doses, it is possible to wait a few weeks before receiving the remaining doses. The risk of contracting the virus when coming to a health care facility for this treatment is higher than any risk of delaying doses five and six for several weeks. If a patient is still on the third dose, the fourth dose should be given before delaying the remaining treatments. If patients are on maintenance therapy, receiving doses one and two and skipping dose three completely is acceptable [11].

For almost a decade urologists have been facing the issue of a worldwide BCG shortage that has limited the numbers of patients receiving adequate induction and maintenance, resulting in higher recurrence and progression rates [14]. Diverse solutions have been proposed [15–17]. A recent report published in *European Urology Oncology* is of utmost interest because of the possible implications in this scenario. In an in vitro study, Brooks and coworkers [18] assessed the viability of the TICE strain of BCG in terms of colony-forming units and demonstrated that viability remains constant for at least 8 h after reconstitution. While the viability at 24 h was lower, it did not decrease to a level below that of a one-third does of BCG and remained close to

50% for at least 72 h. Although the in vivo correlation remains theoretical at this stage, the implications could be immense, allowing more patients to be treated from a single vial.

Urologists have always been at the forefront of advances in medicine; here it is ironic that one of our oldest immunotherapies might help against the newest threat facing civilization.

Conflicts of interest: The authors have nothing to disclose.

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