ISSN 1669-9106

BCG *versus* COVID-19?

Countries where annual tuberculosis (TB) rates are lower than 10 new cases per 100 000 inhabitants are considered "low-burden" or with low TB incidence. The BCG vaccination policy targeting newborns and infants has long been discontinued in these countries, based on the high number of vaccinations that would be needed to prevent one TB case, what would render universal vaccination non-cost-effective. Instead, a vaccination strategy has been chosen which targets specific high-risk groups[1]. On the other hand, BCG vaccination of the newborn is a regular component of TB control programs in "medium" (25-50 new TB cases/100 000) and "high-burden" (>50/100 000) countries. The rationale for this is that by getting in contact with the host earlier than the virulent TB bacillus, the attenuated BCG protects from primary TB, in particular its meningeal and miliary forms, which are the cause of high mortality rates and serious sequelae. In Argentina, BCG vaccination demonstrated to provide 98% (70-100) protection from TB meningitis and other severe forms of primary TB[2, 3]. To achieve such efficacy, vaccination coverage must exceed 80%. In our country in 2018, with an incidence of 27/100 000 inhabitants, coverage reached 93%[4].

The estimated duration of protection by BCG when applied to newborns or infants is about 10 years, and it would extend to 15-20 years when applied at school age[5].

Research is ongoing aimed to develop a more effective vaccine, able to prevent secondary forms of TB (such as adult lung TB), boost immunity in already infected subjects who have some resistance acquired by their primary infection, and achieve a better cost-effectiveness ratio than the current BCG. However, although several candidate vaccines are currently under evaluation, none has met all these conditions so far[6].

It has long been observed that BCG vaccination also exerts nonspecific protection against leprosy, leishmaniasis, malaria, and other infectious diseases eliciting mechanisms of cellular immunity, as well as against certain forms of cancer[7-9].

Will the BCG vaccine then be able to prevent or attenuate disease caused by coronaviruses, including COVID-19? How strong is the association "more BCG less COVID-19"?

Researchers at the New York Institute of Technology postulate that the different impact of the COVID-19 pandemic on various countries could be partially explained by the different national policies on BCG vaccination[10]. In their ecological analysis, these authors found an inverse association between COVID-19 mortality rates and BCG vaccination policies in middle- and high-income countries. The observed correlation between the initiation of universal BCG vaccination and protection against COVID-19 suggests that this vaccine may confer long-lasting protection against the current strain of coronavirus. The article has been thoroughly criticized[11]. We point out here some of the inaccuracies it contains.

In the Summary, it is said that BCG vaccination would provide broad protection against respiratory infections. This has never been demonstrated. Later, it is stated that countries like Iran, which started BCG vaccination late (1984), have high mortality from COVID-19, which would be consistent with the idea that BCG protects the elderly population that had been vaccinated with BCG.

However, since the protection conferred by BCG only lasts about 15 years, this population that had been vaccinated in childhood would not be currently protected by BCG. Furthermore, a vaccination coverage higher that 80%, necessary to achieve the herd effect, was attained by Iran already in 1987. China also maintains stable > 80% coverage since 1987, *while India, the prototype of the non-specific protective effect of BCG, only reached 80% coverage in 2004*[4]!

Most Latin American countries had achieved 80% (or higher) BCG vaccination coverage for children under one year of age. Chile, Argentina, and Ecuador maintain > 90% coverage since 1985 or even earlier, and Brazil since 1992[4]. *However, the situation concerning COVID-19 varies among these countries*.

The article suggests that BCG vaccination would also confer some specific protection against COVID-19[10, 11].

Although it is not proven that BCG confers specific immunity against COVID-19, vaccinating people over 60 years of age, regarded as at higher death risk, could be considered, especially in settings with low TB incidence. If they have not had a primary TB infection and/or disease, they have not developed anti-TB immunity, which in turn includes a non-specific component: the "trained immunity", perhaps useful against coronaviruses, including COVID-19.

But we must remember that an unintended beneficial side effect may also occur with other vaccines, not just BCG, and that BCG is not a substitute for a specific vaccine.

Other publications associating BCG vaccination with lower mortality from COVID-19 are discussed in our *News* section, April 7 2020 (*www.medicinabuenosaires.com*)[12-14]. The note concludes*: At the moment, these associations support the idea that the BCG vaccine can provide protection against SARS-CoV-2, which, together with its proven safety, encourages the consideration of more detailed epidemiological studies, clinical trials, on a large scale, about the efficacy of this vaccine on COVID-19. These studies can provide data for the reformulation of health policies.*

In this sense, a project is at the initial stage in Australia, aimed to evaluate BCG-conferred protection against COVID-19 when applied to elderly people and health workers[15, 16]. Also, a joint Germany-India project has just started, where a vaccine called *VPM1002*, developed at the Max Planck Institute for Infection Biology and produced on a large scale at the Serum Institute in India will be tested for its probable protection against TB and COVID-19[17]. Health workers and groups of elderly population will be selected for vaccination. This approach could be useful until a specific active vaccine against SARS-CoV-2 becomes available.

Some issues deserve to be highlighted:

In countries with low TB incidence (< 10/100 000), where BCG vaccination is not in use, very few, if any health personnel have undergone a primary TB infection. Therefore, BCG vaccination can help to build natural immunity against COVID-19 and other pathogens in this high-risk group, due to the effect of trained immunity. It should be remembered that the immune system takes about 3 weeks to develop an optimal response.

Due to senescence, the immune system weakens in the elderly, and BCG can contribute to strengthening it, regardless of TB incidence. Even in low-incidence countries, TB infection is more common in the elderly. A fraction of this population may have even undergone TB disease, in adulthood or more recently, and still maintain natural immunity (memory), although variable by senescence. In these already infected subjects, BCG can produce an early nodule (tuberculin response), eventually of slow resolution, and the consequent doubts in health professionals about whether or not to administer anti-TB treatment.

In conclusion, in Latin American countries, BCG vaccination of newborns and infants under one year of age should be maintained and strengthened. BCG vaccination to protect health personnel and the elderly against COVID-19 could be considered, albeit with caution, due to the possible primary infection already existing in a proportion of them.

But at the difficult stage we are going through, the key strategy is the one currently in force based on social isolation and other protection measures for the groups at higher risk. We must adhere strictly to it at least until a SARS-CoV-2 vaccine and an effective specific treatment for COVID-19 become available.

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