

# New Insights in Aging Immunity and the BCG Vaccine

## Yaşlanma Bağışıklığı ve BCG Aşısı Konusunda Yeni Görüşler

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### ABSTRACT

Influenza and other respiratory tract infections are the main reasons for hospital admissions and death in the elderly. It is suggested that with the strengthening of the Th1 response by means of Bacillus Calmette-Guérin (BCG) vaccination may protect them from many viral infections, including influenza and Coronavirus disease-2019 in the elderly. This review suggests that in future in the event of an outbreak, the BCG vaccine may provide a more powerful immune response against new pathogens in the elderly when applied monthly in a consecutive period of three months.

**Keywords:** Aging, BCG, immunity

### ÖZ

Grip ve diğer solunum yolu enfeksiyonları yaşlılarda hastaneye yatış ve ölümlerin başlıca nedenleridir. Bacillus Calmette-Guérin (BCG) aşısı yoluyla Th1 yanıtının güçlendirilmesiyle, yaşlıların influenza ve Koronavirüs hastalığı-2019 dahil olmak üzere birçok viral enfeksiyondan korunmaları önerilmektedir. Bu derleme, gelecekte bir salgın durumunda, BCG aşısının birbirini takip eden üç aylık bir dönemde aylık olarak uygulandığında yaşlılarda yeni patojenlere karşı daha güçlü bir bağışıklık tepkisi sağlayabileceğini düşündürmektedir.

**Anahtar Kelimeler:** Yaşlanma, BCG, bağışıklık

## Introduction

The immune system loses its power with age and the dimension and volume of the lymphoid organs decrease. Histologically, fibrosis, fatty tissue and the number of germinal centers increase. Wound repair and healing are insufficient. The nervous system, endocrine system and immune system lose power simultaneously. The protective mechanisms of the immune system, both congenital and acquired, progressively weaken with aging. The performances of neutrophils, monocytes, macrophages, and dendritic cells decrease leading to total decrease in chemotaxis, phagocytosis and signaling process along with ageing.

Due to a decrease in the number and function of toll-like receptors, innate immunity signals have difficulty in reaching the levels that would be sufficient to activate

the adaptive immune system. The response of NK cells to inflammatory cytokines is decreased. When adaptive immunity is evaluated in the elderly, there is a decrease in the phenotypes, the number of receptors and components of T and B lymphocytes. The gradual regression and loss of function of the thymus impairs T-cell maturation. The T-cell repertoire decreases and the production of young T lymphocytes with receptor variations and heterogeneity become lower leading to a decrease in reactions against foreign antigens. The co-stimulatory signals such as B7-CD28-CTLA4 and CD40-CD154 pathways, which are important for antigen recognition and rejection/tolerance events, do not function in the elderly.

As the antigenic stimulation and memory function regulation are disrupted, antigen specific immunity decreases and the expected response to vaccinations may not occur. Also, the control of tumor production is impaired



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due to a decrease in immune control and weakened immune regulation. Telomers in the lymphocyte nuclei shorten with aging and DNA repair thus diminishes stimulation and proliferation properties of those lymphocytes regress. The production and number of young B lymphocytes in the bone marrow decreases, while the lifespan of old B lymphocytes increases. Correspondingly, there is a decrease in the variability and quality of the antibodies produced by B lymphocytes and their affinity to the antigen. So, there is a notable weakening in the humoral immune response due to the dysregulation of B lymphocyte activation and proliferation in the elderly leading to susceptibility to infections with high mortality (1). As stated before cellular protection also weakens with immunological ageing decreasing the number of CD3+, CD4+, and CD8+ T lymphocytes beginning from the age of 45-50, together with a substantial shrinkage of the thymus gland. In summary, in the elderly Th1 cells secrete a reduced number of cytokines (IL-2, IFN- $\gamma$  and TNF) where Th2 cytokine production (IL-4, IL-5, IL-10, IL-13) is higher and memory lymphocytes replace active lymphocytes which increase IL-10 production, an inhibitory cytokine.

In the elderly, these changes in the immune system suppress resistance to influenza virus infections and lead to a decrease in the protective effect of vaccines. Conversely, the response to autoantigens is augmented in the elderly, as immune system regulation is impaired and cancer and autoimmune diseases other than infections may be seen more frequently (2).

### Vaccine Immunology

One of the two pathways of the immune response against vaccines is congenital innate immunity, while the other is acquired immunity. The antigenic structure comprising the vaccine is foreign to the immune system and the immune system is correspondingly stimulated. The natural immunity elements recognize the dangerous part of the vaccine antigen through the "pathogen recognition receptor". Subsequently, the vaccine antigens enter the phagocytic cells via the Toll-like receptor-like receptors in the body. Antigen presenting cells activated by mediators of the phagocytic cells present the vaccine antigen to the T lymphocytes and then antibody production is triggered by the addition of stimulation of B lymphocytes. This is the first induction of an acquired immune response by vaccine antigen and when subsequent encounters with the same antigen occur, it will result in more powerful and rapid responses by the MEMORY function of acquired immunity (3).

Normally, a vaccine triggers pathogen specific effector mechanism and provides protection against that pathogen;

however, some attenuated vaccines may also provide protection against different molecules. Currently, the best example of this is the Bacillus Calmette-Guérin (BCG) vaccine.

### The BCG Vaccine

The BCG vaccine is a vaccine used for the protection from tuberculosis and includes attenuated *Mycobacterium bovis* antigen (2). BCG is known to provide protection against tuberculosis in addition to providing protection against acute respiratory infections. This non-active feature of the BCG vaccine is evaluated within the concept of "trained immunity". Trained immunity can be explained as the triggering of innate immune cells to induce the reprogramming of cells. This trigger may occur by causing epigenetic and metabolic changes in the hematopoietic stem cells in the bone marrow. Netea et al. (4) were the first to propose an explanation of the mechanisms of the non-specific effect and benefit of BCG vaccination as "trained immunity" (5).

Arts et al. (6) demonstrated that BCG vaccination provided protection against experimental yellow fever virus in humans through the reprogramming of the monocytes.

BCG vaccines have been in use since 1921 and "early" and "late" vaccine strains were obtained with the passaging of three vaccines (BCG, hepatitis B and polio) administered to newborn babies. The vaccine strains have different immunologic effects and virulence. Early vaccine strains are more effective immune stimulants since they contain methoxy-mycolic acid in the cell wall in contrast to late strains. Due to the mycolic acids, high levels of IFN-gamma, myeloperoxidase and TNF-alpha are produced by macrophages. Thus, mycolic acids may lead to trained immunity. Their ability to stimulate the immune system varies, depending on the BCG vaccine strain (7).

Conversely, BCG can have an immunomodulator effect on some malignancies, as in bladder cancer. As a result of immunization with BCG, Th1 lymphocytes secreting IFN- $\gamma$  and IL-2 cytokines are activated in people with bladder tumors, and the tumor shrinks as a result (8,9).

### BCG and Its Effect on Trained Immunity (Effect on COVID-19)

It has been suggested that one of the reasons for the low number of cases in Asian countries during the Coronavirus disease-2019 (COVID-19) outbreak could be due to BCG immunization. We know that the BCG vaccine can protect the elderly from acute respiratory infections (6). When examined in detail, the differences between Asian countries are conspicuous and it is suggested that these differences are due to the different "BCG vaccine strains". The BCG vaccine strains used in Japan and Russia trigger trained

immunity more powerfully than the strains produced in Iran and China. Another analysis revealed that as the Russian strain was used in Türkiye it had a higher impact on trained immunity and deaths per million of the population were lower compared to others (7). It would be crucial if the validity of this hypothesis continues in a newly encountered pandemics in the future.

### Protection from Pneumonia by BCG in the Elderly

In an article reported from Japan on the preventive effect of BCG vaccine against pneumonia, it was revealed that BCG strengthens the natural immunity and reduces the risk of pneumonia in elderly patients (10). The BCG vaccine has gained popularity, as pneumonia is seen frequently in COVID-19 (10).

Influenza and other respiratory tract infections are the main reasons for hospital admission and death in the elderly. Cytotoxic T-cells play a significant role in clearing the influenza virus from the lungs. Wardhana et al. (2) found a very high prevalence of acute upper rhino-pharyngo-laryngo-tracheitis (AURTI) by physical examinations of the nose, throat, and chest in a six-month observation study. In elderly individuals, scarring occurred in the areas where the BCG vaccines were administered once a month for three consecutive months, and AURTI was prevented in these individuals. The reason for this was the increased Th1 response demonstrated by the increased level of IFN- $\gamma$  and the suppression of Th2 cells. It is suggested that with the strengthening of the Th1 response, protection from many viral infections, including influenza and COVID-19, can be achieved in the elderly (2).

### Conclusion

In the event of an outbreak, the BCG vaccine may provide an efficient Th1 immune response in the elderly when applied monthly in a consecutive period of three months and that this may provide a powerful prevention from viral infections in the elderly.

### Ethics

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Concept: G.I., Design: G.I., A.K.Y., Literature Search: G.I., A.K.Y., Writing: G.I., A.K.Y.

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