

The potential of BCG as vaccine against infection with COVID-2019 in the elderly

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Radboud University Medical Center, Nijmegen, the Netherlands

Aim

To assess whether BCG vaccination influences the susceptibility and severity of the infection with 2019 novel coronavirus (COVID-2019).

Rationale

Bacillus Calmette-Guérin (BCG) was developed as a vaccine against tuberculosis, but many studies have shown its ability to induce potent protection against other infectious diseases: the so called non-specific effects (NSEs)¹. In a combined analysis of three randomised controlled trials (RCTs) in low- birth-weight neonates in Guinea-Bissau, BCG reduced neonatal mortality by 38% (95% CI 17%-54%)². This was not due to protection against tuberculosis, which takes months to years to develop, but rather due to protection against neonatal sepsis and respiratory tract infections³. NSEs of BCG are not limited to children, as a recent study in adolescents has shown a 70% decrease in the incidence of respiratory tract infections in individuals vaccinated with BCG compared to placebo⁴. In addition, a small Indonesian trial has shown that consecutive BCG vaccination for 3 months reduced the incidence of acute upper tract respiratory infections by 80% (95%CI=22-95%)⁵.

We have demonstrated that the non-specific beneficial effects of BCG vaccination are due to epigenetic and metabolic reprogramming of innate immune cells such as myeloid cells and NK cells, leading to an increased antimicrobial activity, a process termed 'trained immunity'⁶. In experimental studies, BCG has been shown to protect not only bacterial and fungal infections, but against viral infections such as influenza as well⁷. To assess whether this effect is exerted in humans as well, we recently performed a study in which placebo or BCG vaccinated individuals were administered yellow fever vaccine virus as an experimental model of viral infection. BCG vaccination resulted in a significantly reduced viremia, and improved anti-viral responses Figure 1⁸.

Hypothesis

Based on the capacity of BCG to: i. reduce the incidence of respiratory tract infections; ii. exert antiviral effects in experimental models; and iii. reduce viremia in an experimental human model of viral infection, we hypothesize that BCG vaccination may induce (partial) protection against susceptibility to and/or severity of COVID-2019 infection.

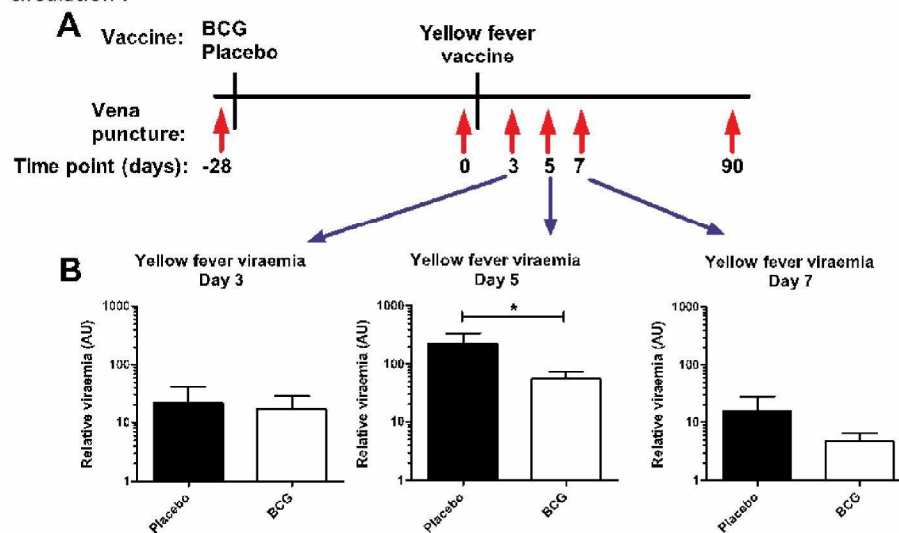
Approach

Randomized clinical studies of BCG vaccination in the elderly.

In areas in which there is ongoing active spread of the virus, we envisage a randomized study of placebo/BCG vaccination in elderly individuals, who represent an important population at risk:

- Elderly individuals above 70 years of age
- 1:1 randomization of BCG vs placebo
- 30% reduction in the incidence of respiratory tract infections by BCG vaccination
- Two groups of elderly individuals can be targeted:
 - o Study 1: Healthy elderly 70+ years old
 - o Study 2: Elderly population in nursing homes
- For each of the two studies, with 300-400 patients/arm, a budget between 500 – 600 k€ would be needed:
 - o Medical and lab personnel
 - o Costs of BCG vaccines
 - o Laboratory tests

Figure 1. A. Healthy volunteers were injected with either placebo (n=15) or BCG (n=15). One month later all volunteers were injected with yellow fever vaccine. B. Viremia was assessed on day 3, 5 and 7 after yellow fever vaccination by PCR in the blood. BCG vaccination significantly decreased the viremia in the circulation⁸.



References

1. Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol* 2013;34:431-9.
2. Biering-Sorensen S, Aaby P, Lund N, et al. Early BCG-Denmark and Neonatal Mortality Among Infants Weighing <2500 g: A Randomized Controlled Trial. *Clin Infect Dis* 2017;65:1183-90.
3. Hollm-Delgado MG, Stuart EA, Black RE. Acute lower respiratory infection among Bacille Calmette-Guerin (BCG)-vaccinated children. *Pediatrics* 2014;133:e73-81.
4. Nemes E, Geldenhuys H, Rozot V, et al. Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination. *N Engl J Med* 2018;379:138-49.
5. Wardhana, Datau EA, Sultana A, Mandang VV, Jim E. The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. *Acta Med Indones* 2011;43:185-90.
6. Netea MG, Joosten LA, Latz E, et al. Trained immunity: A program of innate immune memory in health and disease. *Science* 2016;352:aaf1098.
7. Spencer JC, Ganguly R, Waldman RH. Nonspecific protection of mice against influenza virus infection by local or systemic immunization with Bacille Calmette-Guerin. *J Infect Dis* 1977;136:171-5.
8. Arts RJW, Moorlag S, Novakovic B, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. *Cell Host Microbe* 2018;23:89-100 e5.