


## Comment

# Novel use of an old compound? Urologist-led Bacille Calmette–Guérin vaccine trials in the prevention of coronavirus disease 2019

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## Background and Biological Hypothesis

Amidst the ongoing coronavirus disease 2019 (COVID-19) pandemic, there is a hope for a vaccine to provide effective herd immunity for everyone's lives to return to normal. Several COVID-19 vaccines are under way, some of which have recently entered Phase III trials. Meanwhile, an age-old treatment in daily urological practice may find a novel role in the world's battle against COVID-19, until a COVID-19-specific vaccine is developed.

Intravesical BCG is well-known to all urologists for more than four decades as the 'gold-standard' adjuvant treatment to prevent tumour recurrence and progression amongst patients with high-risk non-muscle-invasive bladder cancer (NMIBC). However, BCG is foremost, an anti-tuberculosis vaccine. In addition to its protection against tuberculosis, some studies suggest that BCG vaccination might provide heterologous beneficial protection against unrelated infections, especially respiratory and viral infections in childhood. The mechanism is called 'trained immunity' [1]. A recent article in the 10 September 2020 issue of the *New England Journal of Medicine* remarkably details this concept of trained immunity, which is a *de facto* innate immune memory. The innate immune system, comprising among others of macrophages, natural killer cells and neutrophils, was supposed to have no such memory in contrast to the 'adaptive' immune system (T cells and antibody producing B cells). When vaccinated either with BCG or with other microbial components, subjects can see the baseline tone of their innate immunity increase, what Mantovani and Netea [1] call as leaving 'an epigenetic scar'. The long-term induction of a memory of the innate immune system has been shown to be due to transcriptomic and epigenetic changes affecting myeloid progenitors in the bone marrow.

## Recent Advances and Ongoing Trials Using BCG and Recombinant BCG Vaccines

The placebo-controlled Phase III randomised control trial ACTIVATE (ClinicalTrials.gov NCT03296423), recently

published in *Cell* on 1 September 2020, sought to explore whether BCG has similar effects in the elderly compared to previous studies that had suggested protection against infections other than tuberculosis in children. In this trial, patients ( $n = 198$ , mean age  $\sim 80$  years) were randomised to either BCG or placebo at hospital discharge and followed for 1 year. In this interim analysis, BCG vaccination reduced the incidence of new infections (25% for BCG [95% CI 16–36%] vs 42% for placebo [95% CI 32–53%]), primarily respiratory tract infections, and with no difference in adverse effects between groups. Furthermore, BCG was able to trigger a robust, non-specific, trained immunity compared to individuals who received the placebo vaccine [2].

While cross-sectional ecological studies need to be interpreted with caution, as there may be multiple unmeasured confounders, the geographical map of European countries less affected by COVID-19 on 22 March 2020 showed some overlap with the map of countries with national BCG vaccination programmes [3]. Given these encouraging immunological data and hypothesis-generating epidemiological data, BCG vaccination has logically been suggested as a possible agent to prevent, or decrease, the severity of COVID-19 [4].

At least 12 randomised studies worldwide are under way to investigate this possibility (Table 1), particularly in protecting front-line workers, including the BRACE trial in Australia (BCG Vaccination to Protect Healthcare Workers Against COVID-19, NCT04327206) and the BADAS (BCG As Defense Against severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2] Study) in the USA (BCG Vaccine for Health Care Workers as Defense Against COVID 19, NCT04348370). Several of these trials are led by, or have active support, from urologists. Dr Ashish Kamat from the MD Anderson Cancer Center in the USA is one of principal investigators for BADAS (<http://bcgbadas.org/>).

Improved vaccination strategies against tuberculosis have included new recombinant BCG (rBCG). The most clinically advanced vaccine is VPM1002, developed at the Max Plank Institute in Berlin. In this rBCG, the urease C gene is replaced with that of listeriolysin O. This pore-forming

**Table 1** Clinical trials utilising BCG vaccine or rBCG

Trial	Location	Population	BCG type
NCT04348370	United States	HCW	BCG vaccine
NCT04328441/2020-000919-69	Netherlands	HCW	BCG vaccine
NCT04362124	Colombia	HCW	BCG vaccine
NCT04350931	Egypt	HCW	BCG vaccine
NCT00417445/2020-001591-15	Netherlands	HCW	BCG vaccine
NCT04327206	Australia	HCW	BCG vaccine
NCT04384549/2020-001678-31	France	HCW	BCG vaccine
NCT04369794	Brazil	HCW	BCG vaccine
2020-001783-28	Hungary	HCW	BCG vaccine
NCT04373291/2020-001883-50	Denmark	HCW	BCG vaccine
NCT04379336	South Africa	HCW	BCG vaccine
NL8547	Netherlands	Elderly adults	BCG vaccine
NCT04439045	Canada	Police, EMS, HCW	rBCG VPM1002
NCT04435379	Germany	Healthy adults (>60 years old)	rBCG VPM1002

EMS, emergency medical services; HCW, healthcare workers.

protein, originating from *Listeria monocytogenes* [5], allows the escape of antigens into the cytosol and thereby enhances the T-cell immune response through the major histocompatibility complex (MHC) class I pathway in addition to the MHC class II. Preliminary data suggest that the rBCG VPM1002 may be more immunogenic and may be safer than BCG. This is why two large studies using this rBCG are underway against COVID-19, one in Germany (Study to Assess VPM1002 in Reducing Hospital Admissions and/or Severe Respiratory Infectious Diseases in Elderly in COVID-19 Pandemic, NCT04435379) and the other in Canada named COBRA (Principal Investigator A. Zlotta; Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 [COVID-19] Infection Rate and Severity, NCT04439045). Finally, the rBCG VPM1002 is currently also studied as intravesical therapy in NMIBC, in particular when BCG has previously failed [6] and the publication of Phase II data is expected in the near future.

The use of BCG in the prophylaxis or treatment of COVID-19 outside of controlled clinical trials is, of course, not recommended.

### Conflict of Interest

Dr Alexandre Zlotta, is the Principal Investigator of ‘Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 (COVID-19) Infection Rate and Severity, NCT04439045’ one of the trials mentioned in the submitted work. Dr Alexandre Zlotta, is a consultant for Verity Pharmaceuticals, the Canadian importer of VPM1002.

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Abbreviations: COVID-19, coronavirus disease 2019; MHC, major histocompatibility complex; NMIBC, non-muscle-invasive bladder cancer; rBCG, recombinant BCG; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.