



## Shortage in BCG Vaccine Impacts Bladder Cancer Treatment

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### Abstract

Bladder cancer is 8<sup>th</sup> most common cancer and 11<sup>th</sup> leading cause of cancer deaths annual. The current gold standard treatment for non-muscle invasive bladder cancer is intravesical BCG vaccine. However, current shortages have necessitated rationing of this life saving medication and affected the treatment of primary bladder cancer with great effect on patients.

### Introduction

The history of BCG begins with a history of tuberculosis- a disease responsible for more human deaths than any other single pathogen. It is estimated over 1 billion people have died from tuberculosis infection [1]. As a disease it is still amongst the top 10 leading causes of death worldwide, with over 1.6 million lives lost annually and an estimated 130 million people currently live with tuberculosis infection [2].

The responsible organism, *Mycobacterium tuberculosis* was discovered in 1882 by German physician Robert Koch, who was subsequently, awarded the 1905 Nobel Prize in Medicine [3]. However, it wasn't until nearly 40 years later a vaccine was created by French scientists Albert Calmette and Camille Guerin. The Bacillus-Calmette-Guerin (BCG) vaccine was created from a closely related organism, *Mycobacterium bovis* extracted from the infected udder of a cow with tuberculous mastitis. Serendipitously Calmette and Guerin discovered the bacterial pathogenicity weakened after attempts to stop the bacterial clumping using a growth medium containing ox tripe, glycerol and potato starch. However, it took another 13 years and 231 serial cultures to create a strain with low enough virulence to be used as a vaccine in humans [4]. The resultant strain is the same used in over 120 million infants and children to vaccinate against tuberculosis to this date.

The concept of using BCG vaccine as a therapy for human cancer arose from pathologists' observation of the lower rates of cancer seen in victims of tuberculosis at autopsy [5]. It was theorized that the infection stimulated an immune response that somehow targeted malignant cells. Given the potential benefit, BCG was the first used in humans to treat acute lymphoblastic leukemia in 1969 [6] and was subsequently used as an intravesical immunotherapy agent against bladder metastatic melanoma in 1974 [7]. This paved the way for the use of BCG against primary bladder cancer which was successfully demonstrated in 1976 [8]. In the intervening 40 years BCG has proven to be the most effective and contain the most favorable side-effect profile compared to intravesical chemotherapy agents [9].

Current indications for intravesical immunotherapy with BCG are for non-muscle invasive bladder cancer including carcinoma-in-situ (Tcis), non-invasive bladder cancer (Ta) and bladder cancer with invasion not beyond the lamina propria (T1) [9,10]. BCG therapy involves reconstitution of lyophilized BCG powder which is subsequently instilled into the bladder via a catheter for a duration of one hour, a process that is repeated weekly for 6 weeks during induction then monthly for 12 to 36 months as a maintenance therapy, and is remarkably similar to the protocol originally described [8,9].

### Discussion

The current shortfall in BCG supply results from a number of factors that impact the supply chain for production of the vaccine. One of these factors is due to Merck being the sole licensed producer of BCG vaccine in Australia. Previously Sanofi held the majority of market share for BCG production but ceased production after a number of contamination issues at their Canadian factory in 2012 leading to a temporary closure. Despite resuming production in 2014, Sanofi determined it was no longer viable to continue production and permanently ceased production in 2017 [11].

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This left Merck, which previously produced roughly a quarter of the market share of BCG to cover not only the gap left by Sanofi's departure but also accommodate the ever increasing demand for BCG due to the number of new diagnoses made. Despite increasing production by over 100 percent to 870,000 vials in 2017, the demand for BCG remains at over 1 million vials per year and rising, creating a significant shortfall [12].

Part of the problem is contributed to by the fact that Mycobacteria are a fastidious slow growing organism and are ill suited to rapidly scaling production. This stems from the long doubling time of the bacteria which is roughly 16 hours, compared to the doubling time of *Escherichia coli* which is a mere 20 min.

In order to ameliorate the impact of a BCG shortage, the American Urological Association released guidelines for the prioritization of BCG to patients based on diagnosis and staging [13], including the reducing in dosage to one half or one third of full dose for certain patients, increasing the indications for intravesical chemotherapies such as doxorubicin or mitomycin and as a last resort offering radical cystectomies to patients with high risk features.

In addition, the Therapeutic Goods Administration in Australia has granted permission for the importation of an alternative BCG vaccine for treatment of bladder cancer via the Special Access Scheme. Namely BCG-medac, produced in Germany by Medac.

Merck itself have altered the distribution of the BCG vaccine to ensure fair allocation and prevent stockpiling by allocating stock to countries based on historical demand as well to wholesalers within each country [12].

## Conclusion

The current shortage in BCG has the potential to have a serious impact on patients living with bladder cancer. The AUA guidelines provide a framework for rationing available BCG according to need; however this may lead to scenarios whereby patients are over treated, such as patients offered radical cystectomy for T1 disease with high grade features. This procedure entails significant risk of morbidity and mortality. In addition there is the potential for patients with non-muscle invasive bladder cancer to receive therapy that results in under

treatment including reduced dosage BCG or alternative intravesical chemotherapy that may be ceased prematurely due to a worse side effect profile. Despite the approval of alternative BCG vaccines there remains doubt about the efficacy of different strains given the high degree of variability demonstrated [14].

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