

## Are there differences among bacillus Calmette-Guérin (BCG) strains regarding their clinical efficacy in the treatment of non-muscle-invasive bladder cancer? The jury is still out but the answer is likely no

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The use of bacillus Calmette-Guérin (BCG) as an intravesical instillation has been a mainstay in the prevention of recurrences, as well as progression for non-muscle-invasive bladder cancer (NMIBC) and in particular, for high-risk disease.<sup>1,2</sup> Whether all BCG strains are equal, or some are more equal than others, as questioned by Noon et al,<sup>3</sup> has become critically relevant at a time of shortages in BCG supply. In Canada, BCG has been supplied by a limited number of companies (currently Merck only). With recent and previous shortages, whether the use of other strains of BCG for prophylaxis would result in similar outcomes is critical in order to increase the availability of BCG for patients and clinicians. We have reviewed the literature both in the tuberculosis, as well as in NMIBC fields. We conclude that, despite differences in genetic composition and immune responses induced, there is no robust evidence that different BCG strains would be associated with different outcomes. This holds true in terms of either protection against tuberculosis or for prevention of recurrence or progression of NMIBC.

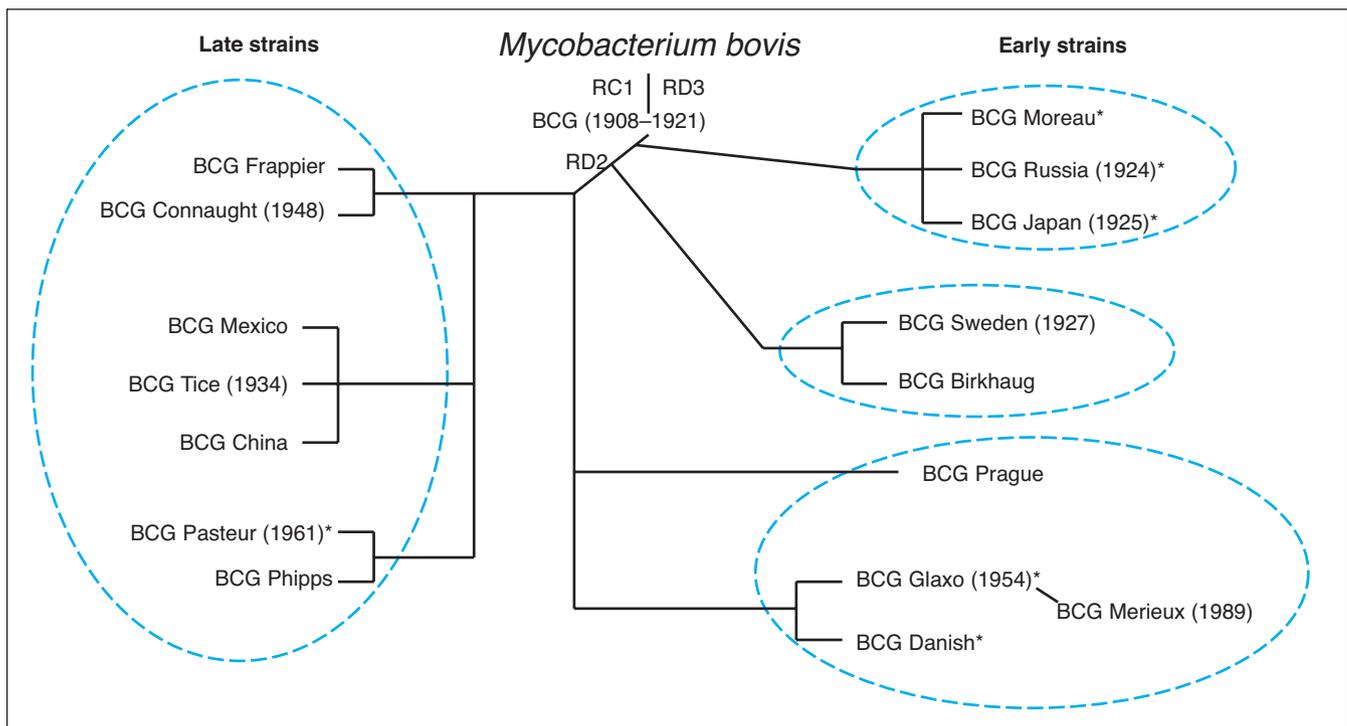
It's worth remembering that when mycobacterium bovis underwent the process of attenuation from 1908 to 1921 to become BCG, it lost one of the key regions, RD1. This was a critical step in its attenuation of the mycobacterium.<sup>4,5</sup> This loss of RD1 is common to all BCG vaccines strains, but these then went on to undergo a series of genomic alterations over time.<sup>6</sup> The various BCG strains can be grouped into early or late strains, as shown in Fig. 1, when they branched off the original BCG. Whether the genomic differences between the early strains (Japan, Moreau, and Russia), and the late strains (Frappier, Connaught, Tice, Pasteur, and Phipps) induce different immune responses and protection against tuberculosis is obviously a very relevant question. We, as urologists, should not forget that BCG was initially introduced to fight a

life-threatening disease affecting millions of men and women in the early 20<sup>th</sup> century, namely tuberculosis.

BCG vaccination against tuberculosis (the six approved strains by the WHO are Pasteur 1173 P2, the Danish 1331, the Glaxo 1077 [derived from the Danish strain], the Tokyo 172-1, the Russian BCG-I, and the Moreau RDJ strains) induces fairly different immune responses according to each particular strain.<sup>7</sup> This may or may not be in keeping with the broad variability in the protection against tuberculosis, which can vary from as low as 0–80%.<sup>8,9</sup> Recent large reviews of randomized control trials didn't support this hypothesis. The key message gathered from the tuberculosis literature is that despite obvious genetic variations and immune response in the host, especially between early and late strains, no study has shown the superiority of one strain over the other.<sup>7</sup>

In bladder cancer, the influence of BCG regimen, schedules, doses, and less often strain on outcomes has been investigated. Direct comparisons between BCG strains are generally lacking. Only one single randomized study<sup>10</sup> compared head-to-head in a small cohort two different strains. Interestingly, although there was a difference in terms of recurrence-free survival of a particular strain over another, the progression rate was actually not statistically different between the Connaught and the Tice strains.<sup>10</sup> Obvious differences between in vitro observations and clinical outcomes exist. For instance, in vitro the Connaught and Russian strains showed the highest direct anti-tumor effects among different BCG strains.<sup>11</sup>

Reviews focusing on this aspect have concluded that despite established genetic differences between strains used in the prevention of NMIBC recurrence and progression, no study supported the superiority of one strain over the others.<sup>12-14</sup> Whole genome sequencing studies taught us that early BCG strains like the Russian strain (used in India in NMIBC), displayed a complete stability of the vaccine substrate genome, whether these were investigated on lots from 1963–1982 or more recently in 2006.<sup>15</sup>



**Fig. 1.** Early and late strains of bacillus Calmette-Guérin (BCG).<sup>18</sup> \*Approved BCGs by the World Health Organization (WHO).

As a summary, not only have several of these BCG strains maintained their stability at the genome level, but differences, which are well-known between strains, never translated either as an anti-tuberculosis vaccine or in NMIBC into meaningful clinical differences. We believe that part of the explanation comes from the mechanism of action of BCG in the prophylaxis of bladder cancer recurrences/progression.<sup>16,17</sup> One should never forget that the doses we instill in the bladder are astronomical compared to the anti-tuberculosis vaccine. BCG are live, attenuated mycobacteria made of numerous subcomponents, which are both antigenic and able to induce very strong cellular immune responses.<sup>16</sup> The key word, as it often is in biology, is redundancy. Many subcomponents of the BCG, irrespective of the strain, are able to drive a robust and necessary TH1 response. This will ultimately lead to the elimination of tumor cells. Because so many components—from the BCG wall, membrane, or secreted by the live attenuated mycobacteria<sup>16</sup>—are able to unleash the immune cascade ultimately resulting in tumor cell killing, it is likely, given all the evidence that is available from the genetics, epidemiology, and clinical perspective, that the variability in sub-strains does not play a major role, if any at all.

We live at a time of shortages in BCG that may affect patients' management and when patients are in dire need of these intravesical treatments. The available evidence does not suggest that the introduction of established BCG strains

from other countries, which have produced adequate prophylaxis in NMIBC, would be in any way harmful or detrimental to the wellbeing of Canadian patients. Ideally though, more research to show equivalence between strains should be encouraged, as only one randomized study with a limited number of patients has addressed this specific issue.

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