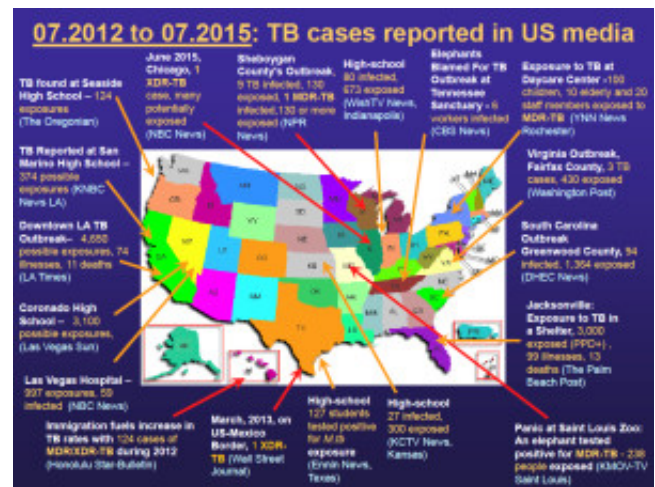


Why does BCG fail to protect against tuberculosis?

Mycobacterium tuberculosis (*M.tb*) is the microbe that causes tuberculosis (TB), a disease that kills one human every 18 seconds. In the last 80 years, only one vaccine has proven somewhat effective at preventing the development of TB disease, and mainly in children. This vaccine is called *Mycobacterium bovis Bacille Calmette-et-Guérin* or BCG.

Efforts to develop a new effective vaccine against TB continue, despite many promising vaccines failing even before entering human clinical trials. This plethora of ineffective vaccine candidates highlights our limited understanding on how the human body responds to prevent TB disease. One problem associated with TB vaccine development is the disparity between how vaccine candidates are tested in the laboratory (as controllers clearing the infection) *versus* human clinical trials (as preventers of TB disease; defined by clinical symptoms); two different concepts with two possible different readouts.



Here we explain some reasons why the BCG vaccine confers very limited protection against TB.

We focused on evaluating the current delivery mechanisms being used for BCG vaccination, on the differences of the many BCG strains being currently used for vaccination, the importance of specific human body responses, and how the environment within the human lung may influence the protective defense generated by BCG. Changing some of these factors could lead to improvements in the efficacy of BCG.

One important consideration is the route of BCG vaccination *versus* the natural route of *M.tb* infection. The natural route of *M.tb* infection is the respiratory tract. As we breathe, bacteria enter the deepest regions of the lung where they infect human cells. However, injection in the arm is the most common route for BCG vaccination. This disparity may be a prevailing factor behind the poor efficacy associated with BCG vaccination. Indeed, data support superior protection against TB if the vaccine is administered directly into the lung. However, undesired lung damage has prevented the development and use of direct TB vaccination of the lung.

A notable problem is the substrain diversity of the BCG vaccine. Following the first vaccination

trials in the 1920s, BCG was distributed to several laboratories across the globe. As continued growth of the original BCG strain lacked standardization guidelines, it resulted in the emergence of over 20 BCG substrains. Currently, public health officials are using different BCG substrains for international TB vaccination programs, leading to large variability in the observed protection against TB in different countries. Further research is needed to assess the differences between substrains to determine why some of them protect more against the development of TB than others.

Sophisticated TB vaccines, based on improving BCG, have been generated in many laboratories. They target certain aspects of host defense mechanisms, particularly communication between infected cells and cells that respond to the infection. However, no vaccine has yet been able to fully prevent infection, highlighting our limited understanding of the defense mechanisms required for protection against *M.tb* infection and the development of TB. In this regard, a major player contributing to generating the defenses against *M.tb* infection is the lung environment. There is nothing known about how this environment may impact the efficiency of any vaccine developed against TB. We conclude that in order to develop a successful TB vaccine, we should first direct our efforts on understanding how human body defenses are built-up and work together against the development of TB, including the contribution of all the factors above discussed.

Publication

[Prospects in *Mycobacterium bovis* Bacille Calmette et Guérin \(BCG\) vaccine diversity and delivery: Why does BCG fail to protect against tuberculosis?](#)

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