MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Frequently Asked Questions

What is the BCG vaccine and how safe is it?
BCG is short for bacillus Calmette-Guerin and is a vaccine for tuberculosis. BCG is a live attenuated bacterial vaccine that contains the avirulent bovine tuberculosis strain *Mycobacterium bovis*. The BCG vaccine is a safe derivative of a strain of a mycobacterial organism. More than 100 years old, the vaccine was originally developed and is still used on a global basis to prevent tuberculosis in high-risk countries. Interestingly, mycobacteria have co-evolved with humans for over 100,000 years, but with today's cleaner modernized human environments, this mycobacterial species is typically not found within humans. This has led many to believe the "Hygiene Hypothesis" of why autoimmune diseases and allergies are on the rise in civilized countries – that humans may have lost evolutionary advantages conferred by living with safe versions of mycobacteria. Over the past century, more than 3 billion people worldwide have received the BCG vaccine, typically at birth. The World Health Organization has heralded BCG as extremely safe as there are few side effects in healthy non-immunosuppressed individuals.

What is effect of the BCG vaccine on the immune system?
It is well established that BCG boosts a cytokine called tumor necrosis factor (TNF). In autoimmune diseases, TNF is beneficial by directly eliminating self-reactive white blood cells (the autoreactive T cells that attack the pancreas in type 1 diabetes) as well as inducing beneficial immune cells called regulatory T cells (Tregs). BCG resets the immune system back to normal immunoregulation. Furthermore, recent data reports that BCG accomplishes this at the level of the patient's DNA, perhaps explaining why limited vaccines doses can have such a durable clinical effect.

How does the BCG vaccine help type 1 diabetics regulate blood sugar?
The specific impact of repeat BCG vaccination on blood sugars in humans is driven by a novel mechanism – a systemic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis (a state of high cellular uptake of glucose) on a tightly regulated level. Glucose uptake and its regulation at the cellular level prevent the potentially lethal hypoglycemia that can be induced by insulin treatment, since the cells stop transporting sugar when blood sugar is in the normal range, resulting in a lowered HbA1c.

What is the significance of Hemoglobin A1c (HbA1c)?
HbA1c refers to a glycated hemoglobin test that is a measure of overall average blood sugar levels over a three-month period. Higher HbA1c is directly correlated with greater risks of developing diabetes-related complications such as blindness, heart attacks, strokes, and renal failure. A significant lowering in HbA1c is a primary endpoint for diabetes clinical trials.

Is this a cure for type 1 diabetes?
We do not label BCG as a cure for type 1 diabetes. No patients in our clinical trials have had their diabetes reversed completely or come off of insulin entirely. Our Phase I trial, which involved limited doses of the vaccine, demonstrates that BCG vaccination creates a lasting blood sugar reduction that is not commonly or safely possible with insulin alone.

How can I enroll myself or my child in a clinical trial using BCG?
We are currently enrolling a Pediatric Trial for children between the ages of 8-17. To learn more about the enrolling pediatric groups and a list of the full participation criteria, please see our postings on clinicaltrials.gov (NCT05180591 and NCT05866536). We are not currently enrolling for any adult clinical trials. If you believe your child may be eligible for the Pediatric Trial, or if you would like to be notified if we open enrollment to adult groups, please register your interest here to hear from us directly. If you have already registered with us and would like to check in, please email us at diabetestrial@partners.org or call 617-726-4084.

How many patients are involved in the BCG clinical trial programs at MGH?
The MGH clinical trial program has been underway for more than 10 years. There have been hundreds of patients – diabetic and control – involved in treatment, placebo, reference and additional study groups for the laboratory and clinical studies. The patients that received BCG in our clinical trials have not experienced major complications nor severe hypoglycemic events compared to placebo groups with long term observations. As of July 2023, we have enrolled approximately 70 pediatric patients that have received two BCG or placebo injections, with more enrolling each week! We plan to enroll a total of 250 pediatric patients.

What is the status of the adult Phase II BCG clinical trial?
The adult Phase II clinical trial will conclude later in 2023 and we are eager to analyze and report the results as soon as we can. This trial included 150 adults with longstanding type 1 diabetes - 100 received six BCG injections over five years, and 50 received six placebo injections over five years.

Where are the BCG clinical trials conducted? Are there multiple clinical trial sites?
The BCG clinical trials are conducted in the Immunobiology Lab at MGH – East. We are located in building 149 near the Charlestown Navy Yards. Boston is currently the only clinical trial site in the United States evaluating BCG in type 1 diabetes.

How long have the patients in your trials had diabetes? Will BCG be viable for everyone with type 1 diabetes?
There are two cohorts of patients in the current Pediatric Trial: children that have had diabetes for at least two years, and children that have had diabetes for at least three months but less than one year. In our adult clinical trial, participants had disease duration ranging from 3 to 41 years at the time of enrollment. We plan to explore differences in how BCG works in those with varying lengths of diabetes duration as we analyze the Phase II data and at the end of the Pediatric Trial.

What are the disadvantages of repeat BCG vaccines and who might not qualify?
Like any live attenuated vaccine, the BCG vaccine cannot be given to someone on immunosuppressive therapy nor to anyone on high-dose steroids. The vaccine requires a normal immune system to be effective and safe. In both type 1 diabetes and multiple sclerosis trials, the BCG vaccine has taken several years for observable clinical effects to appear like lowering of HbA1c or changes in brain disease activity. This is similar to the original disease process of autoimmunity which is known to take a number of years to develop. But the clinical effect in these human trials appears to be durable and long lasting beyond five-year observation periods.

Are all the strains of BCG the same?
BCG strains vary significantly from country to country, and it is known that many strains of BCG are not efficacious against autoimmune diseases.

I have one or more autoimmune diseases. Can BCG help my other autoimmune diseases?
We know there are clinical effects of BCG vaccination in multiple sclerosis, and there are studies ongoing in Italy. Our current focus is solely type 1 diabetes, but we may begin trials in other autoimmune diseases in the future.

What were the key results of your published Phase I study?
The BCG-treated patients showed a durable and statistically significant lowering of HbA1c, the primary clinical marker used to evaluate diabetes therapies that measures average blood sugars. The vaccine also demonstrated no safety issues when used in type 1 diabetic participants.

Where can I find your current publications?
All our papers are publicly available on our website's publications page.

Are your studies controlled for changes in treatment or external factors such as exercise?
In addition to treatment and placebo groups, the studies included large reference groups to help control for changes in treatment and external factors. Several analyses were done to estimate the probability that receiving the BCG vaccine led to an improvement of blood sugars after 8 years as measured by a lower HbA1c level. The statistical tests designed to assess whether this result could have been found by chance found that the studies were highly statistically significant.

How does this durable clinical response compare to data from treatment utilizing insulin pumps and continuous glucose meters?
Insulin delivery by any mechanism will lower blood sugars, but unfortunately insulin alone can continue to lower blood sugars to ranges below normal, risking potentially lethal hypoglycemia. With insulin alone, the safe lowering of HbA1c requires a delicate balance between enough insulin to lower blood sugars but not enough to cause hypoglycemia, which can lead to brain damage or coma. Continuous glucose monitors and insulin pumps can help maintain this balance but are expensive devices that need to be attached to the body and require continuous monitoring. Because of the risks of hypoglycemia, the target HbA1c with insulin pump usage is generally limited to 7 percent. The data from our Phase I trial shows that repeat BCG vaccinations can bring HbA1c down into the

6 percent range without additional mechanical devices and without continuous human-mechanical interface.

How does the amount of insulin used with BCG compare to insulin usage with continuous glucose meters and insulin pumps?
In general, the use of insulin pumps and continuous glucose meters increases the daily use of insulin. In contrast, the lowering of HbA1c with BCG vaccination has not been associated with increased insulin needs and in most cases is associated with decreased insulin usage. We did not design the Phase I trial with repeat BCG vaccines to see if patients could stop taking insulin. That question will be tackled in the upcoming Phase II analysis and the ongoing Pediatric Trial.

Are patients in this trial still using insulin?
At this point, we do not expect patients to completely stop using insulin for extended periods of time. We have documented incidences of patients significantly reducing or temporarily stopping insulin use for varying time periods. These are observations not clinical trial outcomes. The Phase II Adult and Pediatric Trials closely monitor insulin use in all patients.

Is this data consistent with that of the Italian trials in multiple sclerosis, another autoimmune disease being treated with BCG vaccines in clinical trials?
Yes, the positive clinical impact of BCG that we report in type 1 diabetes patients is very similar to the clinical data being observed in new-onset multiple sclerosis patients treated with BCG. In the completed Phase II multiple sclerosis clinical trials, BCG-vaccinated patients similarly showed a two- to three-year delay in the clinical effect and since then, as in type 1 diabetes, have shown a durable and persistent clinical effect lasting greater than five years without the need to revaccinate.

Do you recommend all type 1 diabetics take BCG now?
We do not recommend that anyone take BCG for diabetes, nor do we recommend any "off label" use of BCG. These results are reports from clinical trials and should not be confused with approval from the FDA.

Can BCG prevent type 1 diabetes?
There are interesting studies looking at the historic effects of multiple BCG doses on the incidence of type 1 diabetes in Turkey and Greece. Large pediatric trials are also underway in Australia and Denmark to look at the impact of this drug in resetting the immune system in allergies and in preventing other infectious diseases. The prevention question is partially answered in the Turkish study, in which BCG vaccination dosing could be from 0 to 3 vaccines and there was less diabetes incidence among participants receiving 3 vaccinations. There is also developing data in Greece on whether a childhood BCG vaccine changes the age of onset of diabetes.

Does BCG work in type 2 diabetes?
There is growing evidence that BCG may play a role in metabolic disease, including type 2 diabetes. That data is extremely early but is a mechanism we are very interested in exploring more of in the future.

Could BCG be combined with other therapies?
How to improve and complement the immunoregulatory effect of BCG will be one of the great questions we hope the diabetes community will help us answer. We believe we have demonstrated a mechanism and new basis for beginning a novel type 1 diabetes therapy. Complementary interventions that spur regeneration of insulin-producing cells or long-lasting/low-level insulin dosing options are all very interesting.

Who supports this work? How do I donate to this program?
Our work has relied almost entirely on donations from individuals and family foundations. Donations are critical to sustaining and growing the clinical trial program and are sincerely appreciated. The rate at which these trials can move forward, as well as expanding research into more type 1 diabetic participants, is limited by funding since formal clinical trials with FDA oversight are expensive. If you are interested in supporting this work, please see our donation page to make a gift or learn how to organize a fundraiser event in your community.