In the spring of 1721, Reverend Cotton Mather received frightening news: A sailor from the HMS Seahorse had landed in Boston with smallpox and spread the contagion throughout the city. As the number of afflicted people multiplied, Mather was concerned about the safety of the townspeople, the members of his congregation, and his own children. He had an idea on how to combat the growing epidemic, but it would stir up fierce opposition and endanger his life.

On May 8, town government leaders quarantined the ship in Boston Harbor, and homes with sick residents had guards posted at their doors. Despite these measures, within two weeks, eight more cases appeared throughout Boston. The government had no option other than to let the disease run its course, which meant hundreds of people would die. About a thousand citizens fled when they learned of the growing outbreak. Mather would not give up so easily.

Mather had learned about inoculation from both a slave and a journal published by the British Royal Society, a group of scientists of which he was a member. The procedure involved mixing live smallpox virus with the blood of a patient, who would then suffer a less deadly form of the disease and acquire immunity. When he had learned about inoculation five years earlier, Mather had pledged to himself, “If I should live to see the smallpox again enter into our city, I would immediately procure a consult of physicians to introduce a practice, which may be of so very happy a tendency.”

Smallpox was one of the deadliest diseases in Colonial America. The disease would spread through port cities about once a generation when a population that had not been exposed to the disease enough to develop an immunity existed. Although inoculation existed in parts of Africa, the Middle East, and Asia, the procedure was not used in Europe or America.

In 1721, Puritan minister Cotton Mather and physician Zabdiel Boylston attempted to introduce the procedure to save lives during a smallpox epidemic in Boston. Despite great opposition, they proved that inoculation was a viable medical procedure.

Over time, inoculation slowly became popular in the other American colonies. Although it would continue to arouse animosity wherever it was introduced, the medical discovery saved thousands of lives in Colonial America. By the time of the Revolutionary War, General George Washington would order the procedure for his troops and those wishing to enter the Continental Army.
In June 1721, Mather resolved to introduce the procedure to Boston and proposed the idea to the city's doctors. However, they refused to attempt it because they feared it would contribute to the plague. They also did not want to interfere with what they perceived as God's will in bringing the disease, and doubted Mather's information because it was from a slave.

Mather persisted despite the opposition, and eventually persuaded Dr. Zabdiel Boylston to try inoculation on his own son and two slaves; all survived. In July, several people came to Boylston to be inoculated, but hostility to the procedure grew as doctors published newspaper articles and pamphlets against it. The town government ordered Boylston to stop inoculating people, but he ignored them—he was saving lives.

While the debate raged in newspapers and pamphlets, the death toll mounted. Eleven Bostonians died in July, and 26 the following month. Fear gripped the city, and social interaction ended as people shut their homes against the disease. Businesses closed, boatmen refused to bring firewood, and attendance at church services fell.

Mather prayed for hundreds of sick members of his own congregation. He was the target of abuse from doctors and town publications. In August, a young Benjamin Franklin and his brother, James, started an anti-inoculation newspaper that published attacks on the minister and his medical efforts. Mather faced personal worries when his son returned from Harvard and wanted to get inoculated. Weeks later, he lost a daughter to a fever unrelated to smallpox.

Mather tried to cling to his purpose, but he felt besieged. He complained that his opponents mercilessly attacked him and Boylston. “They rave, they rail, they blaspheme. ... And not only the physician who began the experiment, but I also am an object of their fury – their furious obloques and invective.” He did not quit, however.

The smallpox death toll reached 101 in September, and more than 400 in October. Thousands of Bostonians were afflicted. Furious townspeople confronted Mather in the street and accused him of contributing to the deadly outbreak. Mather and James Franklin angrily met in the street one day in early November and exchanged irate words.

A few days later, an unknown person hurled a homemade bomb through a window of Mather's home. The inhabitants, including some recovering inoculation patients, were startled awake by the breaking glass, but the bomb failed to explode. It carried a note that read, “Cotton, you dog. ... I'll inoculate you with this, with a pox to you!” Mather confided to his diary that he felt like a victim, but he was not to be diverted from his purpose.

The disease faded with the arrival of winter. Mather and Boylston's program resulted in the successful inoculation of nearly 250 volunteers, only six of whom may have died from the procedure. Nearly 1,000 Bostonians who refused the treatment died from the epidemic. An unlikely alliance between a minister and a doctor led to the first inoculation attempts in the American colonies. Mather's purpose and drive to save lives through the procedure strengthened him to persist, even when his life was threatened and the majority of people thought he should stop.