Plague researchers race to beat bioterrorists

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This is Dr. Steve Smiley of the Trudeau Institute. Credit: Trudeau Institute Archives

Given the many pressing concerns of the day, fear of plague probably isn't what causes most Americans to lose sleep. But for those whose responsibility it is to combat bioterrorism, plague is among the highest priorities. Those charged with that mission include scientists like medical researcher Steve Smiley, whose lab at the Trudeau Institute is working to develop a vaccine that will protect the public against weaponized forms of plague. The Institute, which is dedicated to studying how the immune system responds to infectious diseases, is at the forefront of an international effort to protect the public against an ominous foe, whose very name conjures up images of widespread suffering and death.

Caused by the organism Yersinia pestis, plague is a severe and potentially deadly bacterial infection most often spread by rodents. Although rare in the United States, there have been outbreaks of plague in California, Utah, Arizona, Nevada, and New Mexico. Humans typically contract the disease from fleas that spread the bacteria from infected animals like rats, but plague can also spread from human to human, transported in the air through the coughs of the infected.

While plague is usually sensitive to antibiotics, the governments of the United States and Great Britain are concerned that weaponized plague would likely resist such treatment.

During the Middle Ages, resourceful armies hurled plague-infested bodies over castle walls to spread disease and fear, and it is widely believed this early form of biowarfare initiated the "Black Death," the plague pandemic which decimated a third of Europe's population. During World War II, the Japanese experimented with germ warfare by dropping plague-infested fleas on the Chinese. And the former Soviet Union's biowarfare division produced bombs designed to release plague-causing bacteria into the air above American cities. A World Health Organization study concluded that the detonation of a plague "bio-bomb" over a city of five million could cause 150,000 cases of pneumonic plague, leading to 36,000 fatalities.

Small, natural outbreaks of plague continue to this day, and it remains among the deadliest of infectious diseases. Yet there continues to be no effective and reliable vaccine against the disease.

Both the United States and the United Kingdom are funding research aimed at developing an antibody-based vaccine against plague. Why antibodies? Antibodies are special proteins produced by the immune system in response to foreign invaders like bacteria, viruses and other microbes. After the immune system utilizes an antibody to fight off a

dangerous pathogen, it retains a "memory" of the invader, so the relevant antibody can be rapidly reproduced should it encounter that same pathogen in the future. Many vaccines work by simulating exposure to a pathogen, thereby training the body to quickly generate the appropriate antibodies.

Several years ago, however, an enigma arose when the U.S. Army tested the leading plague vaccine candidate in two types of primates. Both produced similar amounts of antibody, but vaccination protected one type of animal much better than the other. Unfortunately, it's not clear whether humans are more like the primates that were, or were not, protected. Most likely, humans will exhibit a range of responses, some similar to the one type of primate and some closer to the other.

In the current issue of the journal *Vaccine*, Dr. Smiley's research group publishes data that may help unravel this enigma and provide a way to predict who will be protected with the plague vaccine being developed by the Army. In collaboration with the U.S. and U.K. militaries, as well as the Northeast Biodefense Center, they have shown that antibodies receive help from another part of the immune system when they protect against plague. Dr. Smiley's laboratory has focused its efforts on pneumonic plague, the form of the disease that attacks the lungs. (Bubonic plague infects the lymph nodes; Septicemic plague infects the blood.)

Using a mouse model of pneumonic plague, they showed that antibodies work together with "cytokines" (proteins used by cells to communicate with one another) to control plague. There are many types of cytokines, each conveying distinct messages to cells that bear cytokine receptors on their surfaces. The two types of primates used in the plague vaccine studies almost certainly produced different amounts of cytokines. "This paper should encourage researchers to determine whether differences in cytokine production may explain why one was better protected than the

other," said Dr. Smiley.

The Smiley lab is now working to produce an improved plague vaccine, one designed to leave the immune system with a memory that instructs it to produce both antibodies and the right mix of cytokines when it encounters plague.

Provided by Trudeau Institute