Jeffery Taubenberger remains hopeful that the 1918 flu virus will hold the key to controlling future pandemics.

How did he come to recreate the virus? By Jeanne Lenzer

Jeffery Taubenberger has been simultaneously criticised for peering into Pandora’s box and extolled as the archetypal virologist credited with “solving the greatest medical mystery” of our time. In 2005, after 10 years of painstaking work, Taubenberger reconstructed the virus that caused the 1918 flu pandemic. The virus was an H1N1 strain that infected almost one third of the global population and killed an estimated 40-100 million people in a matter of months—more than the two world wars, the Korean war, and the Vietnam war combined. Even the black death in the 14th century didn’t cause that much carnage in so short a time.

Taubenberger, a pathologist and currently a senior investigator at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, conducted his research while working for the Armed Forces Institute of Pathology. His quest to reconstruct the virus’s genome triggered protests from groups such as the now defunct Sunshine Project, which monitored biological warfare and the military abuse of biotechnology. In 2003, the group issued a report charging that Taubenberger was able to produce organic molecules. “You don’t create a threat in order to justify defences against it.”

Taubenberger, 46, responds to the charges evenly. He understands the worries. But he also knows the dangers of not doing the research. “I want to know what made this virus so virulent,” he says. And why, he asks, did the 1918 virus kill so many people in their 20s and 30s when most seasonal flu deaths are confined to infants and elderly people? He believes that unlocking the secrets of viral mutation and adaptation could open the door to finding vaccines and drugs that target a universal pathway common to most if not all pandemic influenza viruses. “I want to know,” he says, “how does a virus that is adapted to live in the intestine of a duck become a virus that can be sneezed out of your nose? Which mutations are necessary for influenza virus to go from one person’s sneeze to another person’s lungs?”

While his decision to resurrect the 1918 virus is controversial, there is little dispute among top flu experts that another pandemic will occur—the only question is when. Although some experts say that modern medical care will limit the number of deaths, Taubenberger cautions against complacency. Despite vaccines, antivirals, and social distancing, 500 000 people still die worldwide each year from seasonal flu. Even antibiotics, which weren’t available in 1918 to treat the many patients who died from secondary bacterial infection, may not alter the outcome, says Taubenberger. “We just don’t know the answer to that,” he says. In order to prevent another 1918-style global catastrophe, we need to study the organism that caused the catastrophe.

**Early influences**

Taubenberger came to the attention of scientists at the National Cancer Institute at just 12 years old. For his ninth grade science project, he recreated the Stanley Miller experiment mimicking the way organic molecules, such as amino acids, are thought to have originated from the inorganic molecules of primitive earth. Using inorganic substances, hydrogen, methane, and water, and applying an electric charge, the young Taubenberger was able to produce organic molecules. The institute scientists, particularly the well known microbiologist William Drohan, took him under their wing and encouraged him to conduct further experiments at the institute, and by the age of 16 he was working there part time.

Under Drohan, Taubenberger conducted research on a retrovirus thought to cause breast cancer in mice. Molecular biology was just emerging at the time and he was excited to be able to use cutting edge laboratory techniques and rub shoulders with scientists in the field. With encouragement from Drohan, he completed a joint MD-PhD programme at the Medical College of Virginia. After that he took a research intensive, four year pathology residency at the National Institutes of Health.

For Taubenberger, who wanted to be a bench scientist, the detective work of pathology offered the nearest thing to basic science research. He loved scrutinising pieces of human tissue and hunting for the cause of disease. He relished the progression of his specialty from one in which the gross architecture of tissue was simply observed under a microscope to a deeper understanding as a result of the development of biochemical tests, and from there, to an even more profound understanding of disease processes on a molecular level. As a pathologist, he realised he could go beyond helping individual patients to helping prevent or cure disease in thousands, even millions, of future patients.

**Reconstructing the 1918 virus**

After his residency, Taubenberger moved to the Armed Forces Institute of Pathology in Washington, DC, where he eventually became chief of the department of molecular
pathology. It was there, in 1995, that he and his colleagues hatched the plan to find the cause of the 1918 flu pandemic.

The computerised records of human tissue specimens stored at the institute contained about three million specimens dating back to 1917. He scoured the database but found fewer than 100 samples from 1918 flu victims. Of those, only three still bore any trace of the virus. To make matters worse, what little viral material remained in the 80 year old specimens was in tatters. Of the 14,000 base pairs of nucleotides that comprise the eight genes of the 1918 virus, only tiny fragments of about 100-120 base pairs remained. Taubenberger faced the daunting task of isolating the fragments and piecing each stray bit of the viral puzzle back together. Some doubted it could be done. Others continued to argue it shouldn’t be done.

In 1997, two years into his mission, he received an unexpected boost. Retired San Francisco pathologist, Johan Hultin, contacted Taubenberger after reading an article in Science about his work. As a doctoral student, Hultin travelled in 1951 to Brevig, Alaska, where 85% of the adults had died during the 1918 flu pandemic. He wrote to Taubenberger offering to return to Brevig and dig up the bodies, as he had done 46 years earlier. Taubenberger readily agreed. But when some observers got wind of the project, the reaction was severe. Michael Greger, director of Public Health and Animal Agriculture at the Humane Society of the United States and the physician who later credited Taubenberger with solving “the greatest medical mystery” of our time, was dismayed by the lack of biosecurity. Greger says, “I have a picture of Hultin kneeling over Lucy [one of the exhumed bodies] and he doesn’t even have a mask or gloves on.”

Taubenberger says of his controversial agreement with Hultin: “We had no lawyers. This was just a collaboration between two pathologists.” Taubenberger insists, “We were not being cowboys . . . No one up my supervision chain in the Department of Defense had concerns about the 1918 project.” Part of the reason he believed the risks were “next to nil” is that when Hultin had previously exhumed the same grave site he was unable to grow anything despite having the equipment and knowledge to culture influenza viruses. There was simply no chance of retrieving whole virus, he says. The best he could hope for were more viral fragments.

Whatever the risks of exhumation, the risks of reconstructing the virus and bringing it back to life brought fresh accusations. Ed Hammond from the Sunshine Project says, “Jeffery Taubenberger created a huge problem. Now the Department of Defense and [federal Department of Health and Human Services] have to develop a defence against the 1918 flu and we never had to do that before.” Even if the virus could be safely locked up indefinitely, its resurrection, Hammond and other critics argued, would be a pyrrhic victory. Flu viruses mutate so rapidly that vaccines against seasonal flu that are made in February can be useless by November. What benefit would a vaccine provide against an 80 year old virus that has mutated many times over? And why bring a dead virus back to life in order to defeat it when it had already been defeated by nature itself?

But the risk of the 1918 flu virus accidentally escaping its confines in high containment laboratories or of getting into the wrong hands, says Taubenberger, is extremely low—so low that he and his colleagues believe the potential benefits of reconstructing the virus outweigh the risks. Besides, he says, smallpox, Ebola, and other deadly viruses are also characterised and held in secure labs.

Should the 1918 virus ever escape to infect humans—or if Taubenberger or his protégés do find the cure for pandemic flu—there will be plenty of hindsight to go around. Peer ing into the future is a less certain matter. To date, the payoff for his decade long quest remains elusive. Says Taubenberger, “We had the sequence on paper and we still couldn’t answer the fundamental question of why did this virus kill tens of millions of people? There weren’t any obvious answers just by looking at it on paper . . . It looked just like any other influenza virus.”

Taubenberger is anxious to continue his quest for answers. Should another serious pandemic occur, says Taubenberger, those left behind will surely demand to know why research wasn’t done to prevent a catastrophe. They will ask, “Who was minding the store?” It’s a weight Taubenberger feels daily. Jeanne Lenzer is a medical investigative journalist, New York jeanne.lenzer@gmail.com Competing interests: None declared.

Cite this as: BMJ 2009;338:b264

“How does a virus that is adapted to live in the intestine of a duck become a virus that can be sneezed out of your nose?”