# Master Lecture: The History of Vaccines and Immunization: Familiar Patterns, New Challenges

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The U.S. Department of Defense recently contacted me to work on a national influenza preparedness plan. The project began, and evaluation of the 1918 flu data is underway for the Centers for Disease Control and Prevention (CDC). There are methodological problems of applying historical data to present or future issues, but that was the last great pandemic. The gasping breath and distinctive sounds of whooping cough, iron lung, and braces designed for children attacked by polio, and devastating birth defects caused by rubella inspire dread to Americans while also representing obscure maladies of years past. Yet little more than a century ago in 1890, the mortality data of children in America showed that one out of five children died before their first birthday.

Another one out of five children died before their fifth birthday in the United States, and not only poor children. The cause was invariably infectious diseases, communicable diseases, or contagious diseases. There are historical differences between all those terms. Everyone knew of a child who had died of measles, mumps, rubella, polio, whooping cough, and so on. Many departments of pediatrics are still called Department of Pediatrics and Communicable Disease. At the turn of the last century, communicable disease was a major part of the pediatrician's practice, as well as a major part of the teacher's or social worker's practice, because so many children were stricken by these terrible diseases.

It is an artifact of human society that so much can be done in 2006. Antibiotics became available to the public in 1946 after World War II. Vaccine use began much earlier with Edward Jenner in the late 1790s, but vaccines were not used routinely until the 1920s, 1930s, 1940s, and 1950s. For most of human history, other methods including quarantine were used to try to stem the tide of an epidemic. Today there are antibiotic-resistant strains of bacteria, multidrug-resistant tuberculosis, cholera, and newly emerging infectious diseases such as HIV and a potential avian flu pandemic.

What is considered most readily available will not necessarily work, particularly for avian flu and the vaccine situation. Many great microbe hunters have successfully pounded the globe to eradicate smallpox, but polio is still an issue. If avian flu became human-to-human tomorrow, it would be six to nine months before something resembling a good avian flu vaccine could be developed. Similarly, my entire medical career has been framed by HIV/AIDS. The first question people ask is, "Why is there not a vaccine for HIV/AIDS?" It is a wily, ornery virus, and to find a vaccine is difficult.

The *New England Journal of Medicine* has assigned me to analyze this issue of HIV/AIDS. The virus' ability to hide from our immune system is remarkable. Critics have accused me of anthropomorphizing germs. I love germs, from a distance. There is great hope that the HIV virus will be successfully addressed, but it will take a while. Over time, the span has shrunk between first case of infectious disease and recognition of its cause. The case of HIV is a world record in

human history of epidemics, as it took only three and a half years before they found the ideologic agent HIV that causes AIDS.

It took centuries from first cases of bubonic plague recognized and documented from the middle ages until 1899, when Alexander Yersin discovered the germ that causes bubonic plague. Cholera took centuries before its cause was identified. The next great record in recent history was SARS. Aside from the cases in Guangdong, China which were probably concealed, SARS was not identified until late February 2004 when cases started at the Metropole Hotel in Hong Kong. Eight days after those first cases, physicians, scientists, and microbiologists linked the SARS syndrome to a coronavirus, fingerprinted it, and knew its genome.

People have demanded cures and panaceas since recorded history, and probably before recorded history, framed in how they understand disease. We understand infectious disease to be cause by a particular microbe, either a bacterium or a virus. Then we expect certain methods to help us find out what those germs are and how to subvert, tackle, kill, and prevent them from infecting us; but in the late 18$^{th}$ century, there was a different understanding of infectious diseases. The concept that a tiny microbe could fell a human being was laughable.

At that time, there were concepts of the four bodily humors, taught by people as far back as Hippocrates. There were concepts of miasma, that somehow rotting dead bodies, organic materials, and sewage cause disease. I do not laugh or denigrate people from the past; that is part of the job of being a historian. We call that "presentism" when one judges predecessors by the knowledge or social mores of today. To consider the validity of miasma theory, how foul odors cause disease, spend time in a morgue. It is not a leap to think that foul smells and emanations might cause disease.

In 1796, Edward Jenner began what is called vaccinology. He was a rural doctor in England, where he performed the world's first vaccination by taking pus from a cowpox lesion on a milkmaid's hand and then inoculating an 8-year-old boy. Six weeks later, he variolated two sites on the boy's arm with smallpox. Variolation refers to taking actual smallpox virus, or variola, making a deep gash into somebody's arm, and then injecting that person, or at least introducing that milky pus into his or her arm. One then sees what happens and hopes the immune system takes over. Patients got sick and had a 40 percent chance of either getting smallpox or dying from such a procedure.

Jenner had noted as a country doctor that milkmaids had cowpox lesions on their hands, but they were not getting sick. The cowpox lesions looked rather similar to smallpox lesions, and Jenner had a "eureka" moment to take the pus from cowpox pustules and inject them into a patient. That is where vaccination began, and the word vaccination comes from this initial experiment, because the cowpox is the vaccinia. This concept laid the foundation for modern vaccinology and took the world by storm.

Smallpox was a serious problem back then, and epidemics arose almost annually. About 15 percent of the people who got smallpox died, and those who recovered had terrible scars and lesions. Vaccination carried fewer risks than the older method called variolation, which was

almost as deadly as the disease itself. Even royal patrons got involved. Thomas Jefferson sent for generous cowpox vaccine, and he vaccinated himself and his children for smallpox.

Funding mechanisms in the 18th and 19th centuries were vastly different from today. Expenses and legal issues related to science were stunningly different. The need for a national or international source to produce a vaccine on a regular basis has long plagued work with vaccines. At different points, and particularly in American history, municipal and state departments of health made vaccines. The City of New York had one of the biggest municipal bacteriology laboratories and the first in the world at the turn of last century, making their own vaccines for whooping cough and diphtheria.

Drug companies were heavily involved in vaccines at one stage, particularly in the 1940s, 1950s, and 1960s. They have pulled back somewhat because of litigation issues, despite the National Childhood Vaccine Injury Act of 1986 that made it difficult to sue a pharmaceutical company for a bad vaccine. Risk always exists for things to go awry when handling a biologic. The Act does not provide a free pass, but the flipside of companies not participating on a large industrial scale is painful to contemplate. Remember 2004, when this country faced an influenza vaccine crisis? Only two companies made seasonal influenza vaccines, and one of them had a control problem leading to contamination. Suddenly, there was only half the supply of influenza vaccine.

Philanthropies too have become involved in the production of vaccines, particularly in the 20th century. One of the great examples is the polio vaccine. David Oshinksy's book *Polio: An American Story* won the Pulitzer Prize, describing the quest for the vaccine. The March of Dimes, which was then called the National Foundation for Infantile Paralysis, was not a federal organization, but funded by people either collecting or giving dimes. In 1916, the first major polio epidemic swept through the United States. A safe and effective vaccine for polio was released in 1955. Ironically, the worst polio year occurred in 1953, a few years before the vaccine, with about 60,000 cases of children diagnosed with clinical polio, compared to an average year of 10,000 cases.

Polio severely affected children, resulting in paralysis, use of an iron lung, and so forth. Polio also afflicted wealthy or upper class children far more frequently than poor children. Why? Polio is a gastrointestinal virus and is often present in water supplies lacking effective sewage systems. Until the 1950s and 1960s, sewage systems often ended at the "color line" in poor neighborhoods, particularly in the American south. Where the sewage lines ended, poor children were already ingesting small doses of polio virus and developing an immune response. Wealthier children with access to cleaner water supply did not have the same immunity.

Nonimmune people and those who got polio at an older age experienced greater severity. Franklin Delano Roosevelt was in his late 30s when he contracted polio. He was a co-founder of the March of Dimes National Foundation for Infantile Paralysis with his former law partner, founded in the 1930s. Polio demonstrated this interaction of government and philanthropic concerns, and yet all the donations early on were sent to the White House

It was a unique era in American history, with the rise of the doctor's authority, and the American's trust that the doctor would help them, even if there were problems with vaccines.

Only a few weeks after April 12, 1955 when the polio vaccine was announced as safe and effective, a huge debacle arose at the Cutter Labs, where some bad batches with live polio virus caused 200 cases of polio. On a list of top 10 greatest achievements of medicine, vaccines would be number 1 through 7. Millions of lives have been saved, countless cases have been prevented, and the world has healthier children and healthier adults because of these vaccines.

For anyone concerned with children and their health, the antivaccination movement is a concern. Vaccines have become less popular among people for different reasons. Some of these are good reasons, but we must talk with parents, educators, and all people who care for children. This is a major issue in the history of child health. We need a national agency that makes vaccines, not just a company trying to earn a profit. All children should have access to vaccines and get vaccinated. New vaccines should also be found for other infectious diseases. Antivaccination has been an issue since the 1790s. Parents sometimes blame a shot for an issue experienced by a child at some point after a shot, even if physicians do not think there is a causal relationship. On the autism issue with thimerosal, studies have come out showing no linkage. But to tell that to a parent of a child with autism can be difficult. If one's child got polio from Cutter's bad batch, perhaps that parent would become a strident activist against vaccines. However, some people who distrust vaccines do not rely on scientific evidence.

Doctors promoting vaccination must become better politicians, discussing the issues with people. Doctors must explain the needs. Risks and benefits are different for different things. If there truly is a risk, and risks exist for most biologics, one has to explain what that risk actually means in terms of getting the disease. Those of us promoting vaccination must adeptly change channels for different educational levels. Some people are opposed to some specific vaccinations but not others. It does not necessarily follow that every person who is antivaccinationist is against all vaccines. Nobody wants their child to get a disease, and these discussions can become emotional, requiring patience and thorough explanation.