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What Came Before COVID-19: Two Centuries Of Vaccine Development

by Brenda Sandburg

Infographic timeline looks at key moments in the history of vaccine development, from the first vaccine against smallpox to the polio field trial involving 1.8 million children to the flurry of vaccines created by 'the scientist who saved more lives than all other scientists combined.'

Looking back over the past two centuries of vaccine development puts the development of COVID-19 vaccines in historical perspective and is a reminder of the tremendous advancements that have been made in preventing infectious diseases. (*See timeline below).*

The efforts to make vaccines for the novel coronavirus have been unlike any other in the speed of research, industry collaboration, and government funding to get them on the market in record time. (*See sidebar*). The COVID-19 work joins other pivotal moments in history.

The first vaccine ever created was for smallpox, which was the world's most infectious and deadly disease, killing a third of people who got it and leaving many blind and scarred. Smallpox decimated populations over the centuries, killing an estimated 300 million people in the 20th century alone.

Before there was a vaccine, people tried to prevent the disease by inserting material from smallpox pustules into their arm or vein or grinding up the smallpox scabs and inhaling them through the nose. The process, called variolation, killed some people, but the mortality rate was vastly lower than being infected by smallpox naturally.

In 1796, Edward Jenner, an English physician, developed a vaccine by taking material from a

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cowpox sore on the hand of a milkmaid and inoculating it into the arm of a nine-year-old boy. Jenner subsequently exposed the boy to the smallpox virus a number of times and the child never developed smallpox.

Cowpox, a related, less virulent virus, produced pustules on the udders of infected cows. Milkmaids typically got cowpox pustules on their hands from milking the cows and it was observed that those infected with cowpox did not show any symptoms after being exposed to smallpox.

Jenner published his findings in 1801 and the smallpox vaccine was adopted around the world. In 1958 the World Health Organization launched a global campaign to eradicate the disease, which was intensified in 1967. The last smallpox infection occurred in 1975, and in May 1980, the World Health Assembly declared that the world was free of the disease.

The world's second vaccine, for the prevention of rabies, was developed by the French chemist and microbiologist Louis Pasteur. Until then, anyone bitten by a rabid animal had no chance of surviving. Pasteur made the vaccine with dried material from the spinal cord of rabbits. In 1885, he successfully inoculated a boy who had been severely bitten by a rabid dog. The boy's mother had heard of Pasteur's experiments and brought the child to him desperate to save her son's life.

COVID-19 Vaccines Blaze New Path In the History Of Vaccine Development

By Brenda Sandburg

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Vaccine experts, including R&D leaders at Pfizer and Sanofi, describe what has been unique in developing a vaccine for the novel coronavirus, lessons learned from previous vaccines, and challenges that lie ahead.

Read the full article here

Pasteur knew the agony of such loss. Two of his daughters, aged nine and 12, died of typhoid fever and another died of a liver tumor at the age of two. A vaccine against typhoid fever was developed in 1899.

In 1936, Max Theiler and his colleagues at the Rockefeller Foundation developed a vaccine that protected against yellow fever, which killed about half of those infected. They developed the live attenuated vaccine by growing the virus in chicken eggs and killing it with formaldehyde. Theiler won the Nobel Prize in Physiology or Medicine in 1951, the only Nobel Prize awarded for a virus vaccine.

When Church Bells Rang Across The Country

A pinnacle in vaccine research was Jonas Salk's development of a polio vaccine. In the late 1940s

and early 1950s, the polio virus paralyzed more than 15,000 children in the US every year. It was a terrifying disease. Parents were afraid to let their children go outside or go swimming. Public health officials implemented quarantines on homes and towns where polio cases were diagnosed. Children whose diaphragms were paralyzed were placed in artificial respirators, first known as the Drinker respirator and later as the iron lung, and many died of pneumonia.

Polio vaccine research was able to advance with the creation of the Foundation for Infantile Paralysis, later renamed the March of Dimes, by President Franklin D. Roosevelt in 1937. Roosevelt had been diagnosed with polio, which left him paralyzed from the waist down, in 1921 at the age of 39. The Foundation became the primary funder of vaccine research, raising millions of dollars in donations from the public.

The comedian and Vaudeville star Eddie Cantor coined the name "March of Dimes" when he proposed a radio appeal to raise funds for the organization. He asked listeners to send dimes to the White House to help fight the disease. The response was overwhelming. More than 80,000 letters with dimes and dollars flooded the White House mailroom.

The Foundation funded the 1954 field trial of Salk's inactivated polio vaccine. The trial was the largest medical experiment ever conducted. It included 1.8 million children, of whom 420,000 were injected with the Salk vaccine, 200,000 were injected with a placebo and 1.2 million were observed controls.

Thomas Francis, director of the Poliomyelitis Vaccine Evaluation Center at the University of Michigan, directed the trial. On 8 April 1955, he announced the results before a crowd of hundreds of scientists and reporters gathered in the university's Rackham auditorium. He declared that the vaccine was safe and up to 90% effective in preventing paralytic poliomyelitis.

"By the time Thomas Francis stepped down, church bells were ringing across the country, factories were observing moments of silence, synagogues and churches were holding prayer meetings, and parents and teachers were weeping," Paul Offit, director of the Vaccine Education Center at Children's Hospital of Philadelphia, writes in his book, "The Cutter Incident: How America's First Polio Vaccine Led to the Growing Vaccine Crisis."

Offit noted that Eli Lilly paid $250,000 to broadcast the announcement, which was watched by 54,000 physicians sitting in remote movie theaters across the country.

Polio Vaccine: 'Warp Speed One'

Offit, who is also a member of FDA's Vaccines and Related Biological Products Advisory Committee, provides a riveting narrative of the development of Salk's vaccine and the tragic manufacturing problems at Cutter Laboratories, one of the five companies licensed to make and sell the vaccine.

Salk's polio vaccine consisted of killed poliovirus strains from three poliovirus types. The strains were grown in monkey kidney tissue cultures and inactivated with formaldehyde. Salk provided protocols for developing the vaccine to the manufacturers that received government licenses to make it. One of the manufacturers, Cutter Laboratories, had trouble inactivating the vaccine and live virus remained in several of its lots. Soon after the vaccine was sent out, reports came in of children being paralyzed after receiving it. Ultimately, a total of 200,000 people were infected with live polio virus in Cutter's vaccine. Of these people, about 70,000 had mild cases of polio, 200 were permanently and severely paralyzed and 10 died.

Eli Lilly and Company, Wyeth Laboratories, Pitman-Moore, and Parke-Davis were the other manufacturers licensed to make the vaccine. Offit noted that they also had difficulties making it, but Wyeth was the only other company whose vaccine was linked to cases of paralysis following its adminstration. Wyeth recalled one lot of its vaccine.

Offit wrote that a series of events at Cutter resulted in the polio vaccine containing live virus, and that all of these events had to occur for children to be paralyzed. They included Salk's use of the Mahoney strain of type 1 polio, which is the most deadly; the type of filter used to remove the cells in which the virus was grown was inadequate so virus remained hidden in the debris; the filtered virus was stored too long before it was inactivated; and the company failed to determine how long to treat the virus with formaldehyde. In addition, he said Cutter never told other researchers or the government that it was unable to consistently kill the virus.

Offit noted in an interview that this incident led to the birth of vaccine regulation, which until then had been done rather haphazardly by a handful of people. It also led to the creation of the term "consistency lots," meaning you had to consistently show that you would make a certain number of lots consecutively that had the same characteristics.

"I think if there's a lesson here, it's that it's hard to mass produce" biologics, Offit said. "There are problems that come up in mass production that weren't necessarily encountered when you were making much smaller batches of the vaccine."

The polio story is the closest to that of COVID-19, Offit said. While the US government has taken the risk out of development of COVID-19 vaccines for pharmaceutical companies by paying for trials and mass production, a private philanthropic organization did so for the Salk vaccine.

"You could argue that the [polio vaccine] was Warp Speed One," he said, since companies mass produced a vaccine at risk not knowing whether the field trial was going to show that the vaccine was safe and effective. The government's current Operation Warp Speed has provided billions of dollars to five companies to support development of their COVID-19 vaccine candidates.

Surge Of Vaccines

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The US switched from Salk's vaccine to Albert Sabin’s oral attenuated polio vaccine in 1962. But Sabin's vaccine was found to be unstable and about one in 7500,000 children immunized with the vaccine were paralyzed. In 1998, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommended that Salk’s vaccine be used exclusively and Sabin’s vaccine is no longer available in the US.

In the decades following the launch of the polio vaccine, vaccines were developed for measles, mumps, rubella, chickenpox, hepatitis A, hepatitis B, pneumococcus, meningococcus, and Haemophilus influenzae type b (Hib).

These nine vaccines were all made by Maurice Hilleman, who began his career at Walter Reed Army Institute of Research before becoming director of virus and cell biology at Merck Research Laboratories in 1957. Offit wrote a book about Hilleman’s life and work, “ Vaccinated: One Man’s Quest to Defeat the World’s Deadliest Diseases,” in which he describes Hilleman as the “the scientist who saved more lives than all other scientists combined.”

Hilleman developed the mumps vaccine after his then five-year old daughter, Jeryl Lynn Hilleman, woke him up one night, sick with a sore throat. He saw a lump on her face and looked through The Merck Manual of medical information to confirm that it was mumps. He drove to his laboratory at Merck, gathered cotton swabs and a vial of nutrient broth, went home and swabbed his daughter’s throat, and then returned to the lab to put the sample in a freezer. Offit recounts how Hilleman developed a vaccine by growing the virus in the membrane of a chick embryo and then passing it through several other eggs to weaken the virus.

Offit also describes how Hilleman's work was based on the findings of scientists before him. One of these was the discovery of the ability to grow poliomyelitis viruses in cultures of various types of tissue by a research team at Boston Children’s Hospital. The three researchers, John Enders, Thomas Well, and Frederic Robbins, won the Nobel Prize in Physiology or Medicine in 1954 for the discovery.

The 21st Century has also seen significant breakthroughs, including Pfizer’s development of a pneumococcal conjugated vaccine, Prevnar. The vaccine initially offered protection against seven serotypes, which was advanced with Prevnar-13 to provide protection against 13 serotypes.

William Gruber, senior VP vaccine clinical research and development at Pfizer, noted the impact these vaccines have had. A pediatric infectious disease specialist, he treated patients and taught medical graduate students before working in industry. He said that in the 1970s and 1980s, pediatric hospital wards always had patients with complications of pneumococcal disease, including meningitis, sepsis, and pneumonia. Now, he said such occurrences are so rare they have become teaching cases, as have incidences of Haemophilus influenza type B.

The emergence of COVID-19 has brought renewed attention to the importance of vaccines, which could rejuvenate a field that has been reduced to only five top vaccine manufacturers.

“I think there’s a certain complacency in the public’s mind about infectious pathogens,” John Shiver, Sanofi’s head of vaccines R&D, said. “To have another pathogen amongst us where suddenly we all feel a degree of vulnerability, it’s really an unusual experience for most people today.”

Hopefully, that will help support continued new vaccine research and development, he added, “because there are certainly pathogens that we do need to address.”

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