Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/covid-19-frontlines/a-look-at-immunizations-through-time/11580/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

A Look at Immunizations Through Time

Dr. Russell:
Coming to you from the ReachMD studios, this is *COVID-19: On the Frontlines*. I'm Dr. John Russell. Today I'll be discussing immunizations through time.

The process of variolation began in the 1100s in Asia. This was a direct inoculation with smallpox. Dried scabs from smallpox were blown into the nose. Patients got a milder form of smallpox with 1–2% of patients dying of smallpox as opposed to 30% that would die with natural infection, and those who lived were often left scarred. By the 1700s, this technique spread to Africa, India, and the Ottoman Empire.

By the time this reached Europe, the technique changed. In 1717, Lady Mary Montagu, the wife of the British Ambassador, learned of this procedure in Constantinople. In 1721, in England, several prisoners and some orphaned children had smallpox inserted under their skin. They were exposed to smallpox several months later. The Royal Family were then inoculated, and it became fashionable across Europe. It was not without risk. The son of King George died from the procedure. Slaves from Africa introduced the procedure to North America. Interestingly enough, George Washington ordered variolation done on the troops at Valley Forge.

Next up with smallpox was Edward Jenner. Edward Jenner was an English physician who was looking for an alternative to variolation. Jenner noticed that dairy maids were immune to smallpox from having cowpox infections. In 1796, he took the material from a cowpox on the arm of Sarah Nelms and infected his gardener's son, James Phipps. He then exposed the boy to smallpox, which he did not contract. He repeated this procedure on other children, including his own son. He published his findings in 1798 entitled *On the Origin of Vaccine Inoculation*. The procedure spread, and in 1803, the term "vaccination from cow" came into use. Thomas Jefferson was an advocate of Jenner's work, and he wrote a letter to Edward Jenner that says, "You have erased from the calendar of human afflictions one of its greatest. Yours is the comfortable reflection that mankind can never forget that you have lived. Future nations will know by history only that the loathsome smallpox has existed and by you as been extirpated."

But the vaccination procedure wasn't without controversy. In 1807, the Bavarian Army made it compulsory. As governments began to feel compelled to have their citizens get vaccinated, objections arose. The author, George Bernard Shaw, called it "a filthy piece of witchcraft." This battle raged for over 100 years as the procedure spread. In 1905, the US Supreme Court in Jacobson versus Massachusetts upheld compulsory vaccination. The case said that the state may be justified in restricting individual liberty under pressures of the great danger to safety of the general public. So, variolation was akin to smaller amounts of poison to lessen the effects, much like we saw in the book *The Count of Monte Cristo* or *The Princess Bride*. Whereas Jenner's vaccine gave us similar, less virulent strain to patients, it was attenuated in humans.

So, overall, some of the concepts in modern vaccinology: There are similar processes for vaccines. One, you need to generate antigen, so you need to grow it in some sort of medium before you inactivate it. You need to then release and isolate from the cells it is grown in, purify the antigen through chromatography or ultra-filtration and then inactivate it, strengthen the vaccine through the use of adjuvants, add chemicals to increase shelf life, maintain sterility, and then distribute through growth in a single-lot, consistent vaccine that is packaged and shipped out.

So the next great mind in vaccines was Pasteur, who used attenuation to develop vaccines. Attenuation was an accidental discovery in Pasteur's labs. His team was working with chicken cholera. They would inject the chicken cholera into chickens, and they would die. A research assistant was away from the lab for a month. When he returned, he injected the chickens with old inoculum. The chickens only developed mild symptoms of the disease. When the chickens got healthy, he injected them again with fresh inoculum, and they did not get sick. Pasteur reasoned that the air over time made the bacterium less virulent. This was attenuated, and this could be

considered the birth of immunology, and this technique led him to discover a vaccine for sheep against anthrax.

Pasteur's first human vaccine that he worked on was rabies. Pasteur could not find a causative organism because rabies was a virus, and virus is very small and not detectible. For Pasteur, he passed the virus through a different species, and he discovered the virus would weaken, so Pasteur, passed rabies through rabbits to make it less dangerous to human host. After finding success in testing with dogs, Pasteur tried the vaccine on a 9-year-old boy who was bitten extensively by wild, rabid dogs. The boy was given a series of stronger and stronger doses. He survived, and he ended up working his adult life at the Pasteur Institute. It was originally called Pasteur's Treatment, but he honored Jenner by calling it a vaccine. So, our definition of vaccine today comes from Pasteur, a suspension of live, usually attenuated or inactivated microorganisms, bacteria or viruses, or fractions thereof, administered to induce immunity and prevent infectious disease or its sequelae.

Next up came the vaccine BCG. So, Calmette and Guerin passed bovine tuberculosis through artificial media 230 times to weaken it to protect against tuberculosis. The same technique was used for the development of the yellow fever vaccine as they passed it through mice and chicken embryos.

The next thing that came up was the use of serum. So, Emil von Behring worked with a bacteriologist, Koch. They developed techniques to inject serum from immunized animals into nonimmunized animals, and this protected the nonimmunized animals from fulminant infection. The first successful treatment of humans was with diphtheria. So, diphtheria prior to that was 50% fatal, and about 50,000 children died yearly from diphtheria in Germany. So, von Behring developed serum in large animals, sheep and horses. This was injected into infected children. It only lasted a short time, but it decreased the fatality from that 50% down to about 5%, and they called it antitoxin. von Behring won the Nobel prize in medicine in 1901. Eventually, he developed a vaccine that contained both toxins and antitoxins. von Behring used similar techniques in the vaccine against tetanus. The Iditarod dog race honors the race to get diphtheria antitoxin from Anchorage to Nome.

Towards the ends of the 19th Century, researchers learned that heat or chemicals can inactivate pathogens like typhoid, plague and cholera. In the 20th Century, researchers used formalin to inactivate pertussis bacteria and later diphtheria, and chemical inactivation occurred with influenza vaccines that came around in the mid-20th Century.

Our next great researcher was Jonas Salk. In 1942, Salk went to the University of Michigan on a research fellowship to develop an influenza vaccine. He soon advanced to the position of Assistant Professor of Epidemiology. He also reconnected with his NYU friend and mentor, Thomas Francis, Jr., head of the epidemiology department at Michigan's new School of Public Health, who taught him the methodology of vaccine development. In 1947, Salk was appointed Director of the Virus Research Laboratory at the University of Pittsburgh School of Medicine. With funding from the National Foundation for Infant Paralysis, now known as the March of Dimes Birth Defects Foundation, he began to develop the techniques that would lead to a vaccine to wipe out the most frightening scourge of its time, paralytic poliomyelitis.

So, contrary to the era's prevailing scientific opinion, Salk believed his vaccine composed of killed polio virus could immunize without risk of infecting the patient. Salk administered the vaccine to volunteers who had not had polio, including himself, his lab scientist, his wife and their children. All developed anti-polio antibodies and experienced no negative reactions to the vaccine. Salk grew the polio virus vaccine in the kidney cells of chimpanzees that was then killed with formaldehyde.

In 1954, national testing began on 1 million children age 6 to 9 who became known as the polio pioneers. On April 12, 1955, the results were announced. The vaccine was safe and effective. In the 2 years before the vaccine was wildly available, the average number of polio cases in the US was more than 45,000. By 1962, that number had dropped to 910. Held as a miracle walker, Salk never patented the vaccine or earned any money from his discovery, preferring it to be distributed as widely as possible. When the reporter Edward R. Murrow asked Salk why he did not patent the vaccine, he said, "Can you patent the sun?"

By the 1940s, researchers had been passing material through mice and chicken embryos to make vaccines. The problem was it wasn't always sterile. This led to a discovery of growing cells in culture as a substrate for viral growth. This helped in the development of live vaccines of measles, mumps, rubella, varicella and oral polio through the selection of clones passed through cell culture. To grow in the cells, infectious agents often lose the ability to infect. Occasionally, passage through the gut lost this adaptation, and about 1 in 500,000 got polio through the oral polio vaccine that was discovered by Sabin.

Our next great name, who many of you may not know, is Maurice Hilleman. Maurice Hilleman was responsible for developing more than 40 vaccines, including measles, mumps, hepatitis A, hepatitis B, meningitis, pneumonia, H flu and rubella. His vaccines have been credited with saving millions of lives and with eradicating common childhood diseases. The measles vaccine alone has prevented approximately 1 million deaths. Among other accomplishments, he succeeded in characterizing and isolating many viruses, including the hepatitis A vaccine and culture.

Despite Hilleman's many breakthroughs in immunology and vaccinology, he has never been a household name. Dr. Anthony Fauci, Director of the US National Institute of Allergy and Infectious Diseases, said Hilleman had little use for self-credit. Dr. Fauci told the BMJ that Hilleman's contributions were "the best kept secret among the lay public. If you looked at the whole field of vaccinology, nobody was more influential."

Hilleman characterized several viruses and identified changes that occur when a virus mutated. This concept, which he worked out while he was at the Walter Reed Institute of Army Research, helped prevent a huge flu pandemic of Hong Kong Flu in 1957. Learning that the flu was a new strain, 40 million doses of vaccine were rapidly made available to the United States.

Hilleman joined Merck on New Year's Eve 1957 as director of a new Department of Virus and Cell Biology research. Under Hilleman's leadership, by 1984, Merck had garnered 37 product licenses with an additional 3 vaccines ready for development. He retired from Merck at the age of 65 but stayed on as a consultant.

Hilleman's style of working was iconoclastic. Dr. Paul Offit from Children's Hospital in Philadelphia said, to give an example of how he worked, that in 1963, when his daughter had the classic symptoms of mumps, he swabbed the back of his daughter's throat, brought it to the lab to culture, and by 1967 there was a vaccine. The mumps strain was named Jeryl Lynn after Hilleman's daughter.

A challenge in creating his vaccine involved avoiding the use of human blood products, as did Hilleman's first hepatitis B vaccine. Therefore, Merck used an enzyme to remove the virus's surface protein. Researchers inserted the code for the antigen into yeast cells, which produced more of the surface protein. The yeast-derived surface protein produced immunity to the hepatitis B virus.

During his more than 60 years in basic and applied research, he earned a reputation as an often harsh, impatient fellow who tangled with industry and government bureaucracies. Hilleman defended his pushy and prickly behavior, which offended some colleagues and coworkers, as crucial for science to advance. He argued that politics, not science, determine which breakthroughs were brought to the marketplace.

Next up came the work on capsular polysaccharides. Early bacteriology showed that many pathogens were surrounded by a polysaccharide capsule and that antibodies can promote phagocytosis. This led to the development of vaccines, first against meningococcal disease, then pneumococcus and HIB. These polysaccharide vaccines did not have much of a response in infants. The development of conjugate vaccines allowed a T-cell as well as B-cell responses. Conjugate vaccines can decrease nasal carriage as well as which helps with herd immunity to the major bacterial diseases of infancy.

For the protein-based vaccines, most flu vaccine is grown in eggs, and then the virus is broken up with detergents. The viral hemagglutinin in protein is purified. An acellular pertussis vaccine replaced the whole-cell pertussis. The virus is broken into fragments in the hope of similar immunogenicity without the febrile reaction that often plagued the pertussis vaccines.

Then comes genetic engineering. So, starting with Hilleman's hepatitis B vaccine, multiple vaccines have developed using genetic engineering. The HPV vaccine has been developed growing the L1 protein of the virus. This protein produces protective antibodies and produced in yeast or insect cells. New recombinant technology can grow flu vaccine through inserting hemagglutinin and protein into a baculovirus of the fall armyworm. A new meningococcal B vaccine is produced using reverse vaccinology of the proteins that then induces an antibody response.

So, which of these many different ways will the COVID vaccine go? Hopefully, researchers will find a vaccine that is safe and effective and will help lead the world into the light after all this darkness of the pandemic.

For ReachMD, this is *COVID-19: On the Frontlines*. I'm your host, Dr. John Russell. For continued access to this and other episodes and to add to your perspectives towards the fight against this global pandemic, visit us at ReachMD.com and Become Part of the Knowledge. Thanks for listening.