

[Maurice Ralph Hilleman \(1919–2005\)](#) ^[1]

By: Ross, Christian H.

Maurice Ralph Hilleman developed vaccines at the Merck Institute of Therapeutic Research in West Point, Pennsylvania, during the twentieth century. Over the course of his career at Merck, Hilleman created over forty vaccines, making him one of the most prolific developers of vaccine in the twentieth century. Of the fourteen vaccines commonly given to children in the US by 2015, Hilleman was responsible for eight of them. Hilleman's most widely used vaccine was his measles, mumps, and rubella (MMR) vaccine. Hilleman's MMR vaccine prevented many diseases and also rubella in millions of children and pregnant women. Rubella in pregnant women often led to congenital rubella syndrome in the [fetus](#) ^[2], causing severe malformations.

Hilleman was born on 30 August 1919 in Miles City, Montana, to parents Edith and Robert Hilleman as the youngest of eight children. Neither his mother nor his twin sister survived the delivery. With eight children to raise on his own, Hilleman's father sent him and his older siblings to live on the nearby farm of Hilleman's aunt and uncle. Hilleman grew up during the Great Depression raising chickens and cattle and helping with the family business of making brooms and horseradish. In 1927, at the age of eight, Hilleman nearly died from diphtheria, a bacterial infection that causes fever, swelling of the throat and neck, and potentially fatal damage to the heart and nervous system.

As a student, Hilleman regularly listened to science radio shows and read science textbooks. He also read [Charles Darwin](#) ^[3]'s 1859 *On the Origin of Species*, despite disapproval from the local Lutheran minister. In 1937, Hilleman graduated from Custer County High School in Miles City and took a job at a local department store. Hilleman later said that though he was interested in science, he did not believe that he could afford to pay for a college education. However, in 1938, one of his older brothers told him that there were scholarships available at some Montana colleges and encouraged him to apply for them. Hilleman did so and received a full merit scholarship at Montana State College in Bozeman, Montana, where he enrolled later that year.

At Montana State College, Hilleman double majored in chemistry and microbiology. One of his classmates, Menga Huffman, described Hilleman as solely dedicated to science and said that he often spent his Saturdays working in the chemistry lab rather than socializing. Hilleman graduated from Montana State College first in his class in 1941 and enrolled in a doctoral program studying microbiology at the [University of Chicago](#) ^[4] in Chicago, Illinois. While a graduate student at the [University of Chicago](#) ^[4], Hilleman met and married Thelma Mason in 1943.

Hilleman received his PhD in microbiology in 1944 from the [University of Chicago](#) ^[4] for his dissertation work characterizing the microbe that caused chlamydia, a sexually transmitted infection that causes painful inflammation of the genitals. Hilleman's research overturned microbiologists' prior notions that chlamydia infections were caused by viruses by demonstrating that chlamydia was a bacterial infection. His discovery as a graduate student led to the introduction of antibiotic treatments for the thousands of people infected with chlamydia. According to medical historian Laura Newman, after receiving his PhD, Hilleman's professors urged him to continue his research at academic institutions rather than at a commercial laboratory. His professors claimed that the education he received at the [University of Chicago](#) ^[4] had not trained him for a career outside of academic institutions. But Hilleman believed that pursuing a job outside academia provided him greater resources to push scientific innovations to a consumer market. Therefore, Hilleman left academia in 1944 for the pharmaceutical company E.R. Squibb & Sons in New Brunswick, New Jersey, to study viruses and attempt to create vaccines.

Vaccines protect individuals against viruses by intentionally exposing individuals to mild strains of a virus. When an individual is infected, the immune system produces antibodies, proteins that chemically recognize foreign bodies like viruses. Even after the immune system fights off the viral infection, it continues to produce antibodies specifically against the virus to prevent future infections from that virus. To promote the production of specific antibodies, vaccines expose individuals to a small amount of virus that researchers have made no longer infectious. Because the virus is inactive or weakened, individuals exposed to the milder version of the virus do not experience the full symptoms of infection. Yet, even in response to only a little bit of inactivated or weakened virus, the immune system produces antibodies that protect against infection by the full-strength strains of the virus. As a result, vaccines protect individuals from contracting a specific viral infection.

Hilleman continued to identify and describe microbes as a researcher at E. R. Squibb & Sons. Within his first year there, Hilleman created a vaccine against Japanese encephalitis, a viral brain infection spread by mosquitos, which was killing US soldiers stationed in the Pacific during World War II. In 1948, Hilleman took a job studying respiratory viruses at the Walter Reed Army Institute of Research in Washington, D.C. In 1953, Hilleman discovered and characterized a new family of viruses, later called adenoviruses. Adenoviruses caused infections in the upper respiratory tract that the military identified as the cause of the majority of acute respiratory disease in US military trainees. His discoveries led to the development of an injectable vaccine against two different types of adenovirus in 1956 and oral vaccines in the 1970s.

While working at Walter Reed, Hilleman noticed that various strains of influenza, or flu viruses, can undergo changes from year

to year, resulting in new flu strains. He noted that when only small changes to strains occurred, people's antibodies typically still recognized and provided immunity against the new flu strains. However, when larger changes occurred to flu strains, people's antibodies did not recognize the new strains and did not produce immunity against infection.

Hilleman soon applied his theory of changes in flu virus strains. In April of 1957, an outbreak of avian flu occurred in Hong Kong, China, infecting nearly 250,000 people. Hilleman suspected that a major change to a strain of flu virus caused the outbreak. That change resulted in a new strain that few people's antibodies recognized, meaning most immune systems were unable to protect against the viral infection. At Walter Reed, Hilleman obtained blood samples infected with what was then called the Asian flu virus. Hilleman and his colleagues at Walter Reed worked fourteen-hour days for more than a week to isolate the virus and compare it to known antibodies from blood samples of different people groups from around the world.

Hilleman discovered that almost none of the global blood samples had antibodies that recognized the Asian flu virus, meaning that almost no [humans](#)^[5] had protective immunity against the virus. Without any innate immunity or a vaccine, Hilleman predicted that when the Asian flu virus spread to the US, potentially more than a million people would die from infection. Hilleman sent samples of the isolated flu virus to several US vaccine manufacturers to create a vaccine. The manufacturers grew the Asian flu virus in fertilized [chicken](#)^[6] eggs to weaken the strength of the virus, a process called attenuation, enough for use in vaccines. Growing the virus in [chicken](#)^[6] eggs caused the virus to adapt to [chicken](#)^[6] cells rather than human cells. As the virus adapted more to [chicken](#)^[6] cell biology, it became more infectious for [chicken](#)^[6] cells and less infectious for human cells. That made the Asian flu less likely to cause the full symptoms in people, but it still caused an immune response to create antibodies against the virus.

When the Asian flu virus spread to the US in the fall of 1957, manufacturers had already created 40 million flu vaccines for immediate distribution. By the end of 1958's Asian flu pandemic, 69,000 people had died in the US, but Hilleman's push for rapid mass production of flu vaccines likely saved hundreds of thousands of lives in the US.

In December of 1957, Hilleman left Walter Reed to become the director of virus and cell biology research at the Merck Institute of Therapeutic Research, in West Point, Pennsylvania. After joining Merck, Hilleman's wife gave birth to his first daughter, Jeryl Lynn, in 1958. At Merck, Hilleman oversaw a laboratory studying viruses and vaccine development.

At Merck, Hilleman's co-workers said that they struggled to work with him due to his rough personality and the long working hours needed to meet his expectations.

While working on improving Merck's commercially available polio vaccine in 1960, Hilleman uncovered that a cancer-causing virus, SV40, was present in the polio vaccine. SV40 was a virus found in both monkeys and [humans](#)^[5] and could cause tumors to grow. Hilleman found that SV40 was already present in the monkey kidney cells in which Merck researchers grew weakened versions of poliovirus. When they tried to isolate the weakened polio virus, they also accidentally isolated SV40, both of which they included in the vaccine. Hilleman's findings caused Merck to remove its polio vaccine from the market and led the US [Food and Drug Administration](#)^[7] (FDA), headquartered in Silver Spring, Maryland, in 1963 to establish screening programs looking for other stray viruses in vaccines. Although researchers did not find links between monkey viruses like SV40 and cancer in [humans](#)^[5], Hilleman's findings convinced vaccine researchers to use human cells to develop vaccines.

At Merck throughout the 1960s, Hilleman developed new vaccines. In 1962, Hilleman developed a [viable](#)^[8] vaccine for measles, a highly contagious disease causing rashes, flu-like symptoms, and fever. A year later, the FDA approved the vaccine for commercial production. That same year, Hilleman isolated an inactive, non-infectious strain of the rubella virus, called the Benoit strain, for use in vaccines. The rubella virus caused a relatively mild infection resulting in a rash and often a low-grade fever. However, in pregnant women, the rubella virus transferred to the [fetus](#)^[2], causing congenital rubella syndrome, which resulted in heart defects, blindness, deafness, or other organ malformations in the [fetus](#)^[2]. Hilleman attempted to use the non-infectious strain of the rubella virus to create a vaccine with a lesser risk of infection than vaccines that still used active, infectious virus strains. However, he did not produce a [viable](#)^[8] vaccine from the Benoit rubella strain.

Hilleman's wife Thelma died in 1962, leaving him to raise their daughter alone. Soon after his wife's death, Hilleman enlisted the help of his administrative assistant to begin selecting potential marriage candidates from the pool of Merck job applicants. He instructed his assistant to send one woman to meet with him each week until he found a suitable match. In that manner, in 1963, Hilleman met and married his second wife, Lorraine, with whom he later had another daughter, Kirsten.

Hilleman began in 1963 to make a mumps vaccine. One night in 1963, Hilleman's five-year-old daughter, Jeryl Lynn, had a swollen jaw and fever that Hilleman diagnosed as caused by the mumps. The mumps is a viral infection of the salivary glands, which in some cases led to infections of the brain, causing permanent deafness or death. That night, Hilleman made a late visit to the virus laboratories at Merck to retrieve swabs to collect samples of the mumps virus from his daughter. Hilleman then grew those samples in [chicken](#)^[6] embryos in his laboratory to weaken, or attenuate, the mumps virus strain. Hilleman's daughter eventually recovered from the mumps, and Hilleman used the attenuated mumps virus to create an experimental mumps vaccine in 1965. As a part of testing, in 1966, Hilleman arranged to have his younger daughter, Kirsten, inoculated with the experimental mumps vaccine created from the virus isolated from her older half-sister. Hilleman's vaccine proved successful and, after clinical testing, was approved by the FDA for commercial use in 1967. By 1972, over 11 million doses of Hilleman's mumps vaccine had been distributed in the US.

During the late 1960s, Hilleman worked to develop vaccines for rubella and measles. In 1967, Hilleman abandoned his attempts to create an inactivated vaccine with the Benoit strain of rubella. He switched to an active rubella strain called HPV-77 that virologists Paul Parkman and Harry Meyer had isolated in 1963 at the [National Institutes of Health](#)^[9] in Bethesda, Maryland. The HPV-77 strain caused a greater immune response, which made it a good candidate for use in vaccines. Hilleman attenuated the HPV-77 strain by growing it in [duck](#)^[10] embryos to develop a successful rubella vaccine. In 1969, the FDA approved Hilleman's rubella vaccine.

Hilleman also developed a new version of his measles vaccine in 1968. The measles virus caused a more severe fever and rash than the rubella virus and in some cases caused complications that led to diarrhea, pneumonia, or blindness. Hilleman's improved measles vaccine used a more weakened strain of the measles virus that better protected recipients against the measles virus and caused fewer, milder vaccine side effects. In 1968, the FDA approved Hilleman's more reliable measles vaccine for sale later that year.

Hilleman continued his work in vaccine development at Merck into the 1970s. He created the measles, mumps, and rubella (MMR) vaccine in 1971. The MMR vaccine combined Hilleman's measles vaccine, mumps vaccine, and rubella vaccine. Hilleman's MMR vaccine required only a single injection and minimal medical visits to inoculate children against three of the most widespread childhood diseases in the US. The [Food and Drug Administration](#)^[7] approved the MMR vaccine in 1971. Years later, in 1979, Stanley Plotkin's rubella vaccine, which used the RA 27/3 strain of rubella, replaced Hilleman's in the MMR vaccine. By 2015, physicians have administered more than 500 million doses of the vaccine worldwide. Hilleman's MMR vaccine is one of the most widely used vaccines in history, preventing millions of cases of measles, mumps, and rubella. It also prevents cases of fetal deformation from congenital rubella syndrome caused by the rubella virus in pregnant women.

Throughout the remainder of his career at Merck, Hilleman developed several other vaccines. In 1974, Hilleman created a vaccine against meningococcal disease, caused by bacteria that infect the bloodstream and linings of the brain and spinal cord, resulting in fever, vomiting, or trouble waking from sleep. In 1977, he created another vaccine against pneumococcal disease, also caused by bacteria that infect the bloodstream, often resulting in severe inflammation and fluid accumulation in the lungs. Later, in 1981, Hilleman developed a vaccine for [chicken](#)^[6] pox, a highly contagious viral infection causing fever and itchy skin blisters that scab over. In the same year, he also developed a vaccine for Hepatitis B, a sometimes chronic viral infection of the liver causing abdominal pain, vomiting, and yellowing of the skin. Hilleman retired from Merck in 1984 at the age of 65, but Merck immediately rehired him as a consultant to keep him involved in the vaccine research and development process for diseases like malaria, tuberculosis, and AIDS.

For his contributions to medical research, Hilleman received the Albert Lasker Medical Research Award in 1983. In 1985, the US National Academy of Science elected him to membership for his work in virology and cell biology, and in 1988, he received the National Medal of Science, the highest honor in the US for scientific achievement. The World Health Organization and the Albert B. Sabin Vaccine Institute honored Hilleman with lifetime achievement awards in 1996 and 1997, respectively.

Hilleman continued to be involved with vaccine research and development until his death. Hilleman died on 11 April 2005 in Philadelphia, Pennsylvania, from cancer.

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