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POLIO

- **Polio was a crippling disease until the development of a vaccine in the mid-1950s, an event of such impact that some historians have called it one of the greatest achievements of the 20th century.**
- **In 1916, a polio epidemic began in the U.S. that killed 6,000 people and paralyzed 27,000 others annually. In the early 1950s, more than 20,000 cases of polio were reported each year. By 1979, after polio immunization had become routine, there were only 10 cases reported in the U.S., and in 1991, the Western Hemisphere was declared polio-free.**
- **Worldwide, cases of polio have dropped from 350,000 per year in 1985 to just 480 cases near the end of 2002. Polio is now endemic in only six countries.**
- **The World Health Organization has established a goal of eradicating polio worldwide during the first decade of the 21st century.**
- **Polio survivors, numbering 300,000-600,000, represent one of the largest U.S. populations with disabilities.**

Polio Vaccine Developed, U.S. stamp (3187a) from "Celebrate the Century," a series of fifteen 33¢ commemorative stamps for the years 1950-59 issued in 1999.

- **Post-polio syndrome can occur 10-40 years following the initial onset of polio. It can cause chronic fatigue, debilitating muscle weakness and atrophy, and severe chronic joint pain.**

Background

Poliomyelitis - or infantile paralysis as it was formerly known - was a most feared disease in the U.S. in the first half of the 20th century. However, polio has been known for thousands of years in all parts of the world. The bone formation of an Egyptian skeleton of the period 3700 B.C. indicates the effects of polio, as does an Egyptian plaque from 1300 B.C.

Although polio has existed for thousands of years, it wasn't until 1908 that scientists showed that polio is a contagious disease caused by a virus that attacks the central nervous system[1]. Although the existence of viruses is well-known today, only a few viruses had been isolated before polio was recognized as a distinct disease, and scientists had more questions than answers about viruses.

One of the questions scientists then had to answer was whether polio was caused by just one particular virus or by more than one type. Re-

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NOTE:

Words contained in the glossary (pages 11-12) are highlighted in **bold** the first time they appear in the text.

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search on this question took several years and it was proven in the early 1940s that there are three **strains**, or types, of poliovirus: *bulbar*, *spinal* and *bulbarspinal*[2].

In temperate climates, the spread of poliovirus is cyclical -- winter is the latent season for polio and summer, the high season. In tropical climates, however, polio is a year-round threat.

Ironically, the advanced state of public hygiene in the U.S. and the rest of the developed world contributed to the polio epidemics of the 20th century. Polio is primarily a disease of infants and children. Before public hygiene developments, infants and young children became exposed to poliovirus, but their symptoms were mild and the exposure provided lasting immunity[3]. With the advent of indoor plumbing and modern ideas about hygiene and sanitation, children were not exposed to the poliovirus in infancy and did not develop natural immunity. As a result, outbreaks of polio began to be seen in the mid-1800s.

Pathogenesis and Pathology

The poliovirus enters the body through the nose or mouth and travels to the lymphoid tissue of the throat and small intestine, where it incubates. The **incubation period** is usually between 7 and 14 days, but may range from 2 to 35 days. By 3 to 5 days after exposure, the virus can be recovered from the blood, throat and feces. At this time, most patients either experience no symptoms or experience flu-like symptoms, such as headache, nausea, vomiting, and fever. Also at this stage, infected people can pass on the disease to others. Polio can be spread through contact with infected feces or through infected droplets travelling through the air, in food or in water.

The virus next enters the bloodstream, and the immune system makes antibodies against it. In most cases, this stops the progression of the virus and lifelong immunity is acquired. However, the paralytic form of the disease manifests itself when the virus travels from the bloodstream to the central nervous system and infects nerve cells. Poliovirus invades only certain types of nerve cells, particularly the **anterior horn cells** of the spinal cord, and in the process of multiplying, the virus may damage or destroy these cells.

Paralytic polio is sometimes preceded by fever and a brief illness. The primary symptom is limb paralysis without loss of sensation. Paralysis varies depending upon

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the area of the nervous system affected. Brainstem infections, for example, cause weakness in muscles used for swallowing, talking, facial expression, breathing and blood circulation. Spinal cord infections can cause paralysis of the legs, arms or trunk.

One of of ten people infected develops symptoms of polio, and one out of 100 develops the paralytic form. About one out of four people with paralytic polio incurs permanent disability, and five percent of children and 30 percent of adults do not survive.

Treatment

For survivors of paralytic polio, some recovery from paralytic symptoms may occur gradually over many months. The paralysis that remains after recovery is usually permanent and may be accompanied by severe pain. Other complications of poliovirus infection include diseased heart muscles, high blood pressure, fluid in the lungs, shock, and urinary tract infections.

Treatment of poliovirus infection is generally limited to reducing pain and muscle spasms; maintaining respiration (breathing); minimizing skeletal deformities; anticipating and forestalling other paralytic effects; and allaying patient fears. When fever subsides, early mobilization and exercise are usually begun.

Polio Epidemics

Large **epidemics** spread across the United States and Europe in the first half of the 20th century. The early major epidemics of polio in the U.S. were in the Southeast in 1910 and in the Northeast in1916. The epidemic of 1921 took as one of its victims a future president of the United States. Franklin Delano Roosevelt was infected with poliovirus in the summer of 1921. In 1938 President Roosevelt founded the National Foundation for Infantile Paralysis -- which later became known as the March of Dimes -- to organize laypeople and scientists to conquer polio.

There were serious epidemics throughout the 1930s and 1940s, and again in the early 1950s. In 1952, more than 57,000 Americans contracted polio, the largest number on record in a single year. In 1954, the city of Boston, MA had so many polio cases that parents drove their sick children to Children's Hospital and sat in their cars on the street while resident physicians decided who would go inside for care[4].

During this time, the pattern of polio changed, as increasingly older groups became

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infected. Many polio patients were only able to survive with the aid of large **iron lungs**, and wards full of these machines were a common features of hospitals at that time. In the early 1950s, 16 regional respiratory and rehabilitation centers were established at teaching hospitals across the U.S. These centers acted as hubs of care, research and rehabilitation.

Vaccine Development

Poliomyelitis is one of the most thoroughly studied diseases. Before the development of vaccines, knowledge had advanced to such an extent that scientists understood well the **epidemiology** and the clinical forms of the disease. It was this substantial pre-existing knowledge of polio and the virus that causes it that made vaccination against the disease possible within a relatively short period of time in the 1940s and 1950s.

Immunization against polio began in 1955 with the development of the injectable "killed", **formalin**-inactivated poliovirus vaccine (IPV) by Dr. Jonas Salk. The "live," **attenuated** oral poliovirus vaccine (OPV) of Dr. Albert Sabin soon followed and was first used on a large-scale basis in the former Soviet Union in 1959. It was licensed in the U.S. in 1962.

Wherever the vaccine was used in North America, Europe, Australia, and some parts of Asia, there was a spectacular decline in the number of cases reported. In the U.S., for example, there were 28,000 cases reported in 1955 and 1956. After the first year of vaccine use, the number of cases reported dropped to 15,000. Today, the average annual number of reported cases in the U.S. has been fewer than five.

The two types of **trivalent** polio vaccine currently in use are the oral polio vaccine (OPV or Sabin vaccine) and the inactivated or killed vaccine (IPV or Salk vaccine). The U.S. Public Health Service has specific recommendations about the administration of polio vaccine. Generally, all persons between the ages of six weeks and 18 years must receive the OPV vaccine. The World Health Organization recommends that unimmunized adults travelling to developing countries be immunized with the IPV vaccine.

A primary vaccination series with either vaccine produces immunity to all three types of poliovirus; hence the term "trivalent" is used to refer to the vaccines. The primary OPV series consists of three doses -- 2 doses give 6-8 weeks apart and a third given at least 6 weeks and, customarily, 12 months after the

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second. The primary IPV series also consists of three doses -- 2 doses each given 4-8 weeks apart and a third dose given 6-12 months after the second.

In some people, a condition known as post-polio muscle atrophy or **post-polio syndrome** (PPS) occurs 30 to 40 years after an acute episode of polio[5]. PPS is characterized by progressive weakness and atrophy of muscles, difficulty in breathing, and severe pain in muscles and joints. It is estimated that one-third of the 300,000 to 600,000 polio survivors in the U.S. have PPS.

Several explanations have been put forth to explain post-polio syndrome, including an acceleration of the aging process in polio survivors. As the body ages, it experiences a decrease in the number of anterior horn cells (nerve cells) in the spinal cord. These cells transmit nerve impulses to the muscles and cause them to move. The anterior horn cells are the cells which are destroyed or damaged in an acute attack of poliomyelitis, and survivors of severe polio may have too few left to allow for normal age-related losses.

How have animals helped in the study of polio?

Dr. Albert Sabin's 1956 paper in the *Journal of the American Medical Association*[6] stated that "approximately 9,000 monkeys, 150 chimpanzees and 133 human volunteers have been used thus far in the quantitative studies of various characteristics of different strains of poliovirus." These studies, according to Sabin, "were necessary to solve many problems before an oral polio vaccine could become a reality."

> ***My own experience of more than 60 years in biomedical research amply demonstrates that without the use of animals and human beings, it would have been impossible to acquire the important knowledge needed to prevent much suffering and premature death, not only amongst humans but also amongst animals.***
>
> - Albert Sabin

The viral cause of paralytic polio was proven in 1908 after polio was induced in rhesus monkeys following injection with extracts of the spinal cord fluid of a boy who had died from polio[1]. Several weeks later, the monkeys developed paralytic polio, and the disease was transmissible to other monkeys. Since the spinal cord fluid had been sterilized to kill any bacteria prior to inoculation of the monkeys, this important experiment demonstrated the presence of a virus and provided a crucial animal model for studying the disease.

Monkeys were later used to show the virus infected the anterior horn cells in the spinal cord that normally supply stimuli to nerve cells[7].

Polio research was among the earliest research on viruses and was extraordinarily difficult. Unlike bacteria, which could be seen with a microscope and studied in culture dishes, viruses are so small they could not be

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observed with the instrumentation available in the early 20th century. There were attempts as early as 1913 to replicate poliovirus in tissue culture, all of them unsuccessful. Scientists initially concluded that poliovirus could not live outside nerve tissue, making it even more difficult to work with than other viruses because nerve tissue could not be grown outside the body.

In 1932, the invention of the electron microscope enabled scientists to study extremely small forms of life. With the use of electron microscopy and experiments in mice, the visualization of viruses became possible in 1935. In 1939, a strain of poliovirus established in mice was reported, and progress in polio research began to accelerate.

In the 1940s, scientists were not certain how many types of poliovirus could infect humans. The existence of three poliovirus types, all of which would need to be included in a "trivalent" vaccine, was confirmed by vaccine pioneer Jonas Salk using monkeys. In 1947, Type 2 poliovirus was purified from the brain tissue of infected cotton rats. Researchers subsequently showed that such a virus preparation, when chemically inactivated with formaldehyde and employed as an experimental vaccine, was capable of immunizing cotton rats against poliovirus paralysis. Soon after, using unpurified, inactivated Type 1 virus from the spinal cord tissue of monkeys, researchers demonstrated that nonhuman primates could be similarly protected.

A major breakthrough in the fight against polio occurred earlier in 1949 due to the work of Boston-area scientist Dr. John Enders. Enders and his colleagues showed that poliovirus could be grown in human tissue culture using a suspension of mouse brain infected with a strain of poliovirus[8]. This discovery, for which Enders and his colleagues were awarded the Nobel Prize in Medicine or Physiology in 1954, made possible the large-scale production of sufficient quantities of the three virus types for preparing an inactivated virus vaccine for human use.

Following extensive safety testing in nonhuman primates, preliminary studies carried out in human volunteers in 1952, using poliovirus propagated in tissue culture and then inactivated with formaldehyde, showed that a vaccine could be prepared that was safe and induced a satisfactory immune response. This provided the justification for a large-scale field trial carried out in the United States in 1954. The results, reported in 1955 as 99% effective against Type 2 and Type 3 polio strains, led to the licensing of the inactivated poliovirus vaccine developed by Salk for gen-

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eral application. This groundbreaking development, buttressed by decades of work in animal models, revealed that effective immunity to a virus infection could be induced without the need for experiencing the infection itself.

Albert Sabin subsequently produced a new oral polio vaccine based on the principle of inducing infection with attenuated virus in order to induce immunity. The attenuated live virus vaccine administered orally was tested in the former Soviet Union in 1959. The safe and effective oral vaccine was adopted soon thereafter and is the main polio vaccine used worldwide today.

In polio research, what alternative methods are used in conjunction with animal models?

The study of poliovirus and the development of a vaccine demonstrate how so-called alternative methods of research work together with animal models to provide the broad understanding of a disease and its causative agent that is necessary to develop treatments and cures.

To fully appreciate the interplay between animal models and "alternative" methods, it is important to understand the term "alternative" as it is understood in science. "Alternatives" refers to the "3R's" concept, which was first presented in a 1959 publication entitled *Principles of Humane Experimental Technique*, by W.M.S. Russell and R.L. Burch[9]. It is the definition used by government agencies when referring to "alternatives," and is widely accepted by throughout the scientific community. The "3R's" are:

- **Reduction**, which refers to the use of fewer animals to obtain the same amount or more information. Improving statistical methods to allow use of fewer animals is an example of reduction.
- **Refinement** describes the alteration of existing procedures to minimize any discomfort they may cause to the animals and can also refer to the development of animal models lower on the phylogenetic tree. Use of new, more effective analgesics or closer monitoring for signs of pain are examples.
- **Replacement**, which refers to the use of methods that do not involve whole, living animals. Computer models or cell and tissue culture are examples of replacement methodology.

RNA (ribonucleic acid) was identified as the infectious agent of poliovirus in 1957. Shortly thereafter, the basic steps of how poliovirus replicated were established, and the interaction of poliovirus with its antibody was analyzed. X-ray crystallography and electron microscopic analysis of poliovirus contributed to its further characterization. These advances, in conjunction with work in animals and in culture, contributed to the development of the two vaccines currently available.

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An example of both reduction and refinement in the use of animals to study polio was seen in 1946, when scientists demonstrated that vaccination against polio was possible in human beings after mice were used to create a weakened poliovirus that protected monkeys against the full-strength virus. The major advance from the mouse strain was a cheaper and more accurate diagnostic test to detect whether people had been infected with poliovirus[10]. In the early 1930s, a test had been developed using serum from monkeys, but the test required up to five monkeys per serum and there were doubts as to the accuracy of the test. These new diagnostic tests were indispensable in understanding polio, as they allowed researchers to reliably track how polio epidemics progressed.

Replacement of animals has also been possible in some studies of poliovirus through advances in genetic technology and instrumentation. Major progress has been made in recent years in understanding the poliovirus at the molecular level, particularly through knowledge of its complete **genome** sequence (a complete **DNA** sequence analysis has been made of all three virus types) and the three-dimensional structure of the virus and its cellular **receptor** have been made using x-ray crystallography.

Do we still need to use animals in polio research?

Although the use of nonhuman primates in polio research has decreased considerably, monkeys are still essential to the production of both live and killed polio vaccines, which are routinely produced in monkey kidney cell cultures. Through refinement of animal-based research over the years, a single pair of monkey kidneys produces 350,000 doses of oral Sabin vaccine.

Monkeys are still inoculated to test every lot of the live OPV vaccine for **neurovirulence** and the killed IPV vaccine for safety and efficacy[11]. In an example of replacement methodology, however, a technique that permits identification of mutational changes makes it possible to predict the neurovirulence of vaccine lots. Eventually this research may provide an ancillary method for the testing of polio vaccine for neurovirulence.

The late effects of polio are only beginning to be understood. Post-polio muscle atrophy (PPMA) affects many polio survivors. A 1986 study found that 25% of polio survivors had experienced new problems related to the disease contracted decades earlier. The most commonly reported symptoms are unaccustomed fatigue and new weakness in muscles, pain in muscles and/or joints, sleep problems, breathing difficulties, swallowing problems, and functional decline. At present, little is understood about the late effects of polio, the sum of which are known as **post-polio syndrome** (PPS).

Many scientists believe PPS is a result of persistence of poliovirus in the central nervous system, a hypothesis that must be studied with living animals over a period of time. The search for poliovirus genome sequences in

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the cerebrospinal fluid of monkeys inoculated with **wild-type** poliovirus will help define the link between persistence of poliovirus and post-polio syndrome[12]. A **transgenic** mouse model containing the human poliovirus receptor is also being used in these types of studies[13].

What lies ahead in polio research?

Further Vaccine Development

In May 1985, the Pan American Health Organization adopted the goal of eradicating the indigenous transmission of wild-type poliovirus in the Americas by 1990. The success of this campaign led the World Health Organization (WHO) to make a commitment to the global eradication of poliomyelitis during the first decade of the 21st century.

Eradication efforts will depend heavily on the application of existing vaccine strategies. However, for these efforts to be successful, further research must be conducted. Current objectives guiding vaccine research and development include optimizing immunization strategies and developing new delivery systems; continuing epidemiologic research to improve surveillance techniques; and improving vaccine stability and performance through more basic research.

Some experts believe that the WHO campaign to eradicate polio will only be successful if a new or improved vaccine is developed. While the success rate for the Sabin OPV vaccine is greater than 90 percent in the U.S., it shows only 60-70 percent success rates in the developing world. Although this is due in part to poor immunization programs in many underdeveloped countries, the oral vaccine is also less effective in the tropics. The vaccine is not as stable in hot and humid tropical climates and loses its potency within days. In addition, many children in underdeveloped countries suffer from gastrointestinal diseases that reduce the effectiveness of the oral vaccine.

The genetic technology that ushered in the biotechnology revolution is opening doors in polio research. Ongoing research in the development of new vaccine strains derived from the Sabin vaccine by recombination, further mutation or gene insertion may lead to **recombinant** vaccine strains with greater genetic stability and safety. For example, researchers are working on development of a live poliovirus that cannot mutate to increased neurovirulence. Recombinant viruses with specific alterations in their genomes have been constructed and viral genome sequences responsible for attenutation have been identified[14].

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Efforts are underway to minimize the number of boosters required for polio immunization. These include research into development of a single vaccine with a time-release mechanism.

Scientists are using *Escherichia coli* -- a common bacterium of the human gastrointestinal tract -- as a host for gene cloning. Work is being done to combine the poliovirus genes that code for the synthesis of the protein coat of the virus with *E. coli* genes so that the *E. coli* bacterium can then synthesize the viral proteins to be used in making a vaccine.

Vaccine-related Polio

All organisms undergo some degree of natural mutation, and poliovirus is no exception. In very rare instances, mutation in the oral polio vaccine has produced virus particles that were able to cause paralysis in vaccine recipients. Less than ten polio cases each year in the U.S. are vaccine-related, as no wild-type poliovirus has been isolated in the U.S. since 1979.

Transgenic mice carrying the human poliovirus receptor gene -- *meaning that they are susceptible to poliovirus infection* -- have been used to test poliovirus strains isolated from the spinal cords of patients with vaccine-associated polio. These transgenic mice have also proven to be susceptible to all three strains of poliovirus. They are being investigated as models for alternatives to nonhuman primates in testing oral poliovirus vaccine lots for neurovirulence[15].

Drug Therapies

Infection by poliovirus is initiated by attachment of the virus to specific molecules on cell surfaces called **receptors**. Molecular clones of the poliovirus receptor have been isolated and the receptor has been identified as a new member of the **immunoglobulin** family of proteins. Further study of the normal function of the poliovirus receptor is underway to help researchers develop effective drug therapies to block the entry of poliovirus into cells[16].

Recently, researchers have been able to replicate an entire poliovirus *in vitro*. This important advance will make it easier to analyze the assembly of poliovirus at the cellular level so that drug therapies to block this assembly can be developed.

Post-polio Syndrome

Scientists are working on a variety of avenues that may one day help people with post-polio syndrome (PPS). To understand PPS, it is first necessary to understand how poliovirus infects a cell. The ability of the poliovirus to attack certain cells, such as neurons, depends on the presence of a receptor specific to poliovirus on the surface of the cell. After binding to the receptor, the virus penetrates the cell and releases its genetic material, a single strand of **RNA**. The virus seizes the host cell in order to translate its own RNA into proteins,

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shutting off the host cell's protein synthesis. How the virus is able to shut off protein synthesis in host cells is an area of ongoing study.

Through animal research and biotechnology, the dream of global eradiation of polio is a realistic one. For those still suffering the lingering effects of this deadly and crippling disease, biomedical research offers hope for a better future.

GLOSSARY

Animal model ... an animal used in research that develops or can be induced to develop conditions mimicking a given disease or condition.

Anterior horn cells... motor neurons in the anterior horn of the spinal cord which project to skeletal muscles.

Antibody... a protein produced by the immune system in response to the presence of an antigen. It defends the body against substances identified by the immune system as potentially harmful.

Antigen... a substance that induces the formation of antibodies in the body because it is recognized by the immune system as a threat. It may be a foreign substance from the environment (such as chemicals) or found within the body (such as bacterial or viral toxins).

Attenuate ... reduce the virulence, or potency, of a virus.

DNA... The molecule that encodes genetic information in the nucleus of cells. It determines the structure, function and behaviour of the cell. DNA is a double-stranded molecule held together by weak bonds between base pairs of nucleotides. The four nucleotides in DNA contain the bases: adenine (A), guanine (G), cytosine (C), and thymine (T).

Endemic ... a term term that refers to a disease that occurs continuously and with predictable regularity in a specific area or population.

Epidemic... a disease outbreak ccurring suddenly in numbers in excess of normal expectancy.

Epidemiology... the study of the distribution and determinants of health and disease events in populations.

Formalin... an aqueous (water-based) solution of formaldehyde.

Gene... the smallest unit of heredity. The information from all the genes, taken together, makes up the blueprint or plan for the human body and its functions. A gene is a short segment of DNA which is interpreted by the body as a plan or template for building a specific protein.

Genome... the total set of genes carried by a cell, individual or species.

Immunization... a process used to initiate or enhance resistance to infectious diseases.

Immuno-globulin... a type of protein that is produced by plasma cells to help rid the body of an antigen.

Incubation period... the time from the moment of inoculation (exposure) to the development of the clinical manifestations of a particular infectious disease.

Inoculation... introduction of material (usually a vaccine) into the body tissues. Can also refer to the mode of entry of bacteria into the body.

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Iron lung... a large metal cylinder operated like a pair of bellows to regulate the breathing of polio patients to keep them alive.

Murine... of or relating to a mouse.

Neuromuscular junction... the site where a nerve cell meets the muscle cell it helps activate.

Neuron... a nerve cell.

Neuro-virulence... the potency of a virus toward nerve cells.

Poliomyelitis ... a disorder caused by viral infection that can affect the whole body, including muscles and nerves. Severe cases may cause permanent paralysis or death.

Post-polio muscle atrophy... See **Post-polio syndrome**.

Post-polio syndrome... a condition characterized by new neuromuscular symptoms, including muscle weakness, that develops years after recovery from poliomyelitis. The symptoms may vary from simple nonprogressive deterioration of function, with joint pain, fatigue, and subsequent stabilization, to atypical forms of spinal muscular dystrophy. The new, slowly progressive muscle weakness may occur in muscles that were previously affected by polio and recovered or in muscles that were clinically unaffected by the acute disease.

Receptor... a structure on the surface of a cell characterized by selective binding of a specific substance and a specific physiologic effect that accompanies the binding.

Recombinant... a cell or organism with a new combination of genes not found together in either parent.

RNA... a nucleic acid (ribonucleic acid) found in all living cells. Plays a role in transferring information from DNA to the protein-forming system of the cell.

Strain ... type.

Transgenic... a term describing a plant or animal that has had genes from another organism put into its genome using recombinant DNA techniques.

Trivalent... describes a vaccine which produces immunity to three strains of a virus.

Vaccine... a substance introduced into the body either orally or by injection that "tricks" the immune system into producing antibodies, i.e., immune system particles that protect against the disease-causing agent.

Virus... organisms of a noncellular nature consisting of DNA or RNA and a protein coat. They range in diameter from 20-300nm.

Wild-type... the original parent strain of a virus, bacterium, or other organism.

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