

# HISTORY VACCINES

Events noted represent some (not all) notable milestones in the compelling history of vaccine development and licensure.



Chinese smallpox inoculation

1000

## Early Inoculation and Variolation

A Chinese statesman's son was said to have been inoculated against smallpox by blowing powder from pulverized smallpox scabs into his nostril. Inoculation may also have been practiced by scratching matter from a smallpox sore into the skin. Inoculation and variolation were practiced in Africa and the Ottoman Empire as well, before spreading to Europe and the Americas.



Jenner vaccinating James Phipps

1796

## Jenner's Breakthrough: The Birth of Vaccinology

After observing that cowpox infection seemed to protect humans against smallpox, Edward Jenner inoculated an eight-year-old boy with cowpox matter. He then repeatedly "challenged" the inoculation by exposing the boy to smallpox, who never fell ill. Jenner's method of vaccination grew in popularity and eventually replaced variolation. The term "vaccines" is a reference to the origin of Jenner's breakthrough; vacca is 'cow' in Latin.

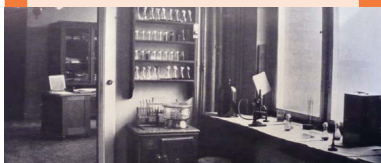


Lab Institut Pasteur

1879

## First Laboratory Vaccine

Having noted that laboratory cultivation led to attenuation of fowl plague bacteria, French chemist and microbiologist Louis Pasteur also observed that it induced resistance to subsequent challenges from virulent bacteria. Further studies gave rise to Pasteur's development of viable and useful vaccines against anthrax, cholera, and rabies based on the concept of "attenuation."



Koch Lab

1882

## Koch Isolates and Cultures Bacilli

Robert Koch, a German physician who helped establish bacteriology as a science, announced his discovery of the agent that causes tuberculosis. For a time called "Koch's bacillus," today it is known as mycobacterium tuberculosis. In 1883, he discovered the vibrio that caused cholera, and then established the microbial basis of disease "Koch's Postulates," which are still used today.



1922 commemorative tag picturing the attack on Joseph Meister

1885

## Pasteur and Roux Develop Rabies Vaccine

Virtually every infection with rabies resulted in death, until Louis Pasteur and Emile Roux developed the first rabies vaccine. This vaccine was first used on a human, nine-year old Joseph Meister, who had been mauled by a rabid dog.

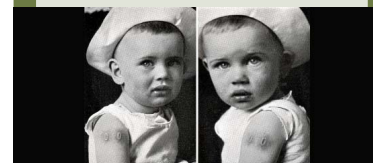


Administering diphtheria antitoxin derived from horse serum

1890

## Discovery of Diphtheria Antitoxin

German physiologist Emil von Behring, who discovered diphtheria antitoxin, was awarded the first Nobel Prize in Physiology or Medicine in 1901 for developing the first successful vaccine for diphtheria and tetanus.

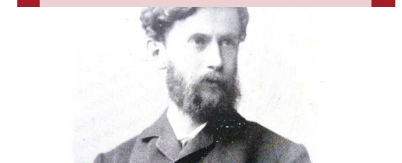


Vaccination Vesicles

1891

## Advances in Vaccine Production

English physician S. Monkton Copeman showed that adding glycerin to lymph acts as a germicide. As glycerin came to be widely used, it reduced transmission of harmful microbes via the lymph.

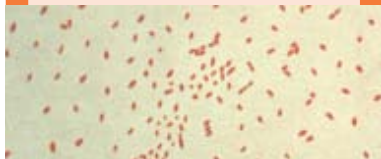


Paul Ehrlich

1896

## Theory of Immunity Developed

German immunologist Paul Ehrlich, who won the Nobel Prize in Physiology or Medicine in 1908, developed the first synthetic pharmaceutical drug for treating syphilis. His receptor theory of immunity, which was used to explain toxin-antitoxin interactions and, later, the relationship between antigens and antibodies, became a cornerstone of 20th century immunology. He also identified the difference between active and passive immunity.

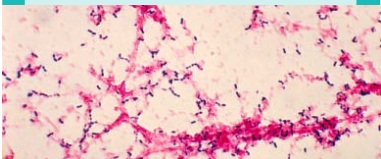


Photomicrograph of Pertussis Bacteria

1906

### Bordet and Gengou Isolate B. Pertussis

Belgian immunologists Jules Bordet and Octave Gengou isolated B. Pertussis in pure culture and developed the first pertussis vaccine. Efforts to develop an inactivated whole-cell pertussis vaccine began soon after, and in the 1920s American pediatrician Louis Sauer developed a vaccine against whooping cough.



Streptococcus pneumoniae, the bacteria responsible for pneumococcal meningitis, is very common, and normally lives in the back of the nose and throat, or the upper respiratory tract

1911

### First Pneumococcal Vaccine Trials

British bacteriologist Almroth Wright and colleagues developed a crude whole-cell pneumococcal vaccine to immunize South African gold miners, a group with an extremely high incidence of serious pneumococcal infections.



Horses and other animals were used to produce antitoxins in a variety of diseases

1914

### Park's Diphtheria Breakthrough

American bacteriologist William H. Park studied the use of diphtheria toxin-antitoxin mixtures to produce active immunity in animals, and then humans. He adjusted substance amounts until achieving a balance between lasting immunity and reactions to the mixture. This method was used in humans until it was replaced by toxoid immunization.



A technician in a Bangladesh laboratory organizing glass vials. Smallpox vaccine would later be placed in the vials, freeze dried in a desiccation machine, and subsequently capped

1918

### Freeze-Dried Vaccine Used in Tropical Climates

The Vaccine Institute in Paris produced a freeze-dried, vacuum-packed smallpox vaccine that addressed problems associated with air-dried vaccine in tropical climates. The product was used in French Guiana and other tropical French colonies. Its use continued for decades and it became crucial to widespread vaccination programs in tropical areas in the 1970s.



A child is given a BCG vaccination by a member of a TB health team in Thailand

1921

### BCG Vaccine Introduced for Human Use

The Bacillus Calmette-Guerrin (BCG) vaccine was introduced for human use, a collaborative breakthrough between fellow bacteriologist Albert Calmette, and his veterinarian colleague, Camille Guerin.



Micrograph of a group of Clostridium tetani bacteria, responsible for causing tetanus in humans

1924

### Tetanus Toxoid Vaccine Developed

P. Descombey developed tetanus toxoid vaccine, a vaccine widely used to prevent tetanus induced by battle wounds during World War II.



Corynebacterium diphtheriae bacteria

1926

### Glenny Develops Adjuvant

Used alone, diphtheria toxoid produced a low level of antibody response and inadequate immunity. Alexander Thomas Glenny increased the effectiveness of diphtheria toxoid by treating it with aluminum salts.



Oswald Avery at his lab

1929

### Antigen Conjugation Introduced

Oswald Avery and Walther Goebel introduced the concept of conjugation of bacterial antigens on a single backbone.



Max Theiler

1936

### Theiler Develops Yellow Fever Vaccine

South African/American virologist Max Theiler and colleagues developed a live attenuated vaccine for yellow fever using tissue cultures prepared from embryonated chicken eggs.



Child receives combination DTP

1942

### First DTP Combination Vaccine

American scientist Pearl Kendrick combined the whole-cell pertussis vaccine with diphtheria and tetanus toxoids to generate the first DTP combination vaccine.



*Ochlerotatus japonicus*, suspected vector of Japanese encephalitis in Asia and West Nile virus in the U.S.

1944

### Vaccine for Japanese Encephalitis

American microbiologist Maurice Hilleman helped develop a Japanese encephalitis vaccine to protect U.S. troops during World War II. Hilleman's vaccine was never widely tested, yet it was given to thousands of U.S. soldiers and likely prevented disease in many. Later, other vaccines replaced it, notably, a JE vaccine developed in China in the 1980s.



*Influenza ward, U.S. Army, Base Hospital No. 88, Langres, France*

1944

### Influenza Vaccine Developed

American virologist Thomas Francis, Jr. developed the killed-virus influenza vaccine, which was first used on soldiers during World War II. Flu is the only vaccine that is continually updated because the virus constantly evolves.



*Polio vaccines being delivered during the epidemic in 1963 in the U.S.*

1949

### Viral Cultures Pave The Way For Polio Vaccine

John Franklin Enders, Thomas Huckle Weller, and Frederick Chapman Robbins succeed in growing polioviruses in non-nervous tissue. The breakthrough allowed poliomyelitis to be harvested in cultures, drastically enlarging stockpiles for study, and later, vaccination efforts. The team would receive the 1954 Nobel Prize in Physiology or Medicine for the discovery.



*Jonas Salk giving the polio vaccine to his son, Peter Salk*

1952

### Salk Begins Early Polio Vaccine Tests

American virologist Jonas Salk and his team began the first human tests of their killed-virus polio vaccine. They tested the vaccine against all three strains of polio, some in combination, others individually.



*A nurse administering oral polio vaccine at a clinic in Freetown, Sierra Leone*

1960

### Sabin's Polio Vaccine Licensed

The U.S. Surgeon General recommended that American medical researcher Albert Sabin's live poliovirus vaccine be licensed. This vaccine provided protection against Type 1 poliovirus, and vaccines against Types 2 and 3 soon followed. By 1963, a single vaccine would combine all three types.



*Boy with measles*

1962

### Attenuated Measles Vaccine Developed

Maurice Hilleman and colleagues developed an attenuated measles vaccine by passing—over 80 times—John Enders' measles virus strain through different cell types. The resulting vaccine was given with a dose of gamma globulin antibodies to reduce reactions.

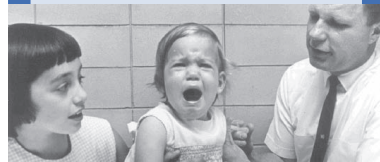


*Smallpox vaccination program in a village near Mandalay, Burma*

1965

### New Delivery Method: The Bifurcated Needle

American microbiologist Benjamin Rubin patented the bifurcated needle for delivery of smallpox vaccine. These needles required less vaccine per dose and were easier to administer than previous methods. This would have significant implications for smallpox vaccination campaigns.



*Robert Weibel, MD, vaccinating Hilleman's daughter while her half-sister looks on*

1967

### Mumps Vaccine Produced

In 1963 Maurice Hilleman cultured the mumps virus from his daughter's throat, and in 1967 a vaccine was produced. The strains used in the manufacture of Mumpsavax contained two distinguishable viral substrains, JL1 and JL2. In the U.S., the strain-based vaccines supplanted the killed-virus vaccine in 1978.



*A child being vaccinated in Yemen*

1969

### Rubella Vaccine Created, Then MMR Vaccine

Maurice Hilleman modified a rubella vaccine virus developed by Paul Parkman and Harry Meyer. The vaccine entered commercial use by 1970. In 1971, the MMR vaccine was licensed to provide protection against measles, mumps, and rubella from a single injection.



*Micrograph of Pneumo*

1977

### First Pneumococcal Vaccine Approved

Work on pneumococcal vaccines began in the early 20th Century but was abandoned with the discovery of antibiotics. In 1977, the first modern pneumococcal polysaccharide vaccine made of multiple strains was approved.



*Neisseria meningitidis* is responsible for causing meningococcal meningitis

1978

### Meningococcal Vaccine Made Available

The first meningococcal vaccine made available was effective against two of the major meningococcus groups. Currently, licensed vaccines provide some protection against all groups except B.



Flyers encouraged parents to vaccinate their children against rubella

1979

### Rubella: An Improved Vaccine is Licensed

The original rubella vaccine was replaced in the U.S. by American physician Stanley A. Plotkin's newly licensed RA27/3 vaccine. While previous rubella vaccines were grown from animal cultures, RA27/3 was isolated from a fetus infected with rubella, and cultured in a cell line derived from human fetal cells. This strain, still in use today, replaced the original rubella vaccine in the MMR shot.



Health worker administering hepatitis B birth dose in Lombok

1986

### First Recombinant Vaccine

Recombinant Hepatitis B vaccine was licensed—the world's first vaccine made by cloning a viral component in yeast, making the vaccine free of association with blood products. The vaccine protects against Hepatitis B acquired during birth and exposure to the virus later in life, thereby preventing viral-induced liver cancer.



Mothers line up with their children to receive vaccinations in Salamanca, Liberia

1995

### Hepatitis A Vaccine Licensed

Hilleman had been working on Hepatitis A for decades and was one of the first scientists to detect the virus and its antibodies. Tests in 1992 showed that his vaccine was 100% effective in preventing the disease and the vaccine was licensed in 1995.



Vaccinators transporting polio vaccines in cold boxes during an Ethiopian polio immunization campaign

2000

### GAVI Launched

The Global Alliance for Vaccines and Immunization (GAVI) is launched, with the Vaccine Fund.

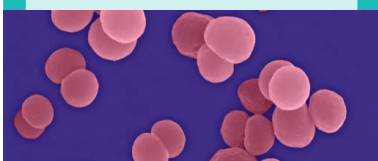


Infant routine immunization

2000

### Conjugated Pneumococcal Vaccine Licensed

A heptavalent pneumococcal conjugate vaccine (PCV7) is licensed in the U.S. and recommended for routine use in infants.



Scanning electron microscope image (3,750 x) of *Neisseria meningitidis*, a bacterium that causes meningococcal disease

2005

### First Conjugate Meningococcal Vaccine Licensed

The first conjugate meningococcal vaccine in the U.S. was licensed in 2005, with a second licensed in 2010.

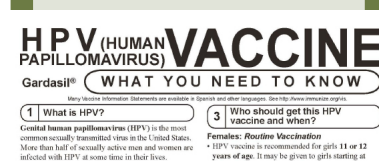


An infant is vaccinated at a newly established clinic in Pakistan's Kyber Pakhtunkhwa province

2005

### MMRV Vaccine Licensed

The U.S. FDA licenses a combined, live attenuated measles, mumps, rubella, and varicella (MMRV) vaccine for use in children aged 12 months-12 years.



HPV Vaccine Information Statement (VIS)

2006

### The Human Papillomavirus (HPV) Vaccine Licensed

Quadravalent HPV vaccine is licensed, the first vaccine against a viral infection that causes many diseases, including genital cancers in both females and males.



By vaccinating children against rotavirus and offering new ways to fight severe diarrhea, Nicaragua is making important strides in protecting children and saving lives

2006

### Pentavalent Rotavirus Vaccines Shown Safe and Effective

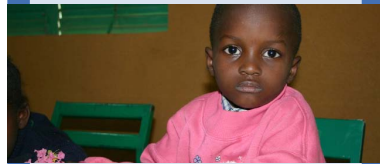
In 2006, two vaccines against Rotavirus A infection, consisting of five human-bovine reassortant strains, were shown to be safe and effective in children. Both are taken orally and contain disabled live virus.



*Modern vaccine production*



*Triage section of the central district hospital in Manhica, Mozambique*



*Little girl in Burkina Faso, Mali, where a country-wide vaccination program of MenAfriVac™ began in December 2010*

2006

### **Shingles Vaccine Licensed**

The U.S. FDA licensed the shingles vaccine, which is similar to the pediatric chickenpox vaccine licensed in 1995, but of a higher potency; it contains approximately 14-times more virus than the pediatric vaccine.

2010

### **13-Valent Pneumococcal Conjugate Vaccine Licensed**

The U.S. FDA licenses a 13-valent pneumococcal conjugate vaccine (PCV13). On the same day, the Advisory Committee on Immunization Practices (ACIP) recommended this vaccine replace the PCV7 vaccine in the infant schedule.

2010

### **Meningitis A Vaccine Introduced in Africa**

MenAfriVac™ (meningococcal A conjugate vaccine) is introduced in sub-Saharan Africa, the result of a collaboration between WHO and PATH, with manufacturing in India. It marked the first time a vaccine had been specifically designed for Africa, where it was introduced before any other region.



# HISTORY of VACCINES