**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’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.

**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.”

### History of Vaccines

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Chinese smallpox inoculation</td>
<td>1000</td>
</tr>
<tr>
<td>Jenner vaccinating James Phipps</td>
<td>1796</td>
</tr>
<tr>
<td>Lab Institut Pasteur</td>
<td>1879</td>
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### History

- **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.

- **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.

- **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.

- **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.

- **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.
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.

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.

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.

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.

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.
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.

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.

American virologist Jonas Salk and John Franklin Enders, Thomas Huckle Weller, and Frederick Chapman Robbins succeeded 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.

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.

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.

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.

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.

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.
### Meningococcal Vaccine Made Available

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

### 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.

### Recombinant Hepatitis B Vaccine Licensed

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.

### Hilleman had been working on Hepatitis A for decades and was...

Tests in 1992 showed that his vaccine was 100% effective in preventing the disease and the vaccine was licensed in 1995.

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

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.

### Quadravalent HPV vaccine is 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.
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.

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.

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.