



Vaccines: The History and Science

A brief overview

Definitions

- **Antigen:** Foreign substance, usually from an infectious microbe, that triggers the production of antibodies in a host. That production process is rapid in a host that has a strong immunity system and has had previous exposure or vaccination, because the body “remembers” the structure of all known antigens.
- **Antibody:** The host body’s response to an antigen, with the production of a blood protein. The protein is specifically structured to neutralize the attack of the microbe and will be triggered rapidly in any subsequent infection by the microbe.
- **Immunity:** The host body’s response to a previously known antigen, which allows it to avoid the symptoms of a disease from an infectious microbe because of the ready presence of antibodies and related mechanisms.
- **Acquired Immunity:** Immunity resulting from exposure to an infectious microbe by natural infection or vaccination
- **Passive Immunity:** Short-term immunity resulting from the transfer of antibody from an immune individual to a non-immune individual. An example includes taking plasma from a recovered patient and transfusing into a diseased patient to help fight serious infection.
- **Recombinant:** Recombination of genetic material. Bringing genes from one source to combine with genes from another source creating gene sequences that are not naturally found.

Definitions

- **Vaccine:** a preparation of killed microorganisms, living attenuated organisms, or living fully virulent organisms that is administered to produce or artificially increase immunity to a particular disease (Merriam Webster)
- **Vaccination:** The act of administering a vaccine
- **Pathogen:** Microorganism (bacteria, virus, fungus, parasite) capable of causing disease in humans
- **Smallpox:** Highly contagious and lethal infection caused by the variola virus. Infected individuals develop fever and distinct rash. The term “large pox” or “great pox” was used in the 15th century to describe the skin sore caused by syphilis



Patient with smallpox
Source: CDC Bangladesh 1974



History of Vaccination Efforts



Early Evidence of Viruses in Humans

- Analysis of variola virus genes suggests that the virus evolved from a cowpox-like virus thousands of years ago in Eastern Africa
- Smallpox lesions have been found on the head of a 3000-year-old Egyptian mummy

Smallpox scars on the head of an ancient mummy.

Photo courtesy of the World Health Organization



Early Efforts to Prevent Illness by Inducing Immunity

- 2000 years ago in China and India **variolation** was used to prevent smallpox
- **Variolation** involved taking a small amount of infectious material from a human smallpox sore (pustule) and scratching it into the skin or inhaling through the nose of a non-immune person hoping to cause a mild but protective infection

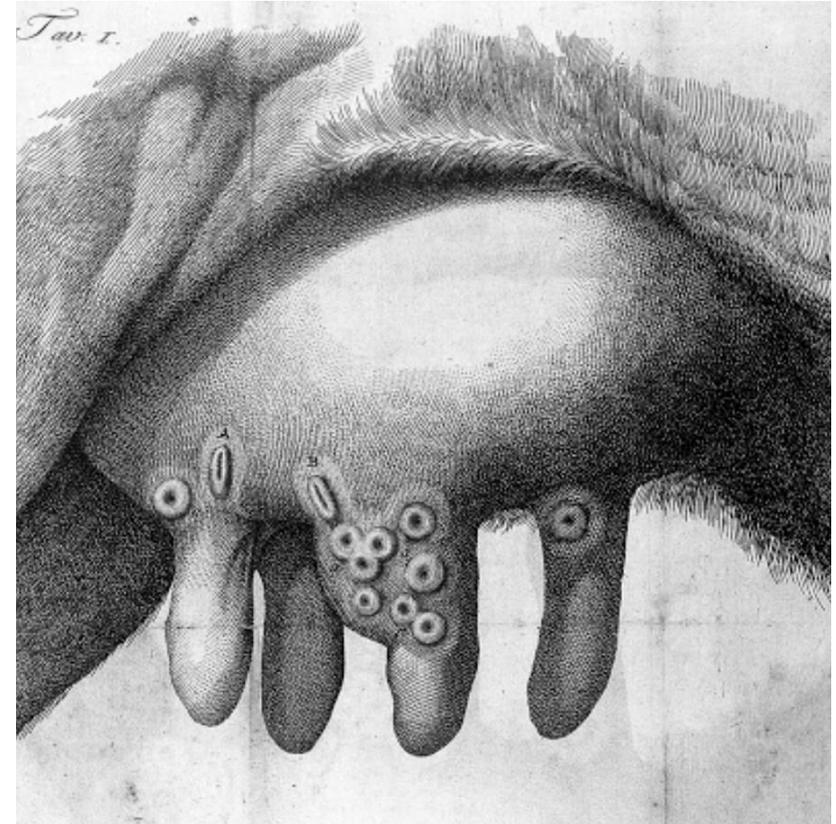


Science Museum.org.uk

Edward Jenner and the The First “Vaccine”

- In 1796, learning that dairymaids were protected from smallpox, Jenner inoculated an 8-year-old boy with material from a fresh **cowpox** pustule. Jenner then exposed the boy to material from a **smallpox** pustule. The boy didn't develop smallpox, and Jenner used that to theorize that exposure to one eliminated risk for the other.
- Jenner decided to call his procedure “vaccination” based on the Latin word for cow (*vacca*) in describing the process of exposure. He chose not to use the process to get wealthy and he received ridicule from some for his ideas.
- However, variolation diminished as a practice and was made illegal in England in 1840.
- In 1977 smallpox was eliminated because of world-wide vaccination.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1200696/>



Cowpox pustules

Understandinganimalresearch.org.uk

Anthrax Vaccination: The Famous Trial In Animals by Louis Pasteur

- Anthrax (*Bacillus anthracis*) has a high mortality rate and kills in a matter of days and can live dormant in soil for years, affecting both animals and humans.
- There's written documentation from China 5000 ago that describes anthrax-like outbreaks, and Virgil describes something similar in 100 BC. In Egypt around 300 BC, anthrax may have been widespread enough to have been labeled one of the plagues in biblical stories, in an outbreak responsible for decimating domestic livestock.
- In 1877, Robert Koch studied the bacterium that causes anthrax.
- 1881 Louis Pasteur weakened (attenuated) *Bacillus anthracis* by chemical exposure in the laboratory. Pasteur set up the experiment with 50 cattle: 25 were injected twice with the attenuated bacteria and 25 cattle were not injected. Within 30 days all non-vaccinated animals died but none of the inoculated ones had, demonstrating the effectiveness of the vaccine. Despite that, a vaccine wasn't regularly used until the 1930s.
- A large outbreak of anthrax occurred near a Soviet military microbiology facility in 1979, which created speculation about whether it was a naturally occurring outbreak.



Pasteur injecting sheep
worldhistoryproject.org

The Human Toll of Viruses

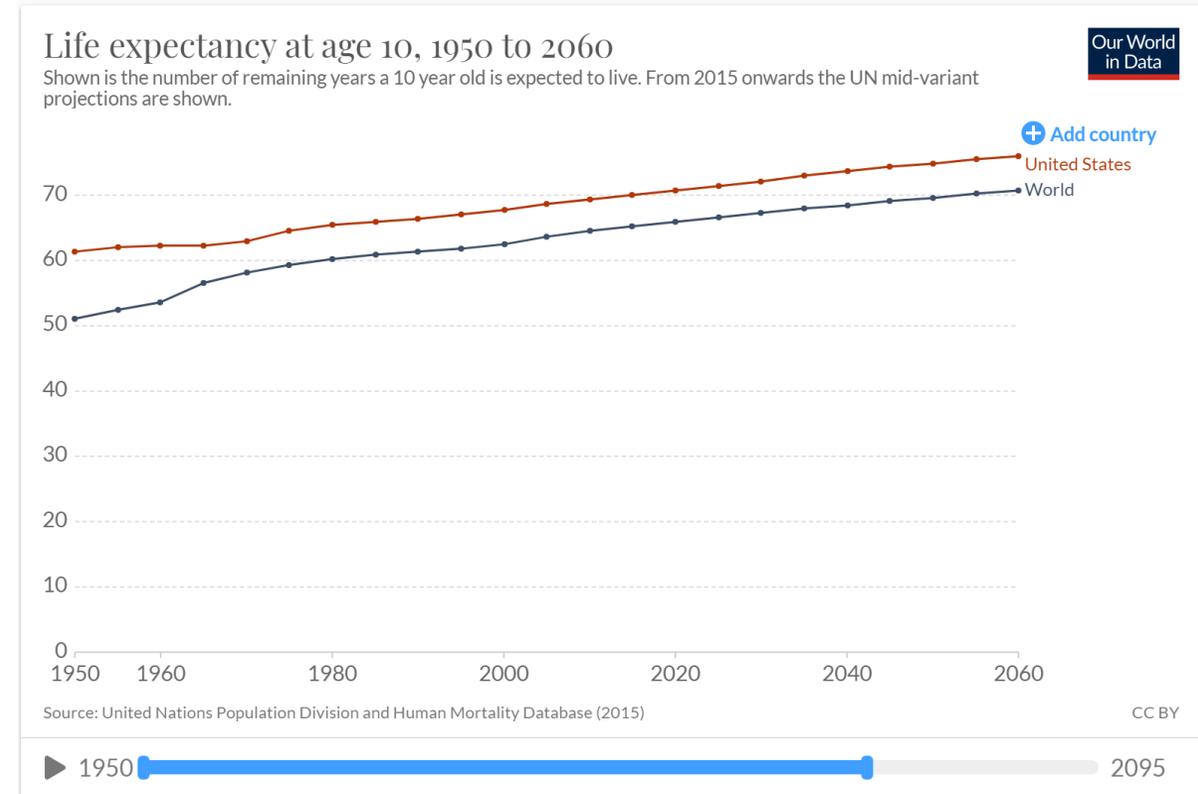
- The 1918, the Spanish Flu killed an estimated 50,000,000 worldwide
- In 1920, the US population was 106 million
 - There were 1,142,558 deaths from all causes
 - 13,400 died from diphtheria
 - 11,000 died from whooping cough (pertussis)
 - 7,700 died from measles
- In 1952 a large polio epidemic in the US occurred
 - 57,000 cases – 21,200 paralyzed – 3,145 died



Influenza precautions – 1918
The morningstarnews.org

Life Expectancy

- Life expectancy of “cavemen” was estimated at 25 years
- Life expectancy 2000 years ago was approximately 40 years, because of early death from injury in heavy labor, childbirth, and disease. But people, even 2000 years ago, lived into their 70s.
- After 1200 AD, humans lived to be between 60-70, if they survived past the age of 10. The exception was the years of the bubonic plague, which reduced the lifespan to 45.
- Between 1700 and 1880, once we factor out childhood mortality, life expectancy remains fixed around 62 years old.
- With the introduction of widespread vaccination programs and use of antibiotics for bacterial infections in the 1920s, we see a consistent climb in life expectancy that continues to this day, with an average life expectancy going from 62 to 78.
 - In 1900, U.S. life expectancy was only 47 y primarily because infant mortality was so high
 - In 1900, 30% of all U.S. deaths were children < 5 y
 - In 2000, U.S. life expectancy was 77 y
 - In 2000, 1.4% of all U.S. deaths were children < 5 y



Selling the Public on the Process: Unvaccinated and Vaccinated Boys with Smallpox



Boy on left was not vaccinated and has severe smallpox while boy on right was vaccinated and has mild smallpox.

This photograph is from a collection of lantern slides used by Philadelphia physicians to illustrate the risks of not vaccinating. Early 1900s.

The Historical Medical Library of The College of Physicians of Philadelphia

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Making and
Manufacturing
of Vaccines



Making Vaccines

Whole Organism Vaccines

Pros: excellent antibody production

Drawbacks: Slow production process, more side effects

- **Live Attenuated:** Growing a pathogen in culture in the laboratory and passing to a new culture over and over lessens or attenuates its virulence. The attenuated strain can then be injected into humans eliciting protective antibody without causing disease
- **Inactivated:** Heating or chemically treating a pathogen kills the microorganism without altering its ability to elicit protective antibody when injected into humans



Iron lungs for Polio epidemic – 1950s

Making Vaccines

Subunit/Partial Organism Vaccines

Pros: average antibody production, fewer side effects

Drawbacks: Slow vaccine production,

- **Inactivated toxin (toxoid):** Purified bacterial toxins can be inactivated by heat or chemical exposure without altering their ability to elicit toxin-neutralizing antibody when injected into humans.
- **Subunit:** Protein and polysaccharide subunits of a pathogen responsible for eliciting antibodies that protect against disease are purified and injected into humans. Because they are only a small portion of the pathogen, they do not cause disease.
- **Conjugated Subunit:** Polysaccharide subunits, which are weak inducers of antibody, can be attached or conjugated to a large protein. The conjugated subunit is a much stronger inducer of antibody.

Making Vaccines

Genetically Engineered Vaccines

Pros: rapid vaccine production, above average antibody production, fewer side effects

- **Recombinant:** Genes taken from a pathogen that make the protein (or polysaccharide subunit) responsible for eliciting protective antibodies are cloned (added) into bacteria (such as *E. coli*). Rapid growth of the *E. coli* produces large quantities of the desired subunit which is purified and used as a vaccine
- **Synthetic gene:** Knowing the molecular sequence of the gene (nucleic acid sequence) allows the gene to be artificially assembled before adding/cloning into an *E. coli* or similar microorganism to produce large quantities for vaccine production

Testing and Manufacturing Timeline

Phase 1 – Is it safe? Dozens of undiseased volunteers given increasing doses to monitor side effects

Phase 2 – 25-100 diseased patients given dosage, determined from phase 1, to evaluate benefits

Phase 3 – Several hundred healthy patients expected to be exposed to the disease given experimental vaccine or control patients given placebo

FDA NDA (New Drug Approval) – review and approval of submitted phase 1-3 data

Large Scale Production and Distribution

Administration and Immunity

Phase 4 – Thousands followed for safety/outcome over time after drug approval

This was a process that traditionally took years to complete. Public pressure and improved processes have reduced the timing.



The Race for the CoVID 19 Vaccine

A GLOBAL EFFORT

Making a Vaccine Against CoVID-19

SARS CoV 2 RNA genome is approximately 30,000 nucleotides in length. There are 4 different nucleotide molecules that occur in sequences throughout the entire genome. Shorter lengths of nucleotides within the genome act as genes providing templates for the synthesis of proteins

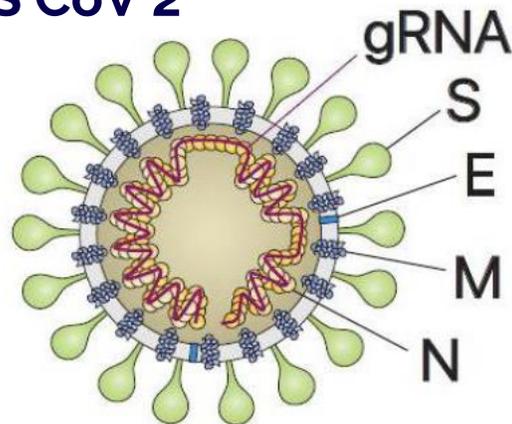
Genomic RNA (gRNA)



10 genes that make proteins



SARS CoV 2



Viral Structural Proteins:

- Spike (S)*
- Envelope (E)
- Matrix (M)
- Nucleoprotein (N)

***Viral Spike protein that vaccination targets**

Viral Accessory Proteins such as enzymes that make reactions happen to construct new viruses

- ORF 1a
- ORF 1b
- ORF 3a
- ORF 6
- ORF 7a
- ORF 8

Making a Vaccine against CoVID-19: Examples of Candidate Vaccines April 2020

Candidate Vaccine	Vaccine Characteristics	How Vaccine Works
Inactivated Whole Organism	Formalin treatment inactivates coronavirus without damaging proteins that elicit antibody production	Inactivated virus delivered by injection. Human recipient produces antibodies to multiple viral components including S-spike protein
Live Attenuated Whole Organism	Knowing the complete viral genome sequence, scientists recode the genome by genetic engineering to produce an attenuated virus that lacks genes responsible for virulence	Attenuated virus is delivered by injection. Human recipient produces antibodies to multiple viral components including S-spike protein without risk of disease
Live Attenuated Viral Vector - Genetically engineered recombinant subunit	Non-pathogenic Adenovirus containing coronavirus gene for S-spike protein	Engineered Adenovirus delivered by injection produces S-spike protein. Human recipient produces antibodies to S-spike protein. No disease caused by the Adenovirus

Making a Vaccine against CoVID-19: Examples of Candidate Vaccines April 2020

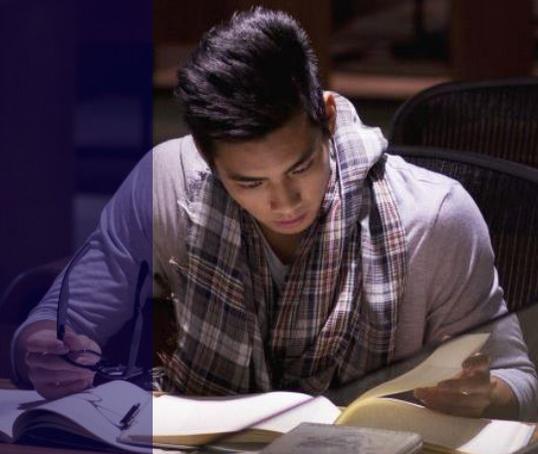
Candidate Vaccine	Vaccine Characteristics	How Vaccine Works
mRNA (messenger RNA) - Genetically engineered synthetic gene	An mRNA copy of a portion of the viral RNA gene encoding coronavirus S-spike protein is encapsulated in small lipid particles	Lipid particles are delivered by injection or nasal spray into human host cells. Human recipient produces antibodies to S-spike protein
DNA - Genetically engineered synthetic gene	A DNA copy of a portion of the viral RNA gene encoding S-spike protein is incorporated into human cells by pulsing an electric current which allows charged molecules such as DNA to transfer across human cell membranes	DNA transferred into human cells produces S-spike protein. Human recipient then produces antibodies to S-spike protein
Protein - Genetically engineered recombinant subunit	Coronavirus S-spike protein gene cloned into E. coli. Large amounts of S-spike protein produced by E. coli grown in laboratory	S-spike protein delivered by injection. Human recipient produces antibodies to S-spike protein

Key Learnings

- Inducing immunity to devastating infectious diseases has been used for thousands of years
- Scientific methods introducing inoculations to prevent specific diseases began approximately 200 years ago
- Modern medicine uses vaccination to prevent scores of life-threatening infections. Life expectancy, partially resulting from vaccination, has been extended from 47 years in 1900 to 78 years in 2020.
- To prevent escalation and continuation of a pandemic of the novel coronavirus (CoVID 19), there is a global effort to produce a vaccine in record time (< 1 year)



Appendix



Impact of Common Vaccines

Journal American Medical Association (JAMA) 298:2155-2163, 2007

Disease	Pre-Vaccine Era Cases and Deaths per Year (before 1980)		Post-Vaccine Era Cases and Deaths per Year (after 1980/2005)	
	Cases	Deaths	Cases	Deaths
Diphtheria	21,053	1,822	0	0
Measles	530,217	440	55	0
Mumps	162,344	39	6,584	0
Polio	16,316	1,879	0	0
Congenital Rubella	20,000	2,160	1	0
Tetanus	580	472	41	4
Hepatitis B	66,232	237	4,713	47
Haemophilus Type B	20,000	1000	208	< 5
Pneumococcus	63,067	6,500	5,169	4,850

Impact of Common Vaccines - 2009

- 4,131,019 U.S. births in 2009 (this is called the 2009 birth cohort)
- Childhood vaccinations given to 2009 birth cohort including:
 - Diphtheria, tetanus, pertussis, *Haemophilus* type b, polio, measles, mumps, rubella, hepatitis B, chickenpox, pneumococcus (pneumonia), hepatitis A and rotavirus
- Estimated morbidity/mortality avoided from birth to death in 2009 birth cohort because of childhood vaccinations
 - 20,000,000 cases of disease (morbidity)
 - 42,000 deaths (mortality from disease)
- Estimated cost avoidance in 2009 birth cohort because of vaccinations
 - Vaccination program costs - \$7.5 billion
 - Direct and indirect cost savings of vaccination program - \$76 billion
 - Net savings of vaccination program - \$68 billion (benefit/cost ratio = 10.1)



Pediatrics 133:577-585, 2014

Human Vaccines Over the Centuries

- **Year 1798**
 - Smallpox – Live attenuated whole organism
- **Years 1885-1897**
 - Rabies – Live attenuated whole organism
 - Typhoid – Inactivated whole organism
 - Cholera – Inactivated whole organism
 - Plague – Inactivated whole organism
- **Years 1900-1950**
 - Yellow fever – Live attenuated whole organism
 - Pertussis – Inactivated whole organism
 - Influenza – Inactivated whole organism
 - Diphtheria – Subunit inactivated toxin (toxoid)
 - Tetanus – Subunit inactivated toxin (toxoid)



Pasteur overseeing boy inoculated with rabies vaccine
PBS.org

Human Vaccines Over the Centuries

- **Years 1950-2000**

- Polio – Inactivated whole organism
- Polio – Live attenuated whole organism
- Measles – Live attenuated whole organism
- Mumps – Live attenuated whole organism
- Rubella - Live attenuated whole organism
- Chickenpox - Live attenuated whole organism
- Meningococcus (meningitis) - Inactivated whole organism
- Meningococcus (meningitis) – Subunit
- Pneumococcus (pneumonia) – Subunit
- Haemophilus type B (pediatric meningitis)– Subunit
- Pertussis (whooping cough) – Subunit
- Hepatitis B – Genetically engineered recombinant



Dr. Jonas Salk responsible for the first Polio vaccine in 1955
Time.com

Human Vaccines Over the Centuries

- **2000s**

- Zoster (chickenpox) – Live attenuated whole organism
- Zoster (shingles) – Genetically engineered recombinant
- Pneumococcus (pneumonia) – Conjugated subunit
- Meningococcus (meningitis) – Conjugated subunit
- Human Papillomavirus (cervical cancer) – Genetically engineered recombinant



Shingles vaccine
Betterhealthfacts.com