Vaccines and Immunity
On Adjuvants, Antibodies, and Herd Immunity

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Innate and Adaptive Immunity

non-specific/innate
- barriers
- phagocytes
  - neutrophils
  - macrophages
  - dendritic cells
- natural killer cells

specific/adaptive
- B cells
- T cells
  - $T_h$
  - $T_c$
- humoral response
- cell-mediated response
Immunology Basics: Essential Information in the Time of COVID-19
https://www.ildcollaborative.org/covid-19/immunology-primer
Vaccines function by safely triggering the kind of immune response that would occur following infection with a pathogen such as a virus or bacterium. This animation takes us through the cellular events that occur from the introduction of the vaccine into the body to the development of immunological memory and the protection that vaccines can offer to the wider population via herd immunity.
Vaccines train the immune system.

- Helper T cell
- B cell
- Killer T cell
- Dendritic cell
Antigens are molecular markers that can stimulate an immune response.
How Vaccines Work

[Diagram showing the process of how vaccines work]
How Vaccines Work

The innate immune system detects the antigen and alarms at the adaptive immune system.
How Vaccines Work

The adaptive immune system starts mounting a bespoke response.
How Vaccines Work

B cells convert to plasma cells, and start creating proteins called antibodies.
How Vaccines Work

The antibodies bind specifically to the antigen.
How Vaccines Work

Phagocytes destroy the antibody-bound pathogen.
How Vaccines Work

The adaptive immune system also produces killer T cells, which detect and destroy infected cells.
How Vaccines Work

To prevent against future infections, the adaptive immune system produces long-lived memory cells.
How Vaccines Work

Memory cells lie ready to produce the right antibodies and killer T cells if the same pathogen is seen again.
How Vaccines Work

Vaccines present the immune system with a killed, weakened, or partial pathogen so that immune cells will respond and eventually make memory cells. Those memory cells will provide protection if the person is exposed to the actual, active pathogen later in life.
How Vaccines Work
Vaccination: From Alchemy to Science

Variolation

In the beginning was ‘variolation’: deliberate ‘controlled infection’ with smallpox (Variola) puss or blister fluid to provide protection.

It was known that people only ever got smallpox once.

Variolation was practiced in China, India and parts of Africa and Europe since hundreds of years ago. But details varied as to how the procedure should be performed.
1721: The First ‘Clinical Trial’ in Immunology

Six prisoners in England were given the choice to either participate with the promise of freedom, or face their judicial execution.

Incisions were made on their legs and arms, and skin and puss from smallpox patient was rubbed in. One participant was instead given the skin and puss up her nose, becoming especially ill.

All participants recovered after about two days of smallpox symptoms and were released from prison.
Cowpox ‘Vaccination’

By 1760, anecdotes circulated in England and elsewhere that prior cowpox infection afforded milkmaids protection against smallpox.

In 1796, country physician Edward Jenner hypothesized that puss from non-fatal cowpox blisters might be used for inoculation instead of dangerous puss from smallpox patients.

Jenner inoculated an eight year old boy with puss from cowpox infection in a milkmaid. When given puss from a smallpox patient, the boy didn’t get ill.
Cowpox ‘Vaccination’

Jenner had difficulties publishing his experiment in a medical journal at the time, and self-published his work after repeating the experiment on others, including his eleven month old son.

The word ‘vaccine’ was later coined by surgeon Richard Dunning to describe Jenner’s process of inoculation with cowpox to protect against smallpox. *Vacca* is the Latin word for cow.

The wider use of the word vaccine is attributed to Louis Pasteur (1822–95).
Cowpox ‘Vaccination’

Jenner believed his work would lead to elimination of smallpox, but at the time he had no deep understanding of how vaccination worked.

At his time, it was not even known that cowpox and smallpox were viral diseases, caused by two related viruses.

The discovery that microbes underlay many known diseases of the time was made a century later by Louis Pasteur and Robert Koch (1843–1910).
Adjuvants and Vaccine Potency

In the 1920s it was discovered that a toxin made by the bacteria which cause diphtheria could be inactivated, and thus potentially used as a safe vaccine against the disease.

However, when injected into animals, the immunity was surprisingly short-lived.

In 1926, Edward Glenny, a London physician, and his research team found that when diphtheria toxoid was purified using aluminum salt, it became an effective vaccine.
Adjuvants and Vaccine Potency

Later other substances were discovered which when incorporated into vaccines help boost the immune response. Collectively they are called *adjuvants*. Aluminum salt remains the most widely used adjuvant.

Glenny proposed that aluminum salt helped the diphtheria toxoid stay in the body long enough for an immune reaction to develop.

To this day, however, it remains unclear how aluminum salt helps vaccines work.
Adjuvants and Innate Immunity

It has puzzled Charles Janeway (1943–2003) why the diphtheria toxoid, a protein that is foreign to the body, did not elicit long-term immunity.

*Why did puss from cowpox blisters work well as a vaccine, but molecules that are isolated from germs did not?*

As we saw last time, Janeway reasoned that the presence of something foreign is not enough for an adaptive immune reaction. There has to be another signal that indicates the presence of actual germs.
Adjuvants and Innate Immunity

This other signal comes from innate immune cells that have pattern-recognition receptors (PRRs) on their surfaces, each able to detect a specific type of germ and switch on an immune response appropriate to the particular threat.

It has become clear that adjuvants are important because they switch on the innate immune system.

As a result, instead of using aluminum salt, adjuvants could be tailor-made, using molecules that had been identified as specific targets for PRRs.
Animation

Vaccines 101: How new vaccines are developed

Vaccines are probably the most successful biomedical intervention in history, but why can they be so effective? The initial selection of the target antigens through to the way it is delivered can all impact how well a vaccine works. What goes into a vaccine and how do we test whether it’s doing its job properly? This animation answers these questions and more.
How New Vaccines Are Developed
Antigenic Target

Most coronaviruses encode only one large surface protein, the *spike protein*, which is responsible for receptor binding and membrane fusion with the host cell.

This is followed by release of the viral genome into the cytoplasm.
Antigenic Target

Antibodies that bind to the spike protein, especially to its receptor-binding domain (RBD), prevent its attachment to the host cell, and thus neutralize the virus.

The spike protein was identified as an antigenic target for the development of a vaccine against SARS-CoV-2 at a very early stage.

Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses
Jiang S, Hillyer C, Du L.
SARS-CoV-2 Vaccines in Development

Vaccine Platforms

More than 180 vaccine candidates, based on several different platforms are currently in development against SARS-CoV-2.

The World Health Organization (WHO) maintains a working document that includes most of the vaccines in development.

Draft landscape of COVID-19 candidate vaccines
https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
The platforms can be divided into

*classical vaccines*: these contain actual pathogens or toxins that have been weakened or killed,

*conventional vaccines*: these contain antigens that can provoke an immune response, and

*next-generation (genetic) vaccines*: these use genetic material taken from pathogens that instruct body cells to make antigens.
Whole-inactivated virus
Example: Polio vaccine

Live-attenuated virus
Example: MMR vaccine

SARS-CoV-2
- nucleocapsid protein
- RNA
- Spike protein

Antigen-presenting cells
Example: Not currently licensed

Viral vector
Example: VSV-Ebola vaccine

Protein subunit
Example: Seasonal

DNA
Example: Not currently licensed

Virus-like particle
Example: Human papillomavirus vaccine

RNA
Example: Not currently licensed
Next-Generation Nucleic Acid Vaccines
Next-Generation Viral Vector Vaccines

Vaccines 101: How new vaccines are developed

Viral vector

Pathogen
SARS-CoV-2 Vaccines in Development

Coronavirus Vaccines
Pfizer and Moderna both developed RNA vaccines.

AstraZeneca’s viral vector vaccine is based on a replication-defective chimpanzee adenovirus expressing a wild-type version of the spike protein.
Current vaccines trials are aiming for approval at roughly 50% efficacy.

Public health measures (distancing, masks, hygiene), and *bridge therapies* (e.g. monoclonal antibodies, antiviral drugs, steroids) will need to complement vaccines.
Herd Immunity

Population Level Protection
When “enough”, i.e. a certain percentage of people, acquire immunity, either through direct infection and subsequent recovery, or through vaccination, this can stop the spread of the infection through the population (“herd”).
**Herd immunity** works to control the spread of disease within a population when a specific amount of that population (threshold) becomes immune to the disease through vaccination or infection and recovery.

When the immunity threshold is reached, susceptible individuals are protected from infection because ongoing spread of disease is limited.

What Is Herd Immunity?
https://jamanetwork.com/journals/jama/fullarticle/2772168
Herd Immunity

Population Level Protection

The percentage, or threshold, of acquired immunity that is needed to reach herd immunity depends on $R_0$, the *basic reproduction number*, which is an estimate measure of the transmissibility of the new infectious agent. $R_0$ is estimated when the infectious agent is new and it can be assumed that (almost) everyone in the population is susceptible to infection.

**Complexity of the Basic Reproduction Number**

*Delamater PL, Street EJ, Leslie TF, et al.*

Herd Immunity

Population Level Protection

$R_0$ is an empirical estimation of the average number of people an infected person would infect.

If $R_0$ is less than 1, the infection will decline in the population, and eventually decay to zero.

If $R_0$ is equal to 1, the infection will stay alive in the population but does not reach pandemic proportions.

If $R_0$ is greater than 1, the infection will likely spread *exponentially* in the population, and can lead to a pandemic.
Herd Immunity

Population Level Protection

Factors influencing $R_0$ are: length of infectious period, contact rate, and mode of transmission.

The higher the $R_0$ of an infectious agent, the higher the percentage of the population that needs to be immune to achieve herd immunity: $100 \times (1 - 1/R_0)$.

Measles has an average $R_0$ of 18, and 95% threshold for herd immunity. 1918 flu had an average $R_0$ of 2, and seasonal flu has an average $R_0$ of 1.3 (reference).
Herd Immunity

Population Level Protection

SARS-CoV-2 likely had a median $R_0$ of 5.7 in the outbreak in Wuhan, China. That’s about double an earlier $R_0$ estimate of 2.2 to 2.7. This raises the threshold for herd immunity to 82%.

High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2
Herd Immunity
Herd Immunity without Vaccines Is Not a Plan
Excess Deaths Associated with COVID-19

CDC Morbidity and Mortality Weekly Report (Oct, 20):

“Overall, an estimated 299,028 excess deaths occurred from late January through October 3, 2020, with 198,081 (66%) excess deaths attributed to COVID-19. The largest percentage increases were seen among adults aged 25–44 years and among Hispanic or Latino persons.”

Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity—United States, January 26–October 3, 2020

https://www.cdc.gov/mmwr/volumes/69/wr/mm6942e2.htm?s_cid=mm6942e2_w
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