Nothing shocks me. I'm a scientist.

INDIANA JONES
Vaccines are our proven best defense against viruses

- Vaccination mobilizes the host immune system to prevent virus infections
  - Immune memory
- Vaccination breaks the chain of transmission
Vaccines stimulate a protective immune response

- Initial immune response
- Protective immunity
- Immunological memory

Antibody prevalence and T cell number over time:
- First infection
- Mild or inapparent reinfection

Time (days) and (years)
• Jenner, 1796

• Pasteur, 1885 - rabies vaccine; introduced the term vaccination from *vacca* (Latin, cow) in honor of Jenner

• Yellow fever, influenza vaccines - 1930s
Large-scale vaccination campaigns can be successful
Vaccines are now an integral part of our existence

- We immunize children, adults of all ages, domesticated and wild animals
- Because of immunization, many childhood diseases are rare
- Vaccines are a major part of the western nations public health measures, but not developing nations (e.g. rubella, measles)
A key concept about how vaccines work: Herd Immunity

- Maintenance of a critical level of immunity
- Herd immunity = population scale immunity
Herd Immunity

- Virus spread stops when the probability of infection drops below a critical threshold
- The threshold is virus (e.g. $R_0$) and population specific
- Smallpox: 80 - 85%
- Measles: 93 - 95%
- No vaccine is 100% effective
- When 80% of population is immunized with measles, 76% of population is immune
$R_0$ for SARS-CoV-2 = 2-3

Number of people who must be vaccinated to prevent virus spread:

$$1 - \frac{1}{R_0}$$

Fraction of people who must be immune to prevent virus spread:

50-70%
Vaccine hesitancy is dangerous to any vaccine program

- "Viral diseases are a thing of the past"
- "Herd immunity has not been proven to work"
- "Polio is long gone"
- "I never get the flu"
- "Measles is just a trivial kid’s disease"
- "Chicken pox only affects kids"
- "Kids should get infected naturally"
- "I’m not injecting anything into my body"
- "Vaccines make you sick, they cause autism, they cause multiple sclerosis, etc etc"
- "I know a guy who got the flu shot and then got the flu"
- "I can’t afford to immunize my kids"
- "I don’t have time this year"

When these attitudes prevail, society has serious problems with large-scale vaccination programs
In some cases, medical exemptions to vaccination are indicated.

These should not exceed 1% of the population, but they usually do as medical exemptions are inappropriately given.

**TWiV 496: Vaccines work, whether or not you believe in them**

https://www.microbe.tv/twiv/twiv-496/
Vaccine programs depend on public acceptance of their value.
Go to:

b.socrative.com/login/student
room number: virus

Herd immunity:

A. Demonstrates the importance of immunizing livestock
B. Emphasizes that not everyone must be immune to protect a population
C. Emphasizes that everyone must be immune to protect a population
D. Describes how group-think can dominate anti-vaccine choices
E. All of the above
Vaccines can be **active** or **passive**

- **Active** - instilling into the recipient a modified form of the pathogen or material derived from it that induces immunity to disease
  - *Long term protection*

- **Passive** - instilling the products of the immune response (antibodies or immune cells) into the recipient
  - *Short term protection*
A natural passive vaccine

![Graph showing the fraction of adult values over time with curves for IgM, IgG, and IgA, indicating changes in antibody levels from conception to adulthood.](image-url)
Passive therapy with convalescent serum

- Jordi Casals infected himself with Lassa virus at Yale in 1969
- Transfused with blood from nurse (Penny Pinneo) who had survived Lassa fever
- Ongoing trials of convalescent plasma for COVID-19 patients
Passive therapy with mAb

- Mouse mAb chimerized into human IgG1 scaffold
- Human mAb isolated from B cells of patients

Zmapp

M. Yuan et al., Science 10.1126/science.abb7269 (2020)

Virology Lectures 2020 • Prof. Vincent Racaniello • Columbia University
Requirements of an effective vaccine

- Induction of an appropriate immune response
  - \textit{Th1} vs \textit{Th2} response

- Vaccinated individual must be protected \textit{against} disease caused by a virulent form of the specific pathogen
  - \textit{Just getting ‘a response’ is not enough (e.g. producing antibodies)}
Requirements of an effective vaccine

- Safety: no disease, minimal side effects
- Induce protective immunity in the population
- Protection must be long-lasting
- Low cost (<$1, WHO); genetic stability; storage considerations; delivery (oral vs. needle)
Replication competent attenuated virus vaccine

Inactivated virus vaccine

Nonrecombinant, purified subunit vaccine

Replication competent virus vector vaccine

DNA vaccine

Protein

Virus-like particle vaccine

Subunit vaccine
### Viral vaccines licensed in the US

<table>
<thead>
<tr>
<th>Disease or virus</th>
<th>Type of vaccine</th>
<th>Indications for use</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Attenuated, oral</td>
<td>Military recruits</td>
<td>One dose</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated whole virus</td>
<td>Travelers, other high-risk groups</td>
<td>0, 1, and 6 mo</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yeast-produced recombinant surface protein</td>
<td>Universal in children, exposure to blood, sexual promiscuity</td>
<td>0, 1, 6, and 12 mo</td>
</tr>
<tr>
<td>Influenza</td>
<td>Inactivated viral subunits</td>
<td>Elderly and other high-risk groups</td>
<td>One dose seasonally</td>
</tr>
<tr>
<td>Influenza</td>
<td>Recombinant proteins</td>
<td>Elderly; those with egg allergies</td>
<td>One dose seasonally</td>
</tr>
<tr>
<td>Influenza</td>
<td>Attenuated</td>
<td>Children 2–8 yr old, not previously vaccinated with influenza vaccine</td>
<td>Two doses at least 1 mo apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 2–8 yr old, previously vaccinated with influenza vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children, adolescents, and adults 9–49 yr old (e.g., FluMist, FluBlo)</td>
<td>One dose</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Inactivated whole virus</td>
<td>Travelers to or inhabitants of high-risk areas in Asia</td>
<td>0, 7, and 30 days</td>
</tr>
<tr>
<td>Measles</td>
<td>Attenuated</td>
<td>Universal vaccination of infants</td>
<td>12 mo of age; 2nd dose, 6 to 12 yr of age</td>
</tr>
<tr>
<td>Mumps</td>
<td>Attenuated</td>
<td>Universal vaccination of infants</td>
<td>Same as measles, given as MMR</td>
</tr>
<tr>
<td>Papilloma (human)</td>
<td>Yeast- or SF9-produced virus-like particles</td>
<td>Females 9–26 yr old</td>
<td>Three doses</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Reassortant</td>
<td>Healthy infants</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>Attenuated</td>
<td>Universal vaccination of infants</td>
<td>Same as measles, given as MMR</td>
</tr>
<tr>
<td>Polio (inactivated)</td>
<td>Inactivated whole viruses of types 1, 2, and 3</td>
<td>Changing; commonly used for immunosuppressed where live vaccine cannot be used</td>
<td>2, 4, and 12–18 mo of age, then 4 to 6 yr of age</td>
</tr>
<tr>
<td>Polio (attenuated)</td>
<td>Attenuated, oral mixture of types 1, 2, and 3</td>
<td>Universal vaccination; no longer used in United States</td>
<td>2, 4, and 6–18 mo of age</td>
</tr>
<tr>
<td>Rabies</td>
<td>Inactivated whole virus</td>
<td>Exposure to rabies, actual or prospective</td>
<td>0, 3, 7, 14, and 28 days postexposure</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Vaccinia virus</td>
<td>Certain laboratory workers</td>
<td>One dose</td>
</tr>
<tr>
<td>Varicella</td>
<td>Attenuated</td>
<td>Universal vaccination of infants</td>
<td>12 to 18 mo of age</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>Attenuated</td>
<td>Adults 60 yr old and older</td>
<td>One dose</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Attenuated</td>
<td>Travel to areas where infection is common</td>
<td>One dose every 10 yr</td>
</tr>
</tbody>
</table>

**Ervebo - Ebolavirus vaccine**
Inactivated vaccines

- Chemical procedures (e.g. formalin, β-propiolactone, nonionic detergents)
- Infectivity is eliminated, antigenicity not compromised
Poliomyelitis

- Polio (grey), myelon (marrow) = Greek
- itis (inflammation of) = Latin

- “A common, acute viral disease characterized clinically by a brief febrile illness with sore throat, headache and vomiting, and often with stiffness of the neck and back. In many cases a lower neuron paralysis develops in the early days of illness”

Poliomyelitis
Inactivated poliovirus vaccine, IPV

- Poliovirus treated with formalin to destroy infectivity
- 1954: National Foundation for Infantile Paralysis-sponsored clinical trial of Jonas Salk’s IPV, 1,800,000 children
- >50% protection, results announced 12 April 1955, licensed same day
- Cutter incident
The diagram illustrates the progression of a virus through the human body. The virus enters the body through mucosal surfaces, enters the lymph node, and then enters the blood. This process is exemplified by the decrease in polio cases from 1940 to 1990, as indicated by the graph in the image. The graph shows the impact of the inactivated oral polio vaccine (IPV) on reducing polio cases per 100,000 population.
Influenza virus

Three types: A, B, C

M1 (matrix protein)
M2 (ion channel)

HA (hemagglutinin)
NA (neuraminidase)

8 RNPs
(-) strand RNA
RNA polymerase
NP (nucleocapsid protein)

Lipid bilayer

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Inactivated influenza vaccine

- 3000-49000 deaths/yr in US due to influenza virus
- Vaccine: virus grown in embryonated chicken eggs, formalin-inactivated or detergent or chemically disrupted virions
- 75-100 million doses manufactured each year US
- 60% effective in healthy children and adults <65 yr
- Protection correlates with serum antibodies to HA, NA
- Vaccines produced in cell culture (Flucelvax)
Inactivated influenza vaccine

- Envelope proteins change each year; new strains must be selected in the first few months for manufacture
- Use reassortants with most RNA segments from high-yielding strain, HA, NA from selected strain
- 2019-20 vaccine: A/Brisbane/02/2018 (H1N1)pdm09-like virus; A/Kansas/14/2017 A(H3N2)-like virus; B/Colorado/06/2017-like (Victoria lineage) virus; B/Phuket/3073/2013-like (Yamagata lineage) virus [quadrivalent]
Selecting an influenza virus vaccine

WHO GISM*  
WHO CC†  
WHO CC-CDC‡/FDA§  
FDA  
FDA  
FDA  
Manufacturers  
Clinic

*World Health Organization Global Influenza Surveillance Network  
†WHO Collaborating Centres  
‡US Centers for Disease Control and Prevention  
§US Food and Drug Administration

http://www.microbe.tv/twiv/twiv-413/ on how strains are selected
Antigenic drift: Influenza virus
Go to:

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room number: virus

Which statement about inactivated viral vaccines is incorrect:

A. Chemicals can be used to inactivate infectivity
B. They do not replicate
C. They can be dangerous if inactivation is not complete
D. Antigenic variation can make them ineffective
E. None of the above are incorrect
Subunit vaccines

- Break virus into components, immunize with purified components
- Clone viral gene, express in bacteria, yeast, insect cells, cell culture, purify protein
- Antigen usually a capsid or membrane protein
Recombinant zoster vaccine - Shingrix

- Recombinant gE produced in mammalian (CHO cells, secreted)
- Adjuvanted with AS01
- Injected

Varicella-zoster virus
HBV vaccine

A cancer vaccine

- Hepatitis B virus (HBV) - HBsAg protein produced in yeast
- Assembles into empty particles
Human papillomaviruses

- Agents of warts (>170 types)
- Some are transmitted sexually, most common STD in USA
- Some cause low risk genital warts
- Others are high risk for cancers: cervix, vagina, penis, anus, oropharynx (31,000/yr; mostly 16, 18)
- Nearly half of Americans infected with genital HPV (18-59)
Human papillomavirus vaccines

*Cancer vaccines*

- **Gardasil** (Merck): types 6, 11, 16, 18 produced in *S. cerevisiae*
- **Gardasil-9** (Merck): types 6, 11, 16, 18, 31, 33, 45, 52, 58
- **Cervarix** (GlaxoSmithKline): types 16, 18 produced in insect cells
- Should be given before becoming sexually active
Future influenza vaccines?

- Virus-like particles: synthesis of HA alone in cells leads to production of immunogenic particles
- Has also been done in plants
- 1 square meter of plants produces 20,000 doses at under $0.20/dose
Subunit vaccine pro and con

• Advantages of a modern subunit vaccine
  - *Recombinant DNA technology: fast*
  - *No viral genomes or infectious virus*

• Disadvantages
  - *Expensive*
  - *Injected*
  - *Poor antigenicity*
Inactivated and subunit vaccines have a common problem

- Viral proteins don’t replicate or infect
- Don’t cause inflammation, poor activation of adaptive responses
- Pure proteins often require *adjuvant* to mimic inflammatory effects of infection
Adjuvants

- Stimulate early processes in immune recognition
- Produce a more robust acquired immune response with *less antigen*
  - *Slow release of antigen as site of inoculation*
  - *Inflammation*
- Licensed
  - *Alum* (aluminum hydroxide or phosphate; in HBV vaccine) - US
  - *AS01* (Shingrix; monophosphoryl lipid A, TLR4 ligand and saponin, stimulates innate immunity)
  - *AS04 in Cervarix* (alum, monophosphoryl lipid A) - US
  - *MF59* - squalene oil-in-water emulsion (depot, innate stimulatory) - Europe
New vaccine technologies

Microneedle patch

Thermostabilization of influenza vaccine in sugars

https://www.nature.com/articles/s41598-019-44020-w
Universal influenza vaccine

By exchanging the HA head domains, but retaining the same HA stalk domain, the antibody response can be redirected towards the otherwise immuno-subdominant stalk region.

Go to:

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room number: virus

What are some requirements for an effective vaccine?

A. Low cost
B. Ease of administration
C. Provides long lasting immunity
D. Minimal side effects
E. All of the above
Replication competent, attenuated vaccines

- Viral replication occurs, stimulates immune response
- Infection induces mild or inapparent disease
Empirically derived attenuated vaccines

Pathogenic virus is isolated from a patient and grown in human cells in culture → The virus is used to infect monkey cells → The viral genome acquires many mutations that allow it to grow well in monkey cells → The virus no longer reproduces well in human cells and may be a candidate for a vaccine
FluMist

- Replication competent, intranasally administered influenza vaccine
- Multivalent
- Reassortants of master donor strain - HA, NA genes from current strains
- Viruses are cold-adapted, temperature-sensitive, and attenuated in a ferret model
- Replicate only in nasopharynx, produce protective immunity
Sabin oral poliovirus vaccine (OPV)

The graph shows the reported cases of polio per 100,000 population from 1940 to 1990. The graph indicates a significant decrease in cases after the introduction of the oral poliovirus vaccine. The vaccine is administered orally, and the virus replicates in the intestines, stimulating an immune response. The inactivated polio vaccine (IPV) is administered intramuscularly and is not replicating.
Attenuation of poliovirus neurovirulence

Albert Sabin’s three strains of OPV licensed in the US in 1961
Determinants of Sabin vaccine strain attenuation

<table>
<thead>
<tr>
<th>Virus</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1/Sabin</td>
<td>5’-UTR nt 480</td>
</tr>
<tr>
<td></td>
<td>VP1 aa 1106</td>
</tr>
<tr>
<td></td>
<td>VP1 aa 1134</td>
</tr>
<tr>
<td></td>
<td>VP3 aa 3225</td>
</tr>
<tr>
<td></td>
<td>VP4 aa 4065</td>
</tr>
<tr>
<td>P2/Sabin</td>
<td>5’-UTR nt 481</td>
</tr>
<tr>
<td></td>
<td>VP1 aa 1143</td>
</tr>
<tr>
<td>P3/Sabin</td>
<td>5’-UTR nt 472</td>
</tr>
<tr>
<td></td>
<td>VP3 aa 3091</td>
</tr>
</tbody>
</table>
## Reversion of P3/Sabin

<table>
<thead>
<tr>
<th>Virus</th>
<th>Base at 472</th>
<th>Time of isolation after vaccination</th>
<th>Histological lesion score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabin vaccine</td>
<td>U</td>
<td>24 h</td>
<td>0.36</td>
</tr>
<tr>
<td>DM1</td>
<td>U</td>
<td>24 h</td>
<td>ND</td>
</tr>
<tr>
<td>DM2</td>
<td>U</td>
<td>31 h</td>
<td>1.58</td>
</tr>
<tr>
<td>DM3</td>
<td>U/C</td>
<td>35 h</td>
<td>ND</td>
</tr>
<tr>
<td>DM4</td>
<td>C</td>
<td>47 h</td>
<td>2.48</td>
</tr>
<tr>
<td>DM38</td>
<td>C</td>
<td>18 da</td>
<td>ND</td>
</tr>
<tr>
<td>P3/119</td>
<td>C</td>
<td>3-4 weeks</td>
<td>3.34</td>
</tr>
</tbody>
</table>
Reported Cases of Paralytic Poliomyelitis, United States, 1961-2003


1 paralytic case/1.4 million doses
Eradication of poliomyelitis

1988 WHA Resolution

2000 Stop poliovirus transmission

2005 Certify Global Eradication

2005-2010 Stop polio immunization
Can viral diseases be eradicated?

- Smallpox eradication program launched 1967, eradicated 1978
- Two features essential for eradication:
  - Replication in only one host
  - Vaccination induces lifelong immunity
(wild type 2 declared eradicated, no type 3 since 2012)
New non-revertible poliovirus strains
nOPV2

The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study


Summary

Background Use of oral live-attenuated polio vaccines (OPV), and injected inactivated polio vaccines (IPV) has almost achieved global eradication of wild polio viruses. To address the goals of achieving and maintaining global eradication and minimising the risk of outbreaks of vaccine-derived polioviruses, we tested novel monovalent oral type-2 poliovirus (OPV2) vaccine candidates that are genetically more stable than existing OPVs, with a lower risk of reversion to neurovirulence. Our study represents the first in-human testing of these two novel OPV2 candidates. We aimed to evaluate the safety and immunogenicity of these vaccines, the presence and extent of faecal shedding, and the neurovirulence of shed virus.
Even if we eradicate a virus from the earth, as long as the nucleotide sequence is known, any virus can be recovered.
Engineering attenuated vaccines

- Yellow fever: first human virus identified, 1901
- Mosquito transmitted flavivirus
- Disease: fever and nausea to failure of major organ systems; high fatality
- Yellow fever vaccine 17D produced 1938 by 176 passages of virulent wild type Asibi strain in chick embryo tissue
- 500 million doses distributed; safe, effective
Building on success of YF 17D vaccine

A

5' UTR

Translation/processing

UTR

C prM E NS1 2A 2B NS3 4A 4B NS5

Replace with dengue virus

B

Yellow fever vaccine DNA

In vitro RNA synthesis

5' (+) strand RNA transcript

Transfection

Cultured cells
Dengvaxia

- E, prM of dengue virus 1, 2, 3, 4 in YF 17D backbone
- Licensed in Mexico, Brazil, Philippines
- No protection against DENV-2
- Lead to worse disease in 2-9 yo
TV003

- Tetravalent, attenuated dengue virus vaccine produced by mutagenesis of infectious clone
- One dose, 100% protection vs challenge

30 nt deletion in 3’-UTR
SARS-CoV-2 virus vaccines (62)

- Codon deoptimized
- Attenuated
- Inactivation

- Replication competent natural virus vaccine
- Formalin inactivation
- Inactivated virus vaccine

- Insect cell VLP
- Plant cell VLP
- Protein

- Virus-like particle vaccine
- Subunit vaccine
- Influenza virus
- Vaccinia virus
- Measles virus
- Horsepox virus

- mRNA vaccine (12)
- DNA vaccine (3)

https://milkeninstitute.org/covid-19-tracker
SARS-CoV-2 mRNA vaccine
Vesicular stomatitis virus vaccine vector

A
(-) strand RNA
3' \hspace{1cm} 5'
Leader RNA
5' \hspace{1cm} 3'
(+) strand mRNA
5' \hspace{1cm} 3'
Replace G gene with transgene
mRNA synthesis
5' \hspace{1cm} 3'
Translation

B
Vaccinia virus encoding T7 RNA polymerase
Infection
4 plasmid transfection
Progeny
Infectious virus
Viral glycoprotein (G)

Ervebo - Ebolavirus vaccine - VSV vector
Next time: Antivirals