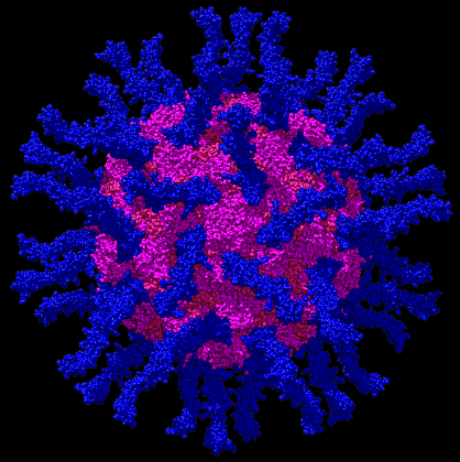


VIROLOGY LIVE

WITH VINCENT RACANIELLO

Vaccines

Session 19

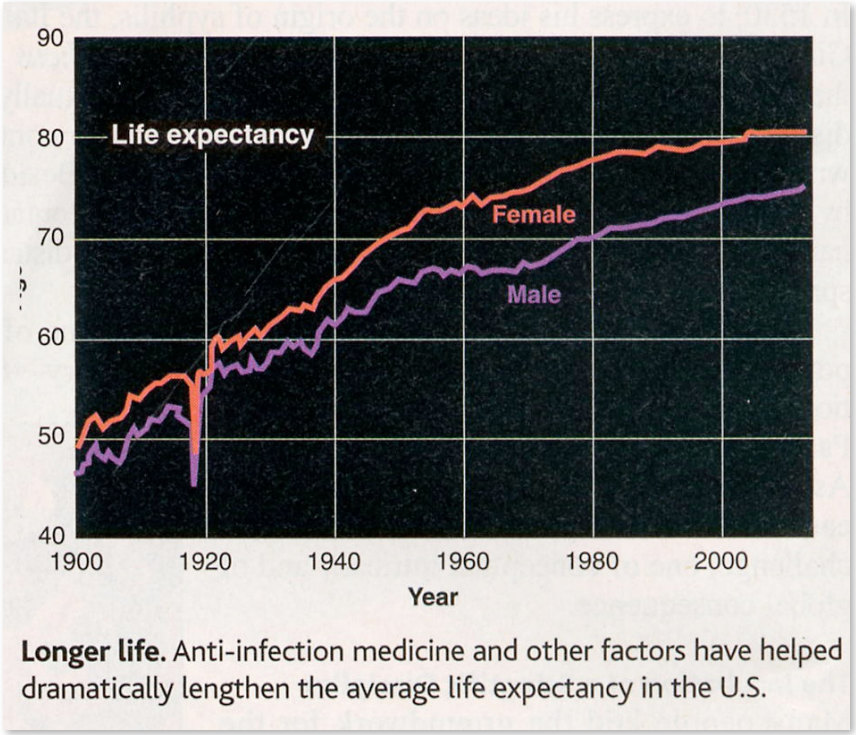
Virology Live

Fall 2021

Nothing shocks me. I'm a scientist.
Indiana Jones

Vaccines are our proven best defense against viruses

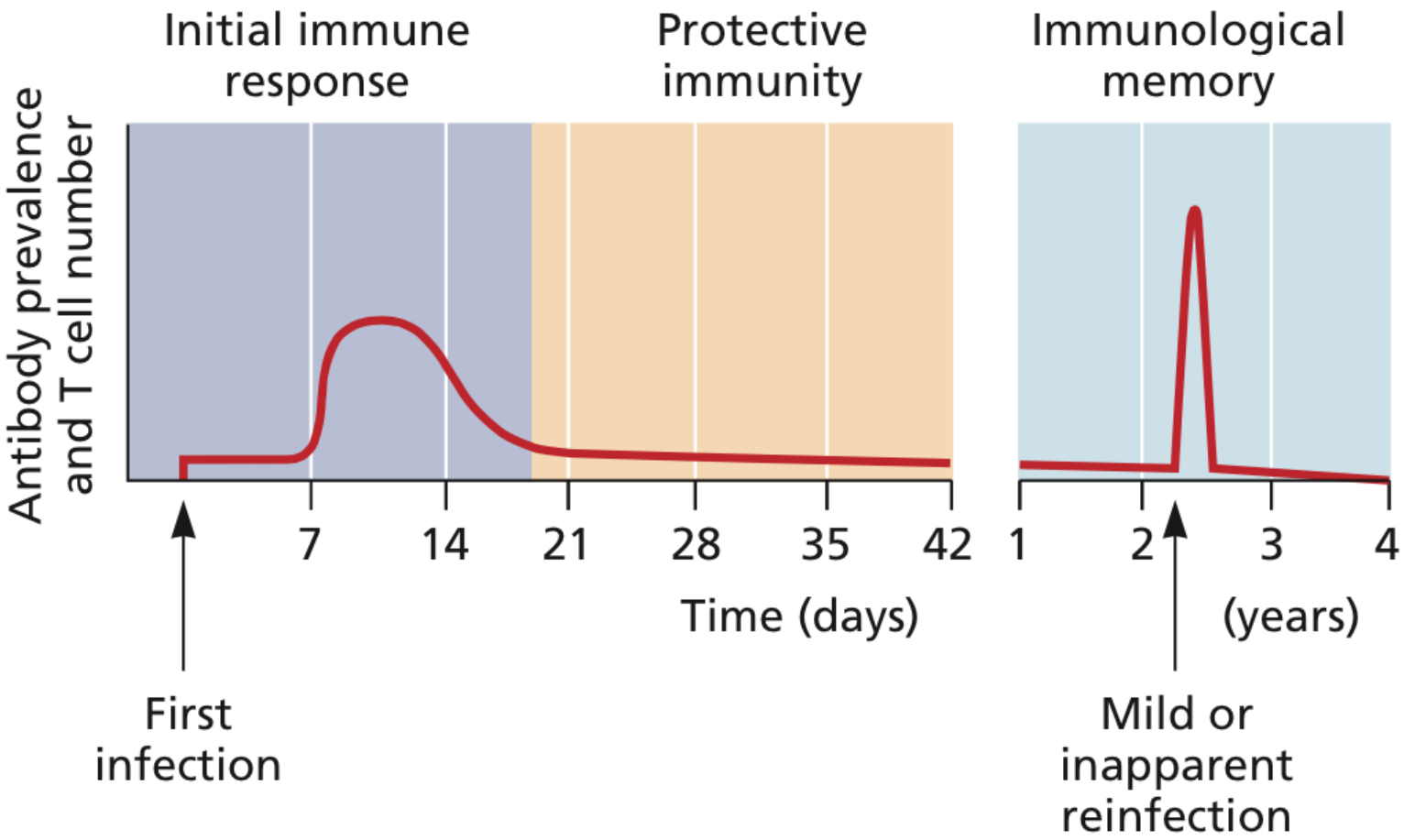
- Vaccination mobilizes the host immune system to prevent virus disease
  - *Immune memory*
- Vaccination breaks the chain of transmission



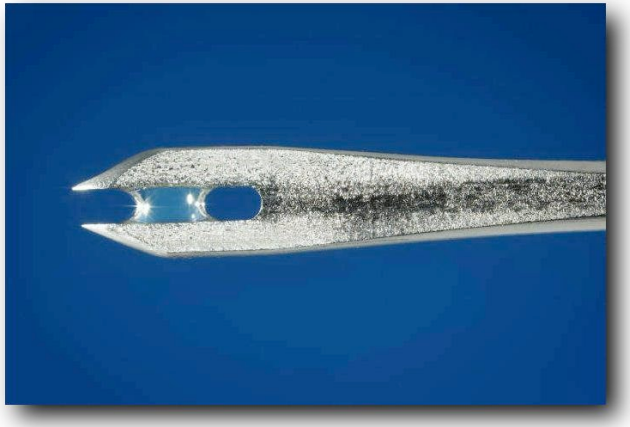
Longer life. Anti-infection medicine and other factors have helped dramatically lengthen the average life expectancy in the U.S.

US life expectancy dropped 1.5 years in 2020

Vaccines stimulate a protective immune response



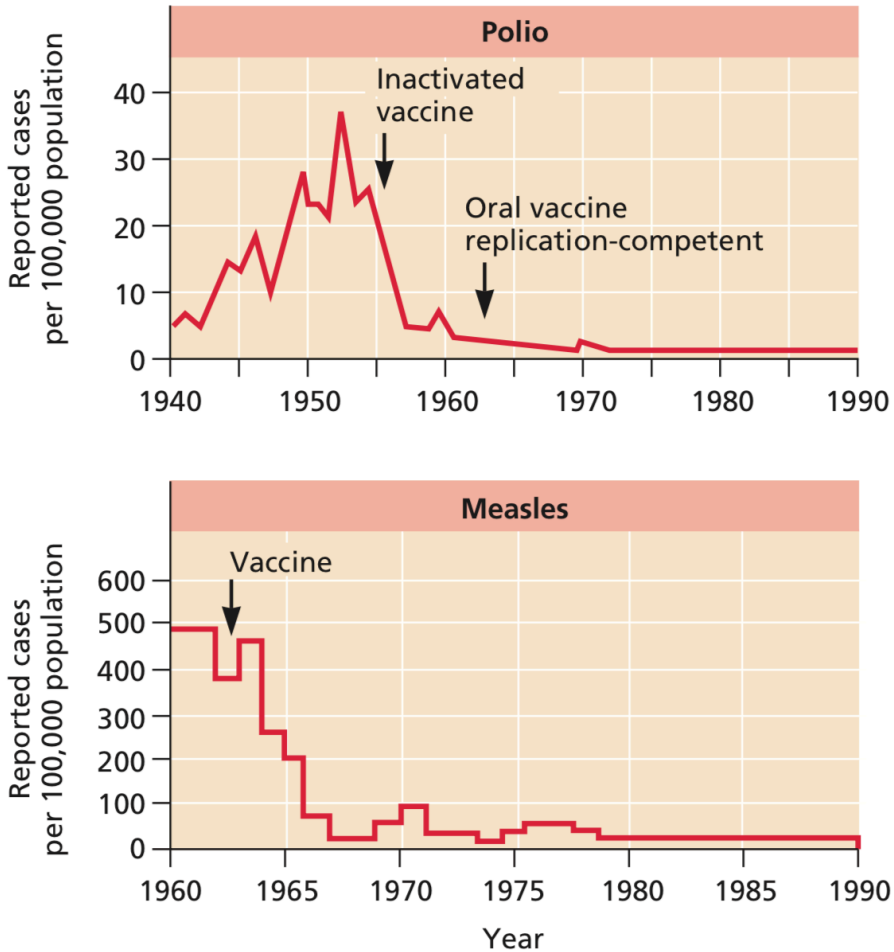
Principles of Virology, ASM Press

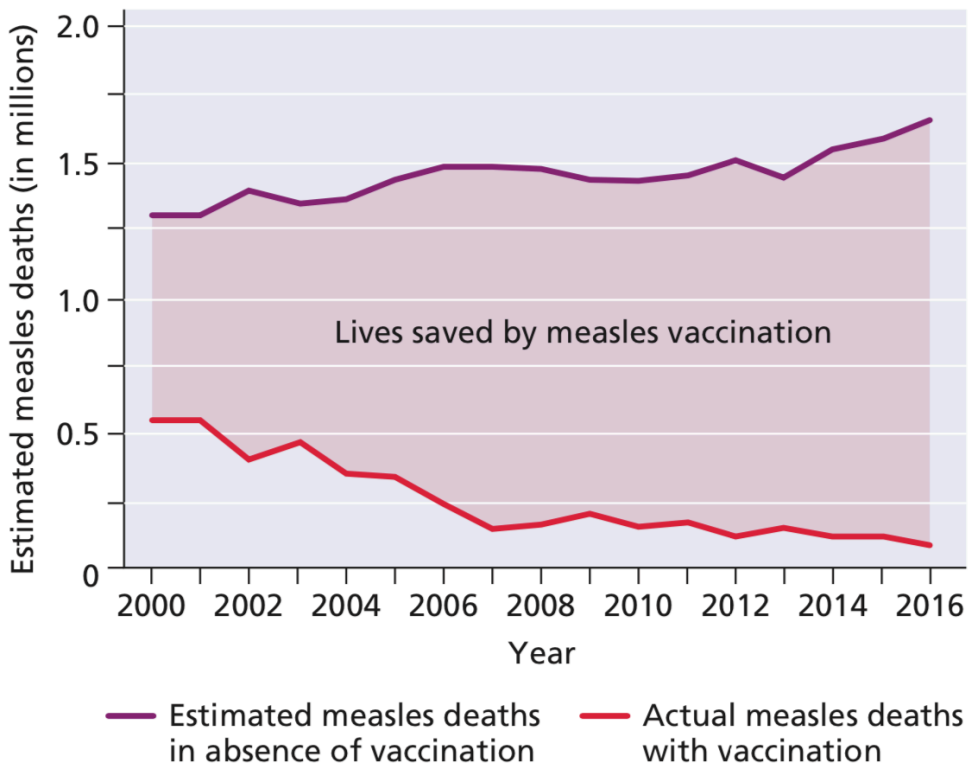


- Jenner, 1796
- Pasteur, 1885 - rabies vaccine; introduced the term vaccination from *vacca* (Latin, cow) in honor of Jenner
- Yellow fever, influenza vaccines - 1930s


The Cow-Pock — or — the Wonderful Effects of the New Inoculation! — Vide the Publications of ye Anti-Vaccine Society.
9994

Large-scale vaccination campaigns can be successful





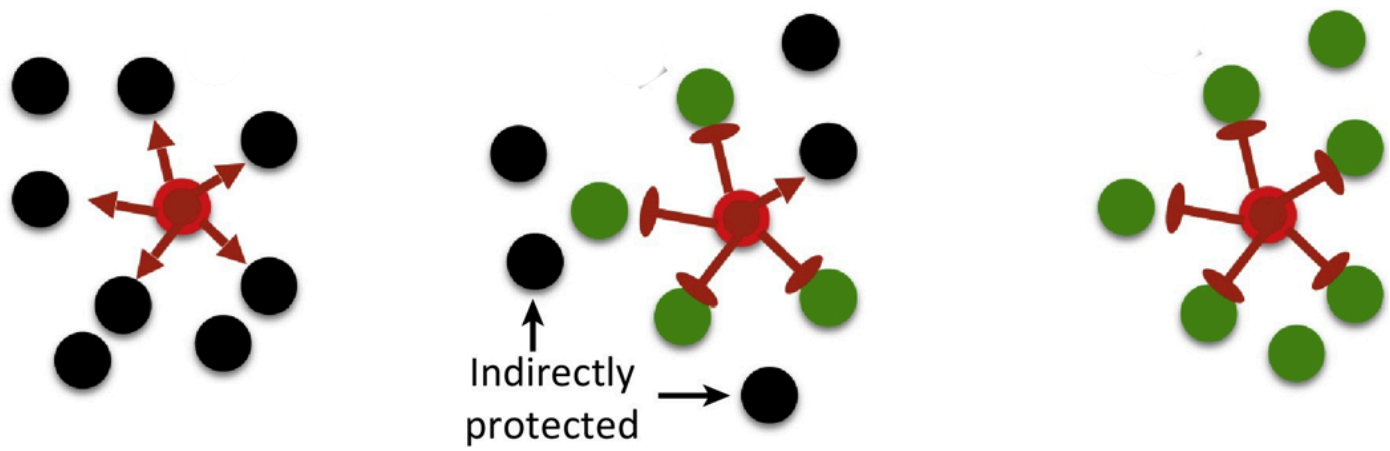
Principles of Virology, ASM Press

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

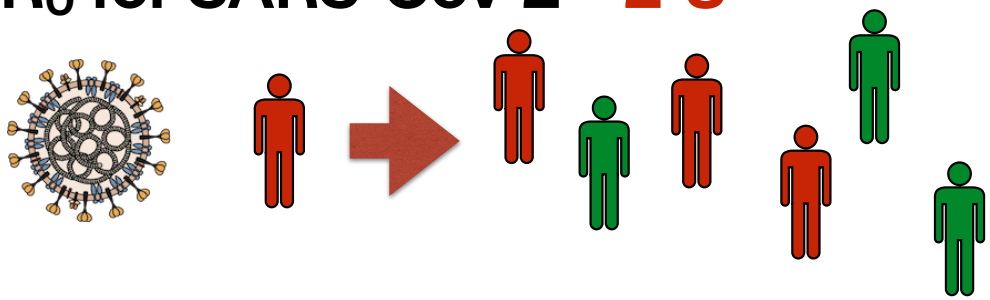


Trends in Immunology Volume 36, Issue 12, December 2015, Pages 753-755

Herd Immunity

- Virus spread drops when the probability of infection falls below a critical threshold
- The threshold is virus and population specific (e.g. R_0)
- 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 impede virus spread:

$1 - 1/R_0$

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

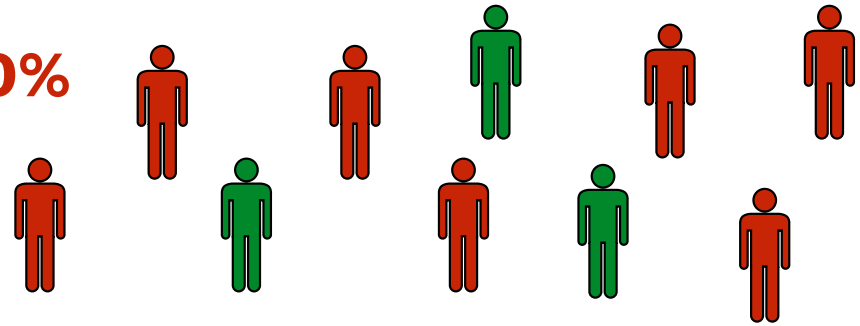
R_0 = tau * c * d

Tau = probability of infection given contact

C = average duration of contact between infected and uninfected host

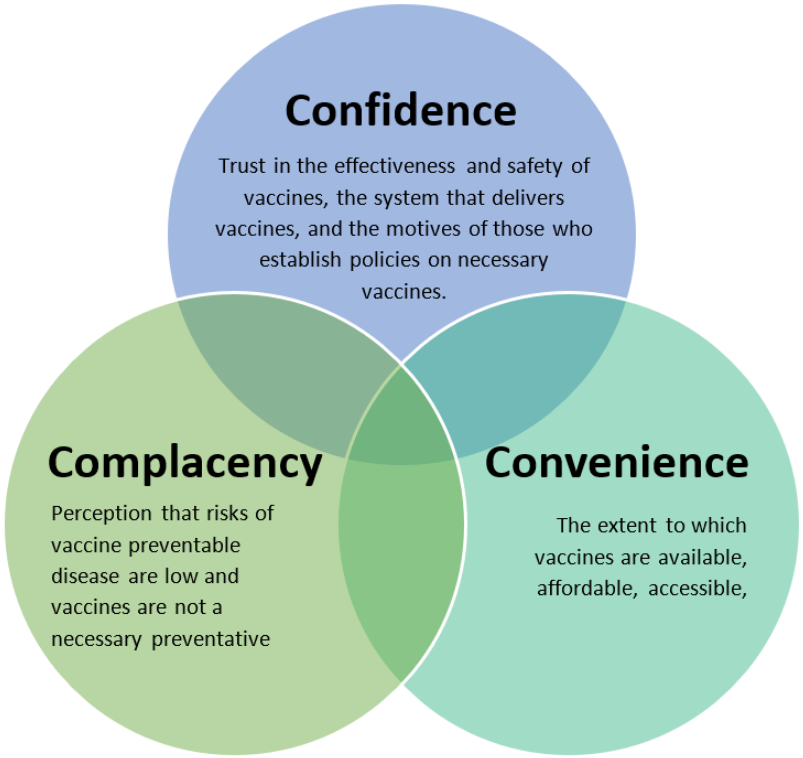
D = duration of infectivity

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

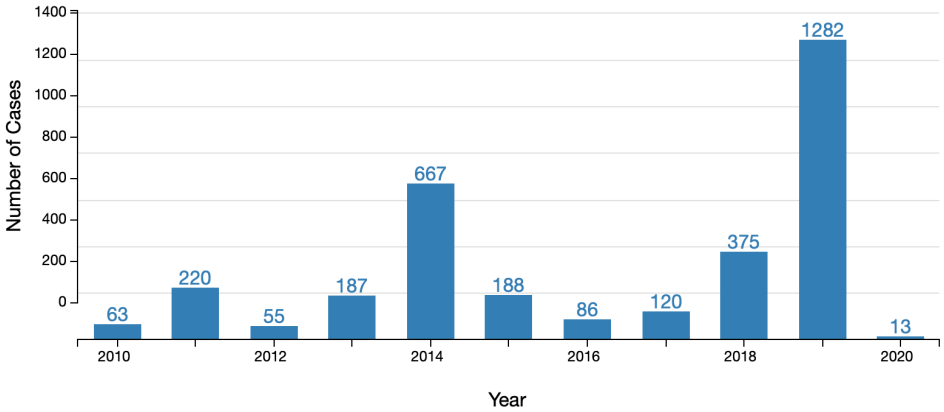
In some cases, medical exemptions to vaccination are indicated

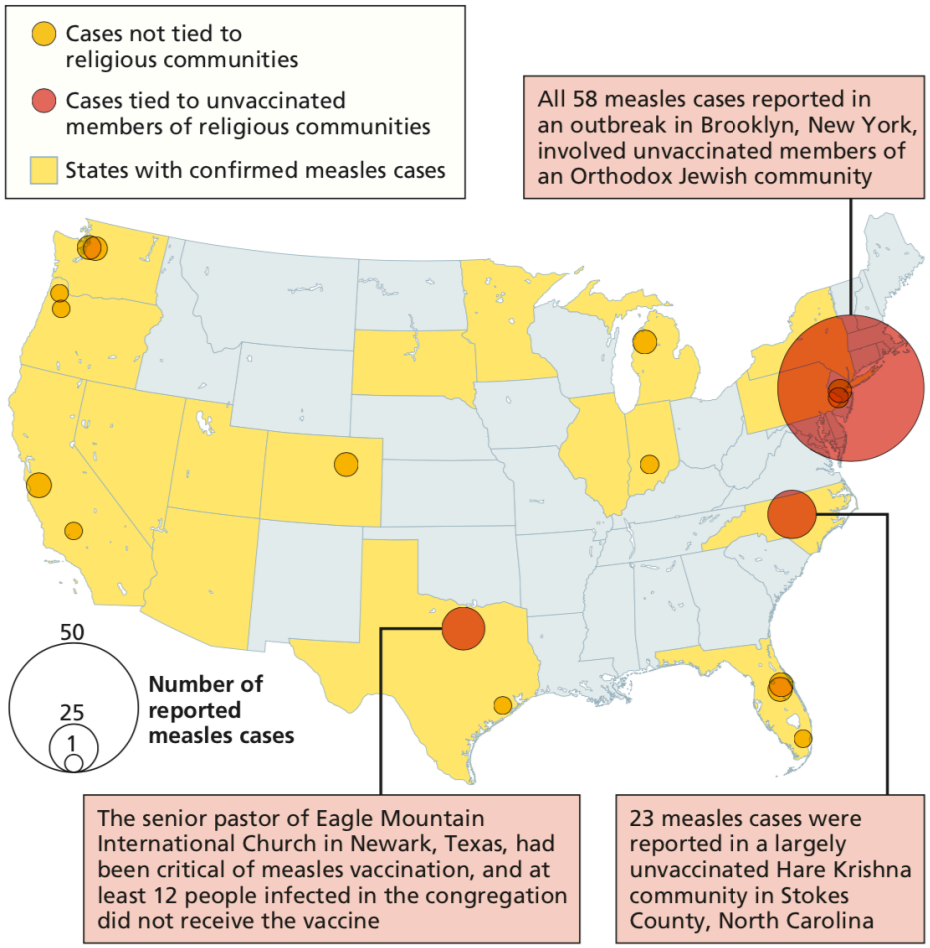
These should not exceed 1% of the population, but they usually do as medical exemptions are inappropriately given

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





Principles of Virology, ASM Press

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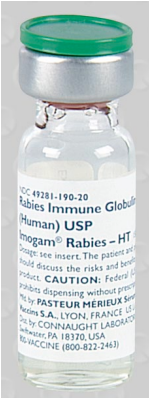
room number: virus

Herd immunity:

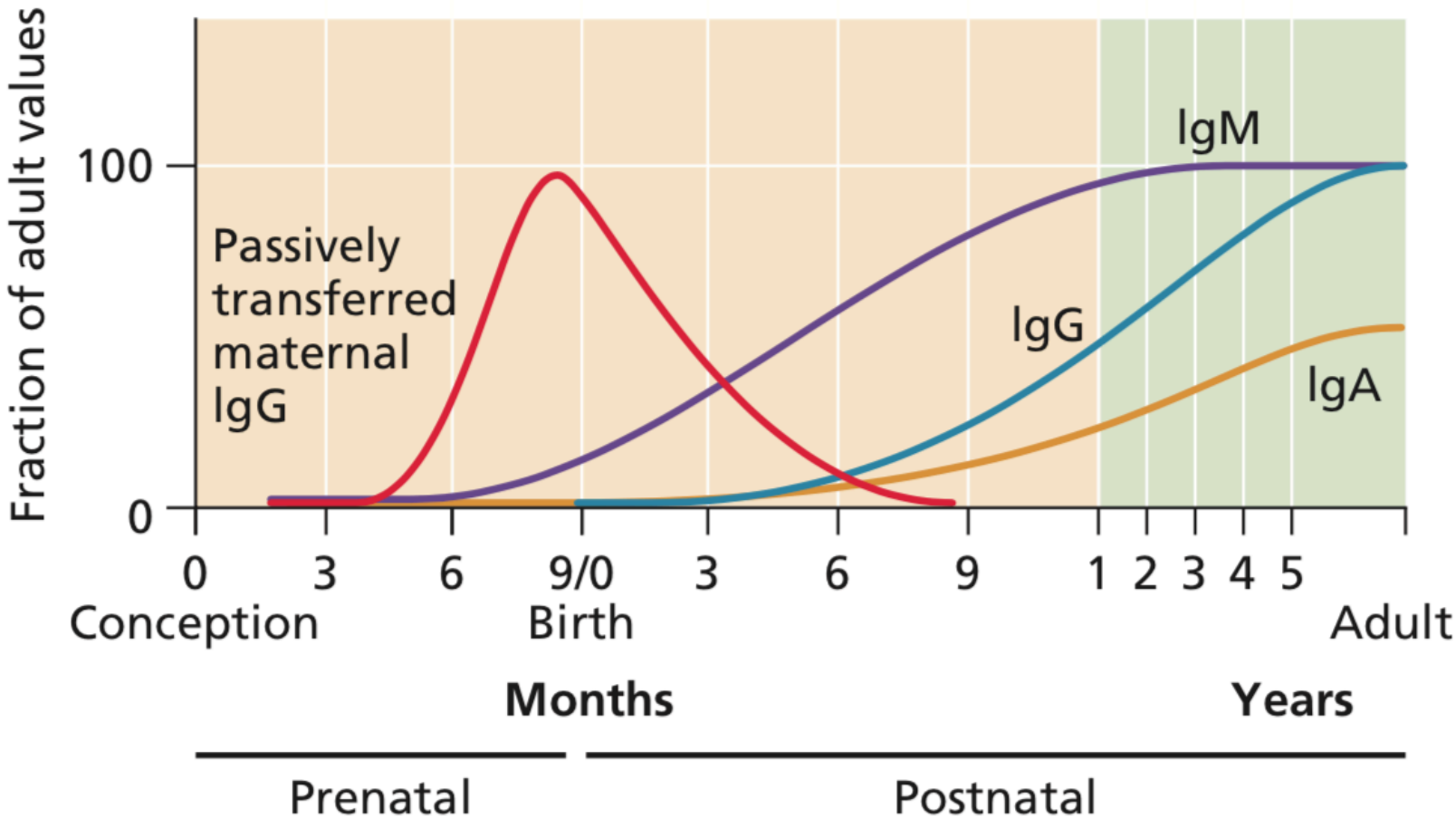
A. Demonstrates the importance of immunizing livestock
B. Emphasizes that not everyone must be immune to protect a population
C. Emphasizes that everyone must be immune to protect a population
D. Describes how group-think can dominate anti-vaccine choices
E. All of the above

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*

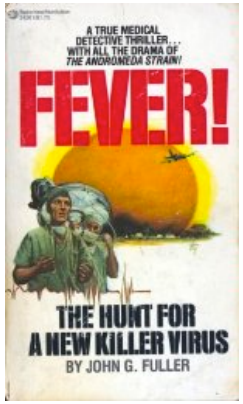


A natural passive vaccine



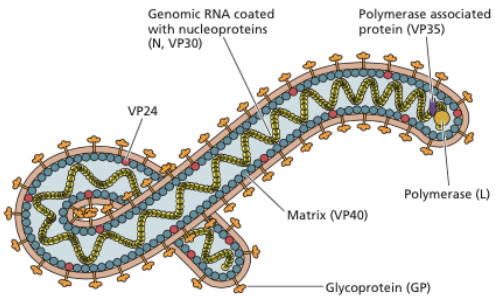
Principles of Virology, ASM Press

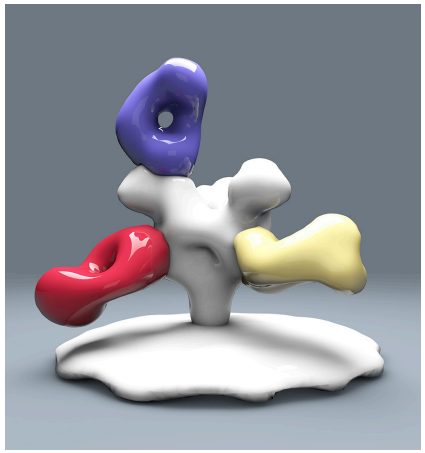
Passive therapy with convalescent serum



- 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





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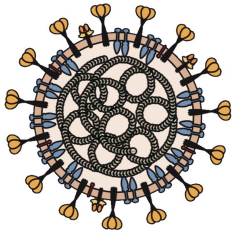
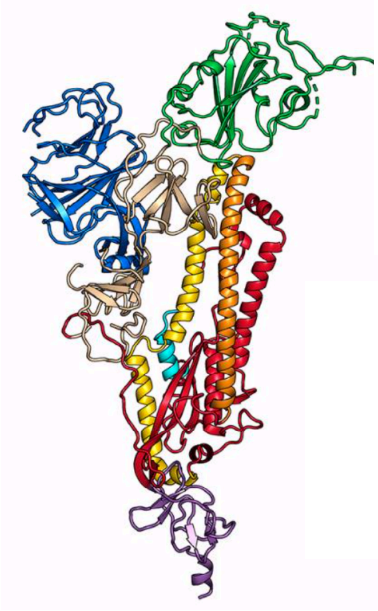
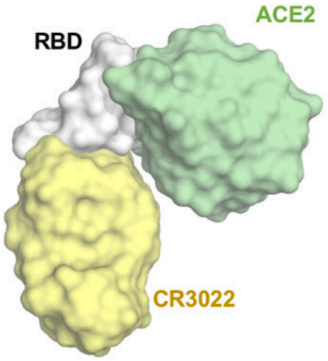




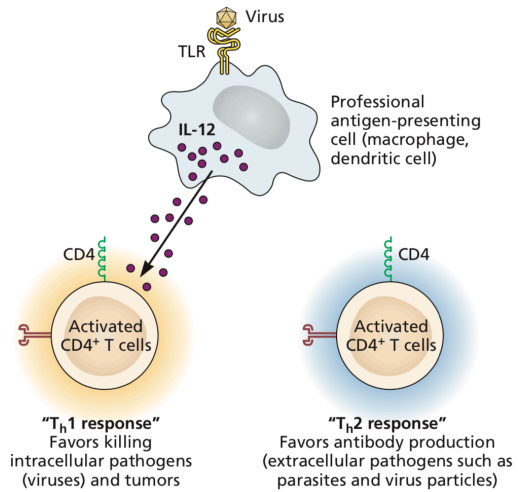


EUA

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

10.1126/science.abb2507
M. Yuan et al., Science 10.1126/science.abb7269 (2020)

Requirements of an effective vaccine

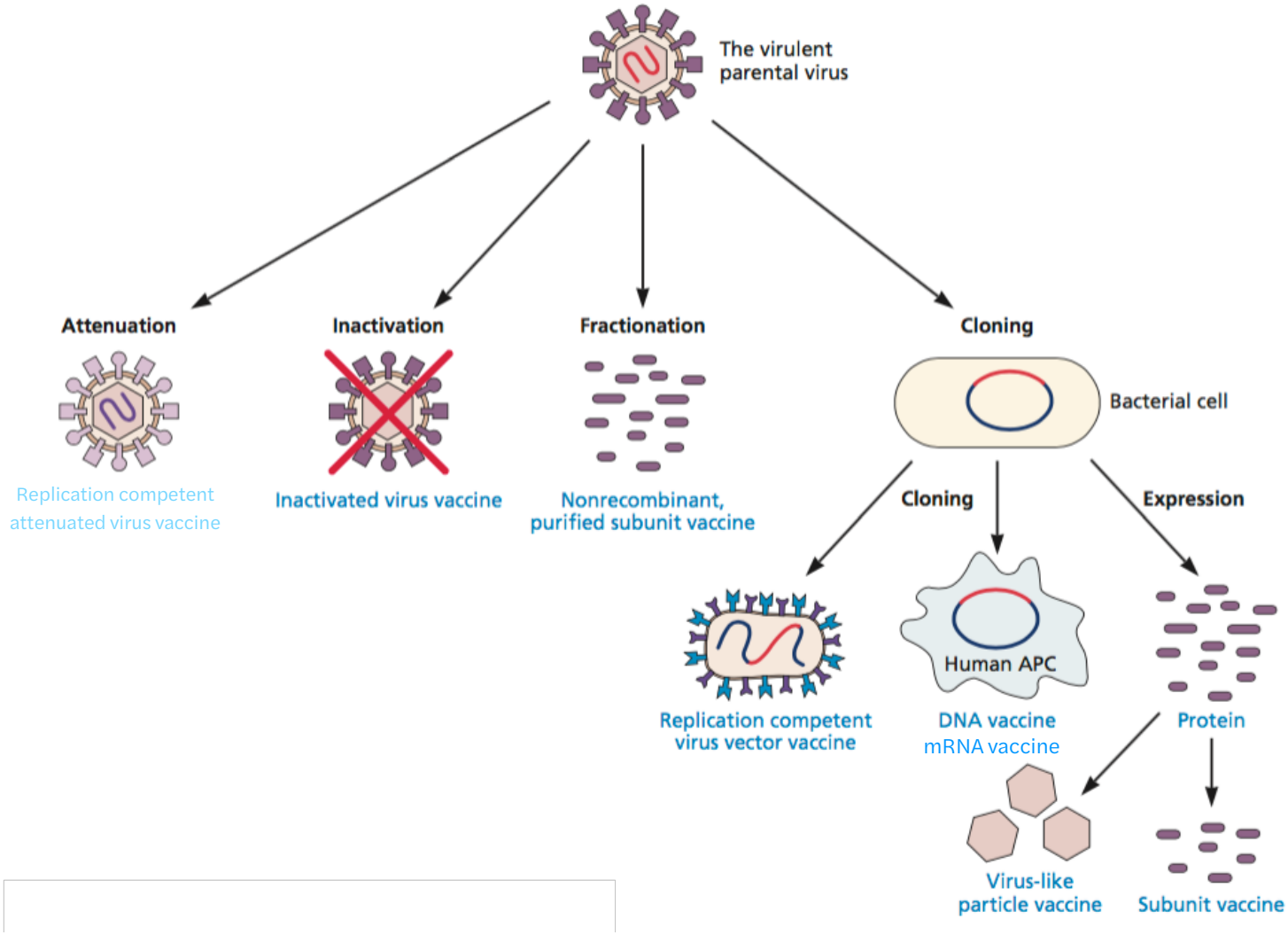


- Induction of an *appropriate immune response*
  - *Th1 vs Th2 response*
- Vaccinated individual must be *protected against disease* caused by a virulent form of the specific pathogen
  - *Just getting 'a response' is not enough (e.g. producing antibodies)*

Principles of Virology, ASM Press

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)



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Viral vaccines licensed in the US

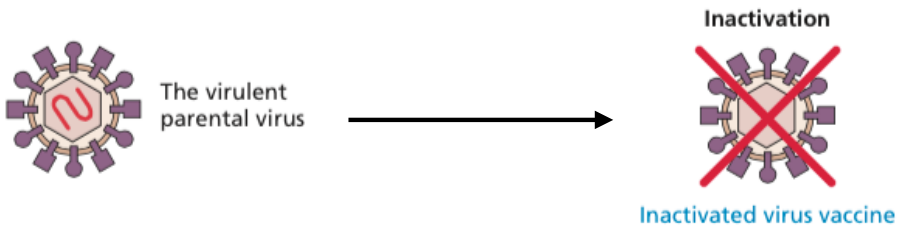
Disease or virus	Type of vaccine	Indications for use	Schedule
Adenovirus	Attenuated, oral	Military recruits	One dose
Hepatitis A	Inactivated whole virus	Travelers, other high-risk groups	0, 1, and 6 mo
Hepatitis B	Yeast-produced recombinant surface protein	Universal in children, exposure to blood, sexual promiscuity	0, 1, 6, and 12 mo
Influenza	Inactivated viral subunits	Elderly and other high-risk groups	One dose seasonally
	Recombinant proteins	Elderly; those with egg allergies	One dose seasonally
Influenza	Attenuated	Children 2–8 yr old, not previously vaccinated with influenza vaccine	Two doses at least 1 mo apart
		Children 2–8 yr old, previously vaccinated with influenza vaccine	One dose
		Children, adolescents, and adults 9–49 yr old (e.g., FluMist, FluBlo)	One dose
Japanese encephalitis	Inactivated whole virus	Travelers to or inhabitants of high-risk areas in Asia	0, 7, and 30 days
Measles	Attenuated	Universal vaccination of infants	12 mo of age; 2nd dose, 6 to 12 yr of age
Mumps	Attenuated	Universal vaccination of infants	Same as measles, given as MMR
Papilloma (human)	Yeast- or SF9-produced virus-like particles	Females 9–26 yr old Males 11-21 yr old	Three doses
Rotavirus	Reassortant	Healthy infants	2, 3, and 6 mo or 2 and 4 mo of age depending on vaccine
Rubella	Attenuated	Universal vaccination of infants	Same as measles, given as MMR
Polio (inactivated)	Inactivated whole viruses of types 1, 2, and 3	Changing: commonly used for immunosuppressed where live vaccine cannot be used	2, 4, and 12–18 mo of age, then 4 to 6 yr of age
Polio (attenuated)	Attenuated, oral mixture of types 1, 2, and 3	Universal vaccination; no longer used in United States	2, 4, and 6–18 mo of age
Rabies	Inactivated whole virus	Exposure to rabies, actual or prospective	0, 3, 7, 14, and 28 days postexposure
Smallpox	Vaccinia virus	Certain laboratory workers	One dose
Varicella	Attenuated	Universal vaccination of infants	12 to 18 mo of age
Varicella-zoster	Attenuated	Adults 60 yr old and older	One dose
Yellow fever	Attenuated	Travel to areas where infection is common	One dose every 10 yr

Ervebo - Ebolavirus vaccine
Comirnaty - COVID-19

COVID-9 vaccines authorized, not licensed
Moderna mRNA
J&J Ad26 vector

Principles of Virology, ASM Press

Inactivated vaccines



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

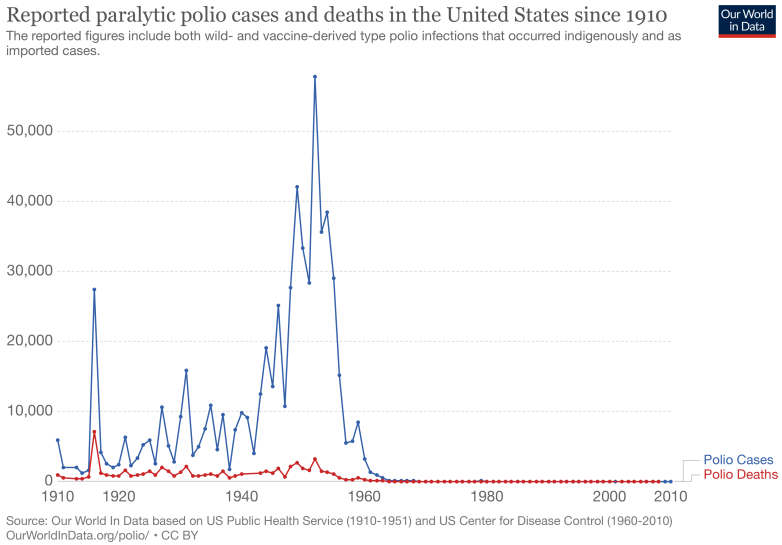
Poliomyelitis

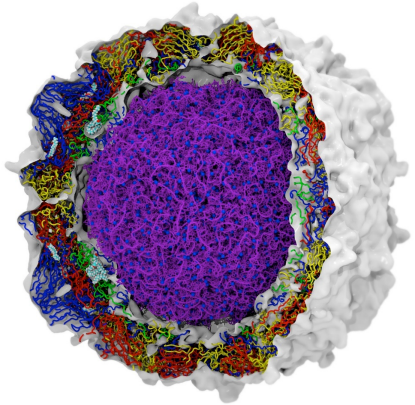
- Polio (grey), myelon (marrow) = Greek
- itis (inflammation of) = Latin

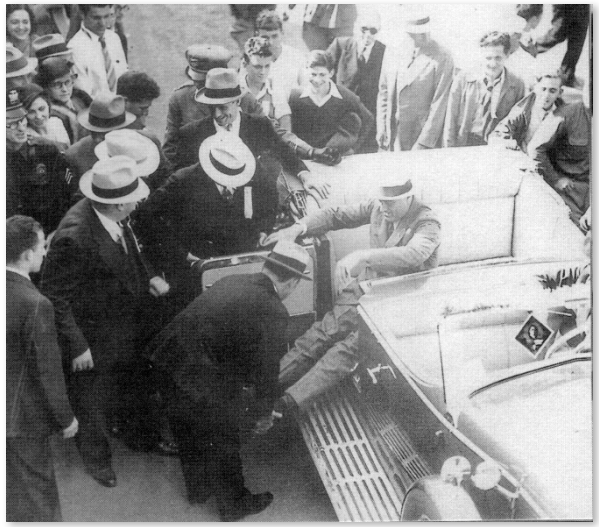
- "A common, acute viral disease characterized clinically by a brief febrile illness with sore throat, headache and vomiting, and often with stiffness of the neck and back. In many cases a lower neuron paralysis develops in the early days of illness"

  —*J.R. Paul, "Poliomyelitis (Infantile Paralysis)", in A Textbook of Medicine, 1959.*

Poliomyelitis

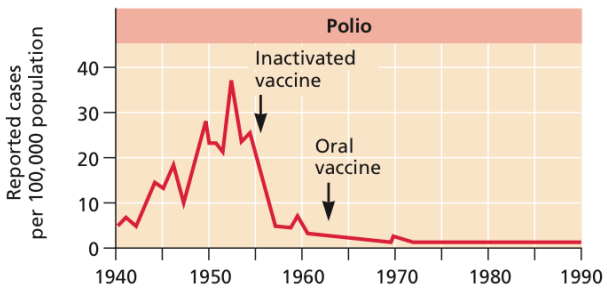


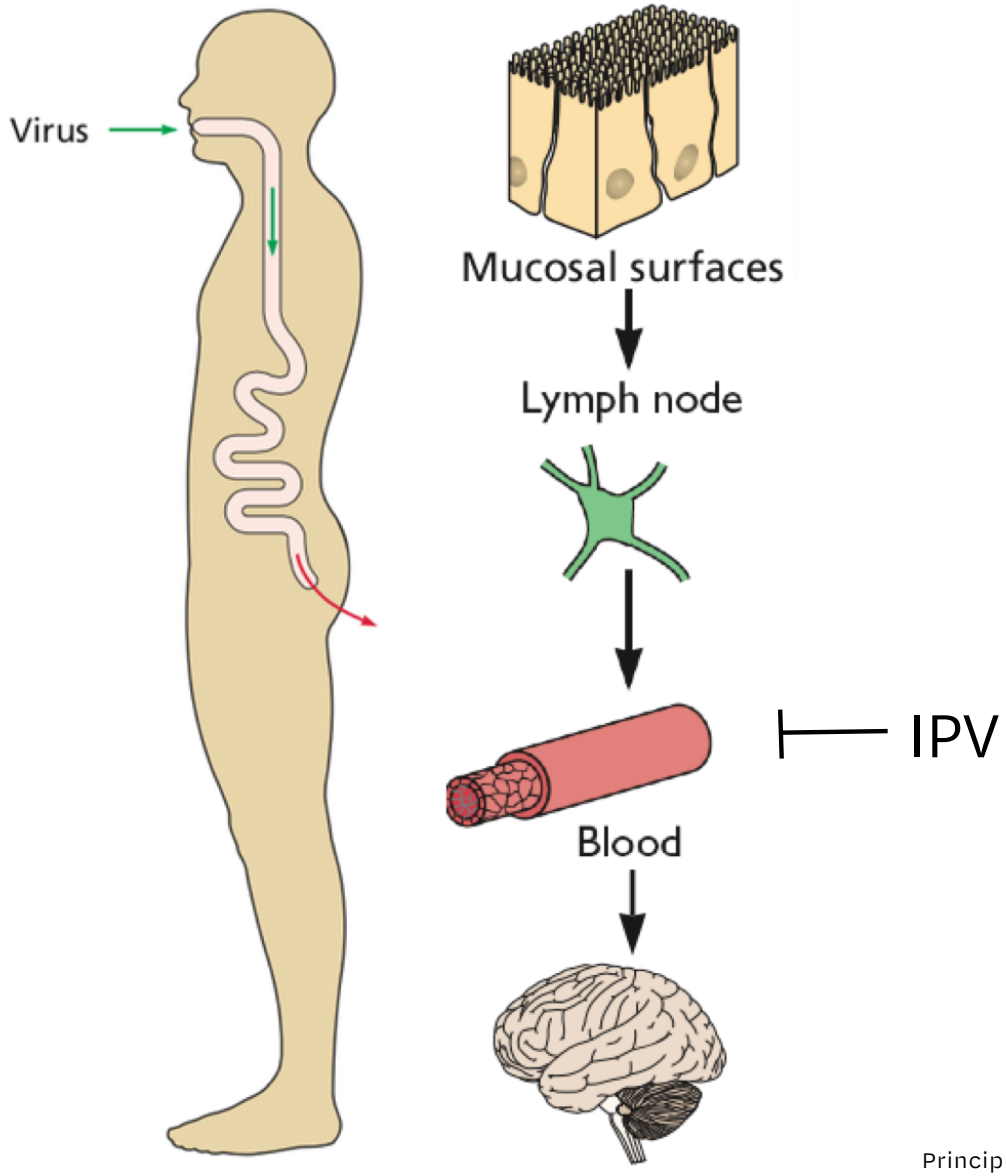




Inactivated poliovirus vaccine, IPV

- 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





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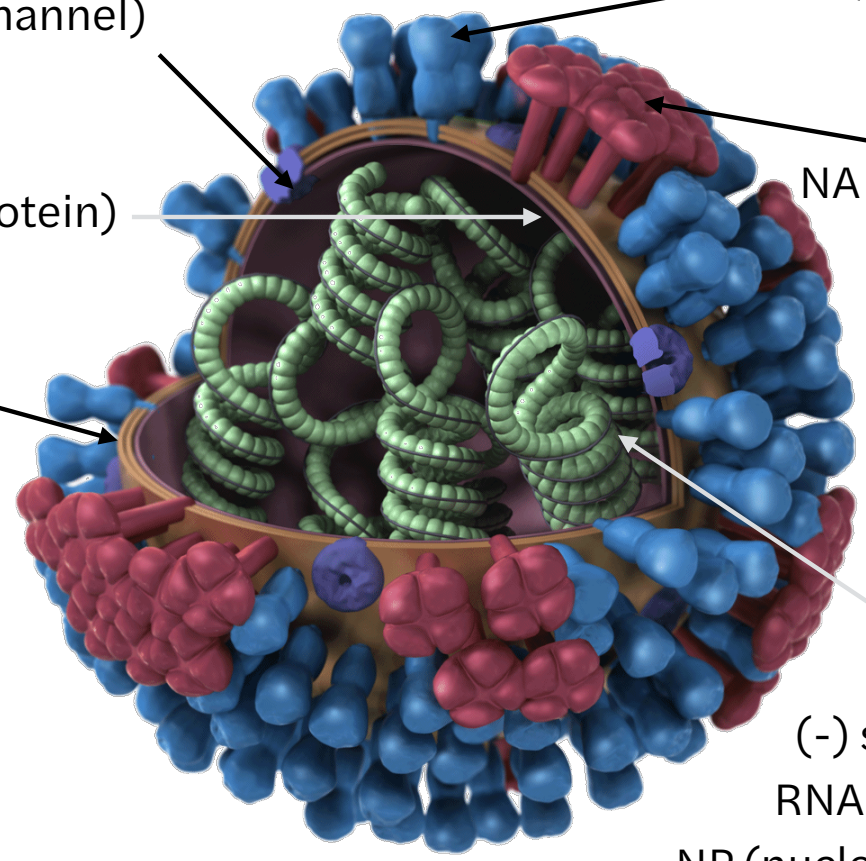
Principles of Virology, ASM Press

Influenza virus

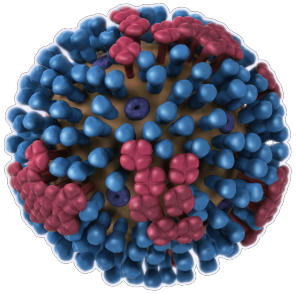


Three types: A, B, C

Inactivated influenza vaccine

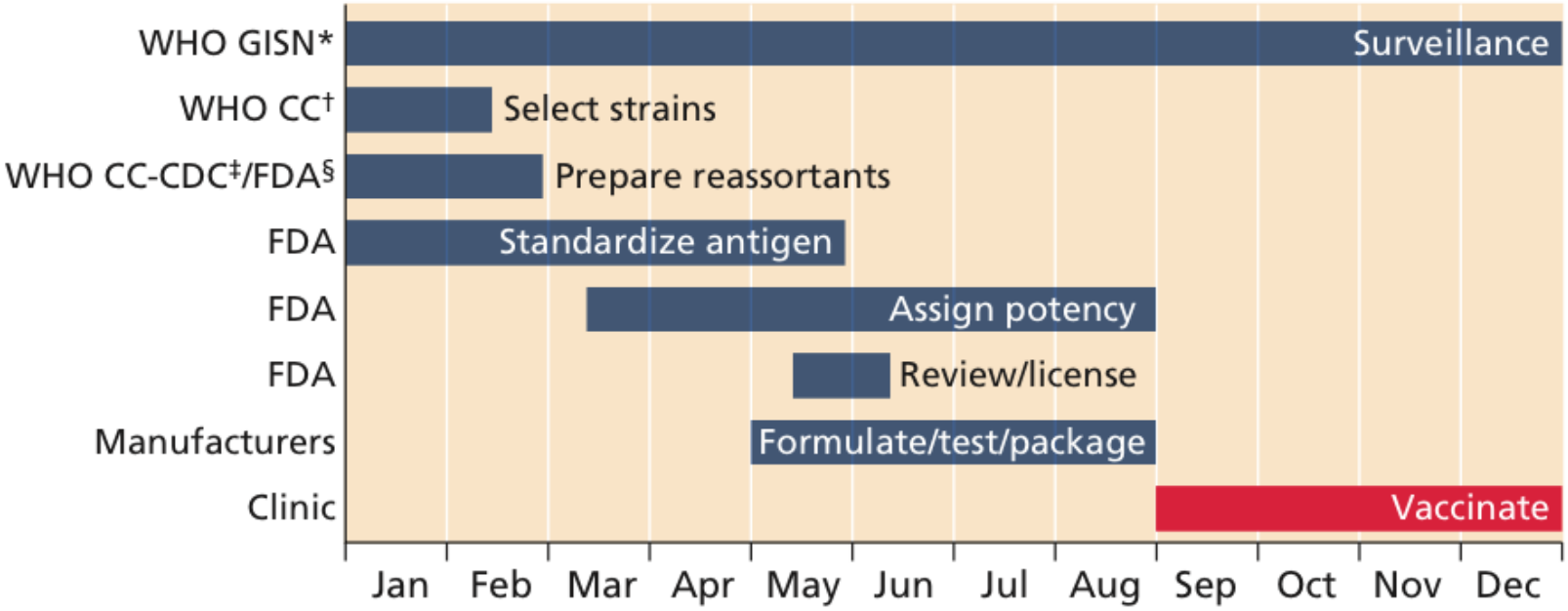
- 3000-49000 deaths/yr in US due to influenza virus
- Vaccine: virus grown in embryonated chicken eggs, formalin-inactivated or detergent or chemically disrupted virions
- 75-100 million doses manufactured each year US
- 60% effective in healthy children and adults <65 yr
- Protection correlates with 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
- 2021-22 egg vaccine: A/Victoria/2570/2019 (H1N1)pdm09-like virus; A/Cambodia/e0826360/2020 A(H3N2)-like virus; B/Washington/02/2019 (Victoria lineage) virus; B/Phuket/3073/2013-like (Yamagata lineage) virus [quadrivalent]

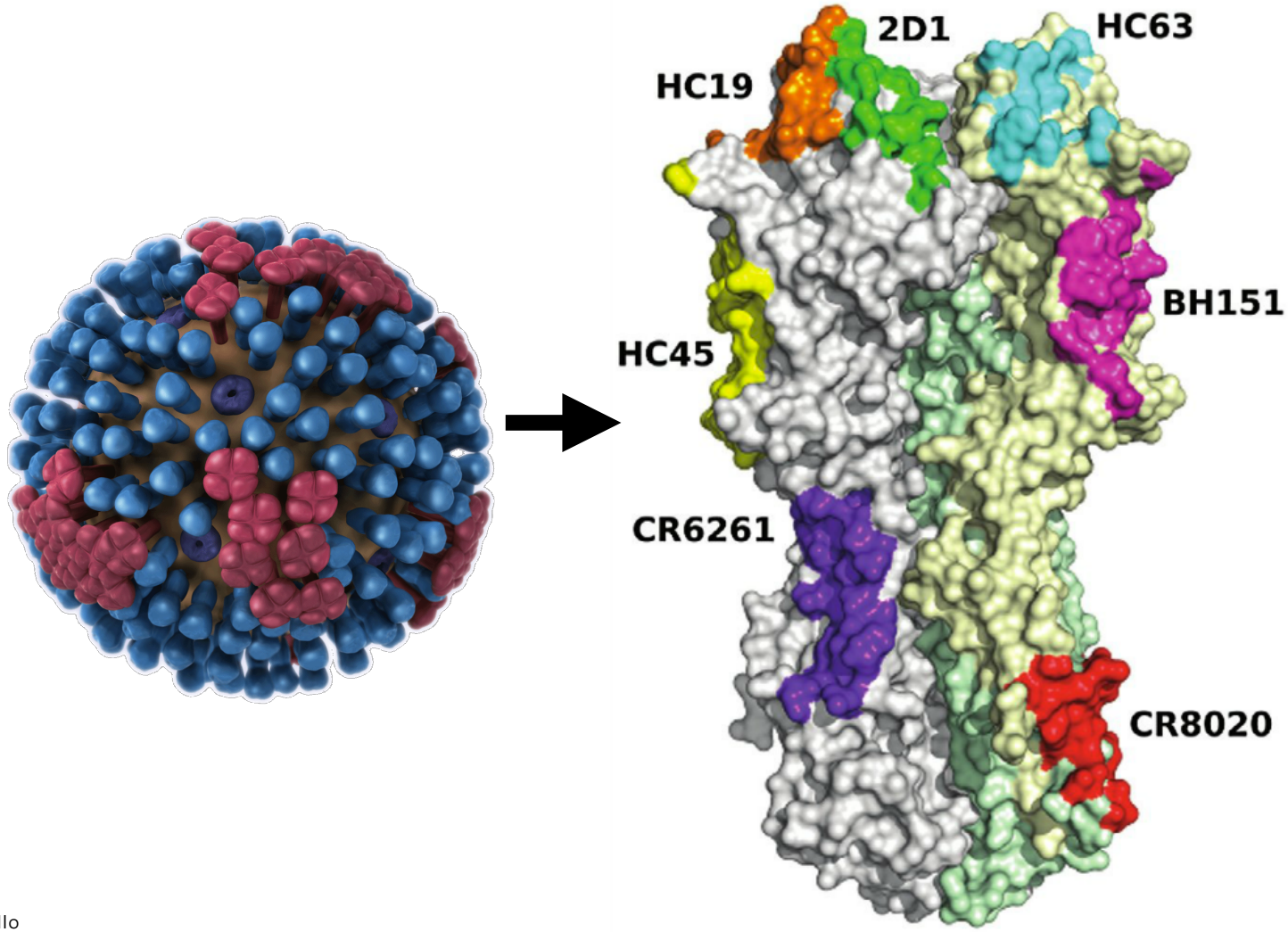
Selecting an influenza virus vaccine



*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



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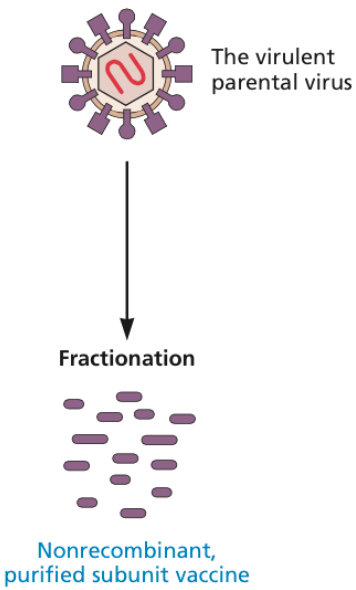
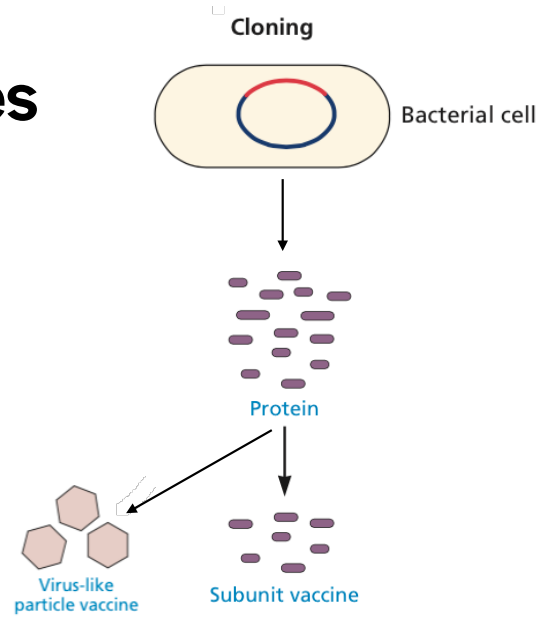
Which statement about inactivated viral vaccines is incorrect:

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

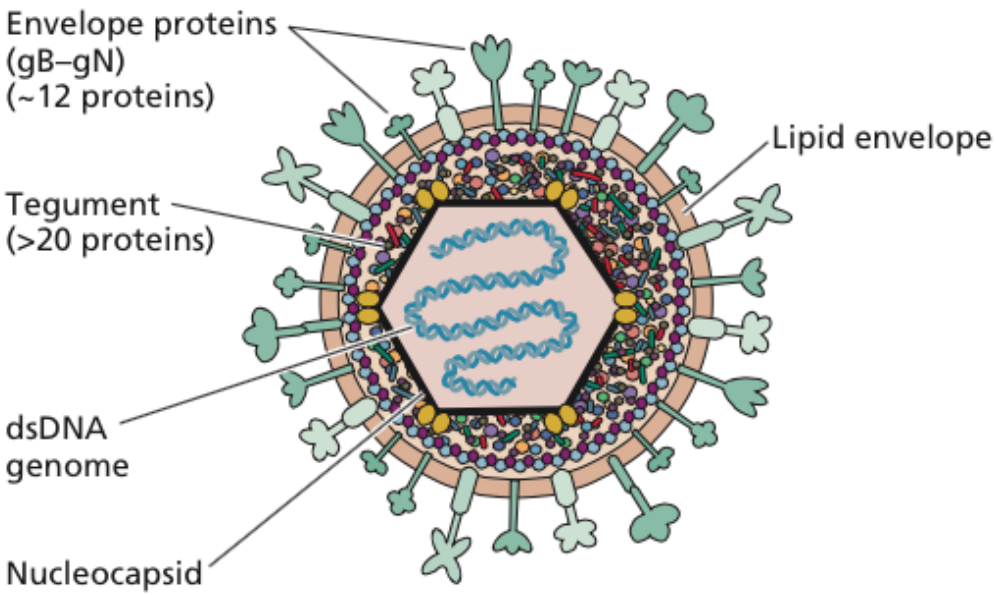
Subunit vaccines





- 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



Varicella-zoster virus

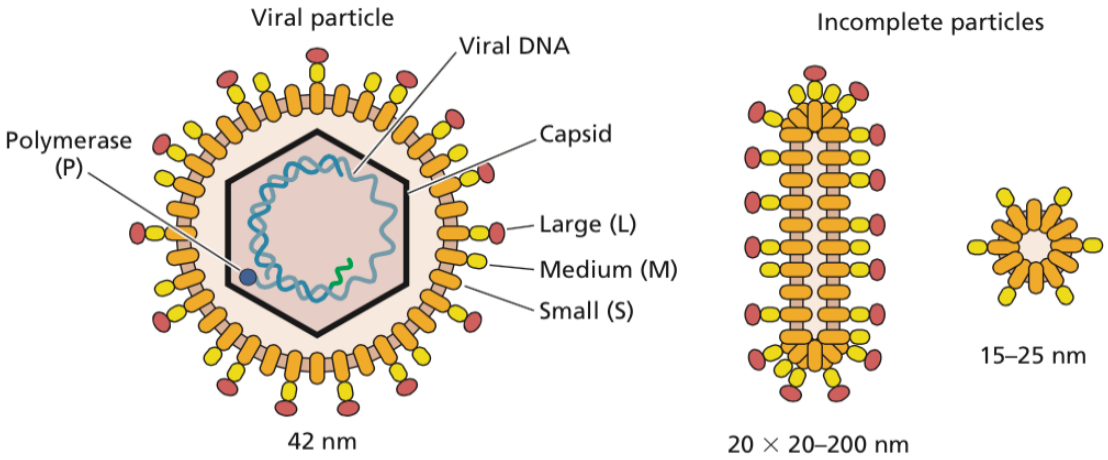
- Recombinant gE produced in mammalian (CHO cells, secreted)
- Adjuvanted with AS01
- Injected

Principles of Virology, ASM Press

HBV vaccine

A cancer vaccine

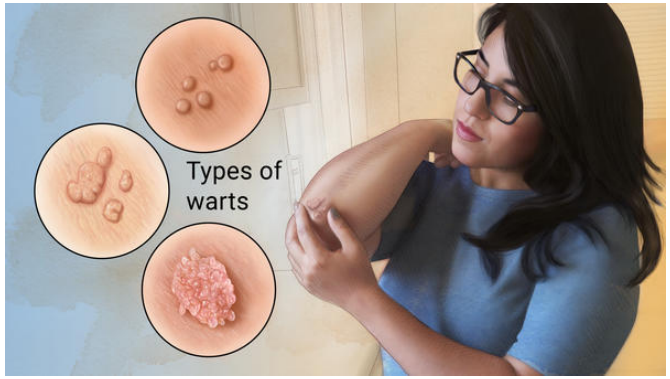
- Hepatitis B virus (HBV) - HBsAg protein produced in yeast
- Assembles into empty particles

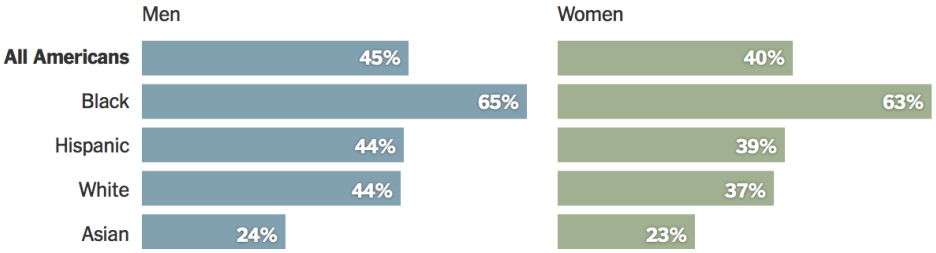


Principles of Virology, ASM Press

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)



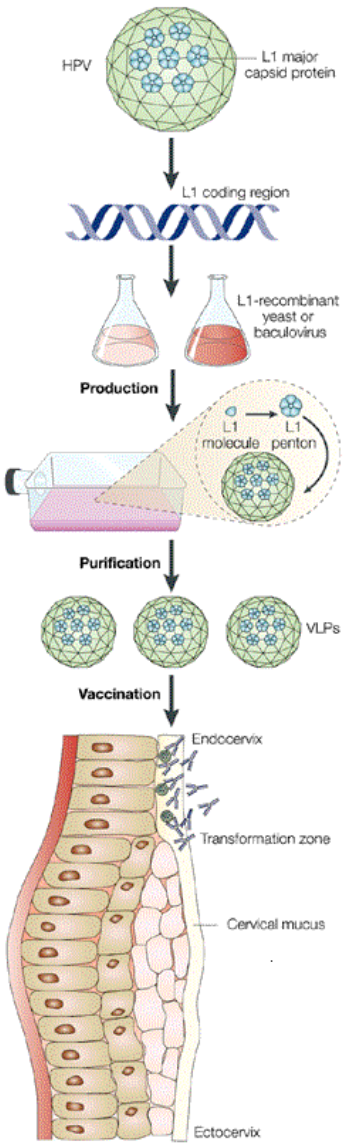


https://nyti.ms/2oFBTM2

Human papillomavirus vaccines

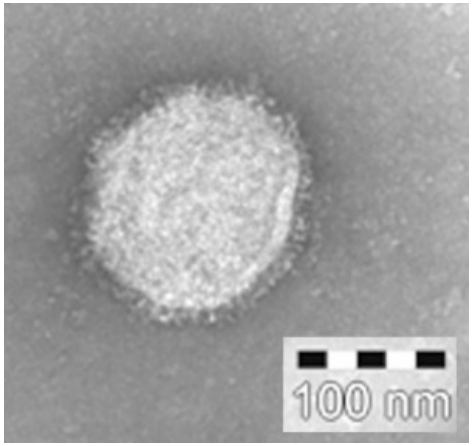
Cancer vaccines

- *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

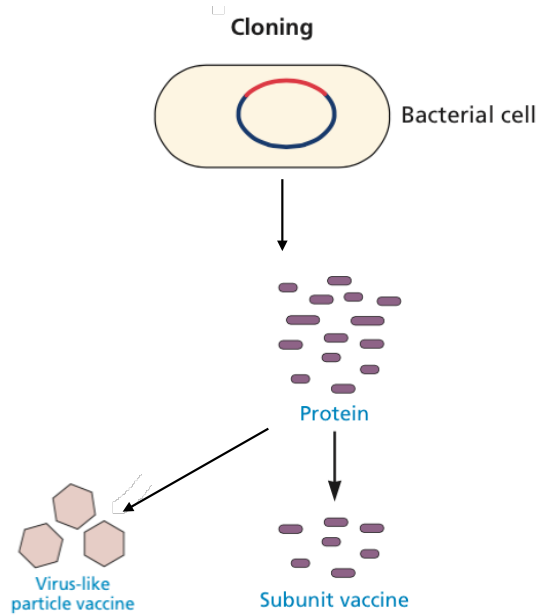


Introduction of HA gene (transient or transgenic) →  → Harvesting and purification of HA

Nicotiana benthamiana

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*



Principles of Virology, ASM Press

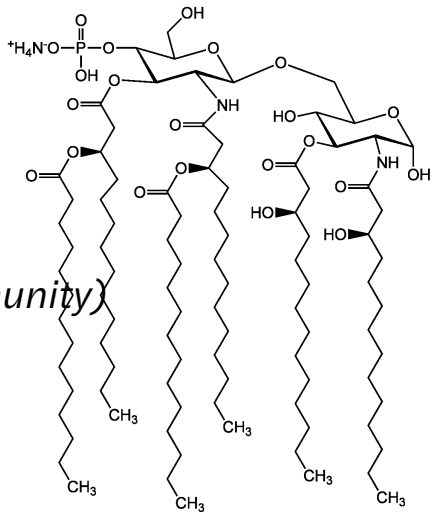
Inactivated and subunit vaccines have a common problem

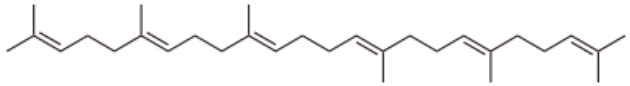
- Viral proteins don’t replicate or infect
- Don’t cause inflammation, poor activation of adaptive responses
- Pure proteins often require* *adjuvant* to mimic inflammatory effects of infection

*Except poliovirus IPV

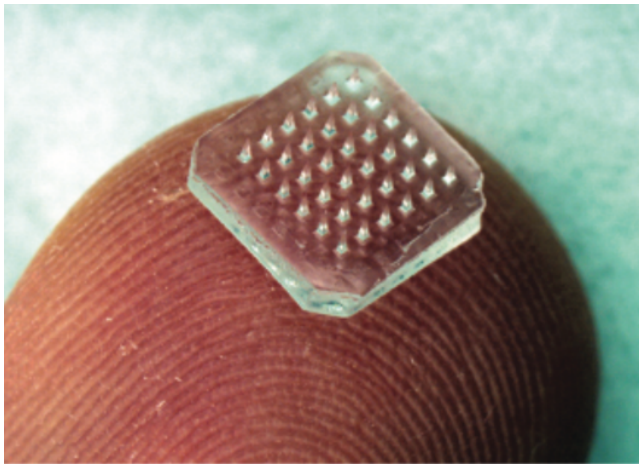
Adjuvants

- Stimulate early processes in immune recognition
- Produce a more robust acquired immune response
  - *Slow release of antigen at 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*

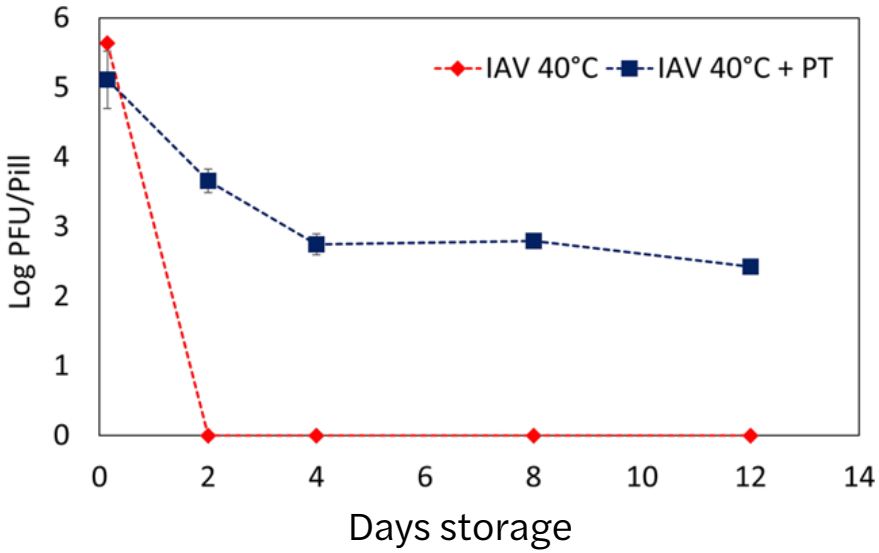




New vaccine technologies



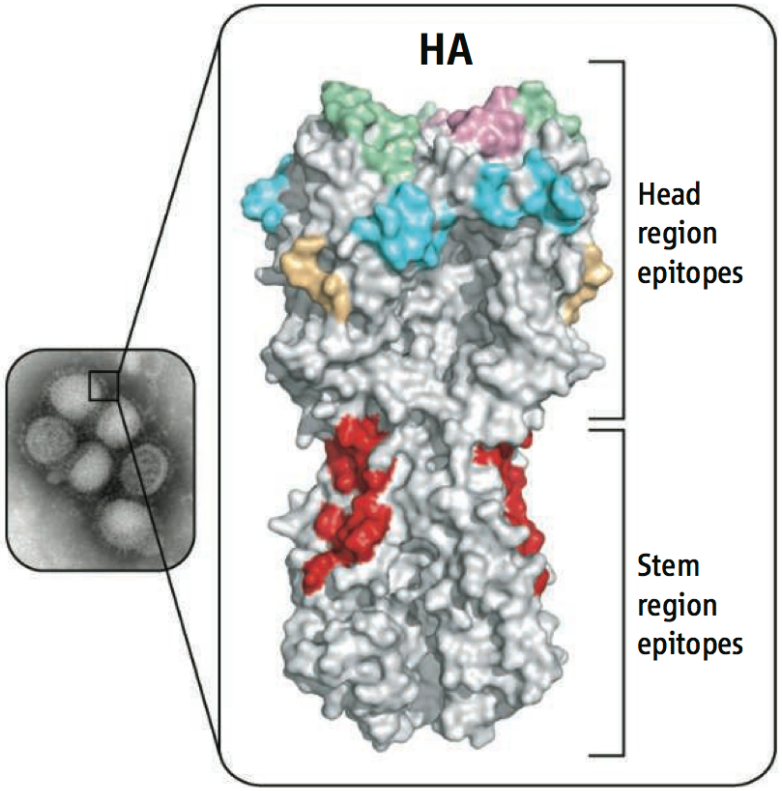
Microneedle patch

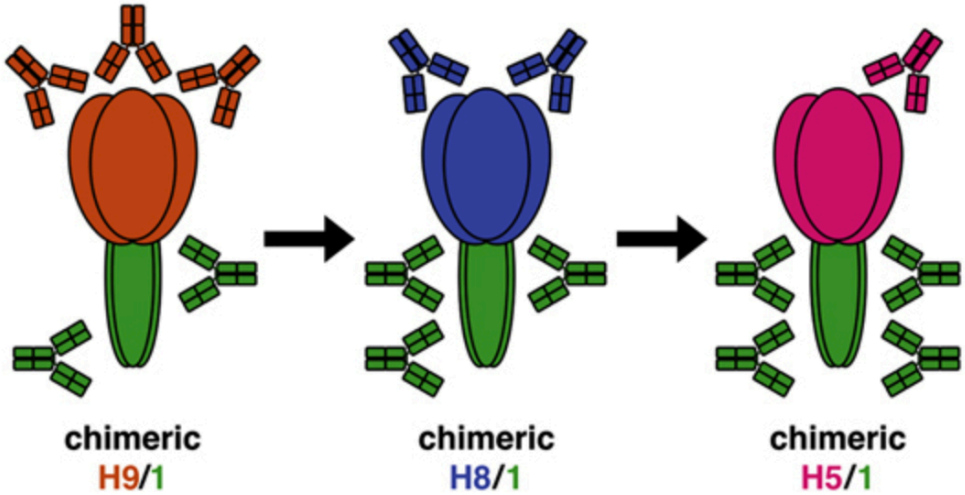


Thermostabilization of influenza vaccine in sugars

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.

NPJ Vaccines. 2017; 2: 26.

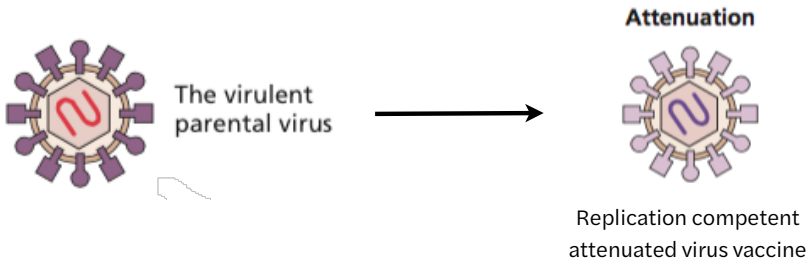
Go to:

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

What are some requirements for an effective vaccine?

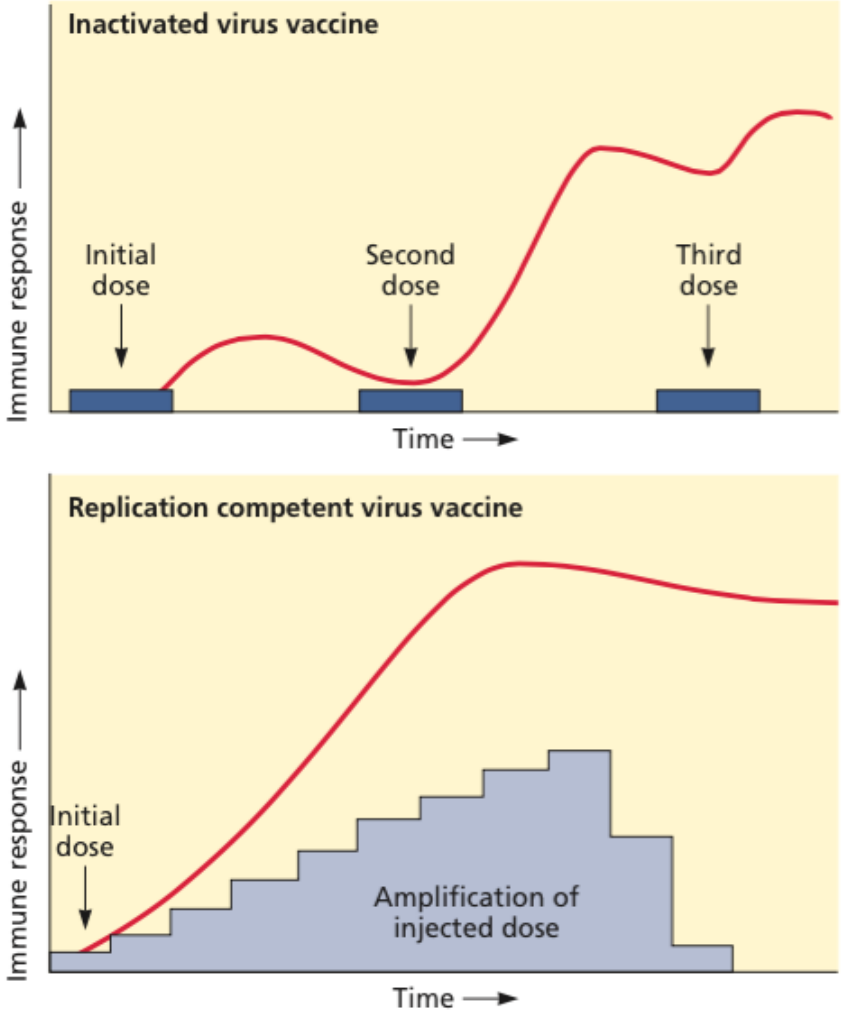
A. Low cost
B. Ease of administration
C. Provides long lasting immunity
D. Minimal side effects
E. All of the above

Replication competent, attenuated vaccines



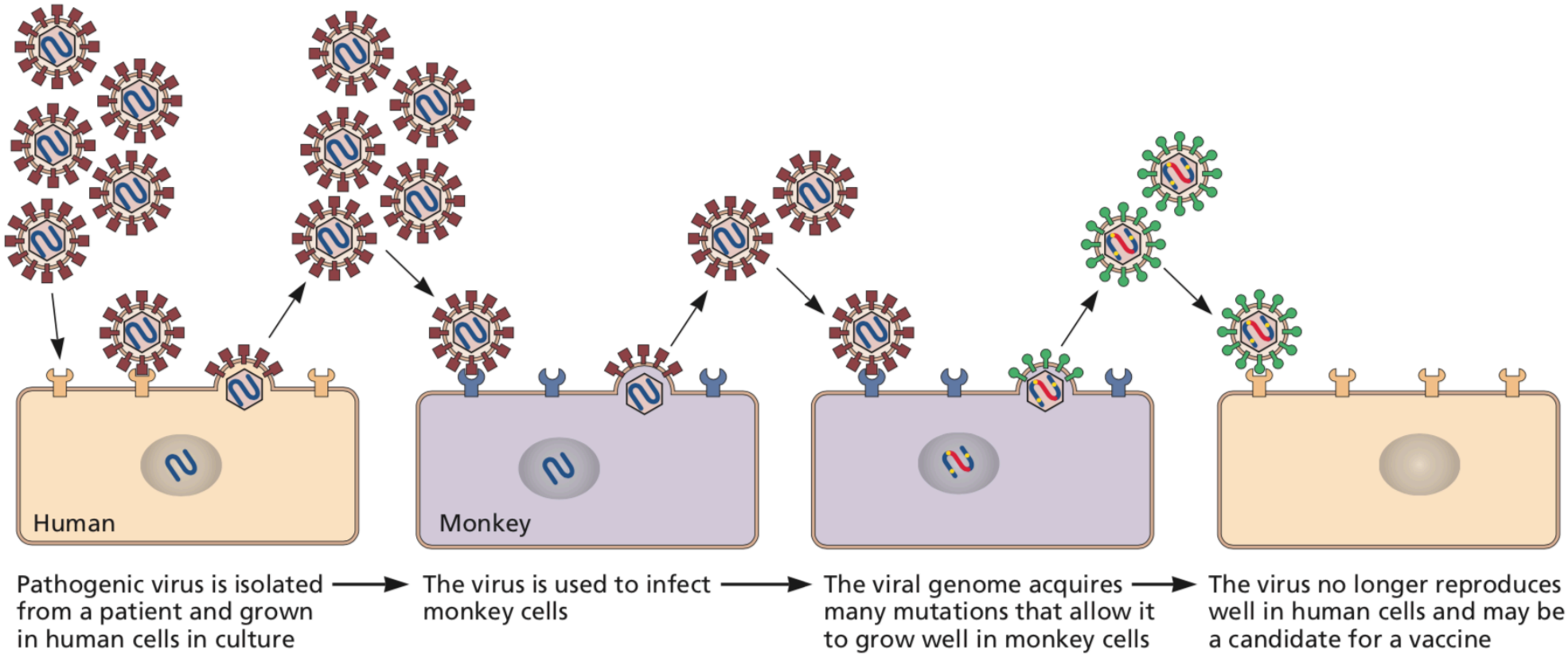
- Viral replication occurs, stimulates immune response
- Infection induces mild or inapparent disease

Principles of Virology, ASM Press

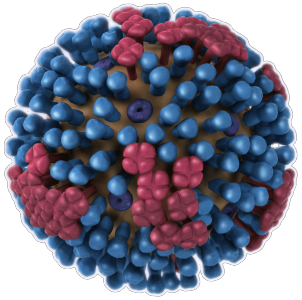


Principles of Virology, ASM Press

Empirically derived attenuated vaccines



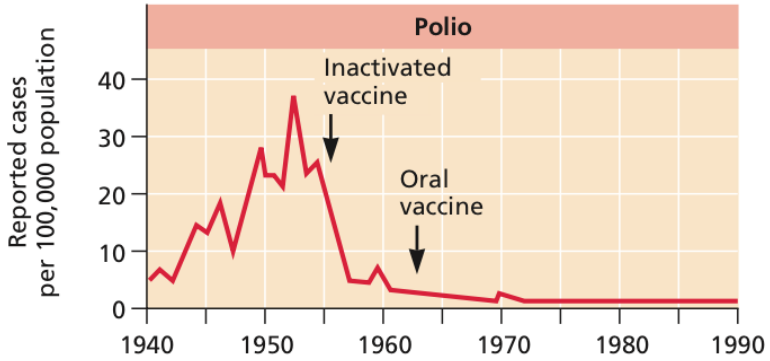
Principles of Virology, ASM Press

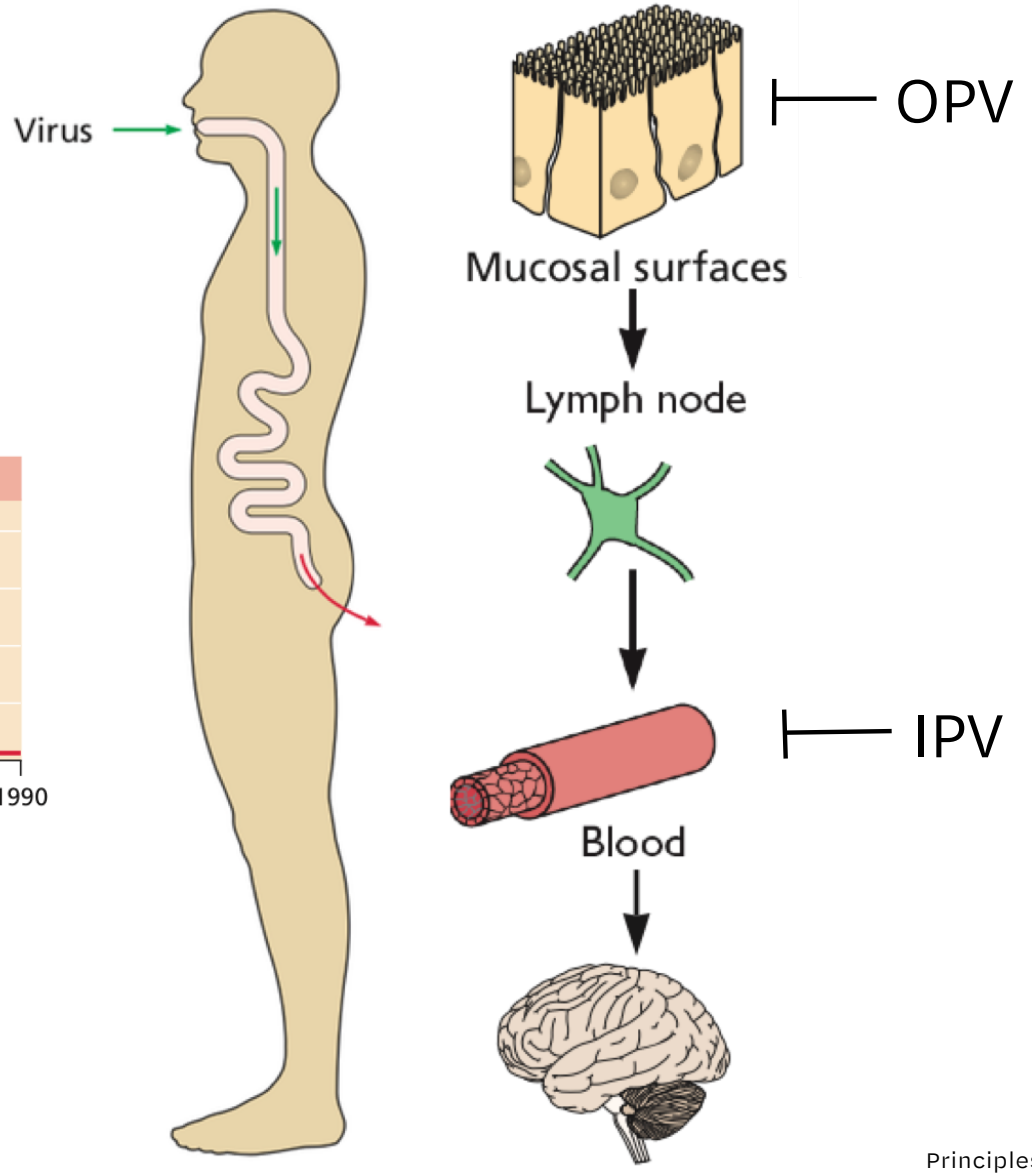


FluMist

- 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

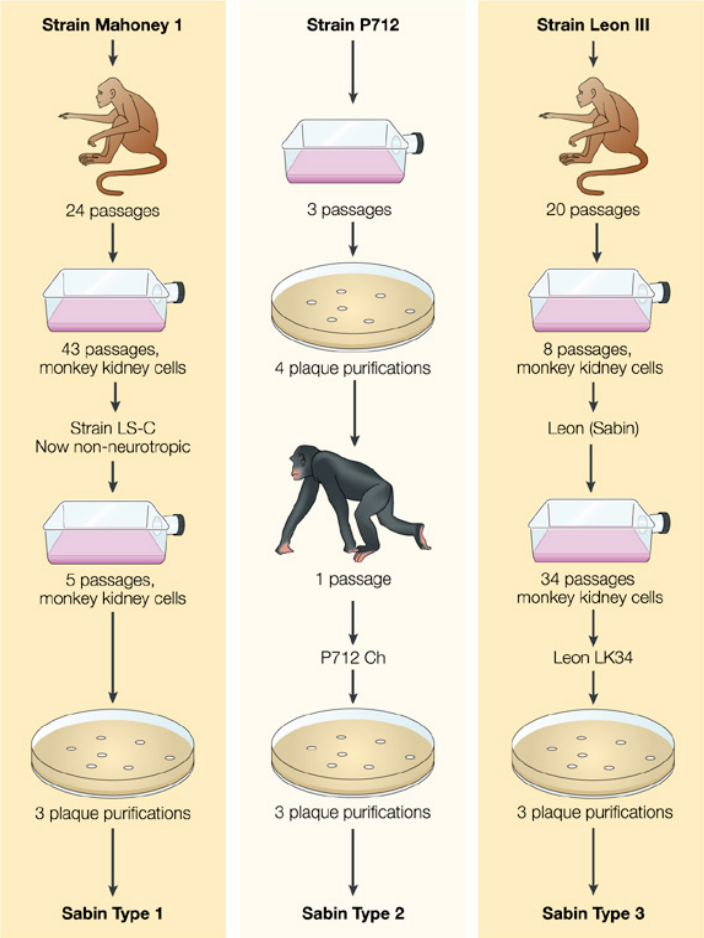
Sabin oral poliovirus vaccine (OPV)





Principles of Virology, ASM Press

Attenuation of poliovirus neurovirulence

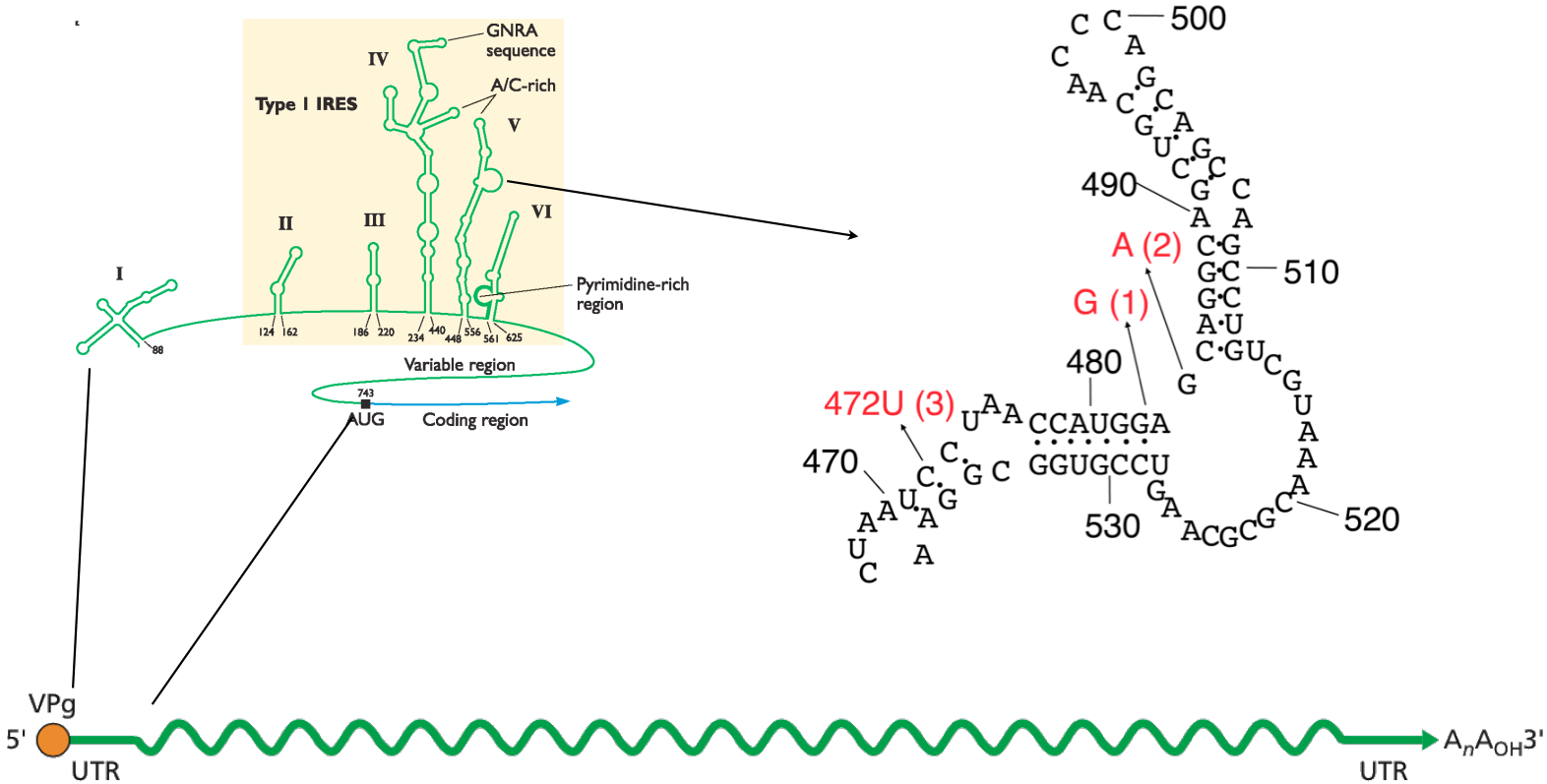


Albert Sabin's three strains of OPV licensed in the US in 1961

Principles of Virology, ASM Press

Determinants of Sabin vaccine strain attenuation

Virus	Mutation
P1/Sabin	5'-UTR nt 480 VP1 aa 1106 VP1 aa 1134 VP3 aa 3225 VP4 aa 4065
P2/Sabin	5'-UTR nt 481 VP1 aa 1143
P3/Sabin	5'-UTR nt 472 VP3 aa 3091

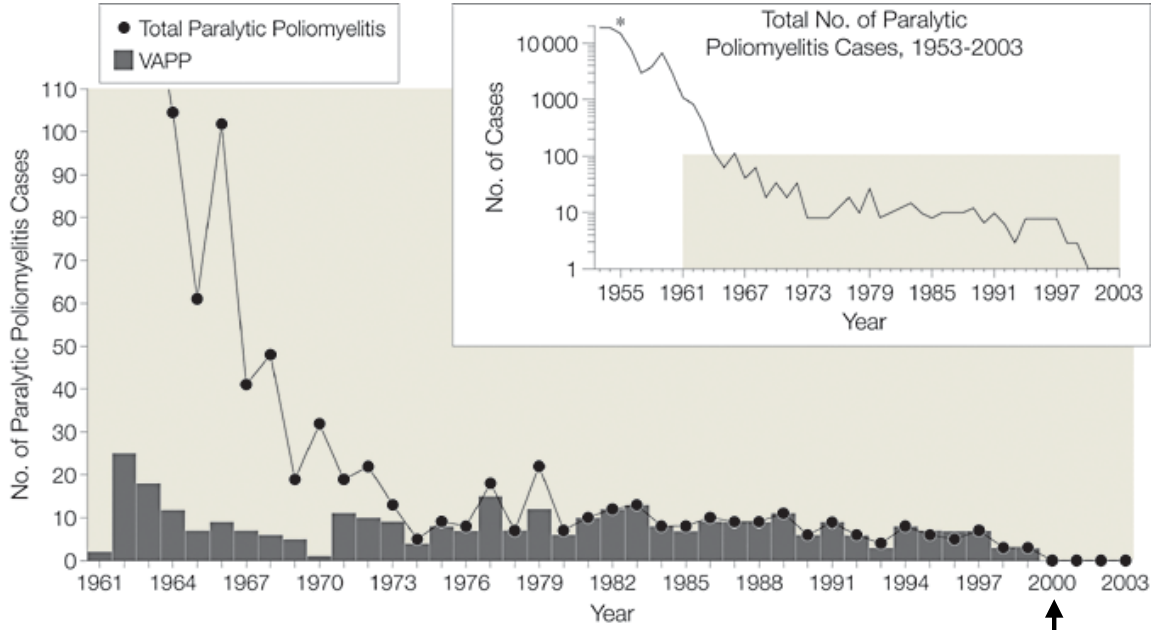

Type I IRES
GNRA sequence
A/C-rich
Pyrimidine-rich region
Variable region
AUG
Coding region
I
II
III
IV
V
VI
88
124
162
186
220
234
440
448
556
561
625
743
500
490
510
520
530
480
470
A (2)
G (1)
472U (3)
VPg
5'
UTR
UTR
$A_nA_{OH}3'$

Reversion of P3/Sabin

Virus	Base at 472	Time of isolation after vaccination	Histological lesion score
Sabin vaccine	U		0.36
DM1	U	24 h	ND
DM2	U	31 h	1.58
DM3	U/C	35 h	ND
DM4	C	47 h	2.48
DM38	C	18 da	ND
P3/119	C	3-4 weeks	3.34

Evans et al., Nature 314:548 (1985)

Reported Cases of Paralytic Poliomyelitis, United States, 1961-2003

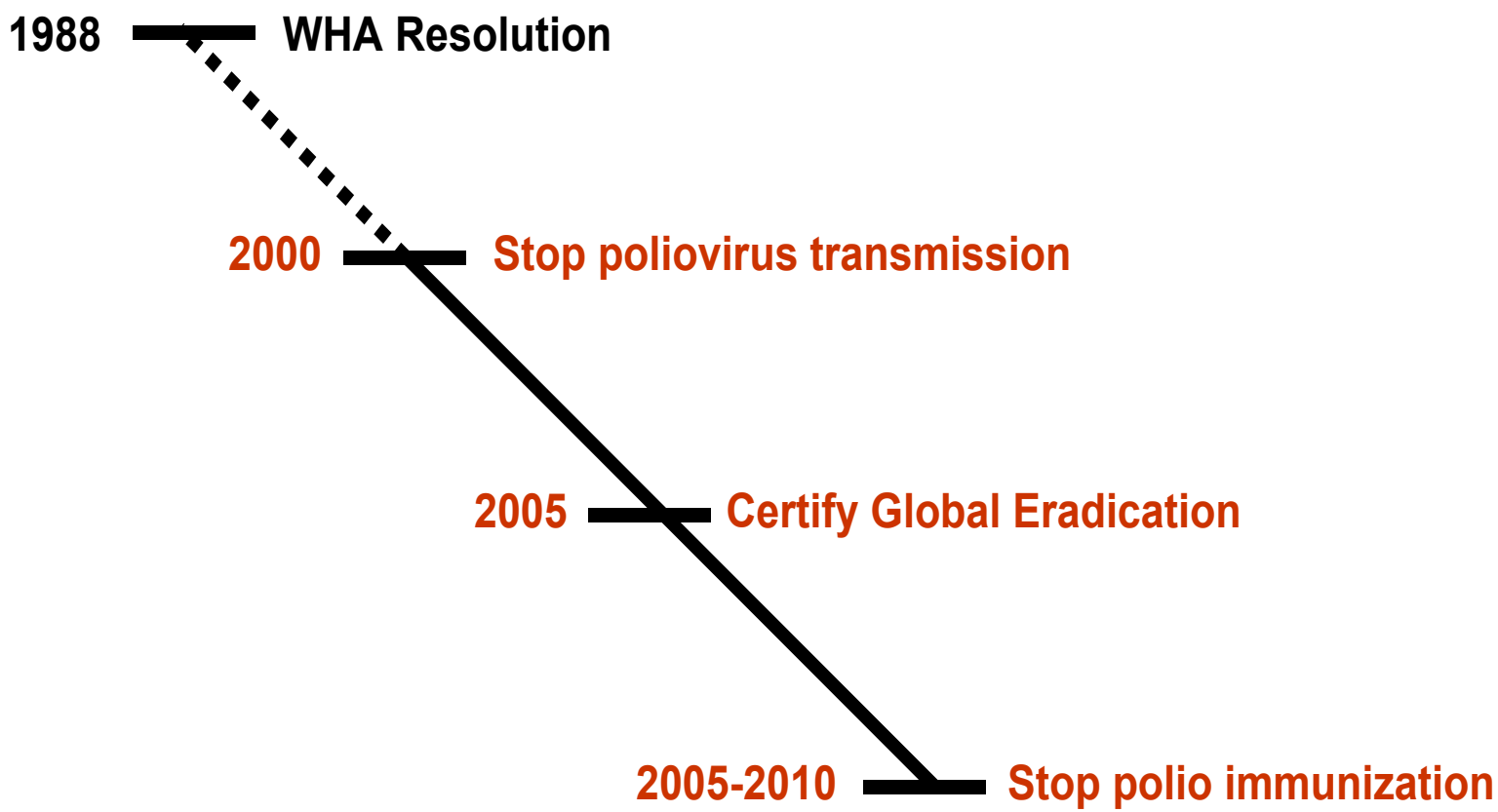


Alexander, L. N. et al. JAMA 2004;292:1696-1701.

switch to IPV

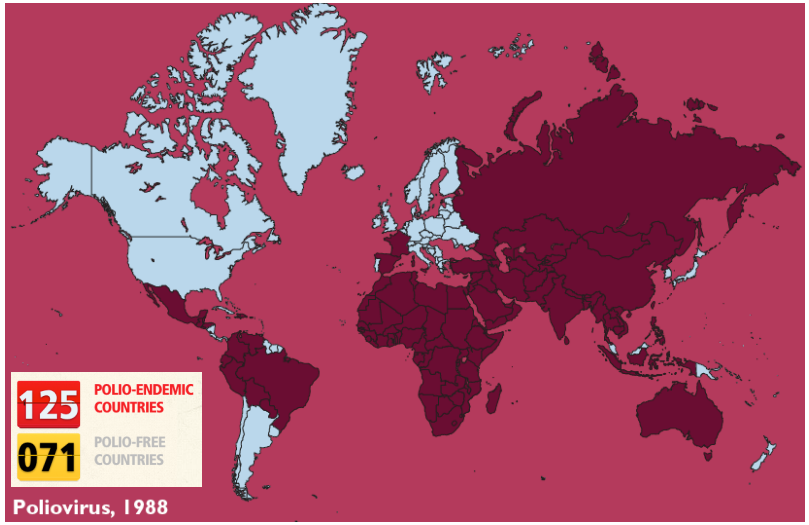
1 paralytic case/1.4 million doses

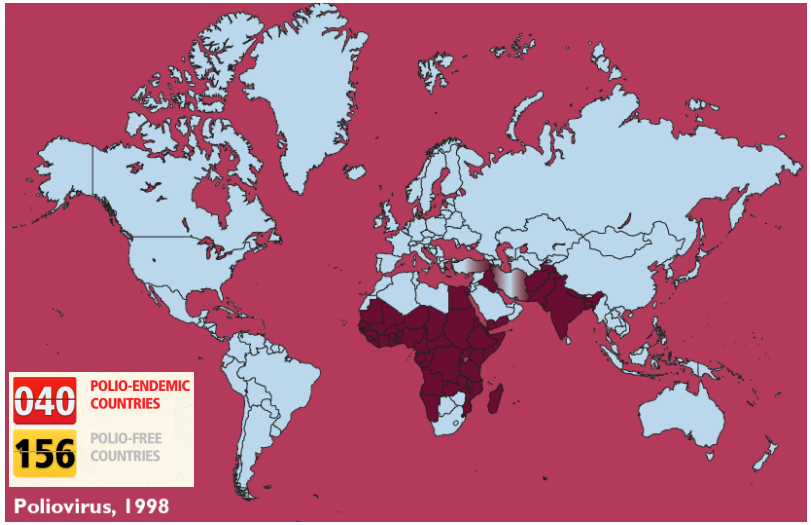
Eradication of poliomyelitis

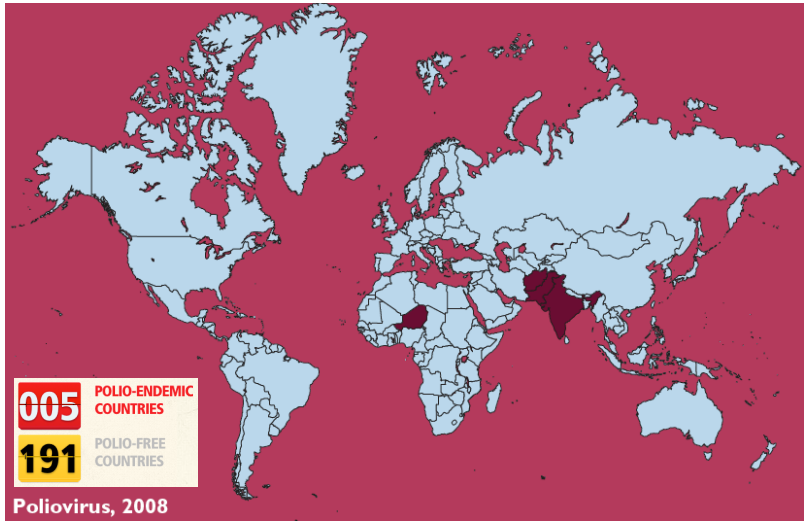


Can viral diseases be eradicated?

- Smallpox eradication program launched 1967, eradicated 1978
- Two features essential for eradication:
  - Replication in only one host
  - Vaccination induces lifelong immunity

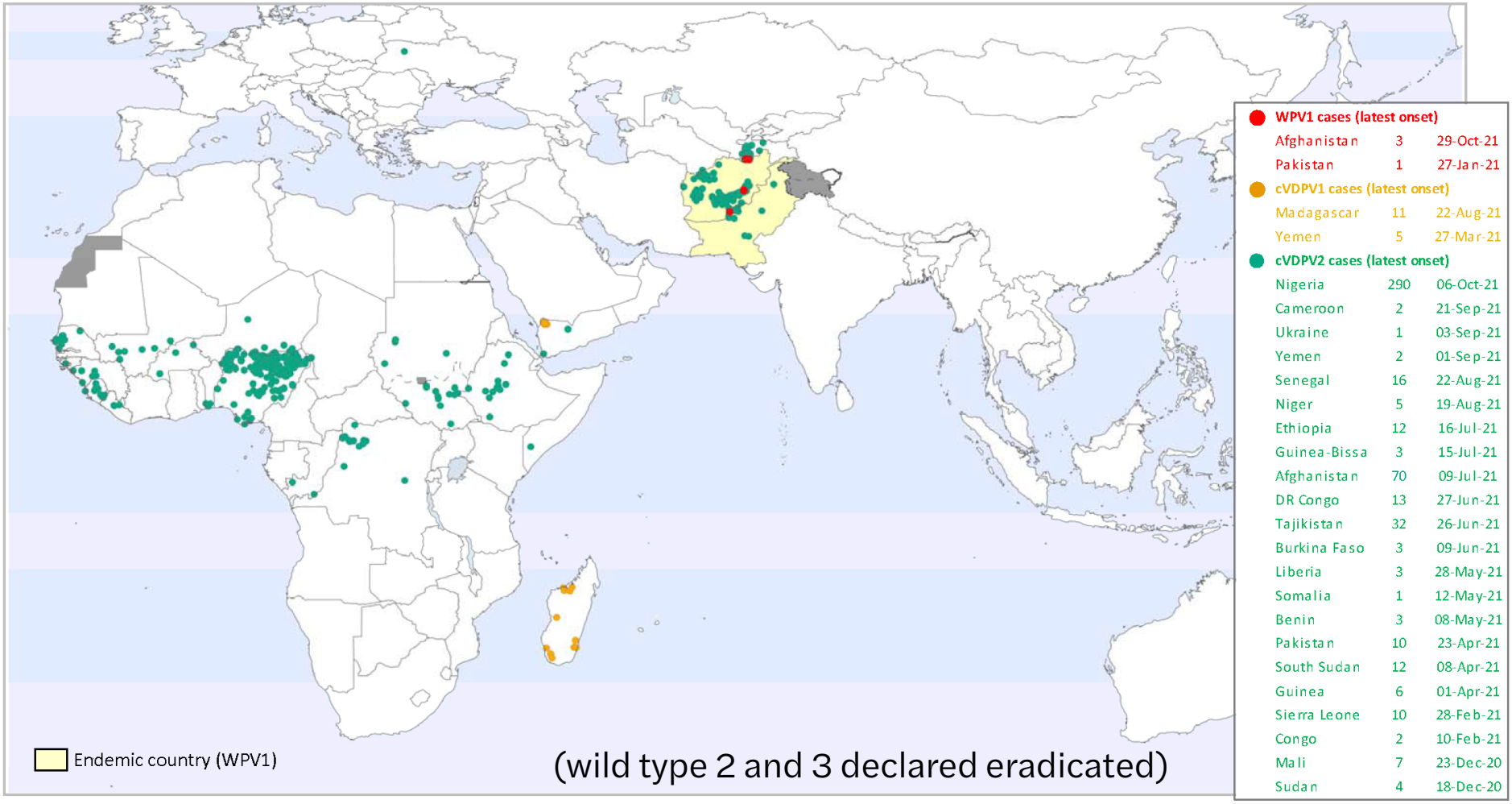

125
POLIO-ENDEMIC COUNTRIES
071
POLIO-FREE COUNTRIES
Poliovirus, 1988


040
POLIO-ENDEMIC COUNTRIES
156
POLIO-FREE COUNTRIES
Poliovirus, 1998


005
POLIO-ENDEMIC COUNTRIES
191
POLIO-FREE COUNTRIES
Poliovirus, 2008

Global WPV1 & cVDPV Cases[1], Previous 12 Months[2]

World Health Organization



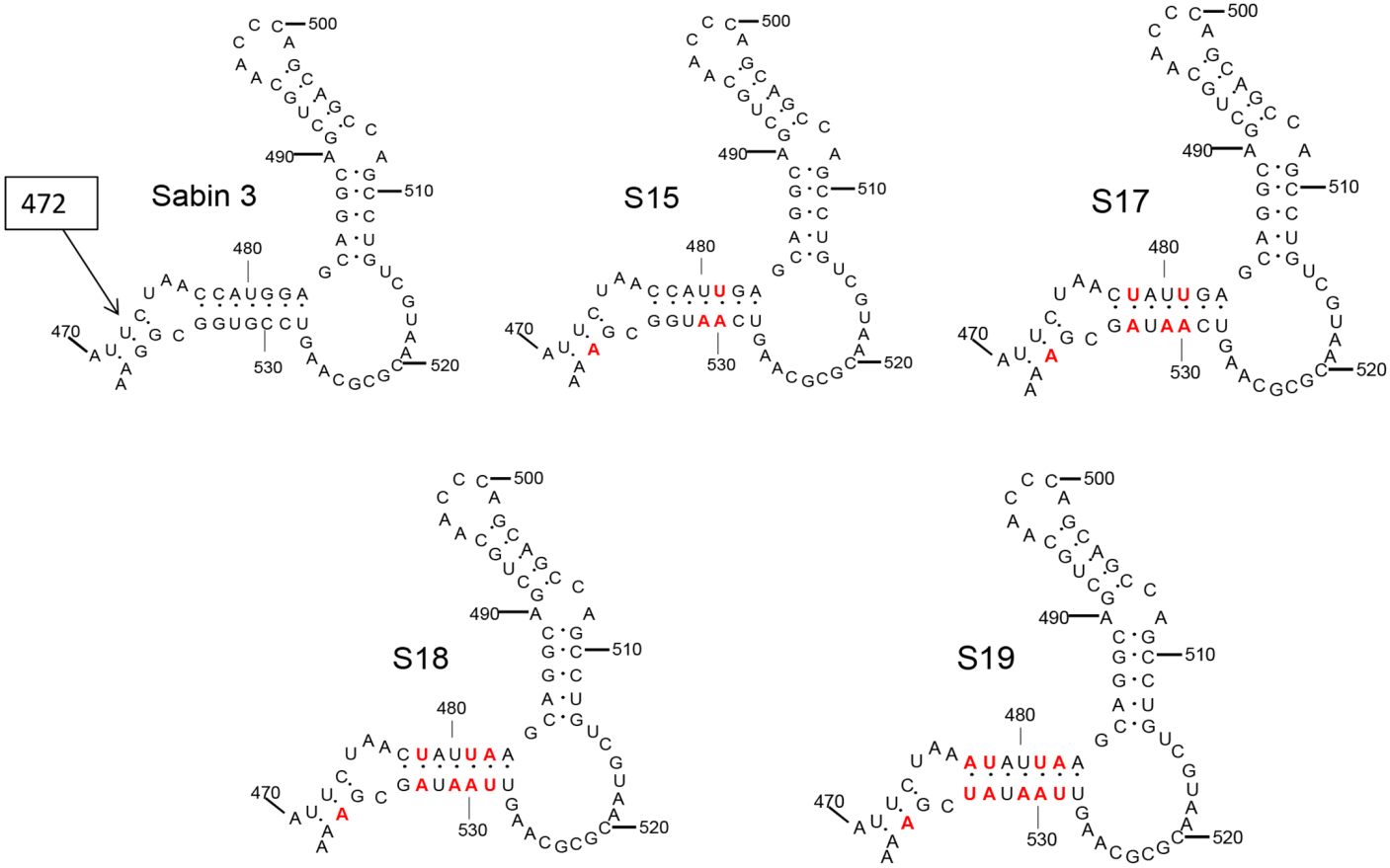
WPV1 cases (latest onset)		
Afghanistan	3	29-Oct-21
Pakistan	1	27-Jan-21
cVDPV1 cases (latest onset)		
Madagascar	11	22-Aug-21
Yemen	5	27-Mar-21
cVDPV2 cases (latest onset)		
Nigeria	290	06-Oct-21
Cameroon	2	21-Sep-21
Ukraine	1	03-Sep-21
Yemen	2	01-Sep-21
Senegal	16	22-Aug-21
Niger	5	19-Aug-21
Ethiopia	12	16-Jul-21
Guinea-Bissa	3	15-Jul-21
Afghanistan	70	09-Jul-21
DR Congo	13	27-Jun-21
Tajikistan	32	26-Jun-21
Burkina Faso	3	09-Jun-21
Liberia	3	28-May-21
Somalia	1	12-May-21
Benin	3	08-May-21
Pakistan	10	23-Apr-21
South Sudan	12	08-Apr-21
Guinea	6	01-Apr-21
Sierra Leone	10	28-Feb-21
Congo	2	10-Feb-21
Mali	7	23-Dec-20
Sudan	4	18-Dec-20

[1]Excludes viruses detected from environmental surveillance; [2]Onset of paralysis 01 Dec. 2020 to 30 Nov. 2021

Data in WHO HQ as of 30 Nov. 2021

source: polioeradication.org

New non-revertible poliovirus strains



http://dx.doi.org/10.1371/journal.ppat.1005316

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

Pierre Van Damme, Ilse De Coster*, Ananda S Bandyopadhyay, Hilde Revets, Kanchanamala Withanage, Philippe De Smedt, Leen Suykens, M Steven Oberste, William C Weldon, Sue Ann Costa-Clemens, Ralf Clemens, John Modlin, Amy J Weiner, Andrew J Macadam, Raul Andino, Olen M Kew, Jennifer L Konopka-Anstadt, Cara C Burns, John Konz, Rahnuma Wahid, Christopher Gast*

Lancet 2019; 394: 148–58

Published Online June 4, 2019

http://dx.doi.org/10.1016/S0140-6736(19)31279-6

See Comment page 99

*Contributed equally

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

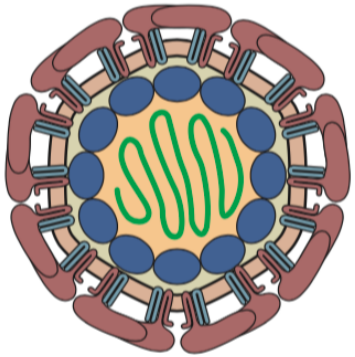
PLOS | ONE

RESEARCH ARTICLE

Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments

Ryan S. Noyce[1], Seth Lederman[2], David H. Evans[1]*

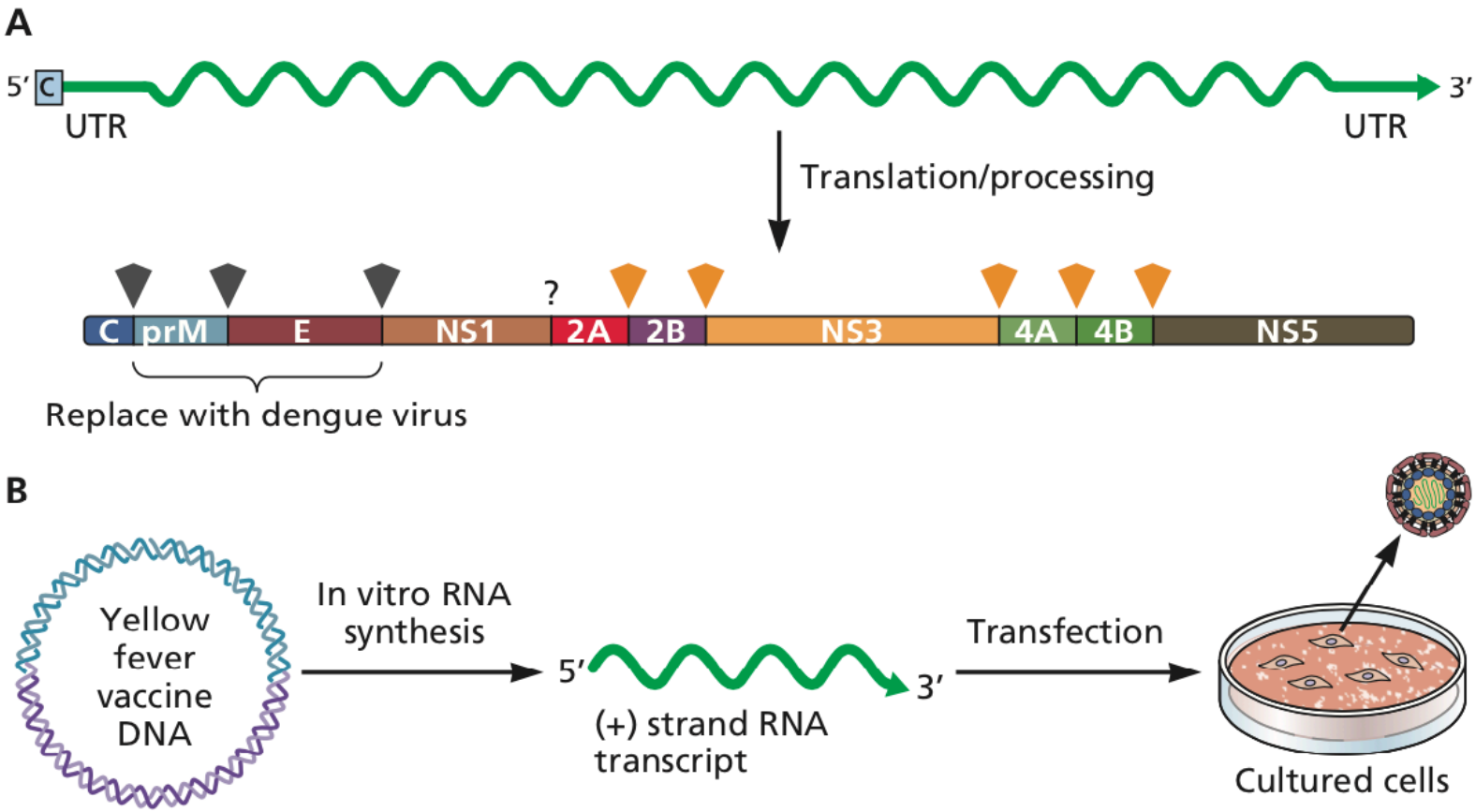
1 Department of Medical Microbiology & Immunology and Li Ka Shing Institute of Virology, University of Alberta, Edmonton, Alberta, Canada, 2 Tonix Pharmaceuticals, Inc., New York, New York, United States of America



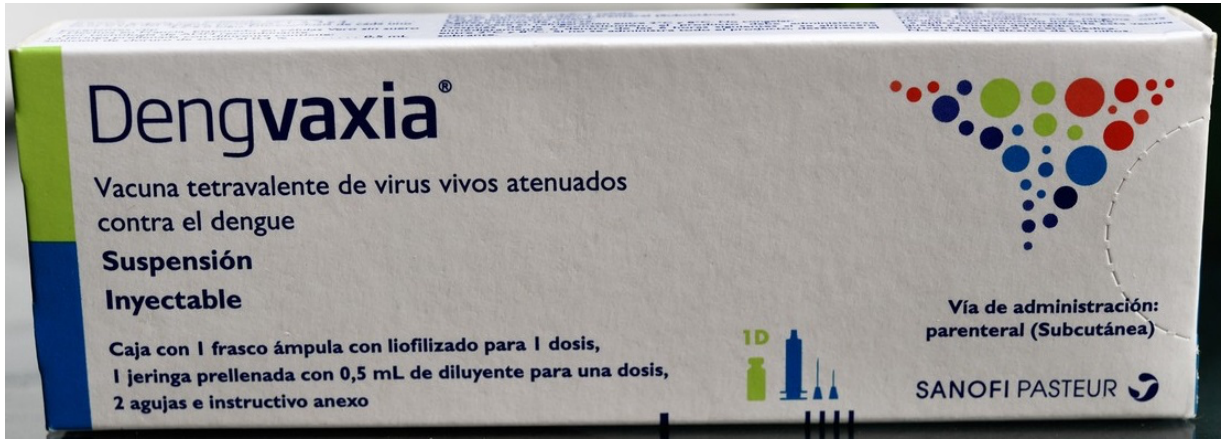
Engineering attenuated vaccines

- 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



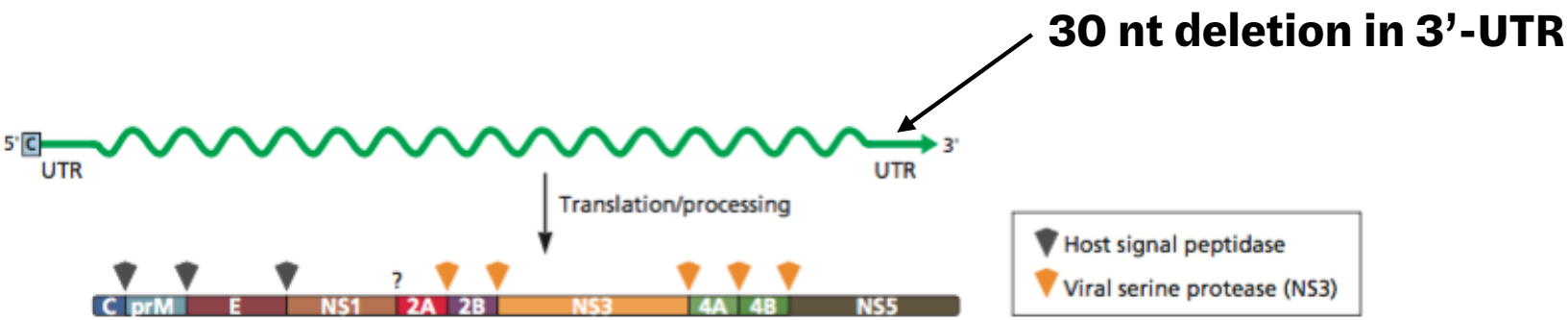
Dengvaxia



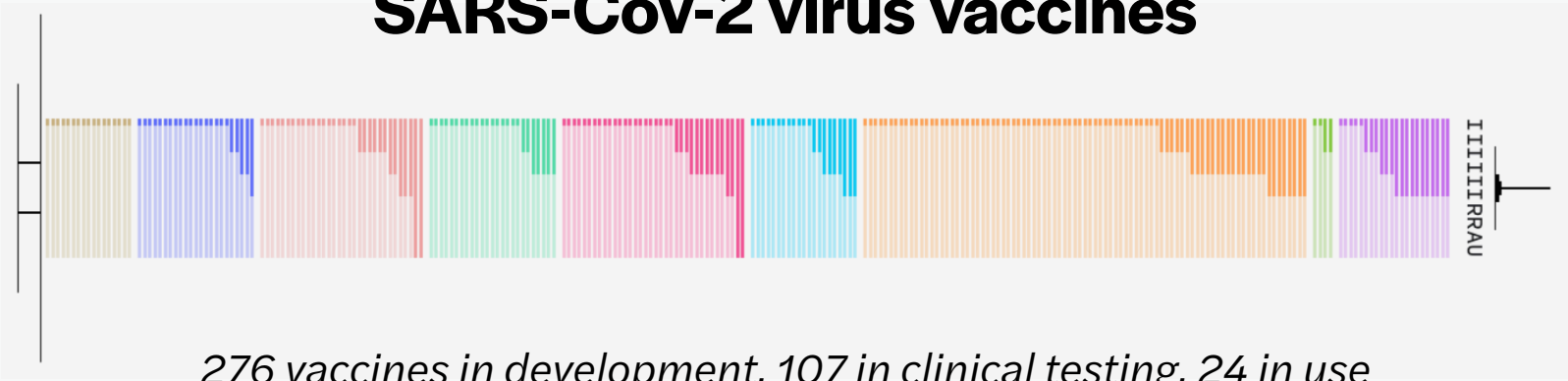
- E, prM of dengue virus 1, 2, 3, 4 in YF 17D backbone
- Licensed in Mexico, Brazil, Philippines
- No protection against DENV-2
- Lead to worse disease in 2-9 yo

TV003

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



SARS-CoV-2 virus vaccines



276 vaccines in development, 107 in clinical testing, 24 in use

Leading Vaccines

BioNTech/Pfizer	Approved
Moderna	Authorized
Oxford/AstraZeneca	Authorized
Janssen Pharma	Authorized
Sinovac/Instituto Butantan	Phase III
Wuhan Inst./Sinopharm	Phase III
Beijing Inst./Sinopharm	Phase III
Gamaleya Research Inst.	Phase III
CanSino Biologics	Phase III
Novavax	Phase III

VACCINE CATEGORIES

- Inactivated Virus
- Live Attenuated Virus
- Protein Subunit
- DNA-Based
- RNA-Based
- Replicating Viral Vector
- Non-Replicating Viral Vector
- Virus-Like Particle
- Other Vaccines

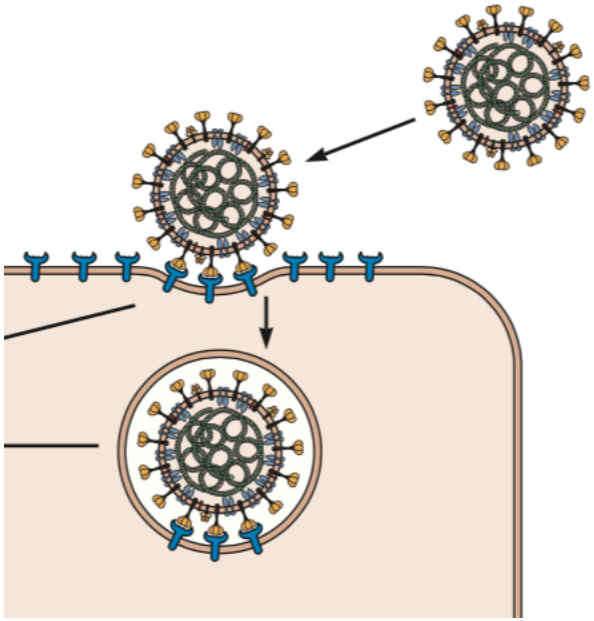
PHASES

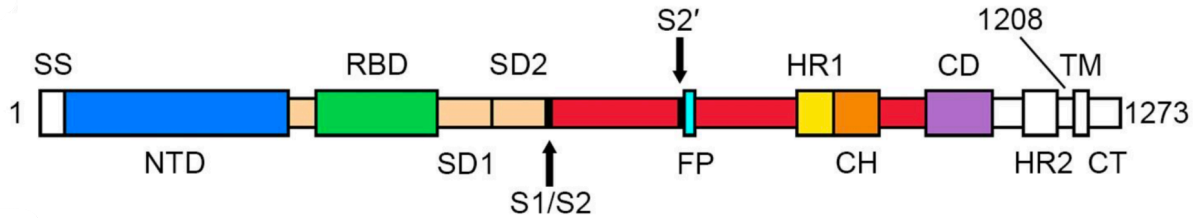
I	Phase One
II	Phase Two
III	Phase Three
RR	Regulatory Review
AU	Authorized

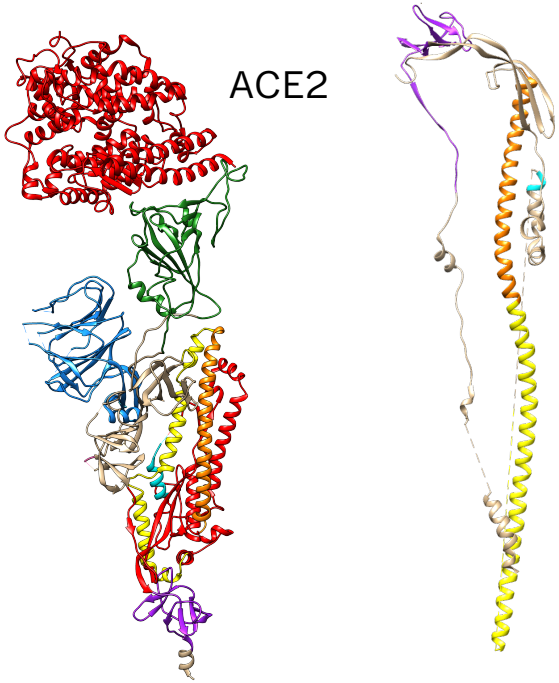
Data as of 12/5/21

https://www.covid-19vaccinetracker.org

SARS-CoV-2 spike protein

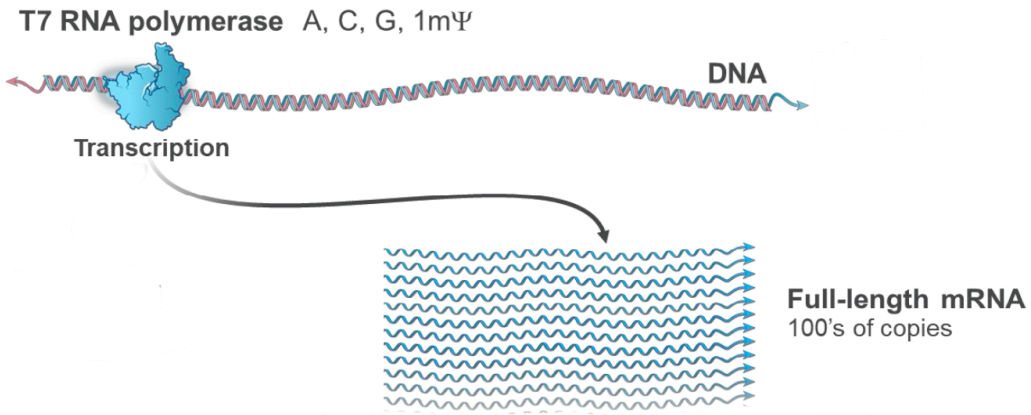


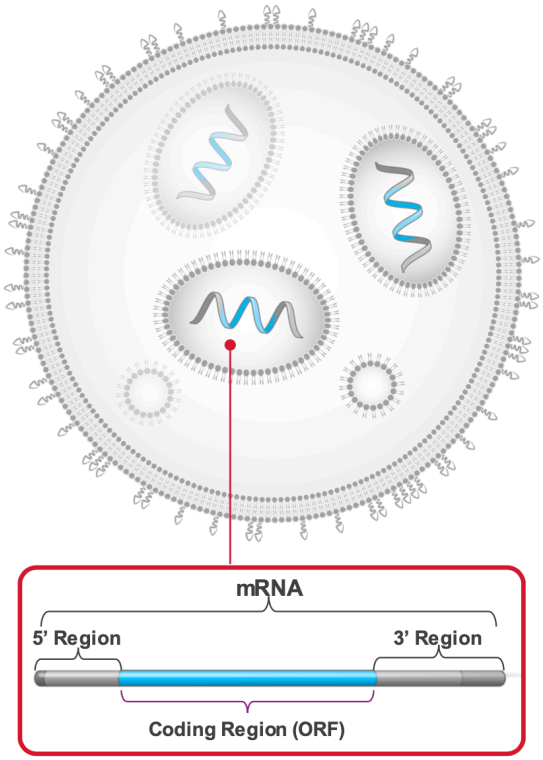




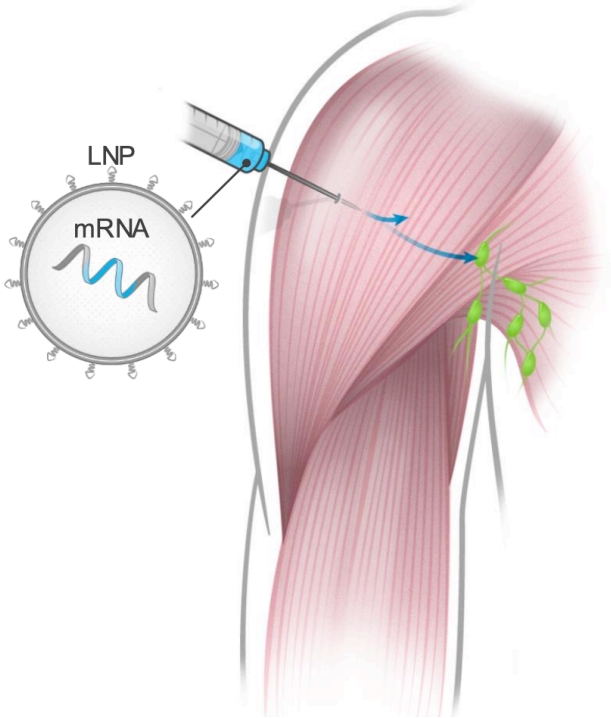
Most vaccines (except inactivated, attenuated, and AstraZeneca) encode a pre-fusion spike
Two prolines added to C-terminal S2

Moderna mRNA-1273

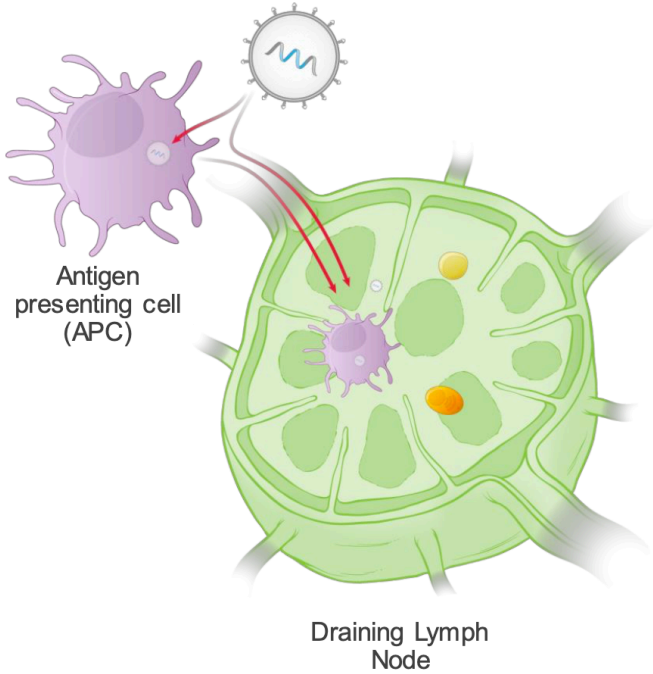




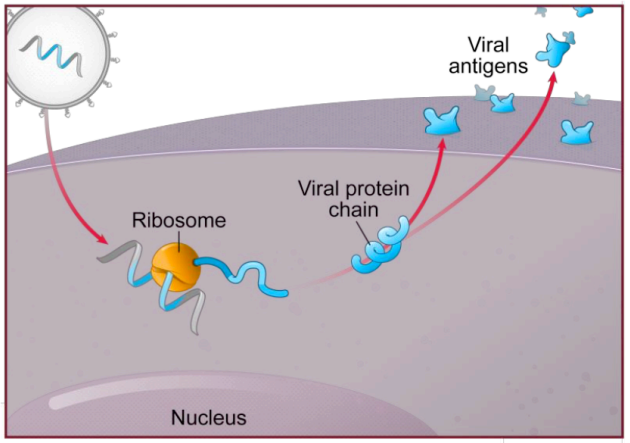
1 Recruitment of immune cells to the site of administration



2 Migration of LNPs and APC to the draining lymph node



3 LNP uptake and antigen expression in cells at the injection site and in draining lymph nodes



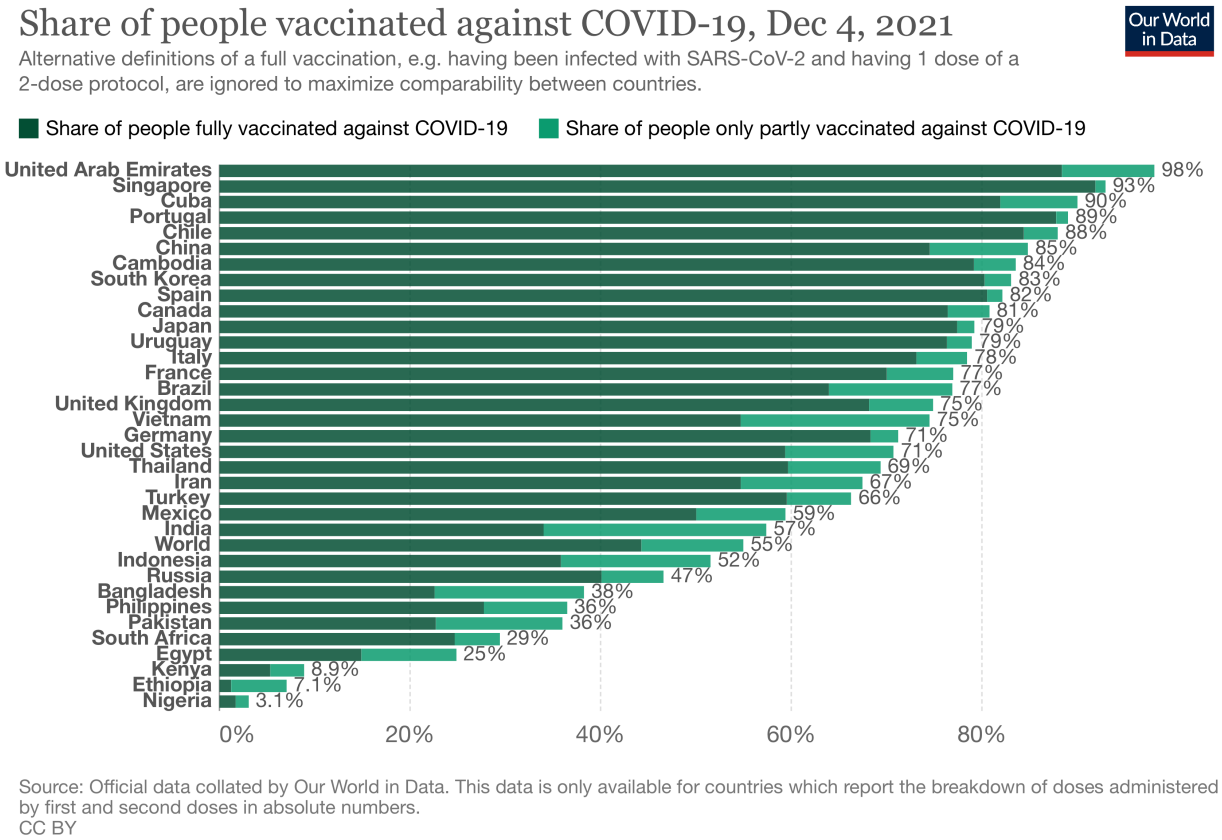
Antigen presenting cell (APC)

Source: Moderna

55% of the world population has received at least one dose of a COVID-19 vaccine.

8.18 billion doses have been administered globally, 34.86 million administered each day.

6.2% of people in low-income countries have received at least one dose.

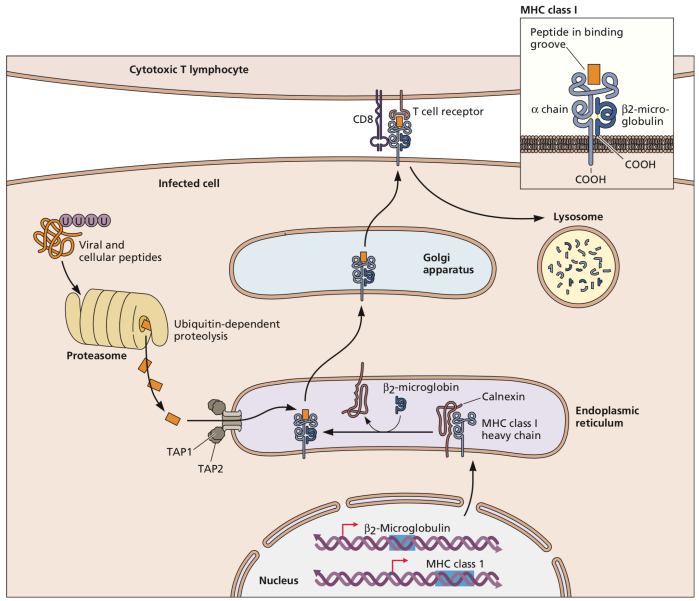


Source: Official data collated by Our World in Data. This data is only available for countries which report the breakdown of doses administered by first and second doses in absolute numbers.

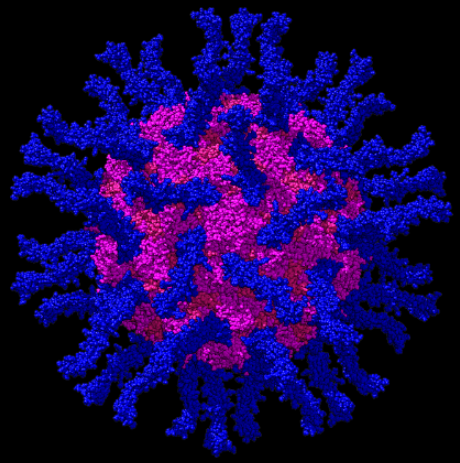
https://ourworldindata.org/covid-vaccinations

Thoughts on COVID-19 vaccines

- Assessed by prevention of COVID-19, not infection
- Focus on induction of neutralizing antibody levels
- Contraction not waning!
- Variants of concern have changes in antibody epitopes
- Most T cell epitopes are not changed
- Reason why vaccines still prevent hospitalization and death even where VOC are circulating



Principles of Virology, ASM Press



VIROLOGY LIVE

WITH VINCENT RACANIELLO

Next time: Antivirals