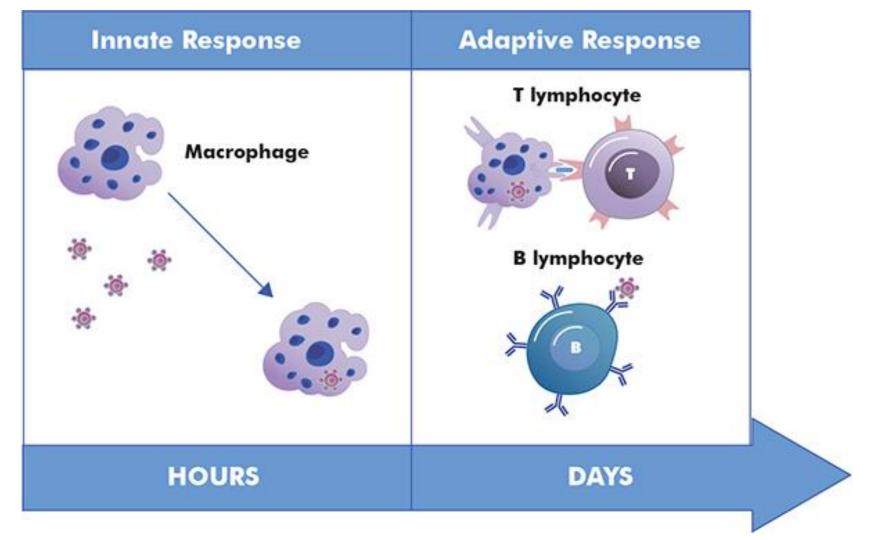
Vaccines: Past, Present and Future

Lynn Lewis, PhD. University of Mary Washington

Why Vaccinate?

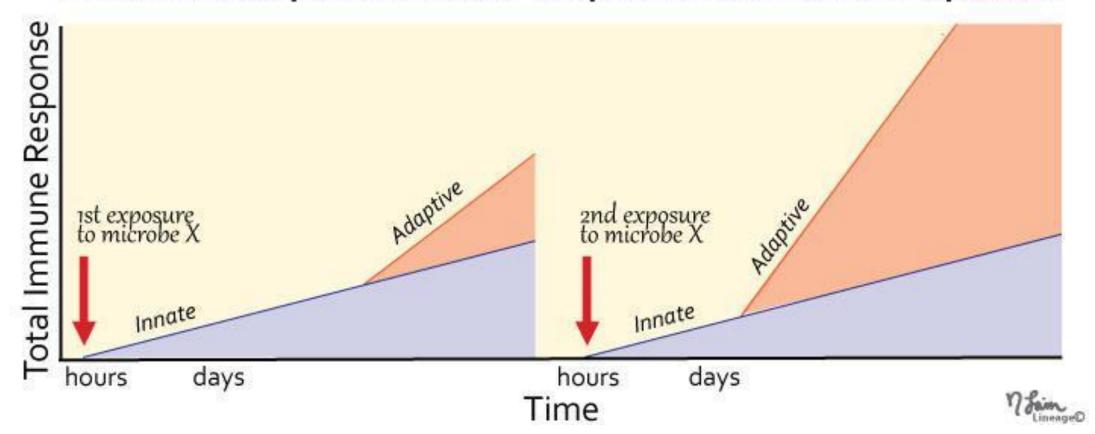
15-5

Immune Response



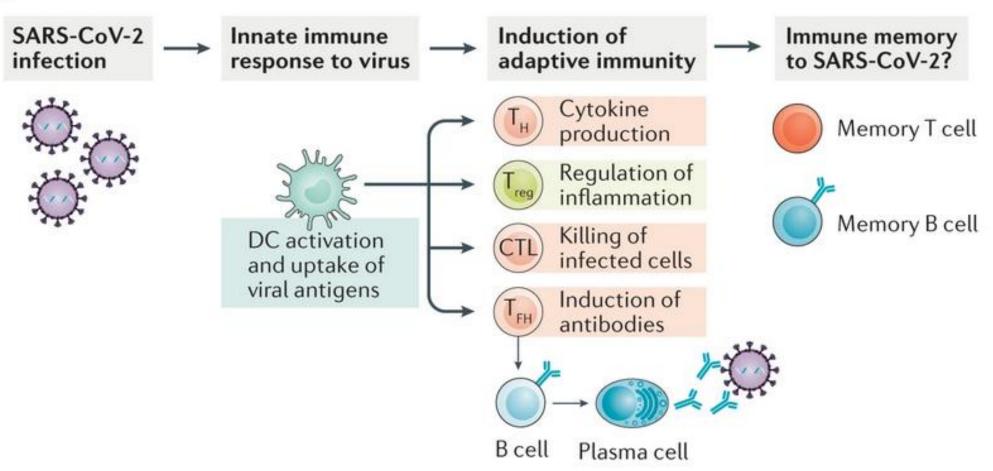
Primary vs. Secondary Exposure

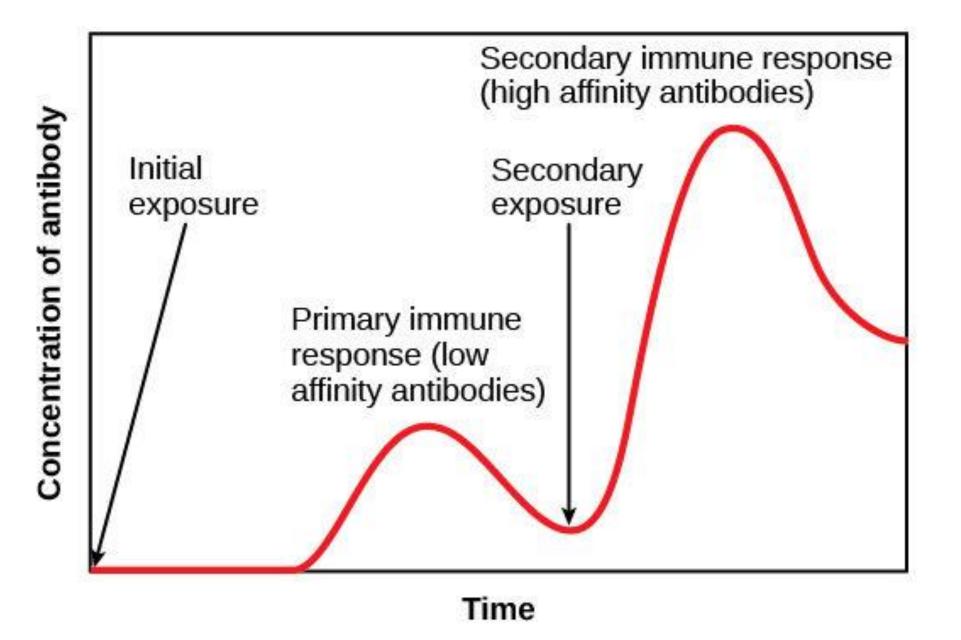
Innate vs Adaptive Immune Response to Microbial Exposure



Immune Memory

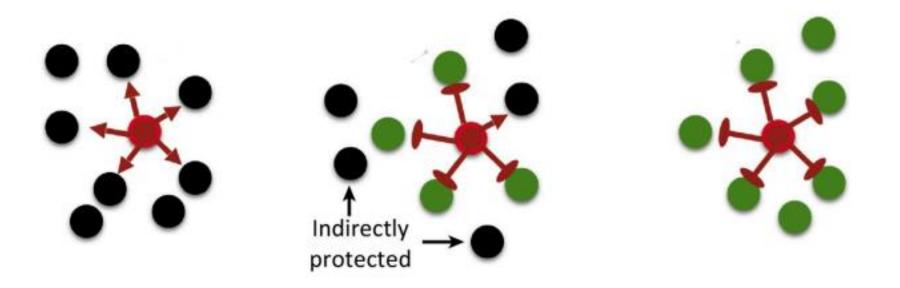
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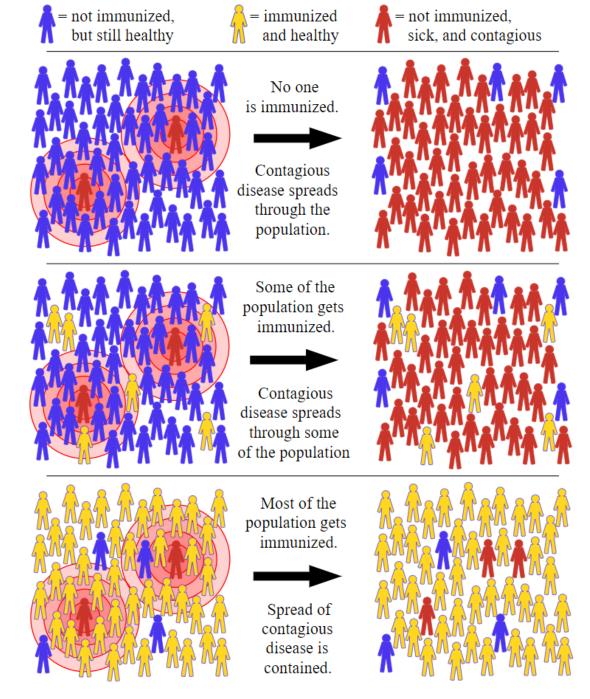




A key concept about how vaccines work: Herd Immunity

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

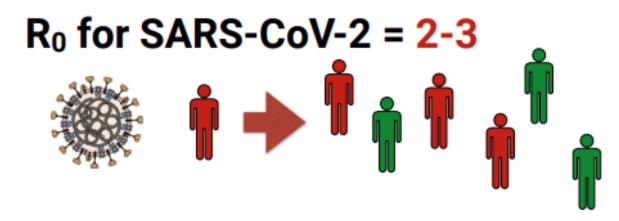




By Tkarcher - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=56760604

Herd Immunity

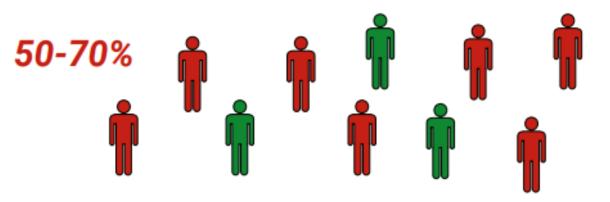
- Virus spread stops when the probability of infection drops below a critical threshold
- The threshold is virus (e.g. R₀) and population specific
- Smallpox: 80 85%
- Measles: 93 95%
- No vaccine is 100% effective
- When 80% of population is immunized with measles, 76% of population is immune



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

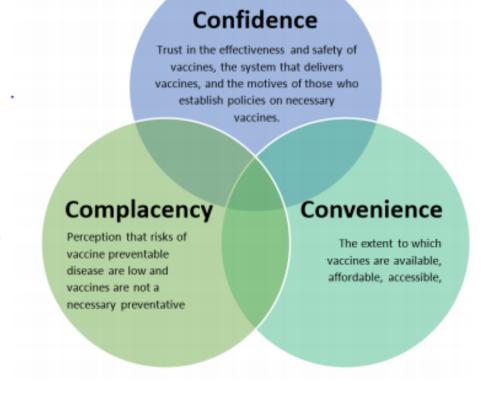
 $1 - 1/R_0$

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



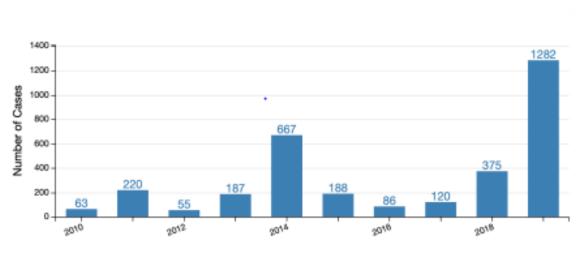
Vaccine hesitancy is dangerous to any vaccine program

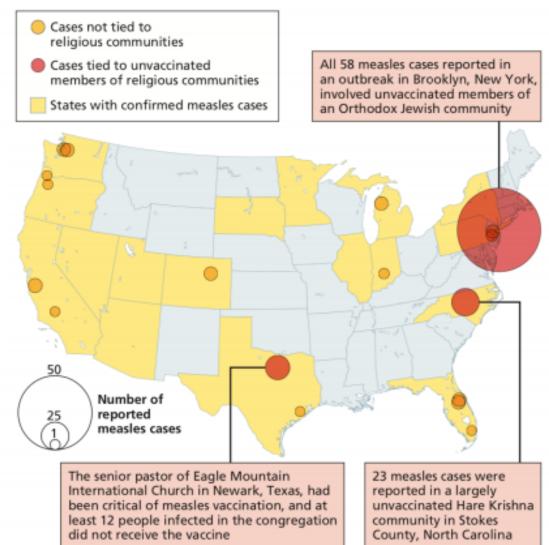
- "Viral diseases are a thing of the past"
- · "Herd immunity has not been proven to work"
- "Polio is long gone"
- "I never get the flu"
- "Measles is just a trivial kid's disease"
- · "Chicken pox only affects kids"
- "Kids should get infected naturally"
- "I'm not injecting anything into my body"
- "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

Vaccine programs depend on public acceptance of their value





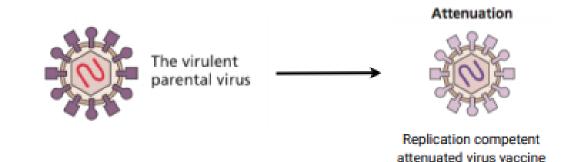
What are Vaccines?

15-5

Pre-exposure to Pathogen

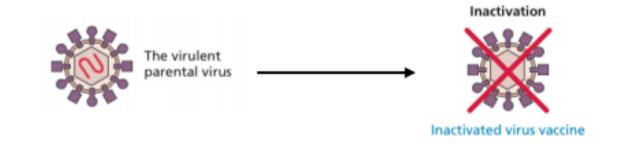
- Typically "live" or "killed"
- Live is weakened or attenuated
- Killed is inactivated
- Newer vaccines may just be a piece of a pathogen
 - "subunit vaccine"
- Or piece of genetic information
 - "DNA" or "RNA vaccine"

Replication competent, attenuated vaccines

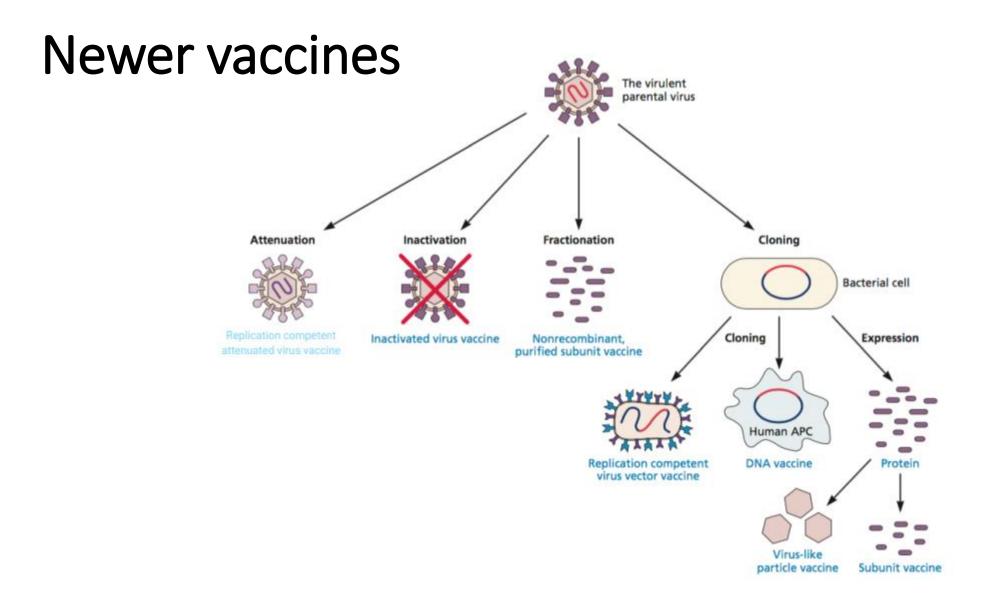


- Viral replication occurs, stimulates immune response
- Infection induces mild or inapparent disease

Inactivated vaccines

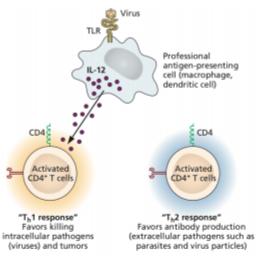


- Chemical procedures (e.g. formalin, β-propriolactone, nonionic detergents)
- Infectivity is eliminated, antigenicity not compromised



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)

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)



History of Vaccines

6500

Earliest Evidence

- May have started as early as 200 BC with Chinese "variolation" against Smallpox
- Approximately 1022 AD



Earliest Evidence



Approximately 1500 AD

Lady Mary Wortley Montagu

- Wife of Ambassador to Ottoman Empire
- 7 year old son was "engrafted" with smallpox in 1717 in Turkey
- 3 year old daughter was engrafted in 1721 in England during epidemic



Edward Jenner and Cowpox



- Jenner developed alternate vaccine using cowpox in 1796
- "Variolated" 8 year old James Phipps with cowpox
- Later challenged with variolation (smallpox = Variola)
- Cowpox virus named Vaccinia
- Effective smallpox vaccine

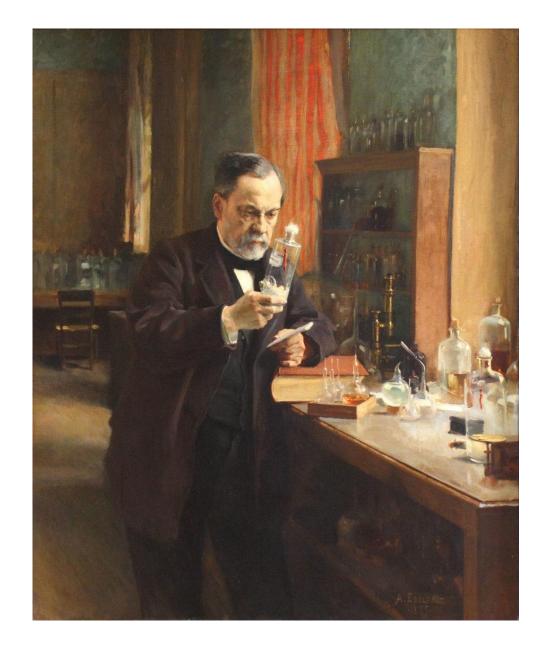
Rise of Antivaxxers (early 1800's)



Benjamin Waterhouse

- Brought vaccination to the US in 1800
- Endorsed by VP Thomas Jefferson
- State of Massachusetts was first to encourage vaccination in 1802
- National Vaccine Agency established in 1813



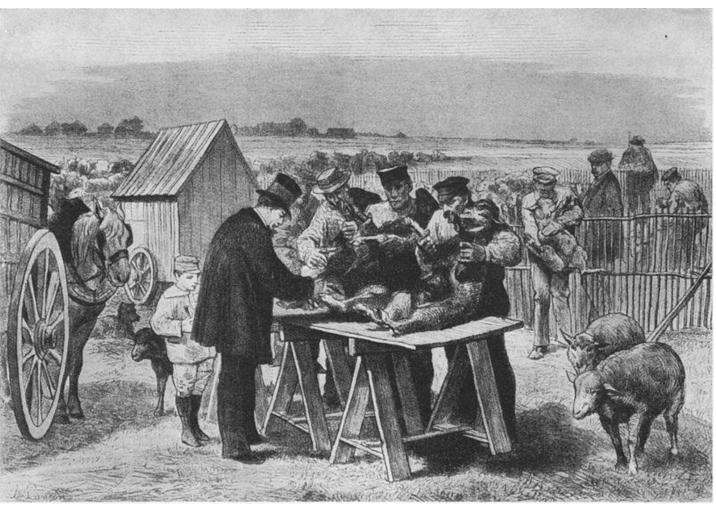


Louis Pasteur and Chicken Cholera

- Fatal disease of chickens
- Determined causative bacterium in 1878
- Developed vaccine accidentally in 1879
- First attenuated vaccine

Louis Pasteur and Anthrax

- Causative agent of anthrax determined by Robert Koch
- Pasteur attenuated *B.* anthracis
- Vaccine trial with 50 sheep and 10 cows in 1881



Louis Pasteur and Rabies



- Attenuated rabies virus by growing in rabbits
- Demonstrated effectiveness in dogs
- Vaccinated 9 year old Joseph Meister in 1885

https://www.awesomestories.com/asset/view/LOUIS-PASTEUR-MEETS-JOSEPH-MEISTER-Louis-Pasteur-and-the-Rabies-Virus

Early Influenza Vaccines



- Early 1940's Thomas Francis, Jr., MD and Jonas Salk, MD developed flu vaccine with US Army support
- Virus grown in chicken eggs and inactivated



Combination Vaccines

- First combination vaccine included diphtheria toxoid and pertussis in 1943
- Next version also included tetanus toxoid in 1947 (DTP)
- Polio was included for a short while



1952 Polio Epidemic United States

- 52,628 Polio cases reported
- Over 21,000 paralytic
- Over 3,000 deaths



https://www.npr.org/sections/npr-history-dept/2015/04/10/398515228/defeating-the-disease-that-paralyzed-america

Jonas Salk and Polio

- By 1952, Salk developed an inactivated polio vaccine
- Vaccinated his family in 1953
- Large scale clinical trial in 1954
- Vaccination paused in 1955 due to "Cutter incident"
- IPV phased out in 1968, back in in 1997



https://www.ksat.com/features/2020/06/23/as-the-world-waits-on-a-covid-19-vaccine-heres-a-peek-at-what-things-looked-like-as-polio-vaccines-surfaced/

Albert Sabin and Polio



- Sabin developed "live" polio vaccine in late 1950's but had to test overseas
- Most of the rest of the world adopted the attenuated oral vaccine
- Vaccine became available in US in 1960

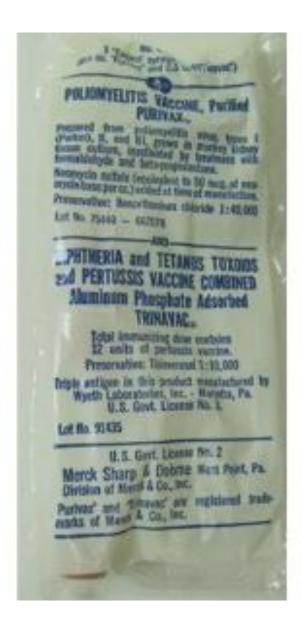
https://www.kake.com/story/41997712/the-other-time-america-desperately-sought-a-miracle-cure-for-a-devastating-disease

Intermission

Co.s

Maurice Hilleman and Polio

- Hilleman worked for Merck
- Discovered contaminant virus in the monkey cells (SV40)
- Moved away from monkey tissue culture to grow polio virus



Maurice Hilleman and Measles



- Hilleman developed attenuated measles vaccine in 1962
- Passaged 80 times through multiple different cells
- Given with a dose of antibodies (gamma globulin)
- In 1968, he passaged 40 extra times, so no lgG needed

Maurice Hilleman and Mumps

- In 1963, Hilleman's 6 year old daughter contracted mumps
- Hilleman isolated the virus from her
- Attenuated it for a vaccine
- Given to his other daughter in 1966



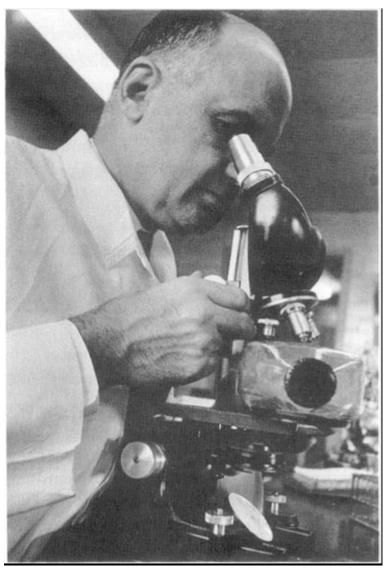
Maurice Hilleman and German Measles



- Rubella caused a major US outbreak in 1967, infecting millions
- Generally mild in children, but caused thousands of miscarriages and 20,000 cases of CRS
- Hilleman developed an attenuated vaccine in 1969

Maurice Hilleman and Other Vaccines

- Japanese Encephalitis Virus in 1944 (for the Army)
- Marek's disease (in chickens) in 1968
- Hong Kong influenza in 1968
- MMR Vaccine in 1971
- Hilleman died in 2005



1970's – 80's

- 1975 & 77 Last wild cases of smallpox (major and minor)
- 1976 Swine Flu vaccine (Guillain-Barré syndrome)
- 1977 Pneumococcal vaccine licensed
- 1978 Measles targeted for Elimination
- 1978 Accidental smallpox infection in a lab
- 1980 Smallpox declared eradicated
- 1985 Polio targeted for Elimination in Americas
- 1985 Vaccine against Haemophilus influenzae B



1980's – 90's

- 1986 Hepatitis B recombinant vaccine licensed
- 1988 Polio targeted for Eradication globally
- 1989-91 Low measles vaccine rate led to 55,622 infections with 123 deaths, 90% in unvaccinated
- 1989 Oral typhoid vaccine licensed in US
- 1990 US military ceased routine smallpox vaccination
- 1994 Polio declared Eliminated in Americas
- 1995 Hepatitis A vaccine licensed
- 1995 Chickenpox vaccine licensed in US



1998 - Andrew Wakefield and MMR

EARLY REPOI

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

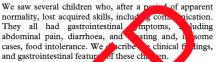
Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rub vaccination in eight of the 12 children, with meas infection in one child, and otitis media in an All : children had intestinal abnormalities rangin from lymphoid nodular hyperplasia to noid ration. Histology showed patchy chronic inflan tion in 11 children and reactive ilea mpho perplasia in seven, but no granulomas. Be vioural diso included autism (nine), disintegrativ JSY. sis (one), ossible postviral or vaccinal encephalitis o). There were no focal neurological ab malities and and EEG tests were normal. Abnor al laboratory results are significantly raised urinary thylmal c acid compared with age-03), low haemoglobin in four matched contro children. m IgA in ar children. cation associated gastrointestinal Inter se and evelopmental regression in a group of , which was generally associated prev possible environmental triggers. in time

351: 637-41

Introduction



Patients and meth. is 12 children, cons red to department rerology paediatric gastre of a pervasive ed skills and intestinal developmenta der with loss arrh symptoms abdomina an, bloating and food ated. All children were admitted to the intolerance), were inv ward for 1 week, accom ed by their parents

nical investigations

took historia including details of immunisations and exposure to infect the diseases, and assessed the children. In 11 case the historia as obtained by the senior clinician (JW-S). Neuro included a psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.¹ Developmental his included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRR), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

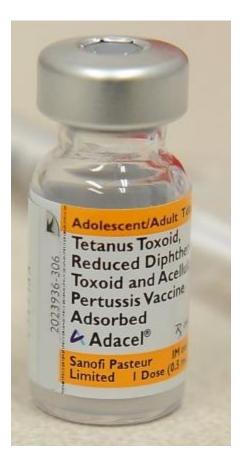
Laboratory investigations

Thyroid function, serum long-chain fatty acids, and

- Andrew Wakefield questioned safety of MMR vaccine, suggesting it caused autism
- His theory has been debunked numerous times, his original research paper was retracted and his medical license was revoked in 2010
- Public perception persists

2000's - 2010

- 1999 DTaP replaces DTP
- 2000 Endemic measles Eliminated from US
- 2000 Salk's IPV added back to US schedule
- 2000 99% reduction in polio cases worldwide
- 2006 HPV vaccine licensed in US
- 2006 HepA vaccine recommended for all children
- 2006 Rotavirus vaccine recommended
- 2008 Measles cases increase in US
- 2009 No diphtheria in US for 5 years



2010 – now

- 2010 California pertussis cases increase 418% over 2009
- 2011 Measles outbreak in US and France
- 2014 2 meningiococcal B outbreaks at universities in US
- 2014 Measles cases increase outbreak at Disneyland (12/15-20)
- 2015 Total of 111 cases from Disney outbreak
- 2016 Zika outbreak
- 2016 Measles Eliminated from Americas (2 of 3 wild strains)
- 2018 Only 3 countries with endemic polio, 17 still at risk



Current State of Vaccines

Com.

15-5

List of Vaccines Used in United States

Links to Clinical info about the vaccine

- <u>Adenovirus</u>
- <u>Anthrax</u>
 - AVA (BioThrax)
- <u>Cholera</u>
 - Vaxchora
- <u>Diphtheria</u>
 - DTaP (Daptacel, Infanrix)
 - Td (Tenivac, generic)
 - DT (-generic-)
 - Tdap (Adacel, Boostrix)
 - DTaP-IPV (Kinrix, Quadracel)
 - DTaP-HepB-IPV (Pediarix)
 - DTaP-IPV/Hib (Pentacel)
- <u>Hepatitis A</u>
 - HepA (Havrix, Vaqta)
 - HepA-HepB (Twinrix)
- <u>Hepatitis B</u>
 - HepB (Engerix-B, Recombivax HB, Heplisav-B)
 - DTaP-HepB-IPV (Pediarix)
 - HepA-HepB (Twinrix)
- Haemophilus influenzae type b (Hib)
 - Hib (ActHIB, PedvaxHIB, Hiberix)
 - DTaP-IPV/Hib (Pentacel)
- Human Papillomavirus (HPV)
 - HPV9 (Gardasil 9) (For scientific papers, the preferred abbreviation is 9vHPV)

- <u>Seasonal Influenza (Flu)</u> only
 - IIV* (Afluria, Fluad, Flublok, Flucelvax, FluLaval, Fluarix, Fluvirin, Fluzone, Fluzone High-Dose, Fluzone Intradermal)
 - *There are various acronyms for inactivated flu vaccines
 - IIV3, IIV4, RIV3, RIV4 and ccIIV4.
 - LAIV (FluMist)
- Japanese Encephalitis
 o JE (Ixiaro)
- Measles
 - MMR (M-M-R II)
 - MMRV (ProQuad)
- <u>Meningococcal</u>
 - MenACWY (Menactra, Menveo)
 - MenB (Bexsero, Trumenba)
- <u>Mumps</u>
 - MMR (M-M-R II)
 - MMRV (ProQuad)
- <u>Pertussis</u>
 - DTaP (Daptacel, Infanrix)
 - Tdap (Adacel, Boostrix)
 - DTaP-IPV (Kinrix, Quadracel)
 - DTaP-HepB-IPV (Pediarix)
 - DTaP-IPV/Hib (Pentacel)
- Pneumococcal
 - PCV13 (Prevnar13)
 - PPSV23 (Pneumovax 23)

- Polio
 - Polio (Ipol)
 - DTaP-IPV (Kinrix, Quadracel)
 - DTaP-HepB-IPV (Pediarix)
 - DTaP-IPV/Hib (Pentacel)
- <u>Rabies</u>
 - Rabies (Imovax Rabies, RabAvert)
- <u>Rotavirus</u>
 - RV1 (Rotarix)
 - RV5 (RotaTeq)
- <u>Rubella</u>
 - MMR (M-M-R II)
 - MMRV (ProQuad)
- <u>Shingles</u>
 - ZVL (Zostavax)
 - RZV (Shingrix)
- <u>Smallpox</u>
 - Vaccinia (ACAM2000):
- <u>Tetanus</u>
 - DTaP (Daptacel, Infanrix)
 - Td (Tenivac, generic)
 - DT (-generic-)
 - Tdap (Adacel, Boostrix)
 - DTaP-IPV (Kinrix, Quadracel)
 - DTaP-HepB-IPV (Pediarix)
 - DTaP-IPV/Hib (Pentacel)
- Tuberculosis

- Typhoid Fever
 - Typhoid Oral (Vivotif)
 - Typhoid Polysaccharide (Typhim Vi)
- <u>Varicella</u>
 - VAR (Varivax)
 - MMRV (ProQuad):
- Yellow Fever
 - YF (YF-Vax)



26 Diseases

Table 1. Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2020

Legend

applicable



50-64 years Vaccine 19-26 years 27-49 years ≥65 years Influenza inactivated (IIV) or 1 dose annually Influenza recombinant (RIV) Flu Blok A or or Influenza live attenuated 1 dose annually (LAIV) Flu Mist Tetanus, diphtheria, 1 dose Tdap, then Td or Tdap booster every 10 yrs pertussis (Tdap or Td) 🕦 Measles, mumps, rubella 1 or 2 doses depending on indication (if born in 1957 or later) (MMR) 🕥 2 doses (if born in 1980 or later) Varicella 2 doses (VAR) 🕦



Zoster recombinant (RZV) (preferred) Shingrix				2 doses	
or <u>Zoster live</u> (ZVL) 🚯				or 1 dose	
Human papillomavirus (HPV) 🚯	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years			
Pneumococcal conjugate (PCV13) 🕡	1 dose			65 years and older	
Pneumococcal polysaccharide (PPSV23) ()	1 or 2 doses depending on indication			1 dose	
Hepatitis A (HepA) 🕦	2 or 3 doses depending on vaccine				
Hepatitis B (HepB) 🕦	2 or 3 doses depending on vaccine				
Meningococcal A, C, W, Y (MenACWY) 🚯	1 or 2 doses depending on indication, <u>see notes</u> for booster recommendations				
Meningococcal B (MenB) 👔		oses depending on vaccine and nendations	d indication, <u>see i</u>	notes for booster	
	19 through 23 years				
<u>Haemophilus influenzae</u> t <u>ype b</u> (Hib) ®	1 or 3 doses	depending on indication			



Chad

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Travelers' Health

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Traveler View Healthy Travel Packing List Chad Chad Chad Chad Cinician View Find a Clinic Fravel Advice and Resources Fravel Advice and Resources Find a Disease Directory Frequently Asked Questions Frequently Asked Questions Find a Clinic Find a Clinic Find a Clinic Find a Clinic CHAD CHAD<	Destinations (245)	—	Traveler View
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Other Destinations			💼 Travel Health Notices
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Where are you going? Be aware of current health issues in Chad. Lea	Where are you going?		Be aware of current health issues in Chad. Learn ho

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On This Page		
Vaccines and Medicines		
Stay Healthy and Safe		
Healthy Travel Packing List		
Travel Health Notices		
After Your Trip		

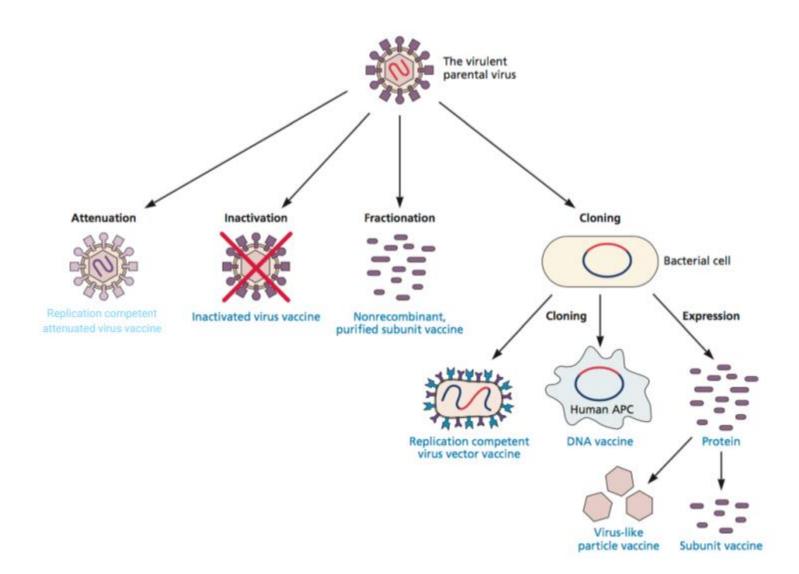
🚏 Clinician View

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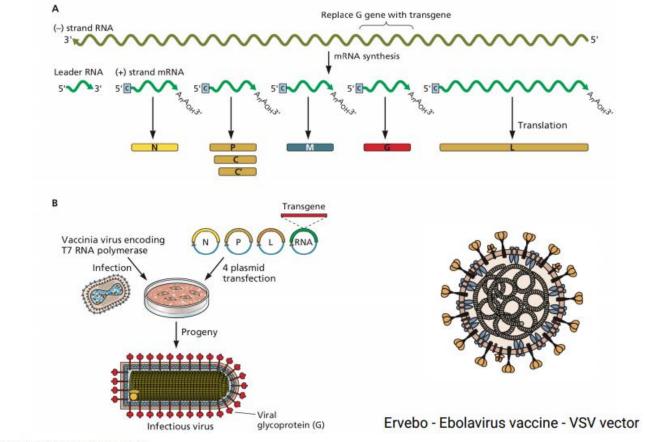
health issues in Chad. Learn how to protect yourself.

Future of Vaccines

15-5

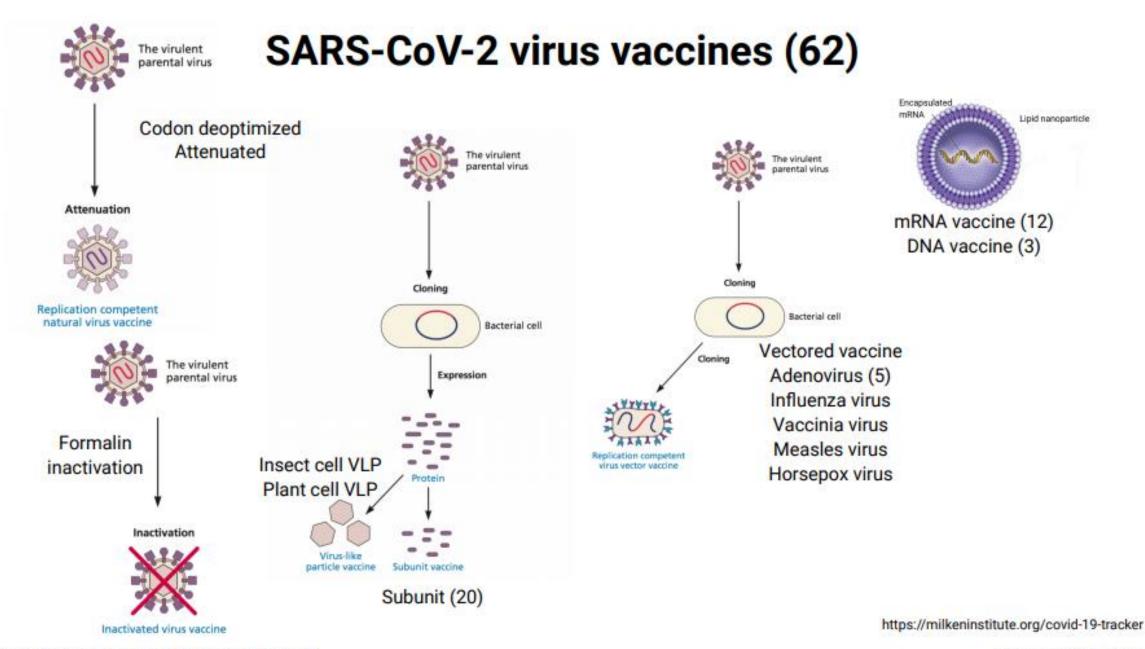


Vesicular stomatitis virus vaccine vector

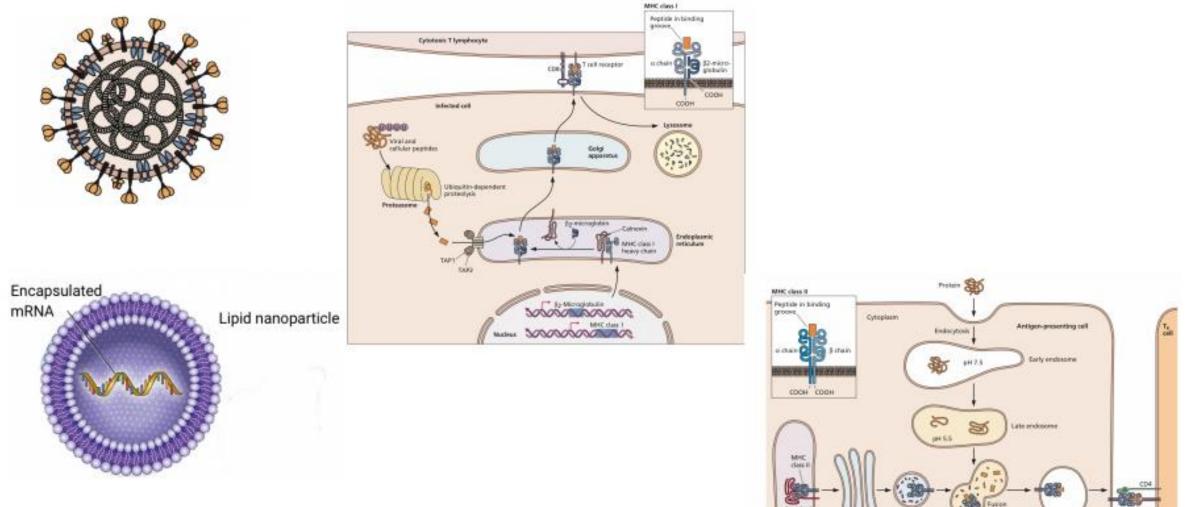


Virology Lectures 2020 • Prof. Vincent Racaniello • Columbia University

Principles of Virology, ASM Press



SARS-CoV-2 mRNA vaccine



Involtion

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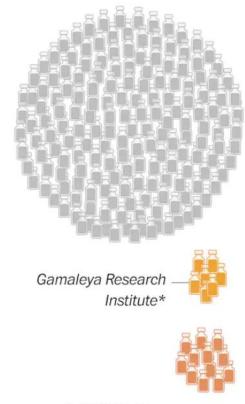
Lynorome

MHC class II vesicle.

invariant chain degraded

Golgi apparatus

11.8





Beijing Institute of

Biotechnology*

Vaccines sorted by how far they have progressed

170+ vaccines

are being tested in animals and lab experiments

7 vaccines

are being tested in a small number of healthy, young people to assess safety and correct dose

12 vaccines

are broadened to a larger group of people, including people at higher risk of illness

7 vaccines

are being tested in thousands of people to check their effectiveness and safety

0 vaccines

have been determined to provide benefits that outweigh known and potential risks

*Vaccine currently in distribution that has not been fully tested.

Vaccine Product Approval Process

The U.S. Food and Drug Administration's (FDA's) <u>Center for Biologics Evaluation</u> <u>and Research</u> (CBER) is responsible for regulating vaccines in the United States.

The sponsor of a new vaccine product follows a multi-step approval process, which typically includes

- An Investigational New Drug application
- Pre-licensure vaccine clinical trials
- A Biologics License Application (BLA)
- Inspection of the manufacturing facility
- Presentation of findings to <u>FDA's Vaccines and Related Biological Products</u> <u>Advisory Committee</u> [] (VRBPAC)
- Usability testing of product labeling

Vaccine Clinical Trials

Phase 1 – Safety & Immunogenicity Small number of people, monitored

Phase 2 – Dose ranging Hundreds of subjects

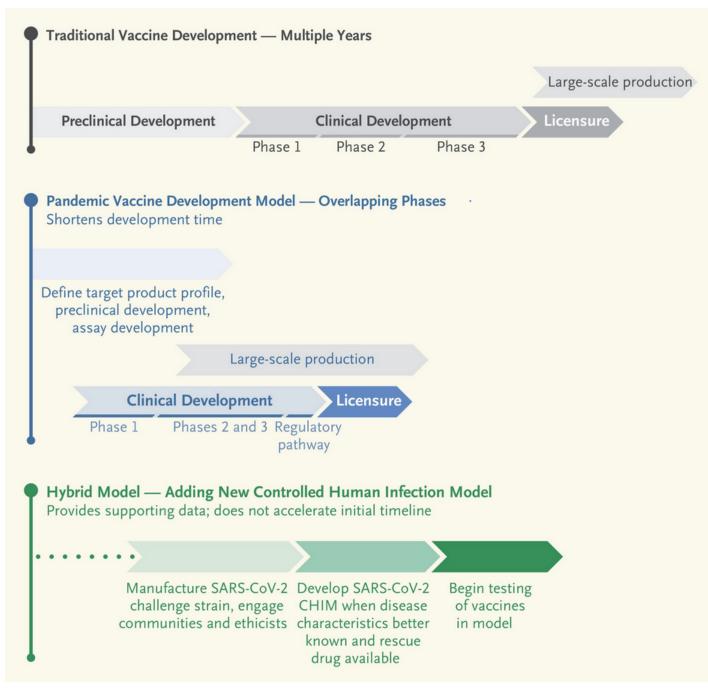
Phase 3 – Effectiveness & more safety Thousands of subjects



Enhancing Public Trust and Health with COVID-19 Vaccination

Why "If We Build It/They Will Come" May Not Apply to Humans and Vaccines and What Can Be Done About It

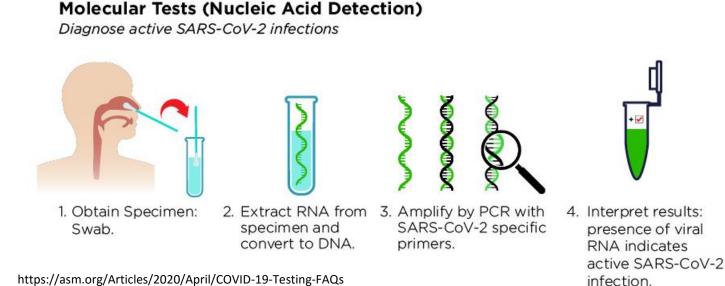
https://www.jhsph.edu/covid-19/articles/enhancing-public-trust-and-health-with-covid-19-vaccination.html

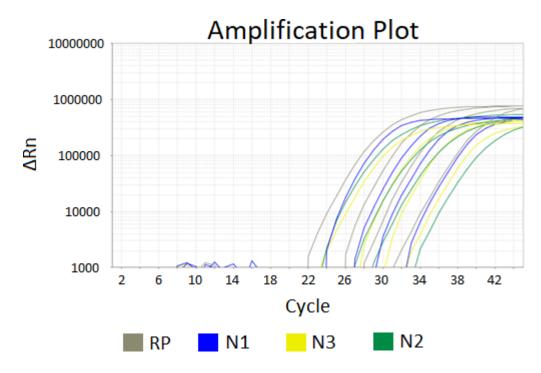


COVID Testing

PCR Test

- "Tickle your brain" test nasopharyngeal swab/nasal swab
- Takes time to process 2-5 days
- Copies RNA from the virus into DNA
- Makes many, many copies

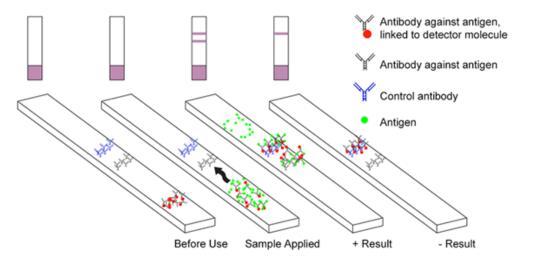




https://www.raybiotech.com/covid-19-rt-pcr/

Rapid Antigen Test (Ag test)

- Nasal swab or saliva
- Takes about 15 min. to process
- Detects pieces of the virus
- Not as sensitive as PCR false negatives





https://www.bd.com/en-us/offerings/capabilities/microbiologysolutions/point-of-care-testing/bd-veritor-plus-system-for-rapid-covid-19sars-cov-2-testing

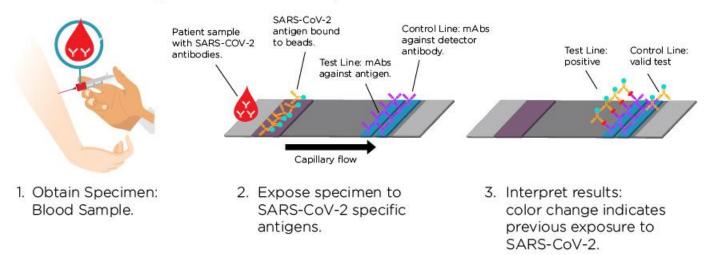
Adapted from: Ian M. Campell, https://commons.wikimedia.org/wiki/File:Diagnostic_Medical_Dipstick.png

Antibody Test

- Detects previous exposure
- May indicate immunity, may not
- Detects 2 different kinds of antibodies

Antibody Tests (Serology)

Detect immune response to SARS-CoV-2 exposure





https://www.firstpost.com/health/covid-19-testing-how-antibodyantigen-rt-pcr- truenat-tests-differ-their-strengths-and-limitations-8548691.html

At Home Test

- "Spit test"
 - In a tube, add paper strip, changes color
 - On the paper, changes color
- Basically instant test
- May have issues with sensitivity





https://6abc.com/rutgers-university-saliva-test-covid-19-fda-testing/6166215/

https://www.nytimes.com/2020/07/03/opinion/coronavirus-tests.html

Questions?

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