HARVARD MEDICAL SCHOOL

Center for Virology and Vaccine Research

How Vaccines Work: The Immunology Underlying Commonly Used Vaccines

Samuel J. Vidal, M.D., Ph.D.
Instructor in Medicine, Harvard Medical School
Associate Physician, Brigham and Women's Hospital Division of Infectious Diseases
Staff Scientist, Barouch laboratory, Center for Virology and Vaccine Research

Massachusetts Adult Immunization Conference
Tuesday, April 4, 2023

Disclosures

- None

Presentation outline

- Historical perspective: back to the future
- Basic immune mechanisms involved in vaccination
- Commonly used vaccine platforms
- Causes of rare but serious vaccine adverse effects

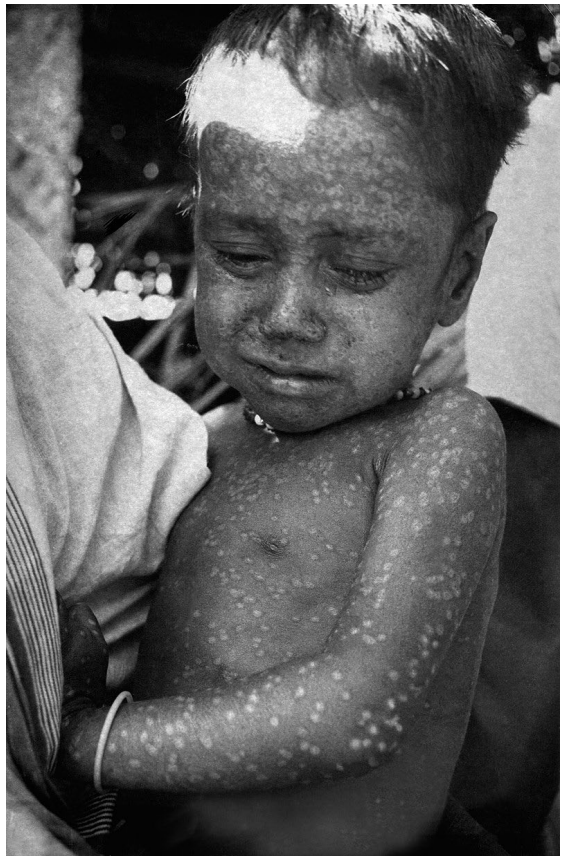
Presentation outline

- Historical perspective: back to the future
- Basic immune mechanisms involved in vaccination
- Commonly used vaccine platforms
- Causes of rare but serious vaccine adverse effects

The first vaccine: vaccinia for smallpox

Smallpox

- Described in Egypt, India, and China >3000 years ago
- Variola major
  - Respiratory tract transmission
  - Flu-like illness followed by dissemination and diffuse pustular rash
  - 30% mortality
- Eradicated in the 1970s after a 20-year WHO-led global vaccination campaign



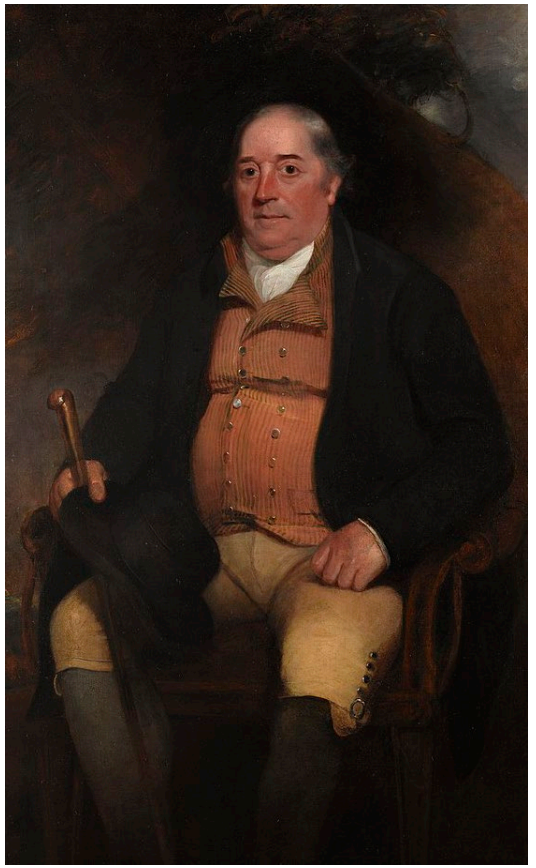
Last known variola major, 1975

Last known variola minor, 1977

The first vaccine: vaccinia for smallpox

- Variolation of healthy individuals with skin secretions from smallpox patients occurred in China and the Ottoman Empire as early as the 1600s
- Lady Montagu introduced variolation to England in the early 1700s after observing it in the Ottoman Empire
- English farmer Benjamin Jetsy inoculated his wife and sons with bovine cowpox in 1774 during a smallpox epidemic

Lady Montagu



Benjamin Jetsy

The first vaccine: vaccinia for smallpox

Edward Jenner (1749-1823)

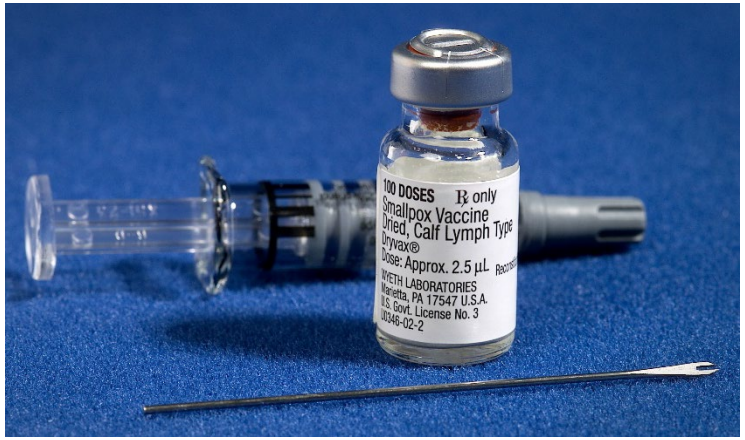
- Also aware that milkmaids contracted cowpox but not smallpox
- After inoculating human cowpox into James Phipps in 1796, variolation produced no disease
- The British government outlawed variolation and provided cowpox vaccination free of charge in 1840

Jenner beginning the first controlled human challenge trial with cowpox vaccination, 1796

The first vaccine: vaccinia for smallpox

Vaccinia virus vaccine

- Precise origin unknown due to record keeping in the 1800s, thought to have originated from cowpox

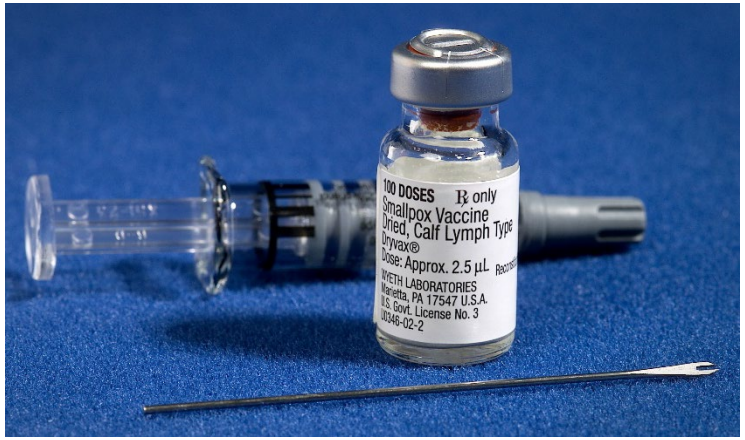


- "Zero generation" vaccine (1800s): Vaccinia inoculated by arm-to-arm transmission
- First generation vaccines (early 1900s): Vaccinia grown on livestock skin (Dryvax)
- Second generation vaccines (1950s): Vaccinia grown in cell culture (ACAM2000)
- Third generation vaccines (1970s): Replication-deficient vaccinia

The first vaccine: vaccinia for smallpox

Vaccinia virus vaccine

- Precise origin unknown due to record keeping in the 1800s, thought to have originated from cowpox

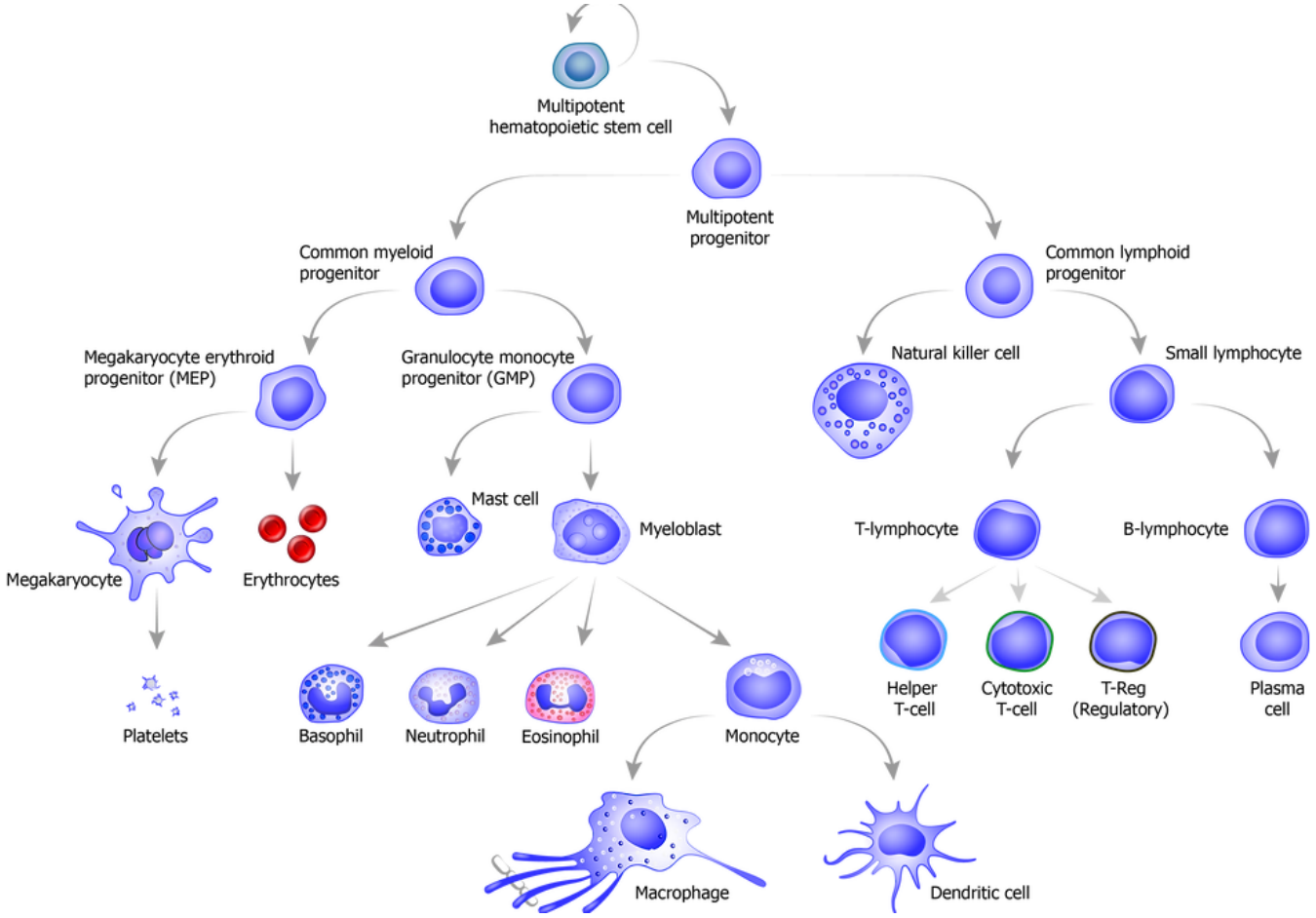


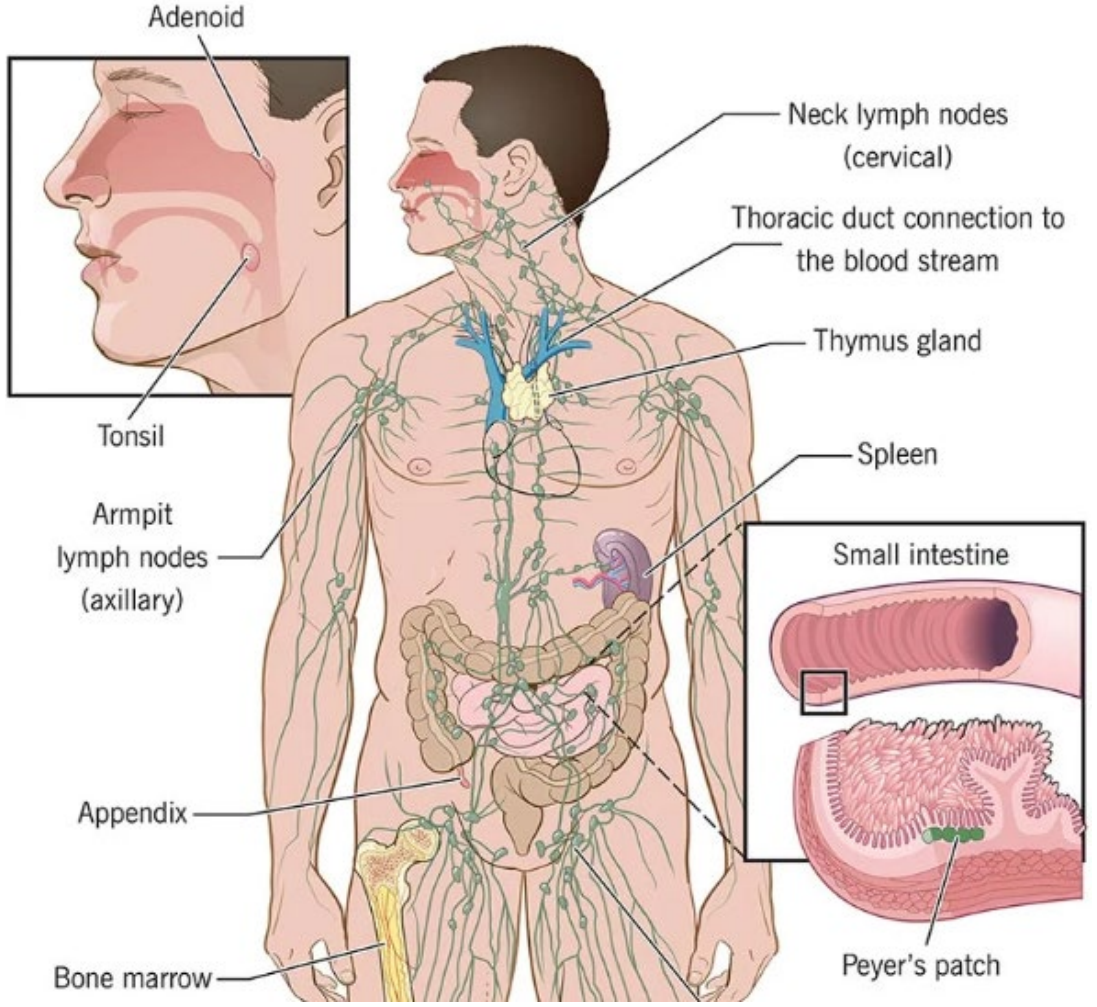
- "Zero generation" vaccine (1800s): Vaccinia inoculated by arm-to-arm transmission
- First generation vaccines (early 1900s): Vaccinia grown on livestock skin (Dryvax)
- Second generation vaccines (1950s): Vaccinia grown in cell culture (ACAM2000)
- Third generation vaccines (1970s): Replication-deficient vaccinia (**JYNNEOS**)

Presentation outline

- Historical perspective: back to the future
- Basic immune mechanisms involved in vaccination
- Commonly used vaccine platforms
- Causes of rare but serious vaccine adverse effects

The immune system is hierarchical and dispersed throughout the body





Adapted from hematopia.com

Adapted from clevelandclinic.org

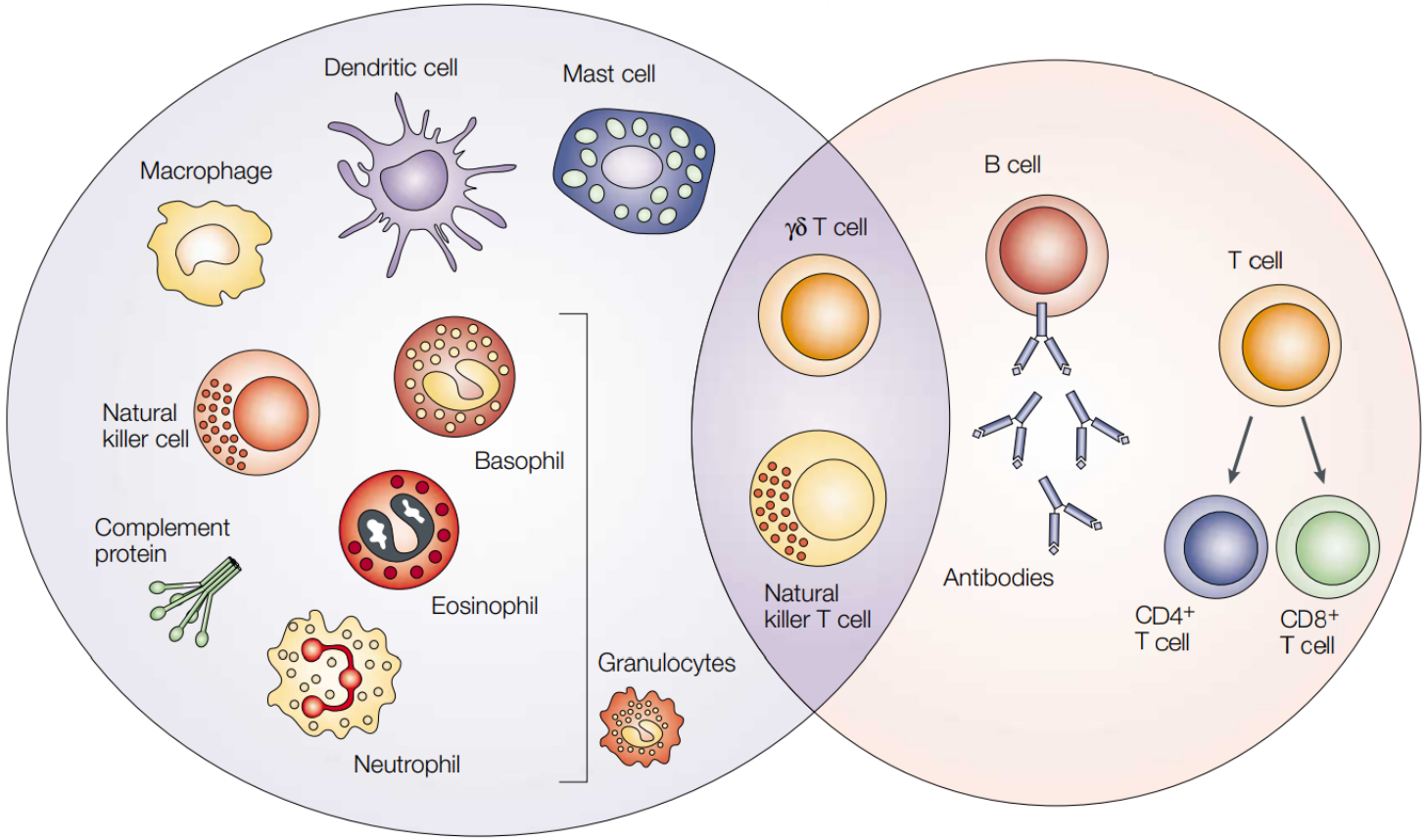
Innate and adaptive immunity

Innate immunity

Immediate (minutes/hours) response to pathogens

Cells/receptors similar between individuals

Example: neutrophils



Adaptive immunity

Delayed (days/weeks) response to pathogens

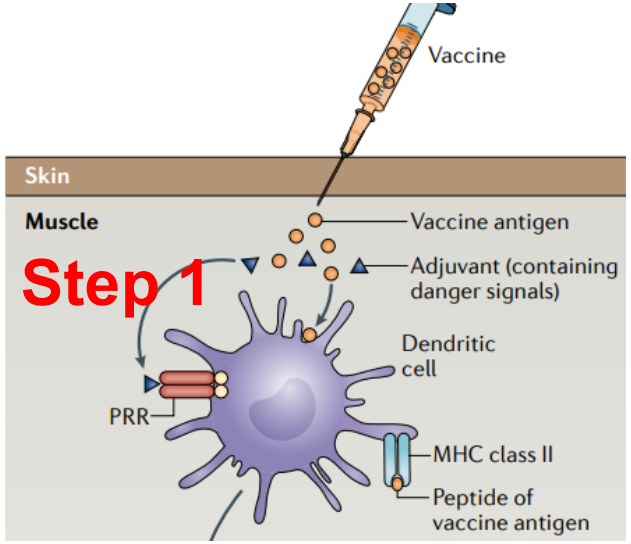
Cells/receptors pathogen- and individual-specific

Example: B cells & T cells

Adapted from Dranoff, Nat Rev Cancer 2004

What happens after vaccination?

Step 1 Vaccine antigens are taken up by muscle-resident innate antigen presenting cells (APCs, e.g. ***dendritic cells***)

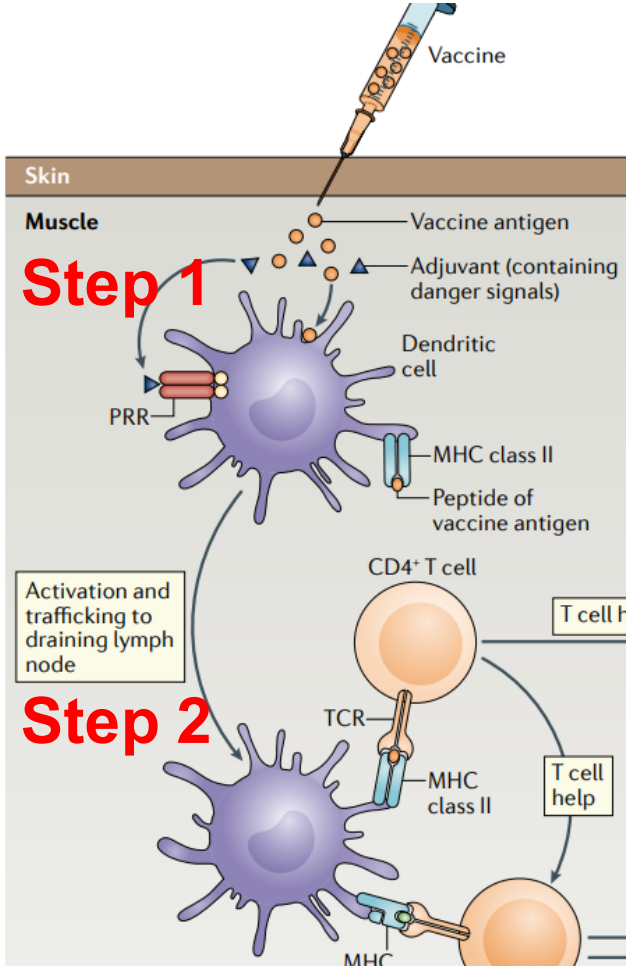


Adapted from Pollard and Bijker, Nat Rev Immunol 2021

What happens after vaccination?

Step 1 Vaccine antigens are taken up by muscle-resident innate antigen presenting cells (APCs, e.g. ***dendritic cells***)

Step 2 Activated APCs migrate to draining lymph nodes (e.g. axillary lymph nodes)



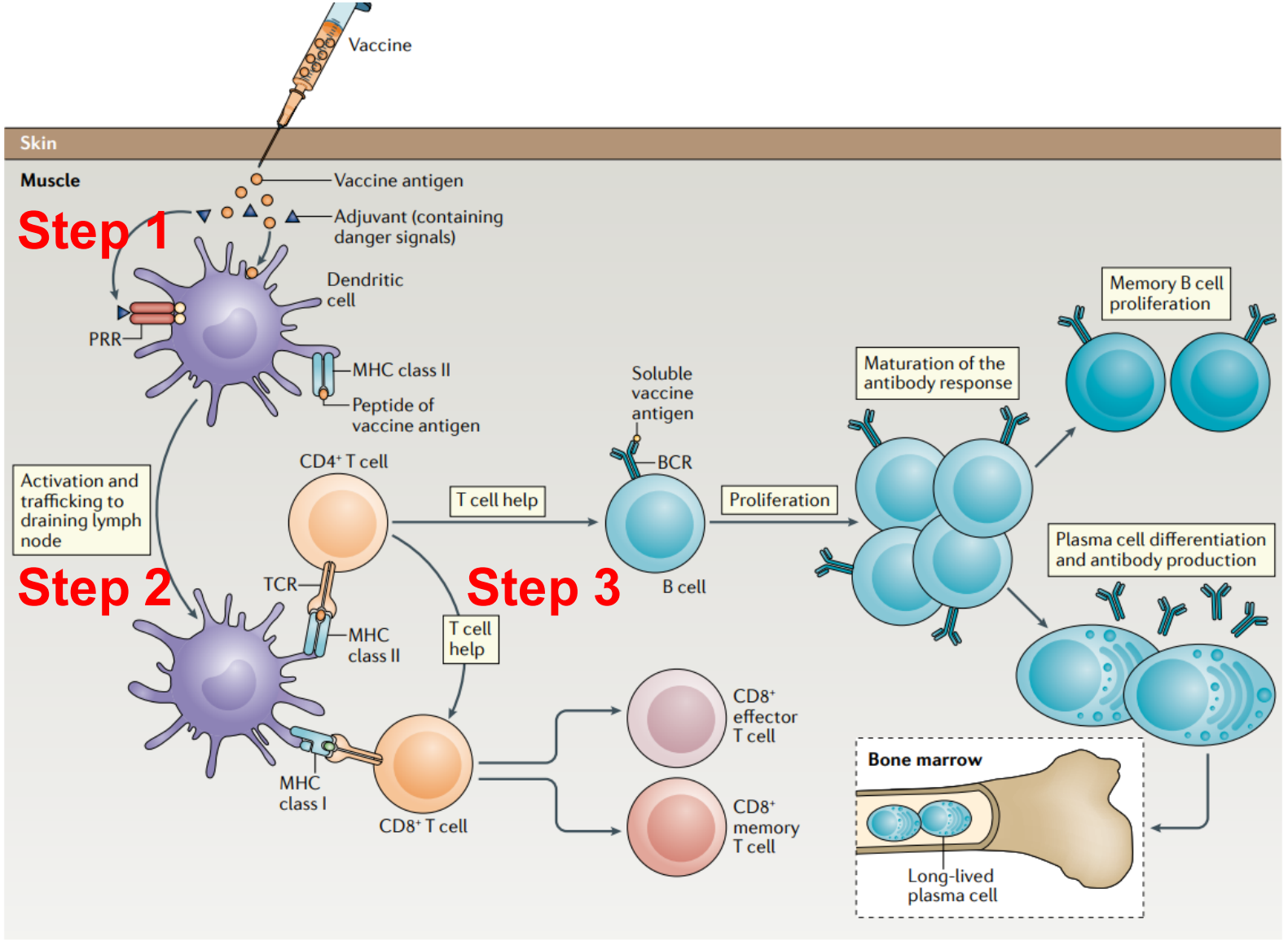
Adapted from Pollard and Bijker, Nat Rev Immunol 2021

What happens after vaccination?

Step 1 Vaccine antigens are taken up by muscle-resident innate antigen presenting cells (APCs, e.g. ***dendritic cells***)

Step 2 Activated APCs migrate to draining lymph nodes (e.g. axillary lymph nodes)

Step 3 APCs activate adaptive antigen-specific ***B cells*** and ***T cells*** in the draining lymph node via their BCRs/TCRs



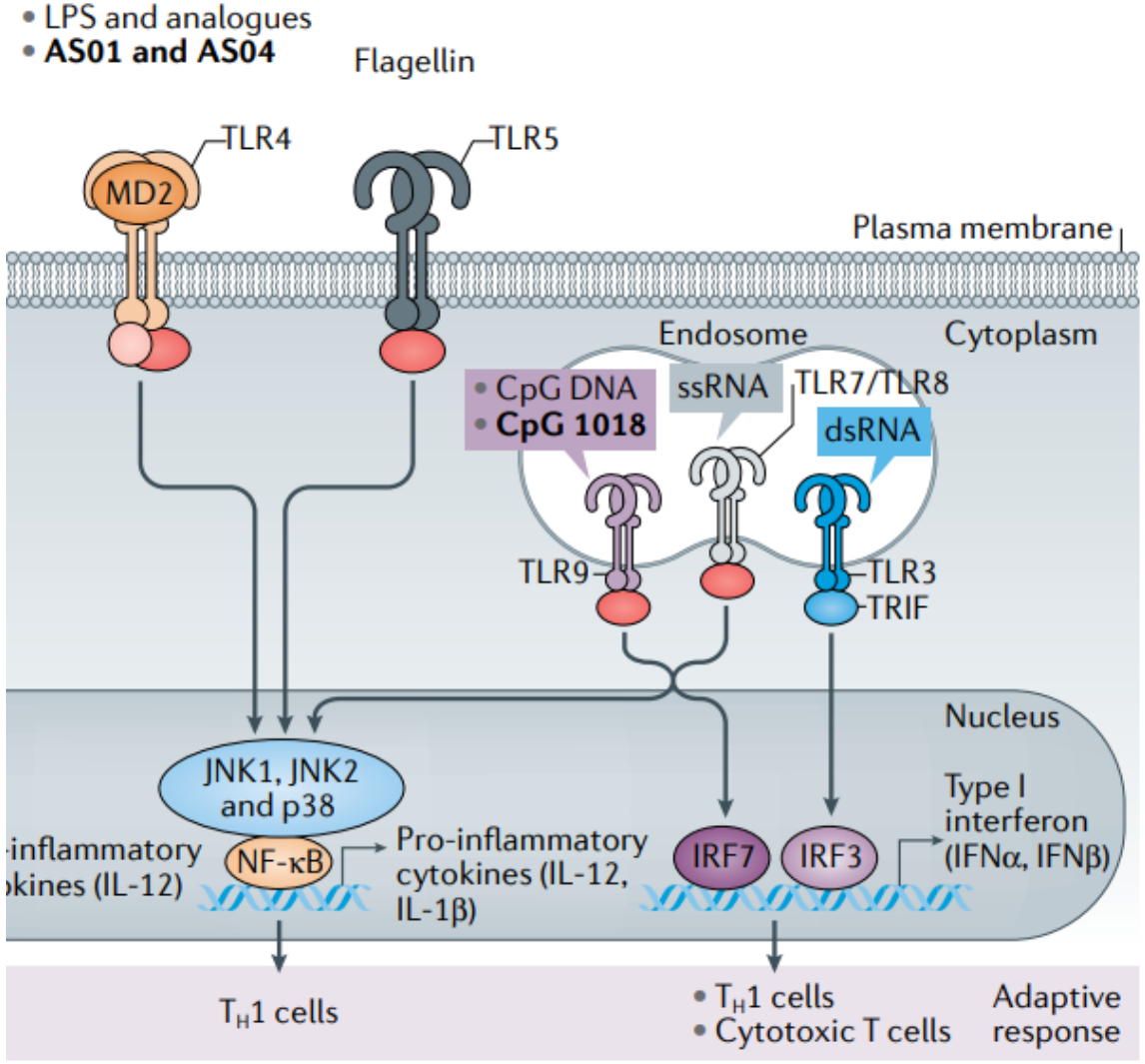
Adapted from Pollard and Bijker, Nat Rev Immunol 2021

What about adjuvants?

Adjuvants are substances that are co-formulated with antigens to increase *immunogenicity*

Some adjuvants are recognized by well-described toll-like receptors (TLRs) on innate immune cells

- AS01
  - Shingrix (shingles)
  - RTS,S (malaria)
- CpG
  - Heplisav (hepatitis B)

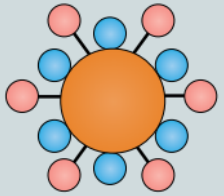


Adapted from Pulendran et al, Nat Rev Drug Discov. 2021

What about adjuvants?

Other adjuvants are less well understood and likely work through multiple mechanisms (non-TLR)

- Alum
  - HepA, HepB
  - TDaP
  - Hib
  - Pneumococcus (Prevnar)
  - HPV (Gardasil)
  - Meningococcus (Bexsero)
- MF59
  - Influenza

Adjuvant	Known knowns
Alum Aluminium hydroxide Aluminium phosphate 	Antibody response independent of TLR signalling[52] Activation of NLRP3 inflammasome in macrophages and DCs[53,54] Activation of DCs is mediated by uric acid[59] Rapid recruitment of neutrophils and formation of NETs[62] Induces cell death that releases DNA, which triggers STING–IRF3 activation, necessary for IgE antibody and T_H2 cell responsed[62]
MF59 Squalene Tween (polysorbate) 80 Span 85 	Activates macrophages and DCs at injection site[68] Induces chemokine secretion[71] Antibody and $CD4^+$ T cell responses depend on transient release of ATP by muscle cells[73] TLR-independent MyD88 activation and NLRP3-independent ASC activation[74,75] Stimulation of antigen-specific $CD8^+$ T cells in tissues is via RIPK3-dependent pathway[74]

Adapted from Pulendran et al, Nat Rev Drug Discov. 2021

Presentation outline

- Historical perspective: back to the future
- Basic immune mechanisms involved in vaccination
- Commonly used vaccine platforms
- Causes of rare but serious vaccine adverse effects

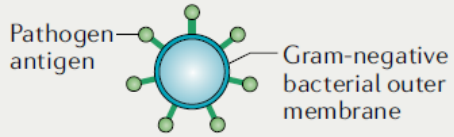
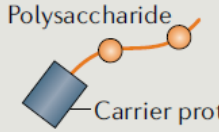
The major vaccine platforms

Type of vaccine	Licensed vaccines using this technology
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid	Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle	Human papillomavirus
Outer membrane vesicle	Group B meningococcal
Protein–polysaccharide conjugate	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Since the live-attenuated vaccinia vaccine was introduced in England in 1840, a multitude of new vaccine platforms have been developed

The major vaccine platforms

Type of vaccine		Licensed vaccines using this technology
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid		Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle		Human papillomavirus
Outer membrane vesicle		Group B meningococcal
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Live attenuated

Pathogens are attenuated, typically by repeated growth in a laboratory

The most widely used is the combination measles, mumps, rubella (MMR)

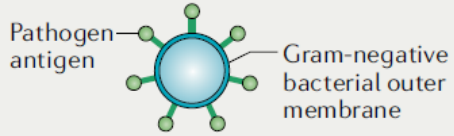
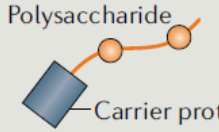
Influenza (intranasal): mostly children

Yellow fever, typhoid: travelers

BCG given at birth to >90% of the world

Oral polio vaccine given in other countries

The major vaccine platforms

Type of vaccine		Licensed vaccines using this technology
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid		Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle		Human papillomavirus
Outer membrane vesicle		Group B meningococcal
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Killed whole organism

Pathogens are killed/inactivated, typically with chemicals (e.g formaldehyde) or irradiation (ultraviolet or gamma)

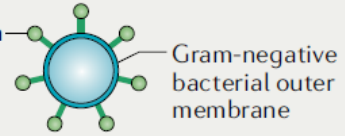
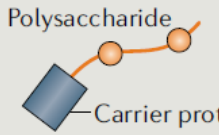
Two widely used vaccines:

Influenza: Revised annually based on epidemiological data

Polio: Jonas Salk vaccine from the 1950s

Other common vaccines include hepatitis A and rabies

The major vaccine platforms

Type of vaccine		Licensed vaccines using this technology
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid		Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle		Human papillomavirus
Outer membrane vesicle		Group B meningococcal
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

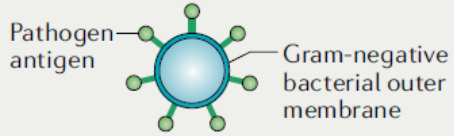
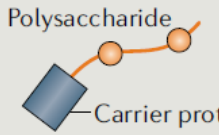
Subunit

A pathogen component ("subunit"), usually a *protein* or *polysaccharide*, frequently combined with an adjuvant

The most commonly used vaccines:

Hepatitis A and B
Pertussis: TDaP
Pneumococcus: Pneumovax
Shingles: Shingrix
Typhoid: travelers

The major vaccine platforms

Type of vaccine		Licensed vaccines using this technology
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid		Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle		Human papillomavirus
Outer membrane vesicle		Group B meningococcal
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Toxoid

Some bacterial diseases are exceptionally dependent on a single bacterial toxin to mediate disease

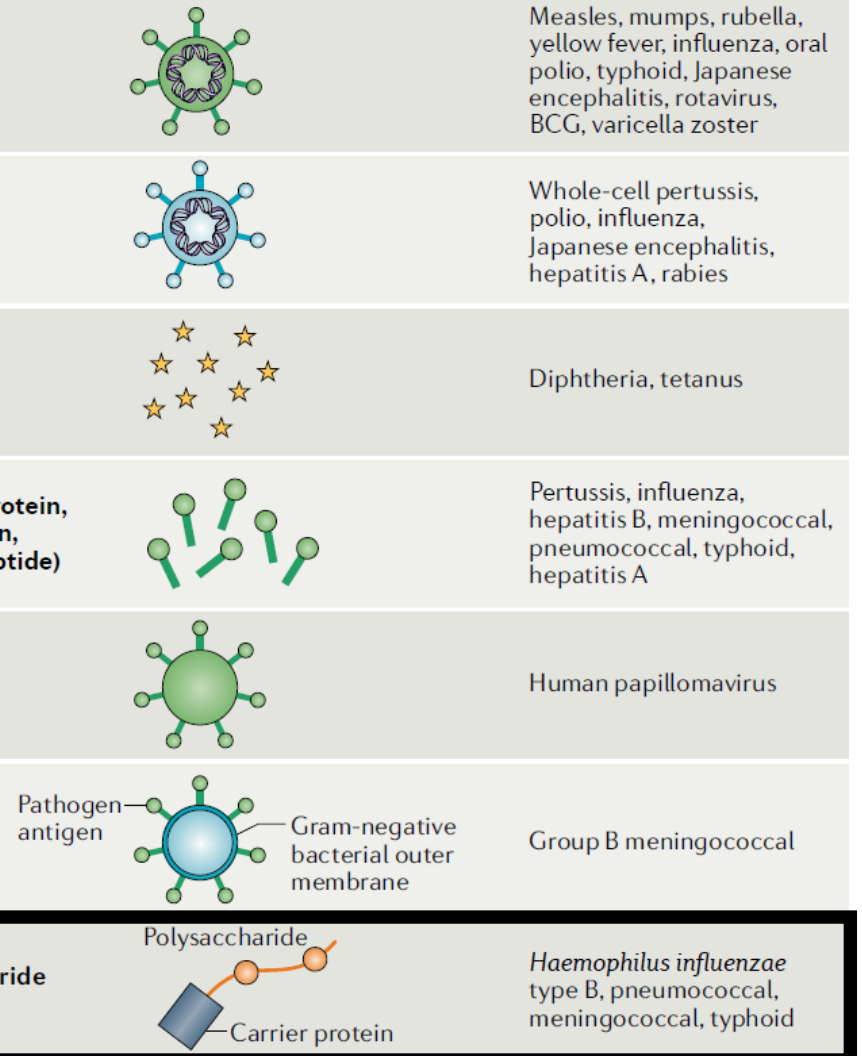
Vaccines may specifically target these toxins rather than the pathogen

Toxins are inactivated by formaldehyde or genetic modification

Tetanus: TDaP
Diphtheria: TDaP

The major vaccine platforms

Type of vaccine	Licensed vaccines using this technology
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid	Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle	Human papillomavirus
Outer membrane vesicle	Group B meningococcal
Protein–polysaccharide conjugate	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid



Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Protein-polysaccharide conjugate

These vaccines combine features of both **subunit** and **toxoid** platforms

A polysaccharide **subunit** component is linked to a **toxoid** to boost the immune response to the polysaccharide

Commonly used vaccines:

Hemophilus influenza: Hib (tetanus toxoid)
Pneumococcus: PCV13/20 (diphtheria tox.)
Meningococcus: Menveo (diphtheria tox.)

The major vaccine platforms

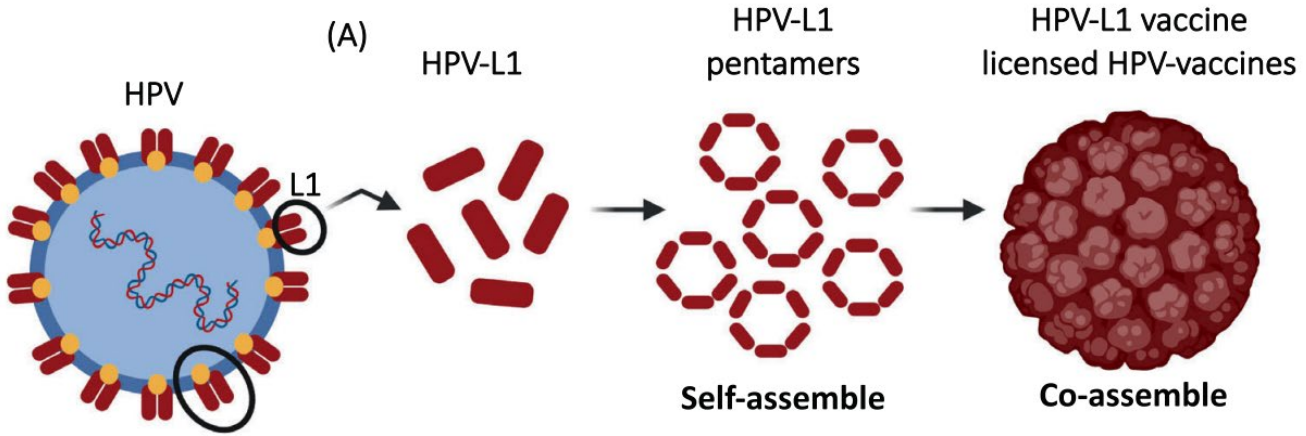
Type of vaccine	Licensed vaccines using this technology
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid	Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle	Human papillomavirus
Outer membrane vesicle (Pathogen antigen; Gram-negative bacterial outer membrane)	Group B meningococcal
Protein–polysaccharide conjugate (Polysaccharide; Carrier protein)	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Virus like-particle

HPV has been difficult to grow in the laboratory, prompting researchers to develop capsid proteins that self-assemble into immunogenic virus-like particles

HPV: Gardasil, Cervarix



Adapted from Mohsen and Bachmann, Cell Mol Immunol 2022

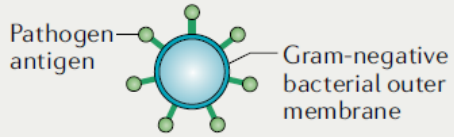
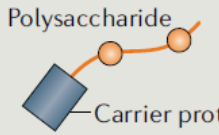
The major vaccine platforms

Type of vaccine	Licensed vaccines using this technology
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid	Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle	Human papillomavirus
Outer membrane vesicle	Group B meningococcal
Protein–polysaccharide conjugate	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

What about vaccines for COVID-19?

The major vaccine platforms

Type of vaccine		Licensed vaccines using this technology
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid		Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle		Human papillomavirus
Outer membrane vesicle		Group B meningococcal
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

The global COVID-19 vaccine effort drew upon these well-known platforms to rapidly generate a vast number of vaccine candidates

Subunit

- Novavax (US)
- Corbevax*

Whole killed organism

- CoronaVac (China)

The major vaccine platforms

The Guardian

Texas scientists' new Covid-19 vaccine is cheaper, easier to make and patent-free

January 15, 2022

Corbevax

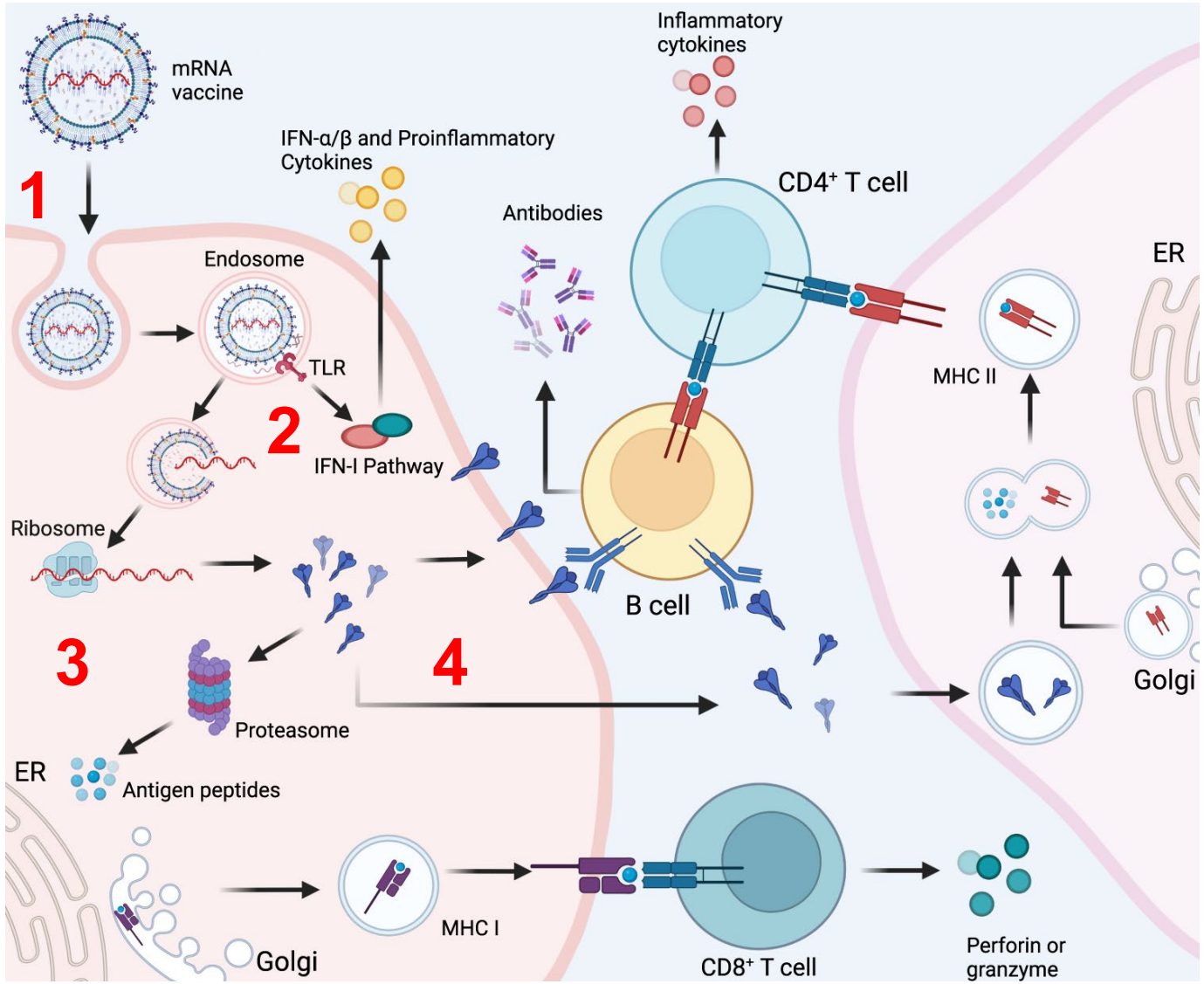
SARS-CoV-2 spike protein formulated with alum and CpG adjuvants

Simple low-cost design similar to hepatitis B vaccines

Distributed to manufacturers without patent protection

>50 million doses given in India as of August 2022

How mRNA vaccines work



1. mRNA is packaged into lipid particles that are taken up into cells via endosomes at the site of administration

2. The lipid particle itself exerts an adjuvant effect

3. mRNA escapes the lipid particle and makes protein

4. The protein induces B cell and T cell responses

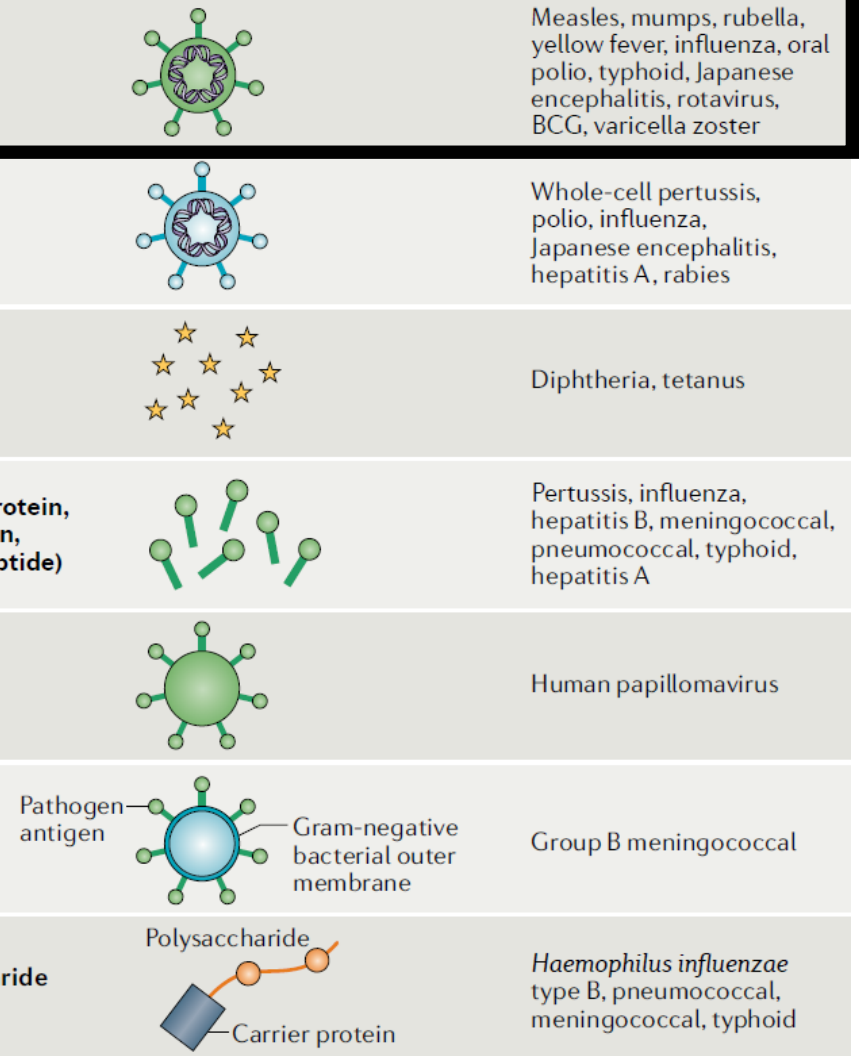
Adapted from Fang et al, Signal Transduct Target Ther. 2022

Presentation outline

- Historical perspective: back to the future
- Basic immune mechanisms involved in vaccination
- Commonly used vaccine platforms
- Causes of rare but serious vaccine adverse effects

The major vaccine platforms

Type of vaccine	Licensed vaccines using this technology
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid	Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle	Human papillomavirus
Outer membrane vesicle	Group B meningococcal
Protein–polysaccharide conjugate	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid



Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Live attenuated

Pathogens are attenuated, typically by repeated growth in a laboratory

The most widely used is the combination measles, mumps, rubella (MMR)

Influenza (intranasal): mostly children

Yellow fever, typhoid: travelers

BCG given at birth to >90% of the world

Oral polio vaccine given in other countries

Oral polio vaccine-derived poliovirus (VDPV)

https://www.unicef.org/immunization/polio

Oral poliovirus vaccine (OPV)

Not given in the United States since 2000

Live-attenuated vaccine that infects the gastrointestinal tract akin to poliovirus

Simple administration more suitable for mass vaccination *and* more immunogenic

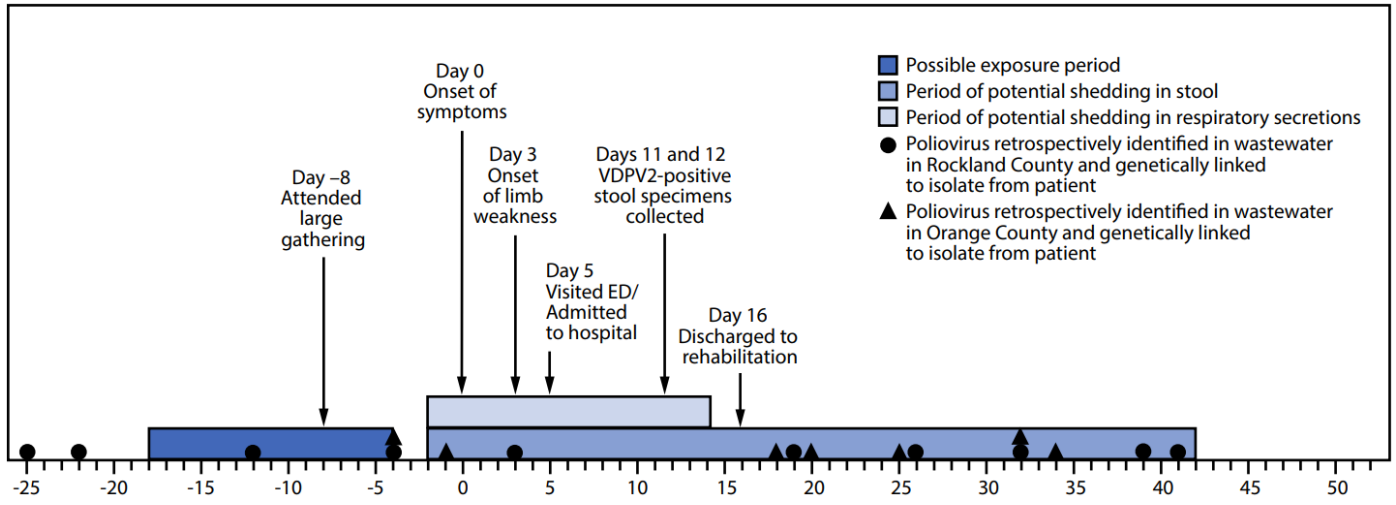
Very rarely OPV may mutate to a poliovirus-like state (VDPV) that can further circulate in an ***under-vaccinated population*** and cause polio

Oral polio vaccine-derived poliovirus (VDPV)

Morbidity and Mortality Weekly Report

Public Health Response to a Case of Paralytic Poliomyelitis in an Unvaccinated Person and Detection of Poliovirus in Wastewater — New York, June–August 2022

Ruth Link-Gelles, PhD[1]; Emily Lutterloh, MD[2,3]; Patricia Schnabel Ruppert, DO[4]; P. Bryon Backenson, MS[2,3]; Kirsten St. George, PhD[5,6]; Eli S. Rosenberg, PhD[2,3]; Bridget J. Anderson, PhD[2]; Meghan Fuschino, MS[5]; Michael Popowich[5]; Chitra Punjabi, MD[4]; Maria Souto, MPH[4]; Kevin McKay, MPH[4]; Samuel Rulli[4]; Tabassum Insaf, PhD[2]; Dustin Hill, PhD[7]; Jessica Kumar, DO[2]; Irina Gelman, DPM[8]; Jaume Jorba, PhD[1]; Terry Fei Fan Ng, PhD[1]; Nancy Gerloff, PhD[1]; Nina B. Masters, PhD[1]; Adriana Lopez, MHS[1]; Kathleen Dooling, MD[1]; Shannon Stokley, DrPH[1]; Sarah Kidd, MD[1]; M. Steven Oberste, PhD[1]; Janell Routh, MD[1]; 2022 U.S. Poliovirus Response Team



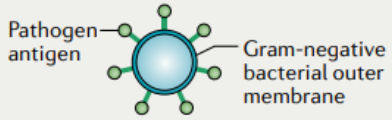
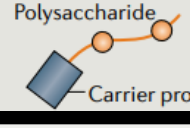
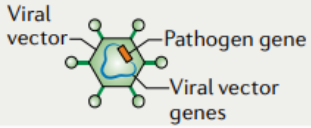
Adapted from Link-Gelles et al Am J Transplant. 2022

Two cases of VDPV-associated polio have been described in the United States since eradication of wild-type virus in 1979

2005: After index case (infant), VDPV discovered circulating in an under-vaccinated community in Minnesota

2022: After index case (young adult), VDPV discovered circulating in an under-vaccinated community in Rockland County, New York

Vaccine-induced thrombotic thrombocytopenia (VITT)

Type of vaccine		Licensed vaccines using this technology
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies
Toxoid		Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A
Virus-like particle		Human papillomavirus
Outer membrane vesicle		Group B meningococcal
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid
Viral vectored		Ebola

Adapted from Pollard and Bijker, Nat Rev Immunol 2021

Viral-vectored vaccines

Similar to subunit vaccines, a pathogen component is delivered using an replication incompetent virus, usually an adenovirus

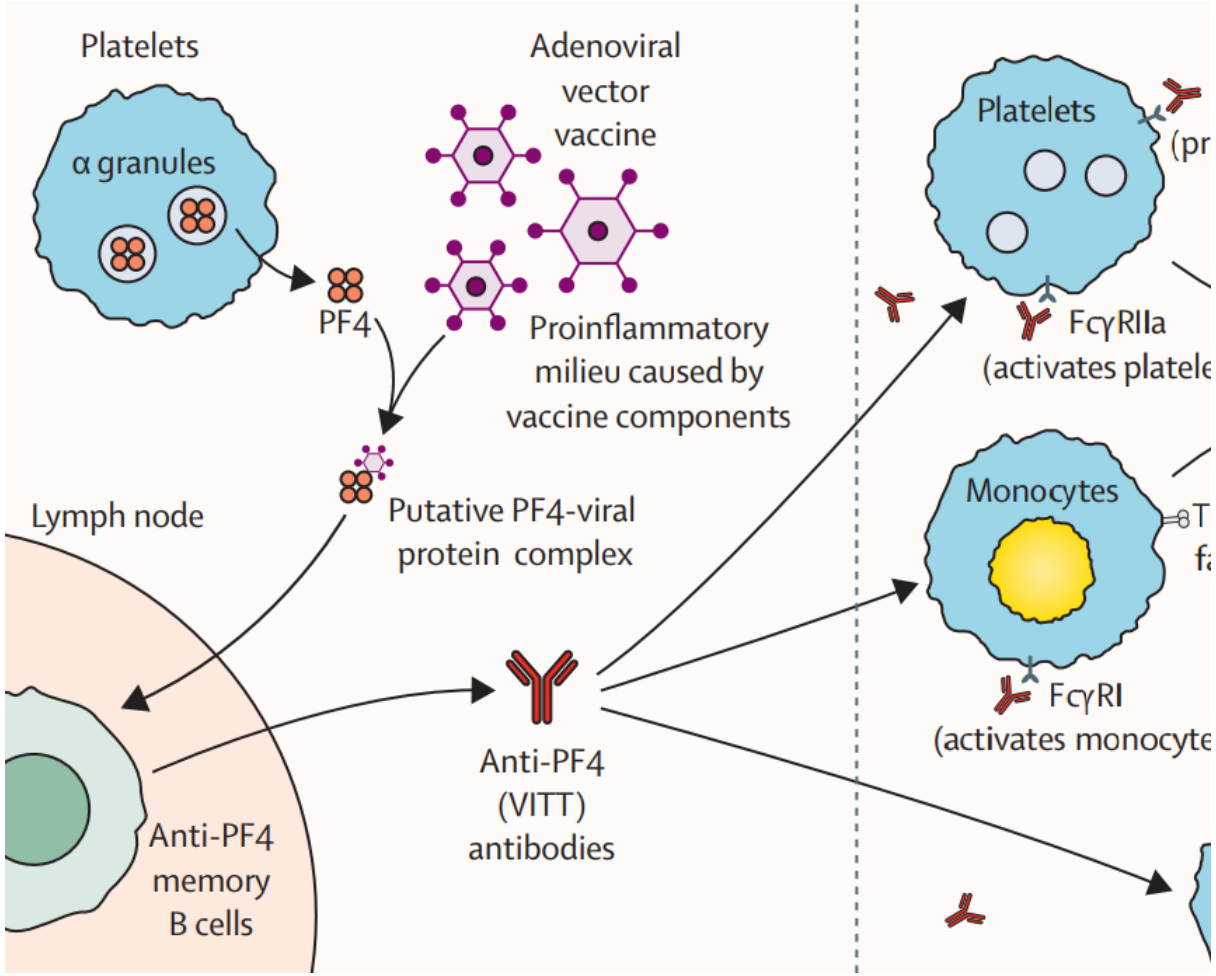
Approved viral-vectored vaccines:

Ebola

COVID-19

- J&J: Ad26.COV2.S
- Oxford: ChAdOx1 nCoV-19
- Sputnik V: Gam-COVID-Vac

Vaccine-induced thrombotic thrombocytopenia (VITT)



Adapted from Klok et al Lancet 2022

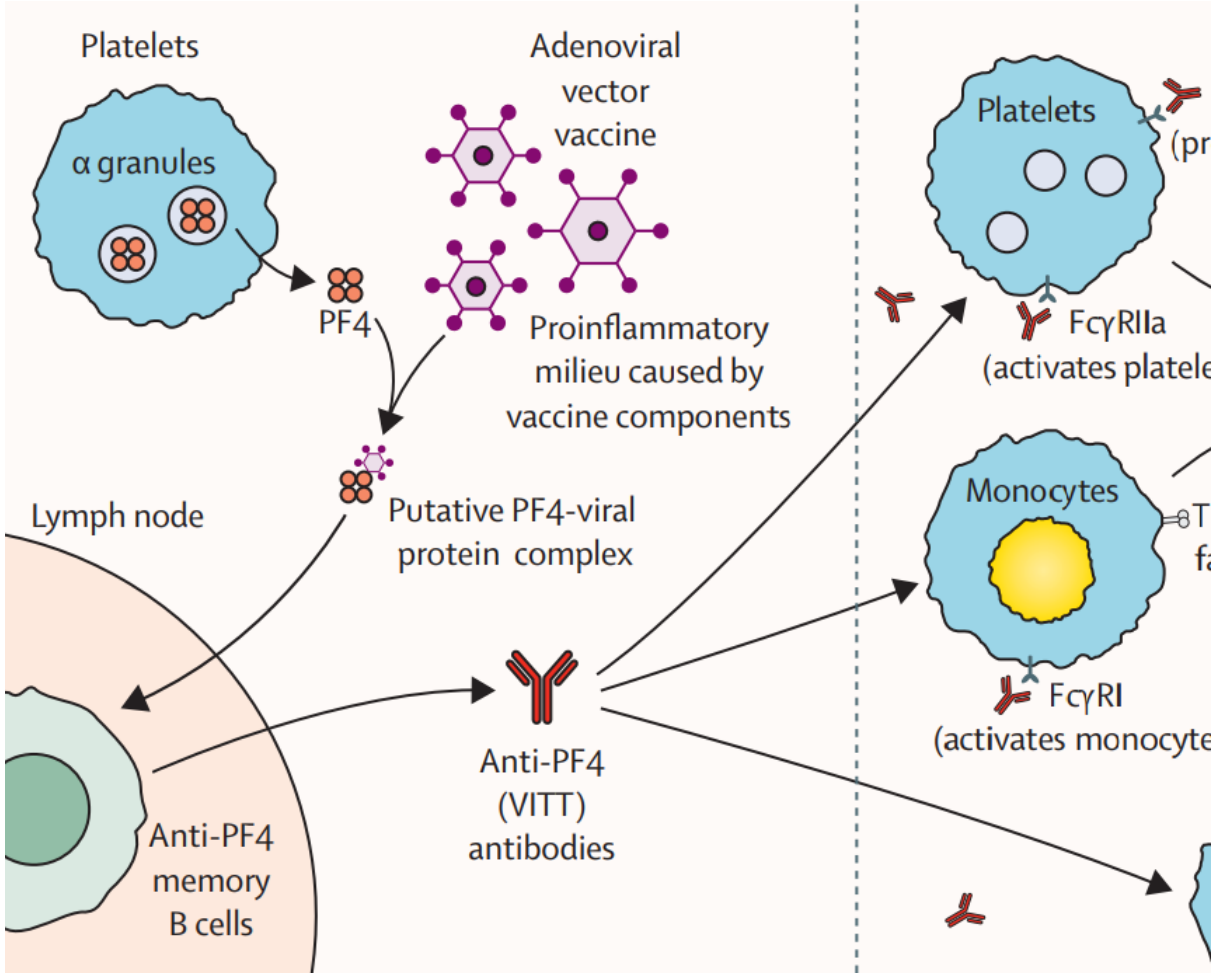
Proposed VITT mechanism

1. Adenovirus vector find directly to circulating PF4, a protein thought to be involved in innate immunity

2. The adenovirus-PF4 complex stimulates the production of anti-PF4 autoantibodies

3. Anti-PF4 autoantibodies bind to multiple cell types causing a consumptive coagulopathy similar to heparin-induced thrombocytopenia (HIT)

Vaccine-induced thrombotic thrombocytopenia (VITT)



Adapted from Klok et al Lancet 2022

J&J vaccine (United States estimates)

- Doses given: >15 million
- Lives saved: >50,000
- VITT mortality rate: 0.6 per million
- VITT deaths: 8

Oxford vaccine (global estimates)

- Doses given: >2 billion
- Lives saved: >6 million
- VITT mortality rate: 1 per million

Oliver et al MMWR Morb Mortal Wkly Rep. 2022
Watson et al Lancet Infect Dis. 2022
Mhase BMJ 2021

Presentation outline

- Historical perspective: back to the future
- Basic immune mechanisms involved in vaccination
- Commonly used vaccine platforms
- Causes of rare but serious vaccine adverse effects

Conclusions

- Variolation has a long history and the first modern vaccination campaign began with cowpox in 1840

- The immune system contains many cell types that can be roughly classified as innate or adaptive
- Innate immune cells carry antigens to draining lymph nodes where adaptive B cells and T cells become activated
- Adjuvants increase the intensity of the immune response

- Five major vaccine platforms account for the great majority commonly used vaccines

- Vaccine adverse effects are well-described but are very rare and vastly outweighed by vaccine benefits

References

Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer. 2004 Jan;4(1):11-22. doi: 10.1038/nrc1252. PMID: 14708024.

Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. Lancet Haematol. 2022 Jan;9(1):e73-e80. doi: 10.1016/S2352-3026(21)00306-9. Epub 2021 Nov 11. PMID: 34774202; PMCID: PMC8585488.

Link-Gelles R, Lutterloh E, Ruppert PS, Backenson PB, St George K, Rosenberg ES, Anderson BJ, Fuschino M, Popowich M, Punjabi C, Souto M, McKay K, Rulli S, Insaf T, Hill D, Kumar J, Gelman I, Jorba J, Ng TFF, Gerloff N, Masters NB, Lopez A, Dooling K, Stokley S, Kidd S, Oberste MS, Routh J; 2022 U.S. Poliovirus Response Team. Public health response to a case of paralytic poliomyelitis in an unvaccinated person and detection of poliovirus in wastewater-New York, June-August 2022. Am J Transplant. 2022 Oct;22(10):2470-2474. doi: 10.1111/ajt.16677. PMID: 36196495.

Mahase E. AstraZeneca vaccine: Blood clots are "extremely rare" and benefits outweigh risks, regulators conclude. BMJ. 2021 Apr 8;373:n931. doi: 10.1136/bmj.n931. PMID: 33832929.

Oliver SE, Wallace M, See I, Mbaeyi S, Godfrey M, Hadler SC, Jatlaoui TC, Twentyman E, Hughes MM, Rao AK, Fiore A, Su JR, Broder KR, Shimabukuro T, Lale A, Shay DK, Markowitz LE, Wharton M, Bell BP, Brooks O, McNally V, Lee GM, Talbot HK, Daley MF. Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine: Updated Interim Recommendations from the Advisory Committee on Immunization Practices - United States, December 2021. MMWR Morb Mortal Wkly Rep. 2022 Jan 21;71(3):90-95. doi: 10.15585/mmwr.mm7103a4. PMID: 35051137; PMCID: PMC8774160.

Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol. 2021 Feb;21(2):83-100. doi: 10.1038/s41577-020-00479-7. Epub 2020 Dec 22. Erratum in: Nat Rev Immunol. 2021 Jan 5;: PMID: 33353987; PMCID: PMC7754704.

Pulendran B, S Arunachalam P, O'Hagan DT. Emerging concepts in the science of vaccine adjuvants. Nat Rev Drug Discov. 2021 Jun;20(6):454-475. doi: 10.1038/s41573-021-00163-y. Epub 2021 Apr 6. PMID: 33824489; PMCID: PMC8023785.

Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Dis. 2022 Sep;22(9):1293-1302. doi: 10.1016/S1473-3099(22)00320-6. Epub 2022 Jun 23. PMID: 35753318; PMCID: PMC9225255.

Questions and contact

svidal2@bwh.harvard.edu