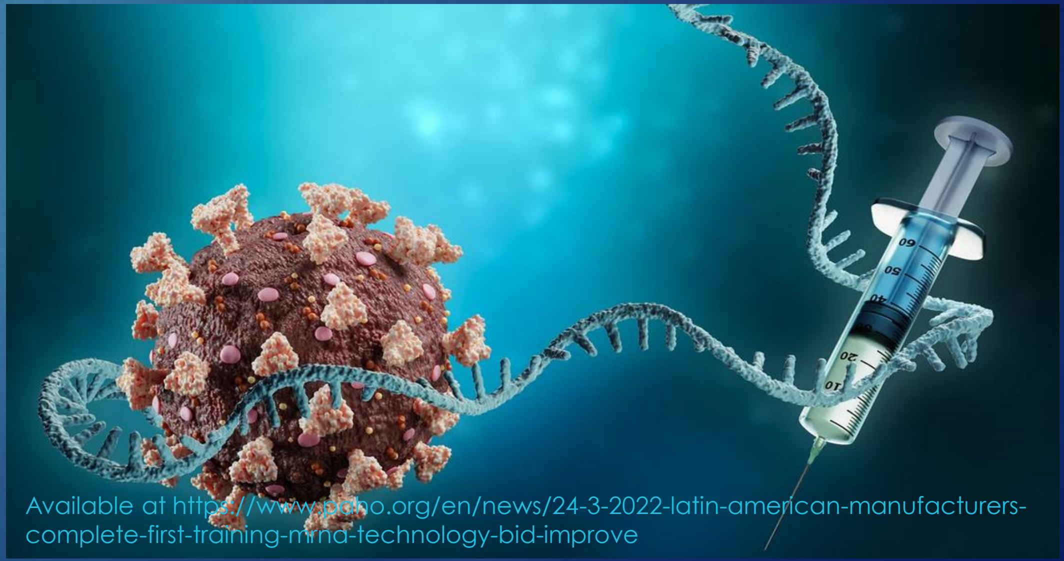
Advances in Vaccine and Immunization Technologies

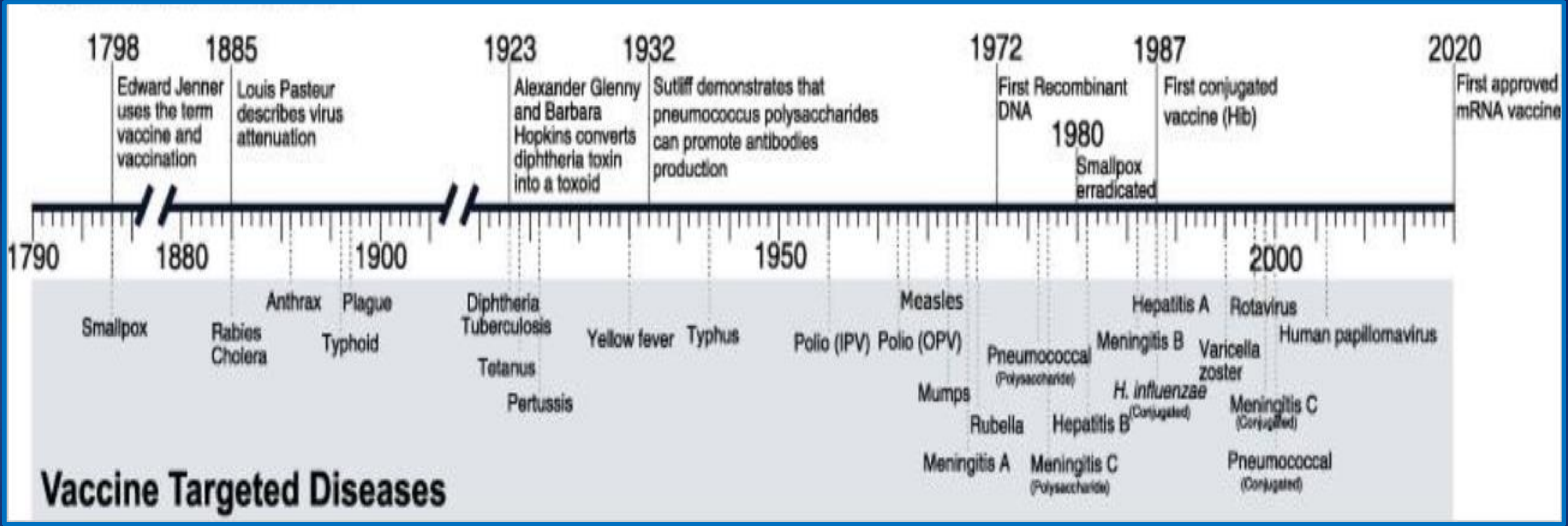
MAYAN LUMANDAS, MD



Outline

- Vaccination Milestones
- Novel Vaccine Technologies
  - New Vaccine Platforms
  - Adjuvants
  - New Vaccine Delivery Systems

Vaccination Milestones



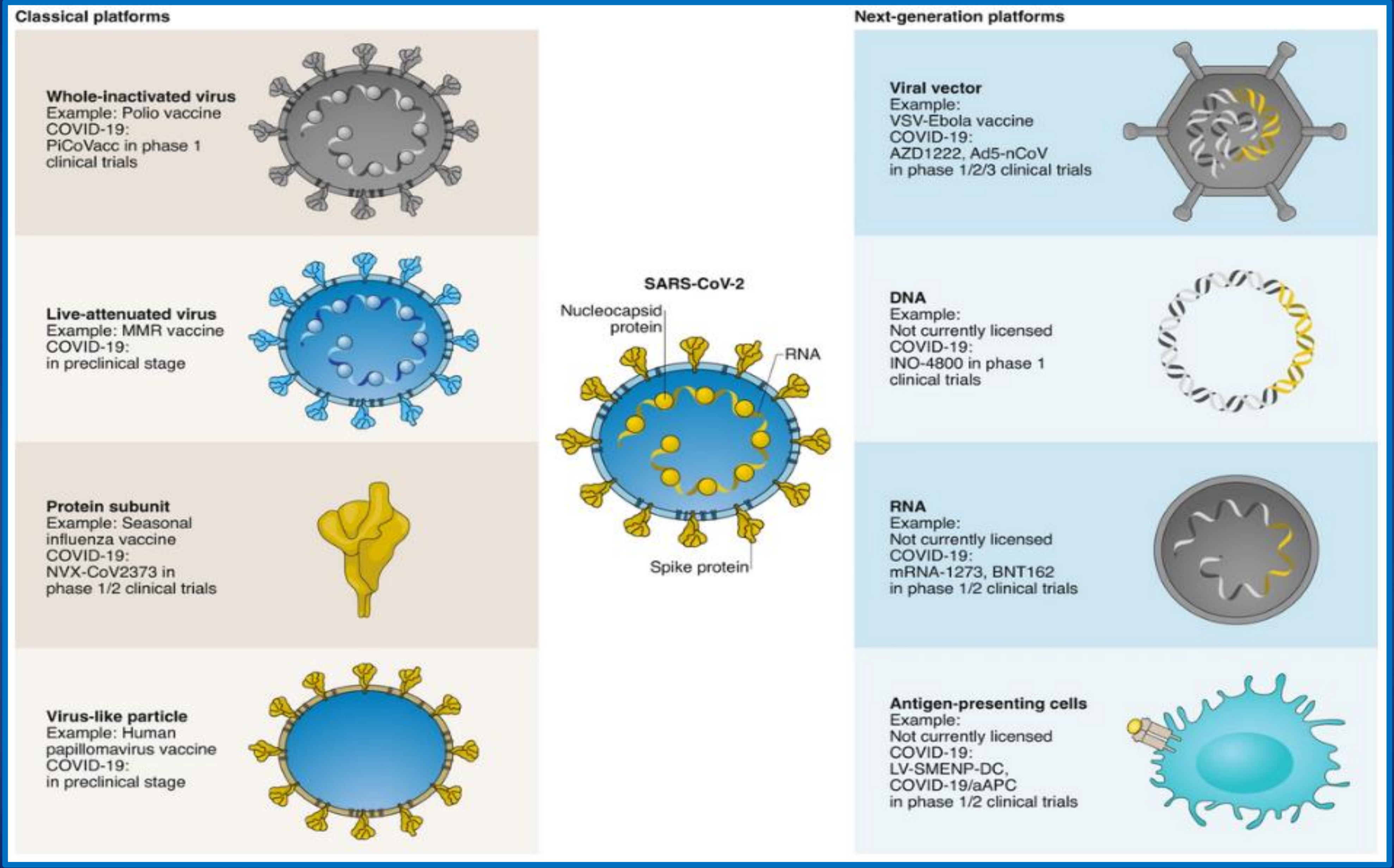
Rosa, S et al. mRNA vaccines manufacturing: Challenges and bottlenecks. Vaccine. 2021 Apr 15; 39(16): 2190–2200.

96-100% reduction in Cases and Deaths

	Cases (All post-vaccine cases refer to 2006)			Deaths (All post-vaccine deaths refer to 2004)		
	Pre-vaccine	Reduction	Post-vaccine	Pre-vaccine	Reduction	Post-vaccine
Diphtheria	**Pre-vaccine:** 158 cases per million per year (1936-45)	100% Reduction	**Post-vaccine:** 0 cases per million per year	**Pre-vaccine:** 13.7 deaths per million per year (1936-45)	100% Reduction	**Post-vaccine:** 0 deaths per million per year
Measles	**Pre-vaccine:** 3044 cases per million per year (1953-62)	99.99% Reduction	**Post-vaccine:** 0.2 cases per million per year	**Pre-vaccine:** 2.5 deaths per million per year (1953-62)	100% Reduction	**Post-vaccine:** 0 deaths per million per year
Mumps	**Pre-vaccine:** 830 cases per million per year (1963-68)	97.4% Reduction	**Post-vaccine:** 22 cases per million per year	**Pre-vaccine:** 0.2 deaths per million per year (1963-68)	100% Reduction	**Post-vaccine:** 0 deaths per million per year
Pertussis	**Pre-vaccine:** 1534 cases per million per year (1934-43)	96.6% Reduction	**Post-vaccine:** 52 cases per million per year	**Pre-vaccine:** 30.8 deaths per million per year (1934-43)	99.7% Reduction	**Post-vaccine:** 0.09 deaths per million per year
Acute Poliomyeltis	**Pre-vaccine:** 141 cases per million per year (1941-50)	100% Reduction	**Post-vaccine:** 0 cases per million per year	**Pre-vaccine:** 10 deaths per million per year (1941-50)	100% Reduction	**Post-vaccine:** 0 deaths per million per year
Paralytic Poliomyeltis	**Pre-vaccine:** 103 cases per million per year (1951-54)	100% Reduction	**Post-vaccine:** 0 cases per million per year	**Pre-vaccine:** 11.8 deaths per million per year (1951-54)	100% Reduction	**Post-vaccine:** 0 deaths per million per year

Samantha Vanderslott, Bernadeta Dadonaite and Max Roser (2013) - "Vaccination". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/vaccination'

Vaccine Platforms



van Riel, D and de Wit, E. Next-generation vaccine platforms for COVID-19. *Nat. Mater.* **19**, 810–812 (2020).

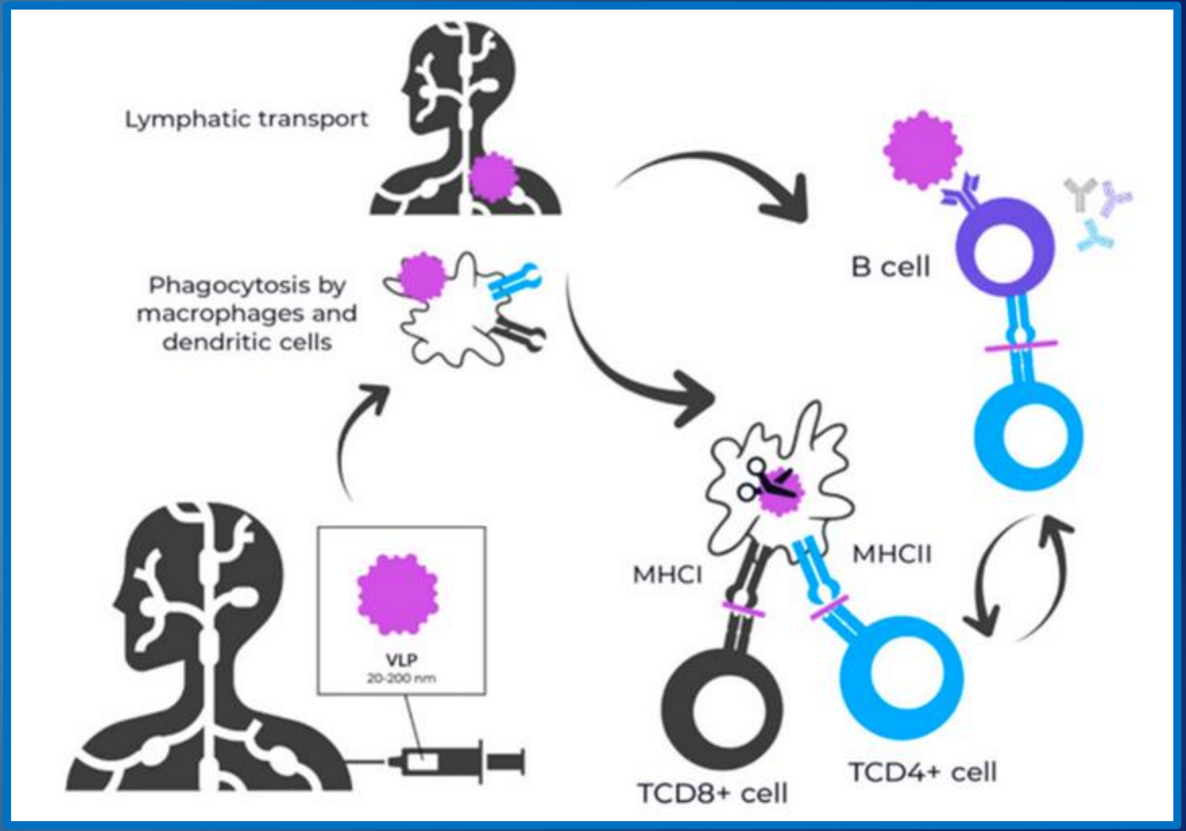
Conventional Technologies

Platform	Description	Examples
Live-Attenuated	Prepared from weakened pathogens	MMR, BCG, cholera, Rotavirus, Varicella
Inactivated	Derived from killed form of virulent pathogens	Poliovirus, Hepatitis A, Diphtheria and tetanus toxoid
Virus-like particles	Macromolecular assemblies designed to mimic the morphology of a native virus	Human Papillomavirus
Synthetic peptides	Identification and synthesis of immunodominant peptide sequences	Meningococcal Group B
Fractional Inactivated	Inactivation of toxins	Diphtheria and tetanus toxoid and acellular pertussis
Polysaccharide and polysaccharide conjugate	Derived from carbohydrate-based polymers	Meningococcal, Typhoid, Pneumococcal, Haemophilus B

Ghattas M, Dwivedi G, Lavertu M, Alameh MG. Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities. Vaccines (Basel). 2021 Dec 16;9(12):1490

Virus-like Particles

- Macromolecular assemblies designed to mimic the morphology of a native virus
- Increased potency due to multivalent interaction
- Manufacturing challenges
- Used in several licensed vaccines such as Hepatitis B and HPV
- Being developed for Chikingunya, Zika and SARS-CoV-2

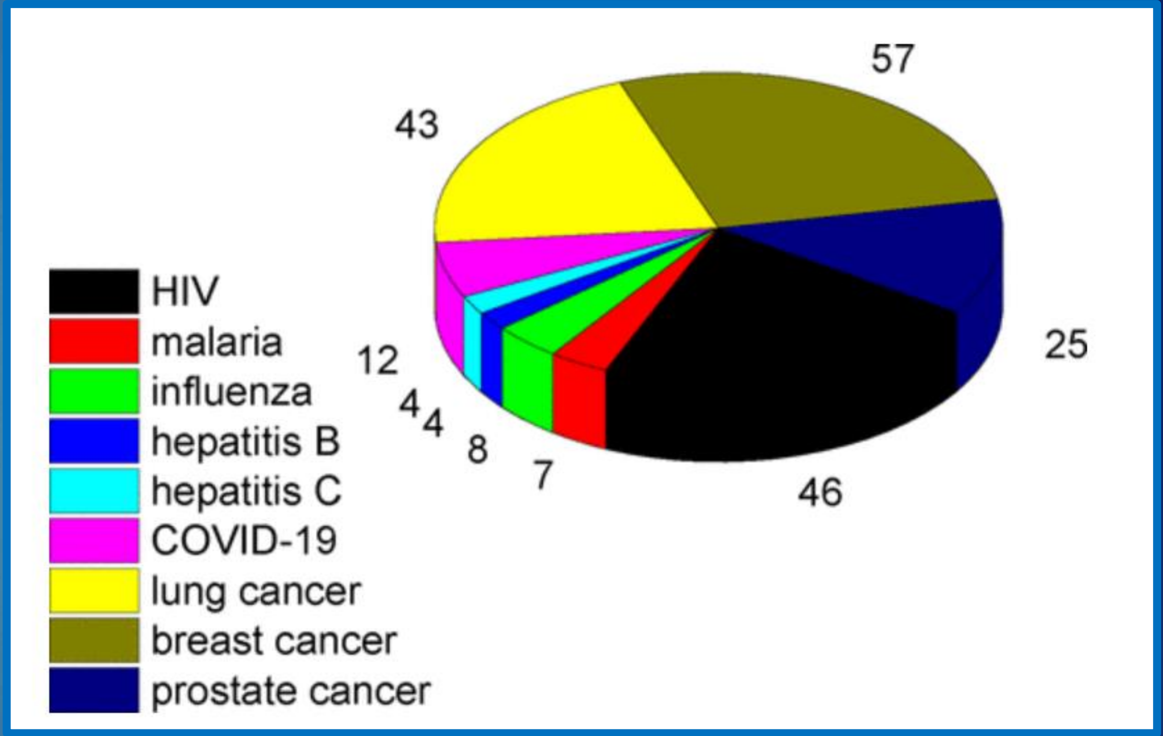


Prates-Syed, W, et al. VLP-Based COVID-19 Vaccines: An Adaptable Technology against the Threat of New Variants. *Vaccines* 2021, 9(12), 1409

Ghattas M, Dwivedi G, Lavertu M, Alameh MG. Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities. Vaccines (Basel). 2021 Dec 16;9(12):1490

Synthetic peptide vaccines

- technology using fragments of protein antigen sequences which are chemically synthesized and assembled into a single molecule[1]
- Example of FDA-approved synthetic peptide vaccine is for Meningococcal B[2]
- used in development of several vaccines for infectious diseases like Malaria, HCV, infuenza virus and HIV[1] and cancer



Hamley, I. Peptides for Vaccine Development.ACS Appl. Bio Mater. 2022, 5, 3, 905–944
Publication Date:February 23, 2022

1.Matic, Z and Santac, M. Current view on novel vaccine technologies to combat human infectious diseases. Applied Microbiology and Biotechnology (2022) 106:25–56
2.Ghattas M, Dwivedi G, Lavertu M, Alameh MG. Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities. Vaccines (Basel). 2021 Dec 16;9(12):1490

Search for Safe and Effective Vaccines Continues….

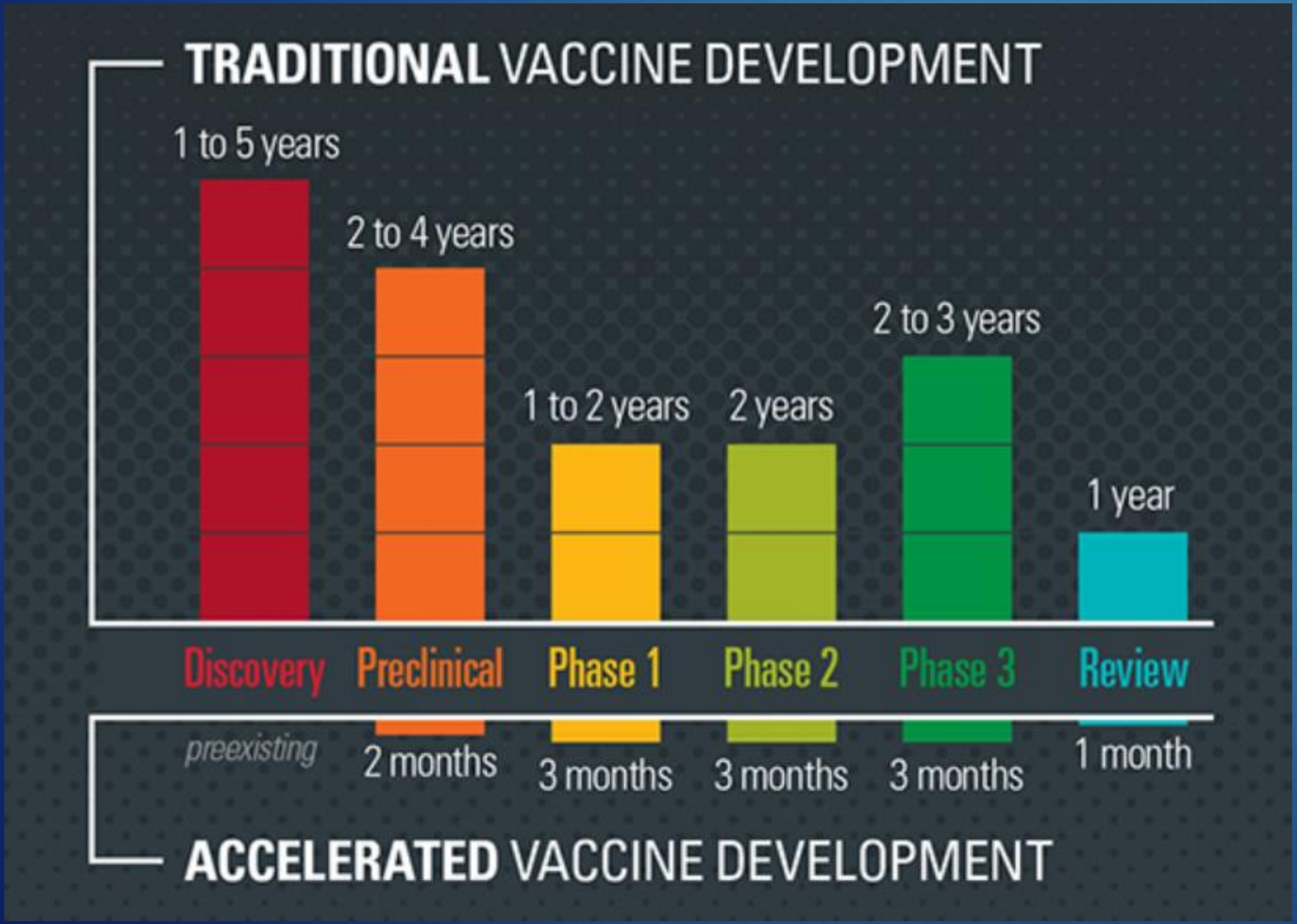
nature > news feature > article

NEWS FEATURE | 18 December 2020

The lightning-fast quest for COVID vaccines — and what it means for other diseases

The speedy approach used to tackle SARS-CoV-2 could change the future of vaccine science.

Philip Ball

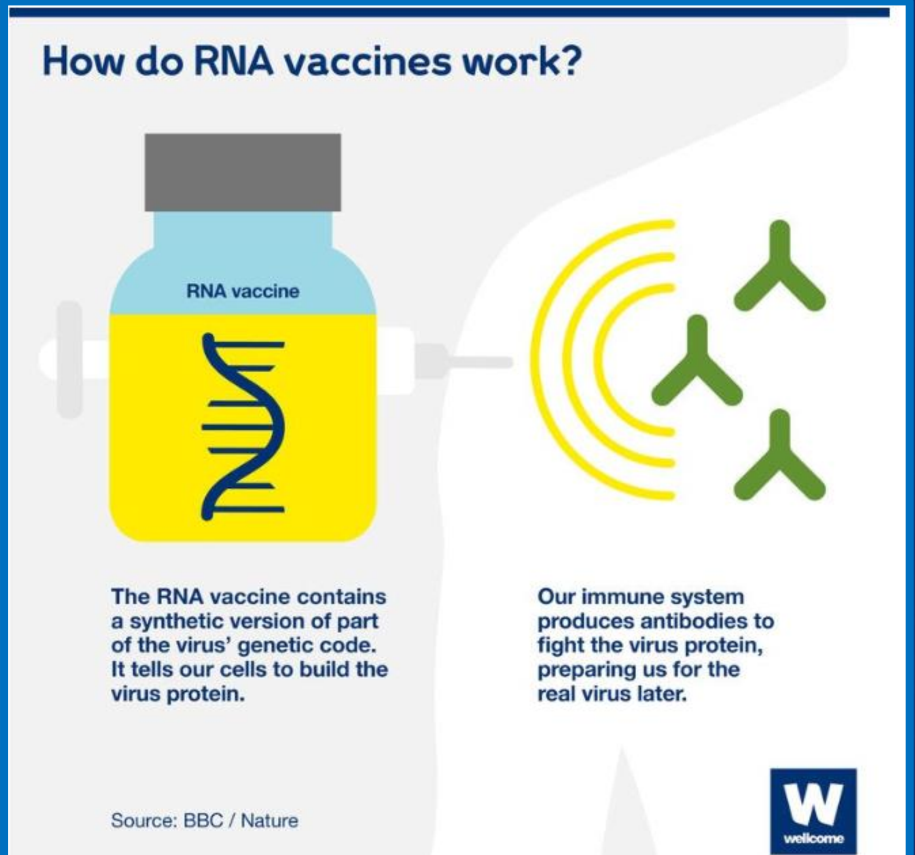


- Research and development has been done for mRNA vaccine for over 10 years
- After sequencing, it took just a few days to make the mRNA vaccine candidates

Available at https://www.nebraskamed.com/COVID/were-the-covid-19-vaccines-rushed

mRNA Vaccines

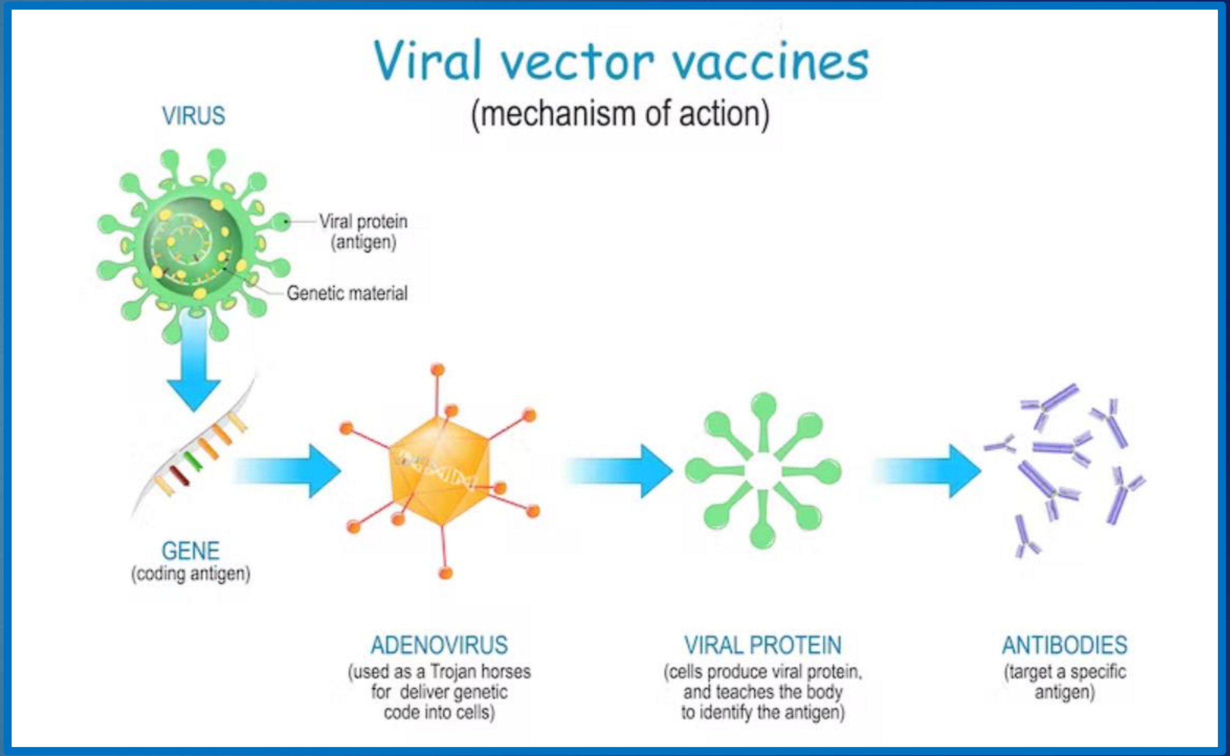
- mRNA vaccines teach our cells how to make proteins in order to trigger an immune response
- mRNA vaccines have several advantages compared to other vaccines such as shorter manufacturing times
- they do not contain a live virus, there is no risk of causing disease.



Available at 7 vital questions about the RNA Covid-19 vaccines | News | Wellcome

Viral vector vaccines

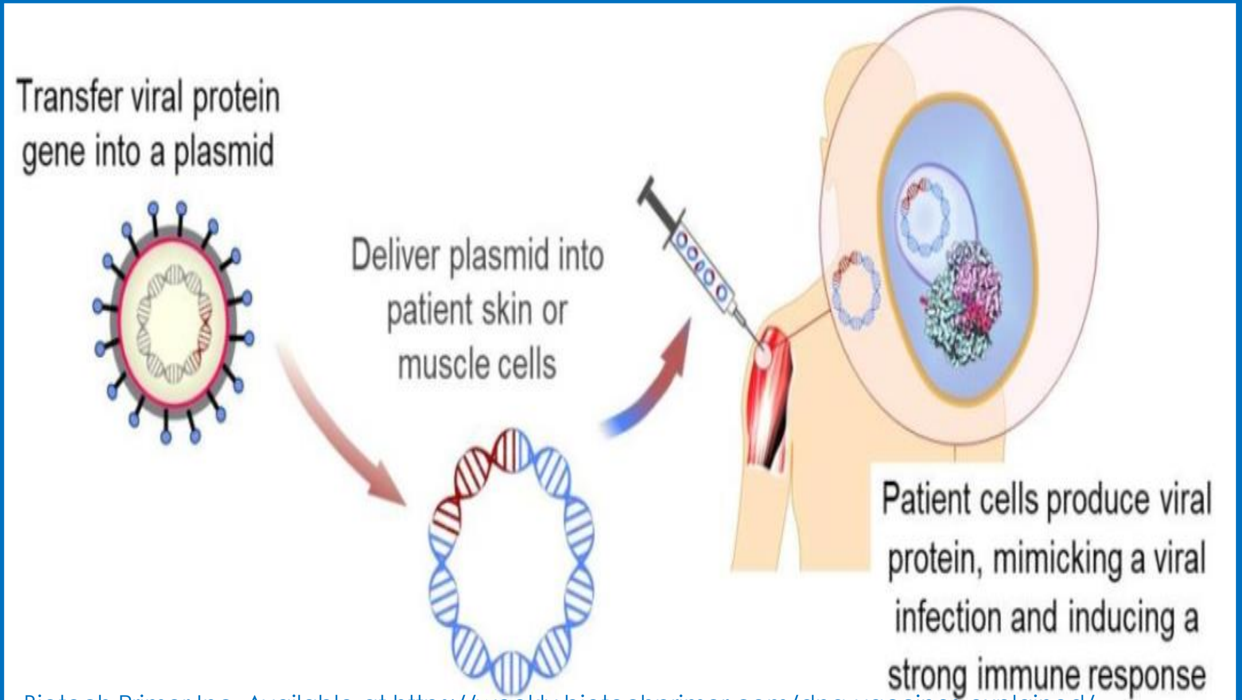
- Viral vector vaccines use a modified version of a different virus as a vector to deliver protection.
- Some examples of viruses that are used as vectors include influenza, vesicular stomatitis virus (VSV), measles virus, and adenovirus. For COVID-19 vaccine, Adenovirus has been used.



Available at https://brighterworld.mcmaster.ca/articles/analysis-how-the-puzzle-of-viral-vector-vaccines-was-solved-leading-to-todays-covid-19-shots/

DNA vaccines

- consist of plasmid DNA (pDNA) containing the transgene encoding the antigen of interest
- beginning of the research of the DNA vaccines, in the early 1990s
- three major limitations of DNA vaccines: (i) low level of intracellular/ intranuclear transport of pDNA, which results in low immunogenicity (Hasson et al. 2015; Klimov 2019), (ii) safety issues regarding the possibility of integration of pDNA into the genomic DNA of the vaccinee and activation of oncogenes (Wurtele et al. 2003), and (iii) potential development of autoimmunity by elicitation of anti-DNA antibodies (Lilic and Ghosh 1994; Zafrir et al. 2012)



Biotech Primer Inc. Available at https://weekly.biotechprimer.com/dna-vaccines-explained/

Matic, Z and Santac, M. Current view on novel vaccine technologies to combat human infectious diseases. Applied Microbiology and Biotechnology (2022) 106:25–56

Bacterial vector vaccines

- Use live bacterial cells as carriers
- Carriers are classified into non-pathogenic and attenuated pathogenic bacteria
- Risk of infection especially in children, elderly and immunocompromised
- Genetic engineering allows attenuation

- Examples of bacterial vectors:
  - Yersinia pestis[1]
  - Mycobacterium bovis[2]
  - Pseudomonas aeruginosa[2]
  - Shigella[2]
  - Salmonella[2]
  - Listeria monocuyogenes[2]
  - Vibrio cholera[2]

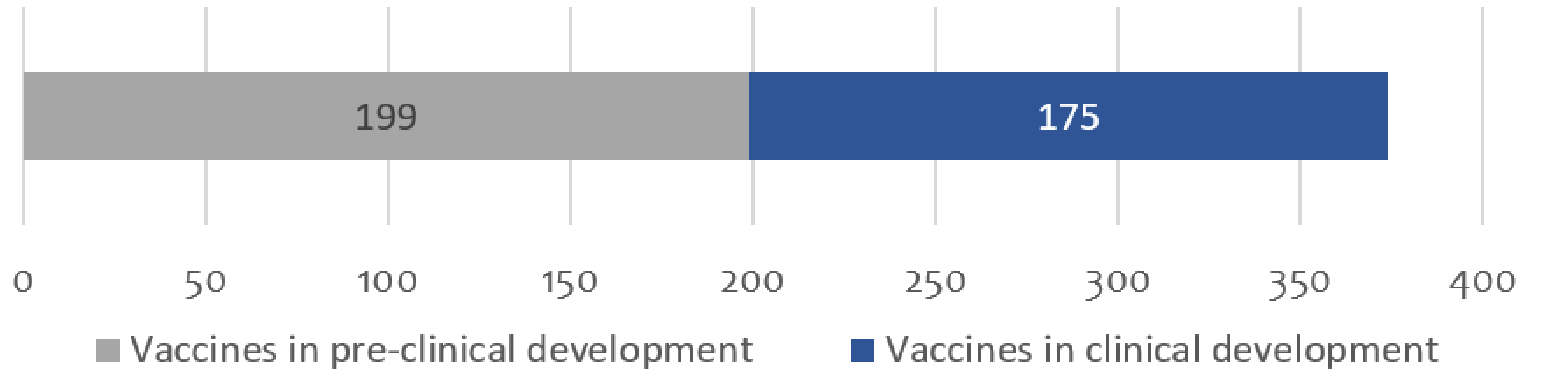
1.Ghattas M, Dwivedi G, Lavertu M, Alameh MG. Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities. Vaccines (Basel). 2021 Dec 16;9(12):1490
2.Creative Biolabs. Avaialble at https://www.creative-biolabs.com/vaccine/bacterial-vector-vaccine-design.htm

COVID-19 Vaccines Authorized by the Philippine FDA

COVID-19 Vaccines	Platform
Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine (nucleoside modified)	mRNA
ChAdOx1-S[recombinant] VAXZEVRIA (COVID-19 Vaccine AstraZeneca)	Viral vector
SARS-CoV-2 Vaccine (Vero Cell), Inactivated [Coronavac]	Inactivated
Sputnik V Gam-COVID-Vac	Viral vector
Sputnik Light COVID-19 Vaccine	Viral vector
Janssen COVID-19 Vaccine (Ad26.COV2-S (recombinant)	Viral vector
Whole Virion, Inactivated Corona Virus Vaccine [Covaxin]	Inactivated
COVID-19 mRNA Vaccine (nucleoside modified) [COVID-19 Vaccine Moderna]	mRNA
COVID-19 Vaccine (Vero Cell), Inactivated [COVID-19 Vaccine Sinopharm]	Inactivated
SARS-CoV-2 rS Protein Nanoparticle Vaccine [Covovax]	Protein Sub-unit

List of COVID-19 Vaccines Authorized by the FDA. Available at https://www.fda.gov.ph/list-of-fda-issued-emergency-use-authorization/

Novel Coronavirus candidate vaccine development



Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	56	32%
VVnr	Viral Vector (non-replicating)	23	13%
DNA	DNA	16	9%
IV	Inactivated Virus	22	13%
RNA	RNA	41	24%
VVr	Viral Vector (replicating)	4	2%
VLP	Virus Like Particle	7	4%
VVr + APC	VVr + Antigen Presenting Cell	2	1%
LAV	Live Attenuated Virus	2	1%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
BacAg-SpV	Bacterial antigen-spore expression vector	1	1%
		175	

Phase 1=53
Phase 1/2=30
Phase 2=14
Phase 2/3=16
Phase 3=49
Phase 4=11

World Health Organization COVID-19 vaccine tracker and landscape. Available at [COVID-19 vaccine tracker and landscape (who.int)]

Creating a Stronger Immune Response

Credit: S. Fenwick / Springer Nature Limited

Adjuvants

- an ingredient used in some vaccines that helps create a stronger immune response
- can cause more local reactions (such as redness, swelling, and pain at the injection site) and more systemic reactions (such as fever, chills and body aches) than non-adjuvanted vaccines
- Aluminum salts, such as aluminum hydroxide, aluminum phosphate, and aluminum potassium sulfate have been for more than 70 years.
- Aluminum salts were initially used in the 1930s, 1940s, and 1950s with diphtheria and tetanus vaccines

Centers for Disease Control and Prevention. Adjuvants and Vaccines. Available at https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html#print

Adjuvants Licensed in the U.S.

Adjuvant	Composition	Vaccines
Aluminum	One or more of the following: amorphous aluminum hydroxyphosphate sulfate (AAHS), aluminum hydroxide, aluminum phosphate, potassium aluminum sulfate (Alum)	Anthrax, DT, DTaP (Daptacel), DTaP (Infanrix), DTaP-HepB-IPV (Pediarix), DTaP-IPV (Kinrix), DTaP-IPV (Quadracel), DTaP –IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (VAXELIS), HepA (Havrix), HepA (Vaqta), HepB (Engerix-B), HepB (PREHEVBRIO), HepB (Recombivax), HepA/HepB (Twinrix), HIB (PedvaxHIB), HPV (Gardasil 9), Japanese encephalitis (Ixiaro), MenB (Bexsero, Trumenba), Pneumococcal (Prevnar 13, Prevnar 20, VAXNEUVANCE), Td (Tenivac), Td (Mass Biologics), Td (no trade name), Tdap (Adacel), Tdap (Boostrix), Tick-Borne Encephalitis (TICOVAC)
$AS01_B$	Monophosphoryl lipid A (MPL) and QS-21, a natural compound extracted from the Chilean soapbark tree, combined in a liposomal formulation	Zoster vaccine (Shingrix)
AS04	Monophosphoryl lipid A (MPL) + aluminum salt	Human papillomavirus, or HPV (Cervarix)

Centers for Disease Control and Prevention. Adjuvants and Vaccines. Available at https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html#print

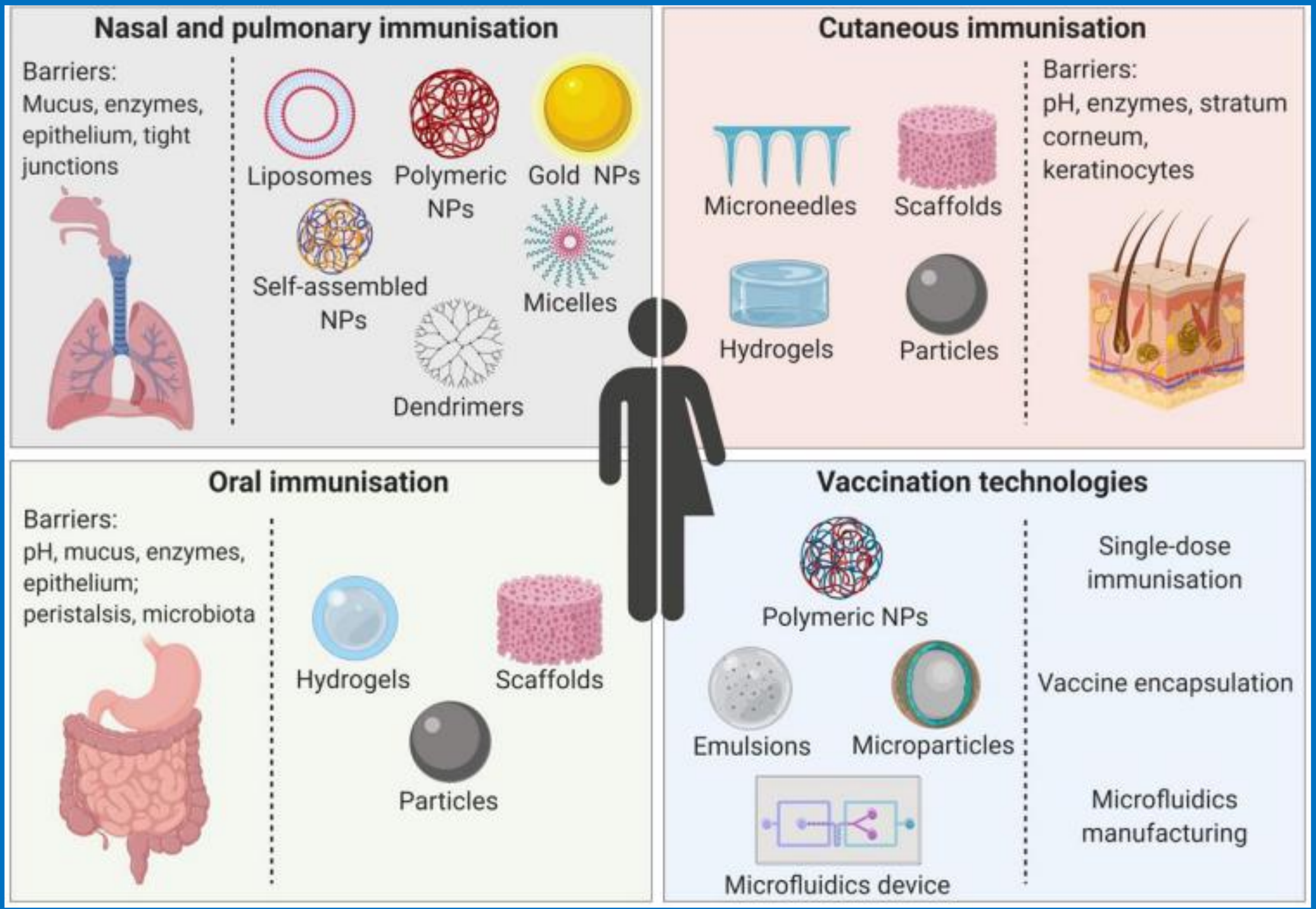
Adjuvants Licensed in the U.S.

CpG 1018	Cytosine phosphoguanine (CpG), a synthetic form of DNA that mimics bacterial and viral genetic material	HepB (Heplisav-B)
Matrix-M™	Saponins derived from the soapbark tree (*Quillaja saponaria* Molina)	COVID-19 vaccine (Novavax COVID-19 Vaccine, Adjuvanted)
MF59	Oil in water emulsion composed of squalene	Influenza (Fluad and Fluad Quadrivalent)

Centers for Disease Control and Prevention. Adjuvants and Vaccines. Available at https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html#print

Can we do more?

Yes, we can!



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Available at https://www.nbcnews.com/health/health-news/flumist-nasal-flu-vaccine-can-come-back-vaccine-advisers-say-n849986

Innovative Vaccine Delivery Systems

Vaccine Platform	Type of Candidate Vaccine	No. of doses	Schedule	Route	Developers	Status
Viral vector (Non-replicating)	Ad5-triCoV/Mac or ChAd-triCoV/Mac, new experimental adenovirus-based vaccines expressing SARS-CoV-2 spike, nucleocapsid and RNA polymerase proteins	1	Day 0	AE	McMaster University	Phase 1
Viral vector (Non-replicating)	MVA-SARS-2-ST Vaccine	1	Day 0	IH	Hannover Medical School	Phase 1
Viral vector (Replicating)	NDV-HXP-S; A Live Recombinant Newcastle Disease Virus-vectored COVID-19 Vaccine	1	Day 0	IN	Sean Liu, Icahn School of Medicine at Mount Sinai	Phase 2/3
Protein subunit	ACM-SARS-CoV-2-beta ACM-CpG vaccine candidate (ACM-001)	2	Day 0 + 28	IN	ACM Biolabs	Phase 1
Protein subunit	A subunit OMV-linked HexaPro spike vaccine. The vaccine platform is based on outer	1	Day 0	IN	Intravacc B.V.	Phase 1
Protein subunit	PepGNP-SARSCoV2, A CD8 T-cell priming adaptive vaccine composed of a Coronaviruses specific peptides mounted on a gold nanoparticle	2	Day 0 + 21	ID	Emergex Vaccines Holding Limited	Phase 1
Viral vector (Non-replicating)	Ad26.cov2.s+bcg vaccine. AD26-BCG	1	Day 0	ID	Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, IRB Chai	Phase 1
Protein subunit	VXS-1223U Microarray patch (HD-MAP) vaccine composed of ARS-CoV-2 spike protein (HexaPro)	1	Day 0	ID	Vaxxas Pty Ltd	Phase 1

World Health Organization COVID-19 vaccine tracker and landscape. Available at COVID-19 vaccine tracker and landscape (who.int)

Innovative Vaccine Delivery Systems

Vaccine Platform	Type of Candidate Vaccine	No. of doses	Schedule	Route	Developers	Status
Viral vector (Non-replicating)	VXA-CoV2-1 Ad5 adjuvanted Oral Vaccine platform	2	Day 0 + 28	Oral	Vaxart	Phase 2
DNA based vaccine	bacTRL-Spike oral DNA vaccine	1	Day 0	Oral	Symvivo Corporation	Phase 1
Protein subunit	CoV2-OGEN1, protein-based vaccine	1-2	Day 0 +/- 14	Oral	USSF/Vaxform	Phase 1
Bacterial antigen-spore expression vector	COVID19 Oral Vaccine Consisting of Bacillus Subtilis Spores	3	Day 0 + 14 + 28	Oral	DreamTec Research Limited	NA
Viral vector (Non-replicating) + APC	LV-SMENP-DC vaccine. Dendritic cells are modified with lentivirus vectors expressing Covid-19 minigene	1	Day 0	SC & IV	Shenzhen Geno-Immune Medical Institute	Phase 1/2

World Health Organization COVID-19 vaccine tracker and landscape. Available at COVID-19 vaccine tracker and landscape (who.int)

What's Next?

- Effective antigens?
- Which genes must be upregulated or downregulated?
- What antigenic constructions can be used to achieve a protective immune response?
- Adjuvant formulations?
- How can vaccines be painlessly delivered?
- Thermo-stable vaccines?
- Cost-effective manufacturing?
- Rapid mass deployment?

→

Safe and Effective Vaccines

100 Days

What if it took 100 days to make a safe and effective vaccine against any virus?

CEPI and the UK Government recently hosted the Global Pandemic Preparedness Summit to explore how we can respond to the next “Disease X”, by making safe, effective vaccines within 100 days.

Coalition for Epidemic Preparedness innovations. Available at https://100days.cepi.net/

Thank you