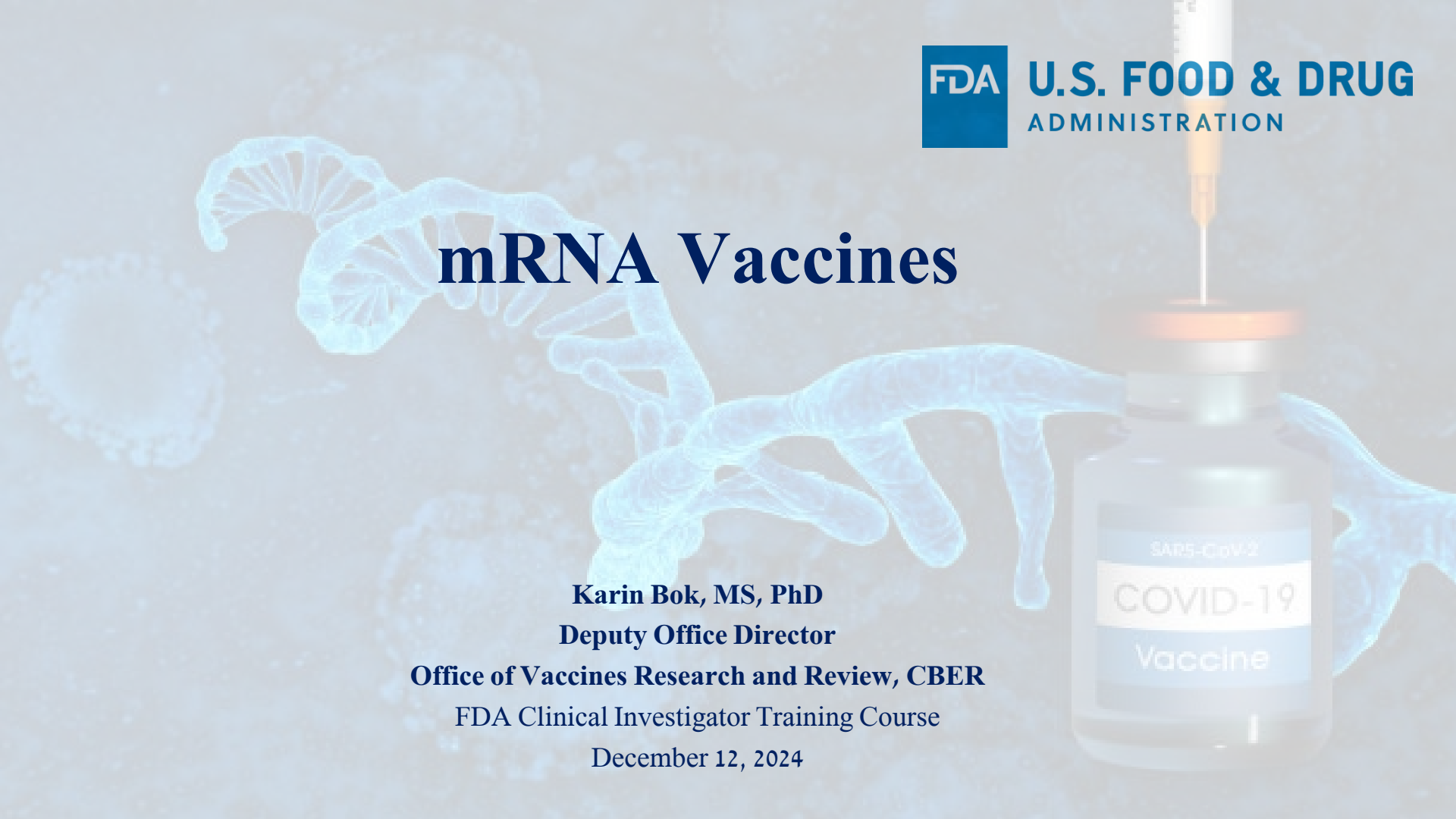
U.S. FOOD & DRUG ADMINISTRATION

mRNA Vaccines



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FDA Clinical Investigator Training Course

December 12, 2024

FDA Disclaimer

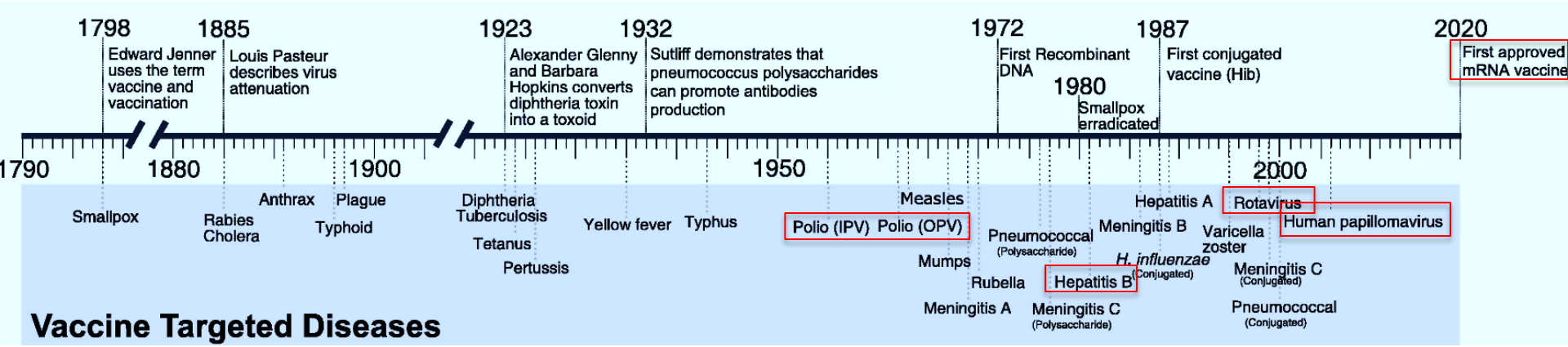
My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.

[**N.B.** No disclosures or conflicts of interest]

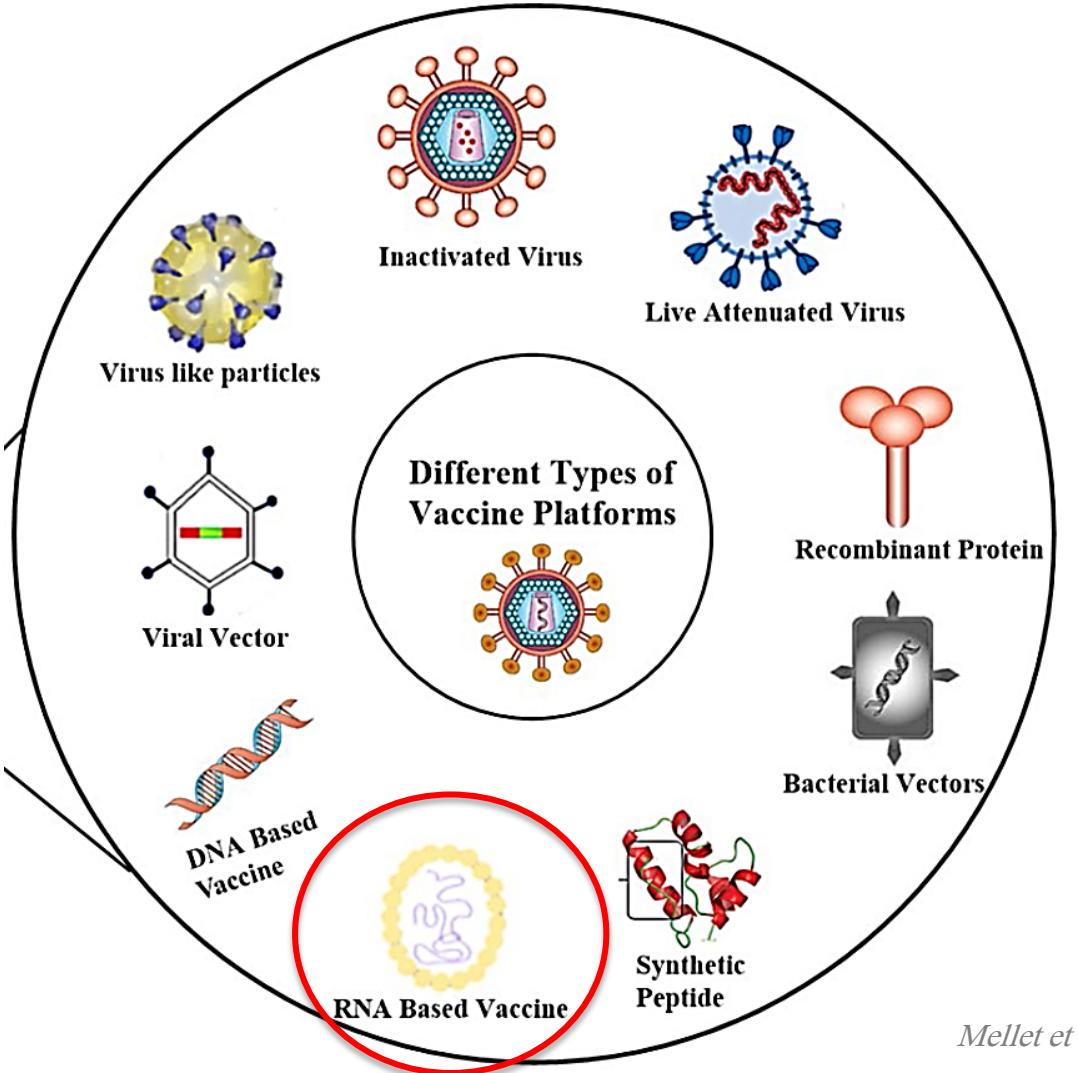
At a Glance

- Introduction
- mRNA Vaccines Technology
- mRNA Vaccines Efficacy
- mRNA Vaccines Biodistribution and Safety
- mRNA Vaccines Durability and Formula Updates
- Approved mRNA Vaccines and mRNA Vaccines in Different Stages of Development
- Summary and Conclusions
- Challenge Questions

Vaccination Milestones



Vaccine Types and Platforms



Mellet et al. 2021. Vaccines

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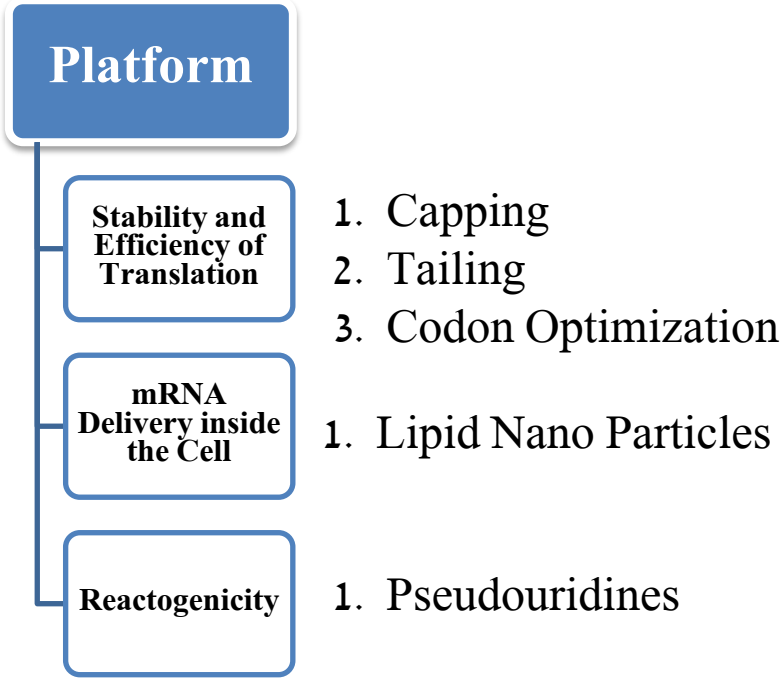
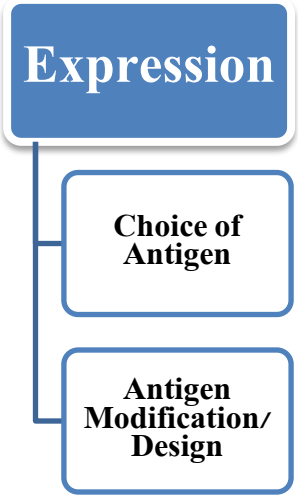
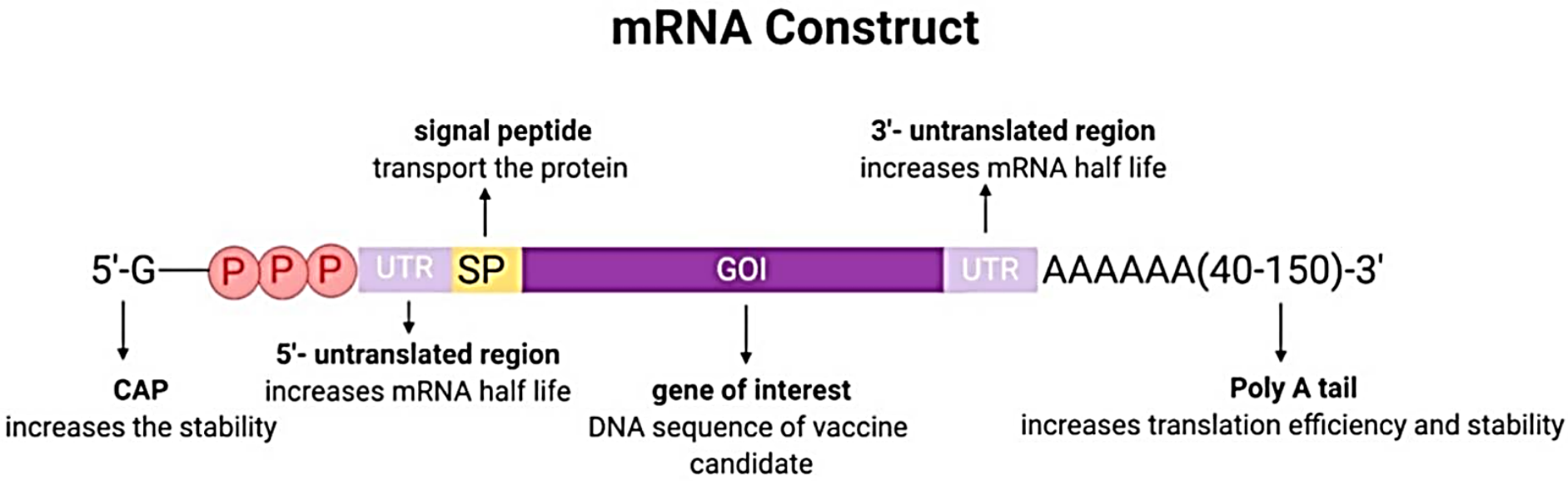
mRNA Vaccines Technology

mRNA Vaccine Technology Breakthroughs



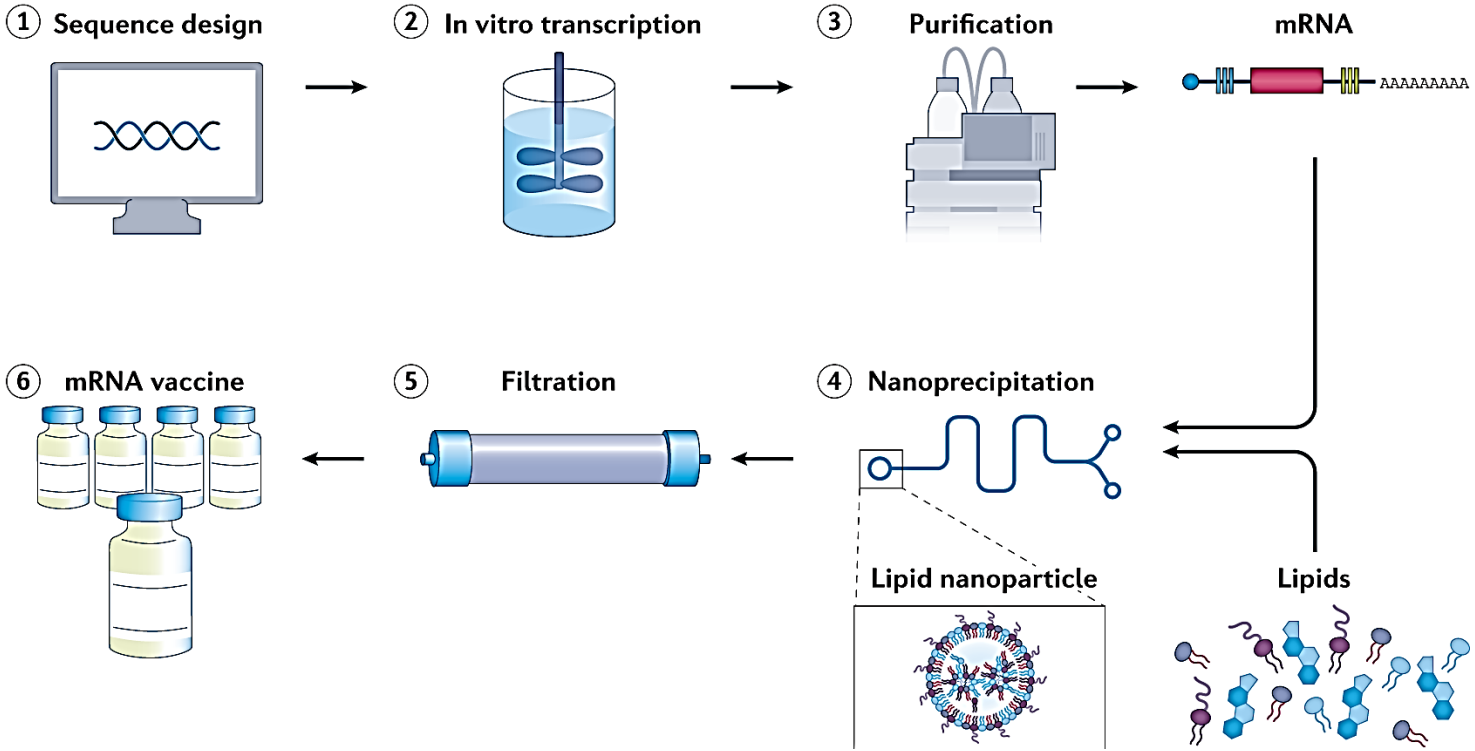


mRNA Construct Overview



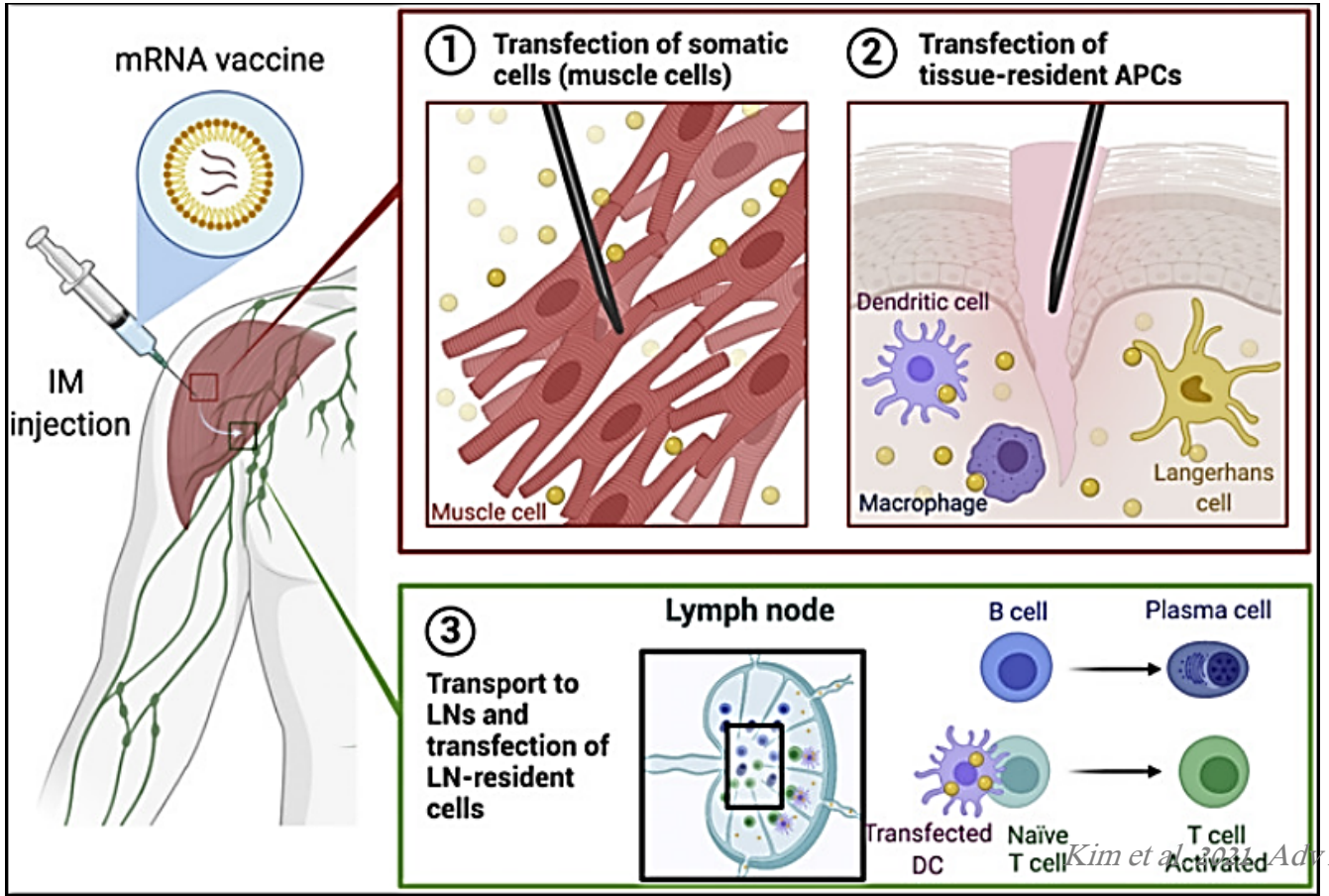
Jamous et al. 2023. Cureus

Manufacturing of mRNA Vaccines



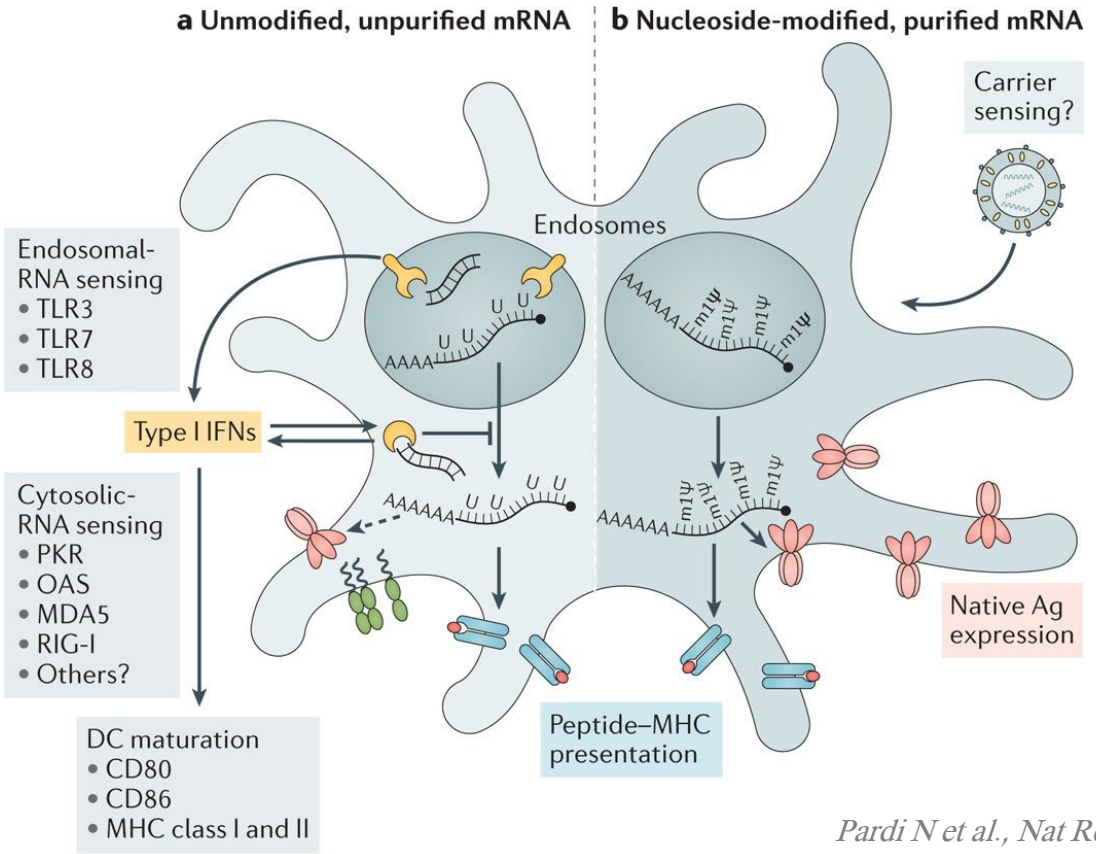
Chaudhary et al. 2021, Nature Reviews

Mechanism of mRNA Vaccines Immunity



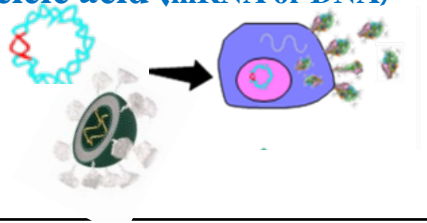
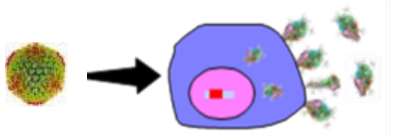
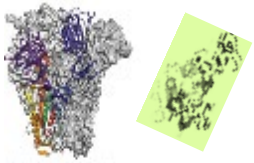
Kim et al. 2021, Adv Drug Deliv Rev

Innate Immune Sensing of mRNA Vaccines

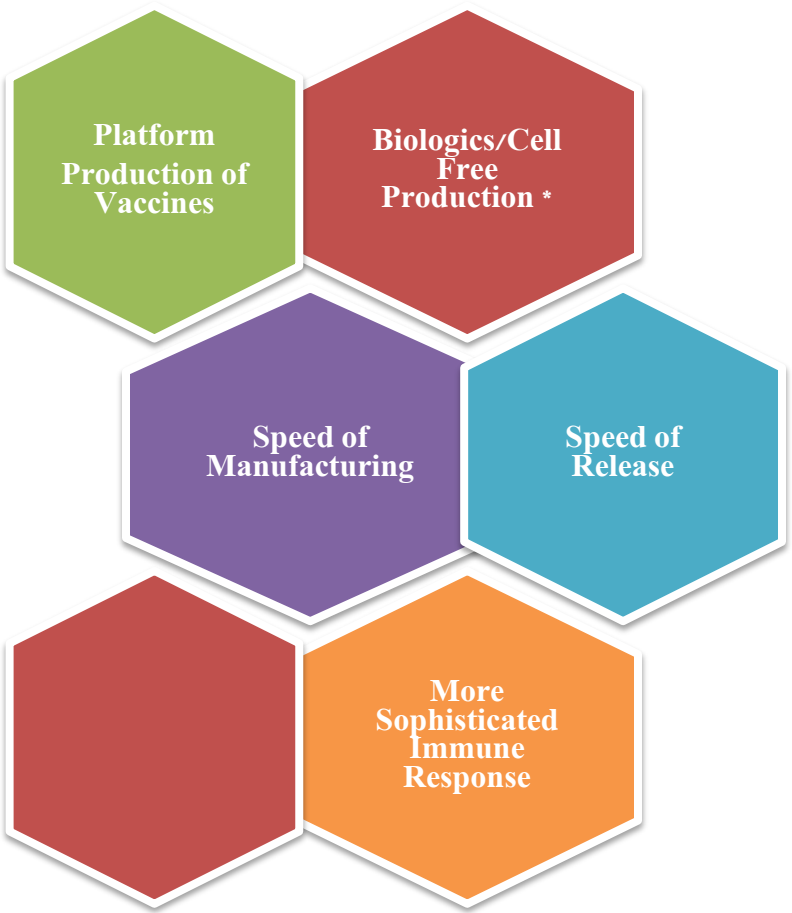


Pardi N et al., Nat Rev Drug Discov. 2018

Tailoring Immune Response by Vaccine Type

	Antibody	CD4	CD8	Pros	Additional Considerations
Nucleic acid (mRNA or DNA) 	+++	++	+	Rapid translation RNA can be modified No prior immunity	RNA-Requires formulation LNP DNA requires electroporation
Adenoviral Vectors 	+*	++	++	Most potent inducer CD8 T cells	*Influenced by prior immunity from natural adenovirus exposure Potential safety concern with Ad vectors
Protein + adjuvant 	+++	++	-	Gold standard for high antibody titers	Adjuvant is critical No CD8 T cells

Overall Advantages of mRNA Technology for Vaccines



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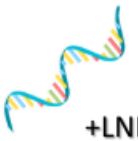
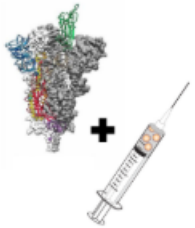
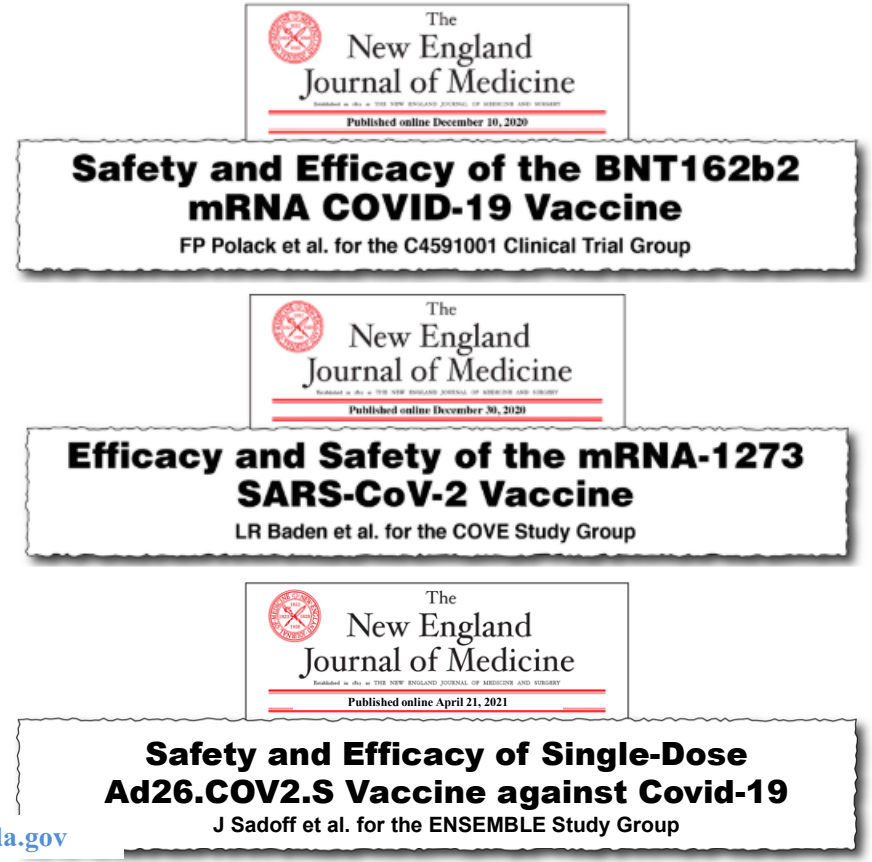
mRNA Vaccines Efficacy

COVID-19 Vaccines in US Government Portfolio

Nucleic acid	moderna	mRNA		→	VRC S2P Ag
	BIONTECH Pfizer	mRNA +LNP		→	VRC S2P Ag
Viral vector	AstraZeneca	Adenovirus vector		→	WT
	janssen	Adenovirus vector		→	VRC S2P Ag
Protein subunit	NOVAVAX Creating Tomorrow's Vaccines Today	Recombinant protein + adjuvant		→	VRC S2P Ag
	gsk SANOFI	Recombinant protein + adjuvant		→	VRC S2P Ag

First Vaccine Efficacy Results - Starting Nov 2020



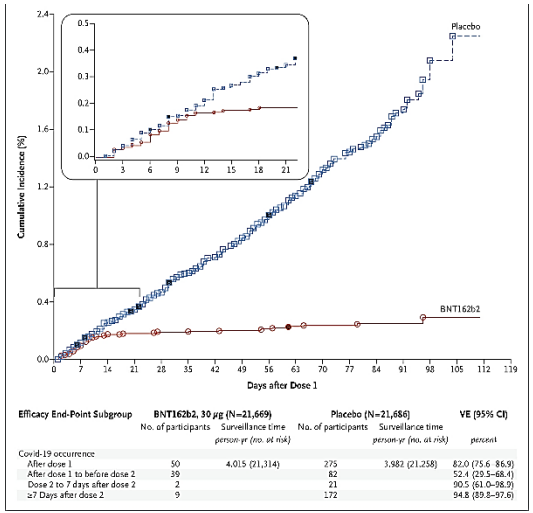
- 2-dose regimen of BNT162b2
- 43,548 participants randomized
- 95% Ve (95% CI 90.3; 97.6)
- EUA issued December 11, 2020
- FDA approval August 23, 2021

- 2-dose regimen of mRNA-1273
- 30,420 participants randomized
- 94% Ve (95% CI 89.3; 96.8)
- EUA issued Dec 18, 2020

- 1-dose regimen of Ad26.COV2.S
- 44,325 participants randomized
- 66.1% Ve (95% CI 55.0; 74.8) overall
- US: 72% Ve (95% CI 58.2; 81.7)
- EUA issued Feb 27, 2021

Efficacy Results: COVID-19 vaccines

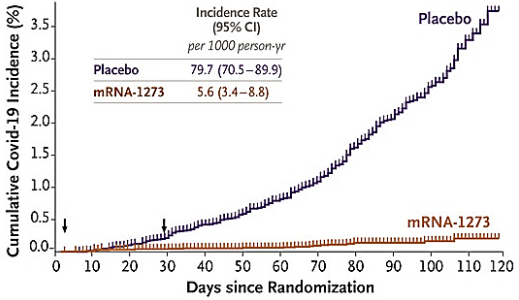
BIONTECH Pfizer



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	Surveillance time person-yr (no. at risk)	Placebo (N=21,686) No. of participants	Surveillance time person-yr (no. at risk)	VE (95% CI) percent
Covid-19 occurrence					
After dose 1	50	4,015 (21,314)	275	3,982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.3–97.6)

FP Polack et al. N Engl J Med 2020;383:2603-2615.

moderna



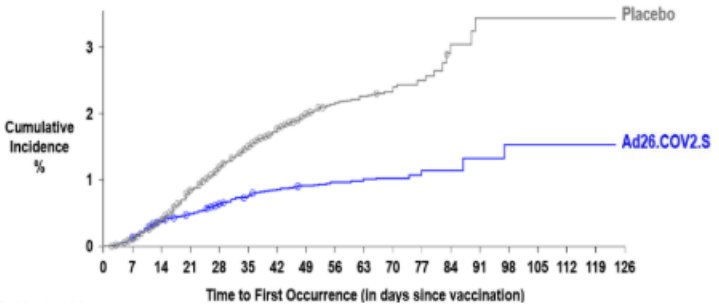
	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

Vaccine efficacy of 94.1% (95% CI, 89.3–96.8%; P<0.001)

LR Baden et al. N Engl J Med 2021;384:403-416.

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Cumulative Incidence of Molecularly Confirmed Moderate to Severe/Critical COVID-19 Cases with Onset at Least 1 Day after Vaccination up to Day 126, Full Analysis Set (Study COV3001)

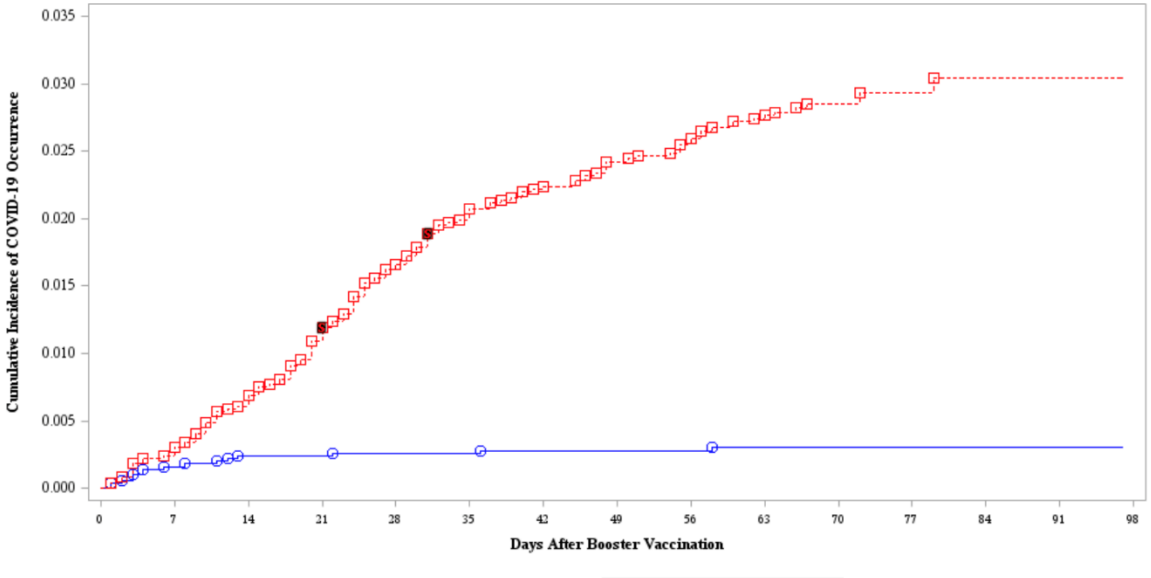


Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19
J Sadoff et al. for the ENSEMBLE Study Group

BNT162b2 mRNA COVID-19 Vaccine: Effectiveness of 2 vs 3 Doses

Cumulative Incidence Curve for First COVID-19 Occurrence After Booster Vaccination – All Available Efficacy Population

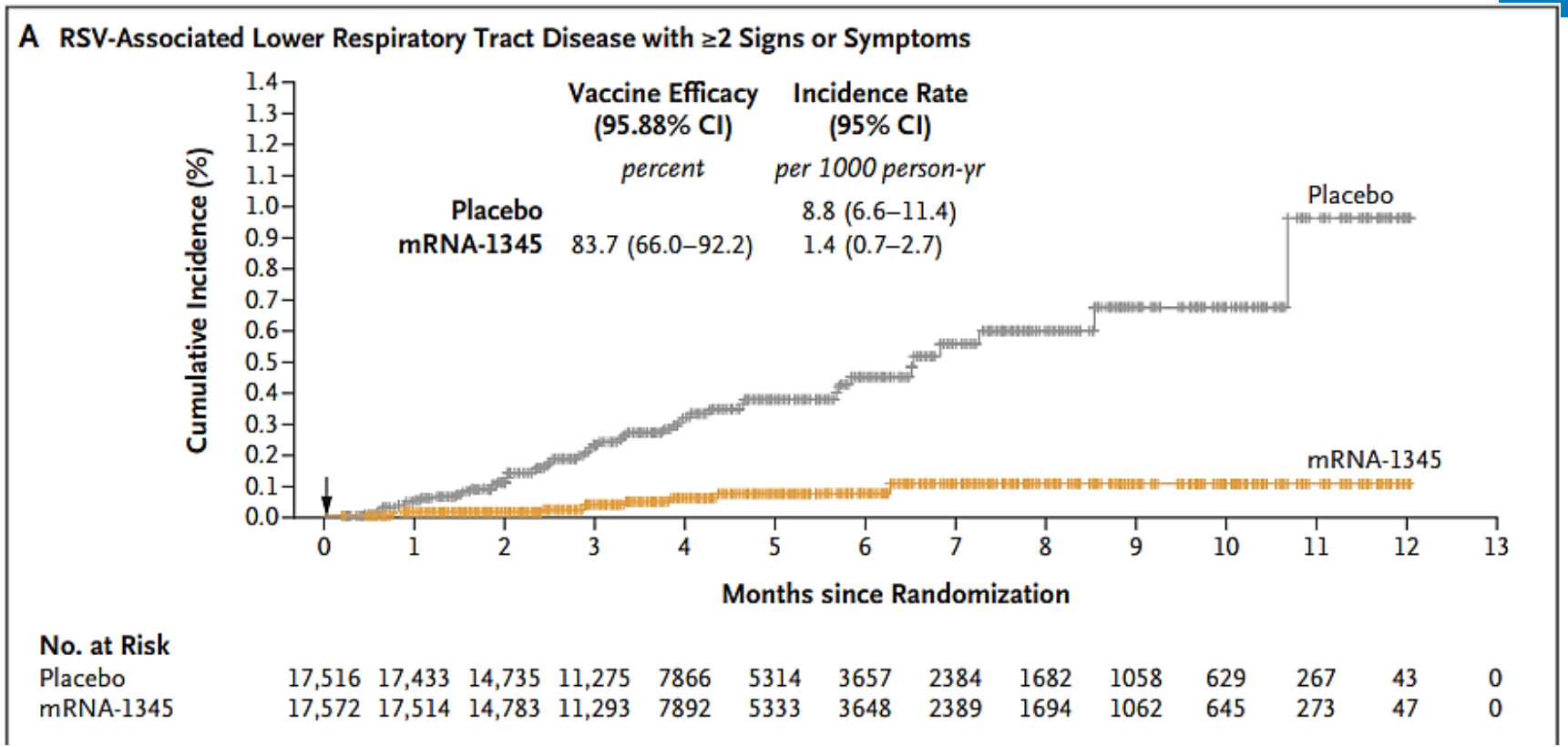
Curves diverge rapidly, starting even before 7 days after booster



Note the 2 severe cases met the FDA definition only, based only on SpO2 <93%. They were not hospitalized

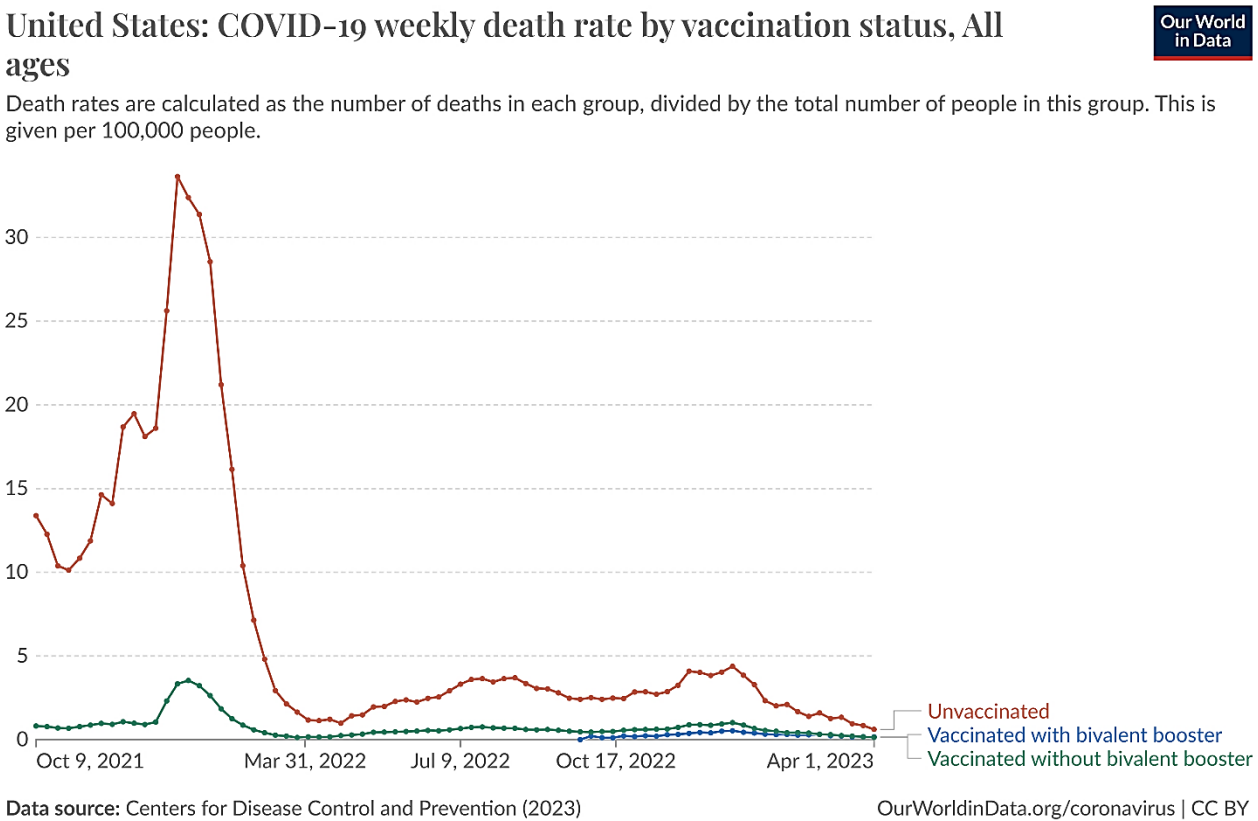
123 vs 6 cases, no hospitalizations

Other mRNA Vaccines Efficacy-RSV



Wilson et al. 2021, NEJM, 2023

COVID-19 Vaccine Effectiveness in the US



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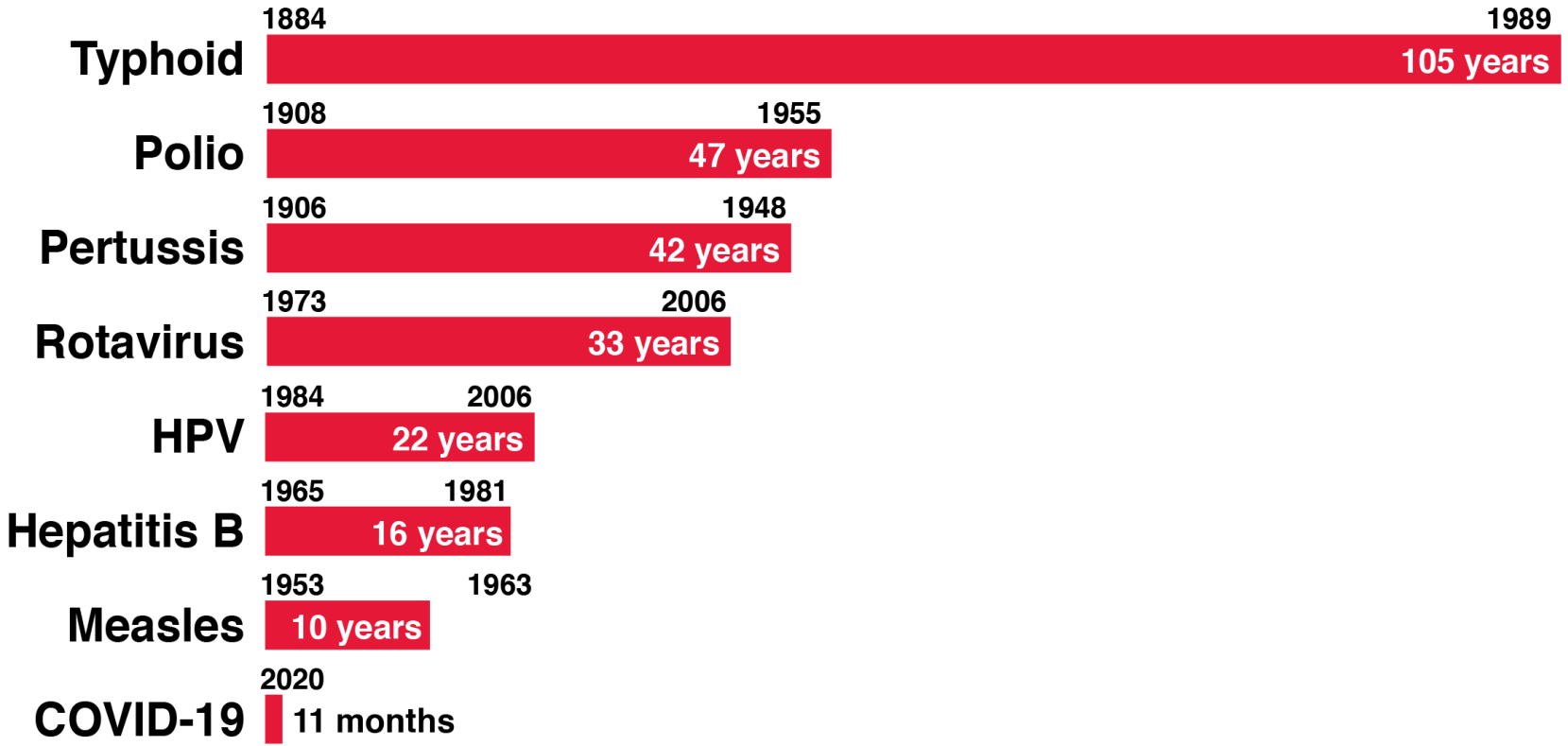
mRNA Vaccines Biodistribution and Safety

Safety-Biodistribution of mRNA Vaccines

- **mRNA** does not travel to the cell nucleus (as opposed to DNA)
- **Antigen** can be detected in blood as soon as 24 hours after vaccination, but detection is rarer after the second dose of vaccination
- Some studies show spike **antigen** detectable in germinal centers up to day 120 post vaccination
- **mRNA** vaccine is found in blood within hours and for approximately a month after vaccination
- **mRNA**-LNP is initially detected on the injection site and liver
- LNPs, mRNA, and/or protein products can be detected in various organs and tissues (including testes and breast milk (48 h); *animal and human data)
- Biodistribution seems to be correlated with type of LNP formulation

Pateevet al. Biomedicines 2023

Safety as a Priority #1: Time to Develop a Vaccine



twen discovery of microbiologic cause of selected infectious diseases and development of a vaccine.

Adapted from AVAC

First in Human SARS-CoV-2 Vaccine: mRNA-1273

PREPAREDNESS

RESPONSE

moderna

VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

NIH NIAID

BARDA

FDA

THE UNIVERSITY OF TEXAS AT AUSTIN

CEPI

~ 10 years

Jan-5: 5 days

March 16: 65 days

May 29: 139 days

July 27: 198 days

November 30: 11 months

Studies Leading to mRNA-1273 Antigen Design and Selection

McLellan, Graham, et al

Kirchdoerfer, Ward, et al

2008 — Response to CoV Outbreaks

2013 — RSV FP stabilization

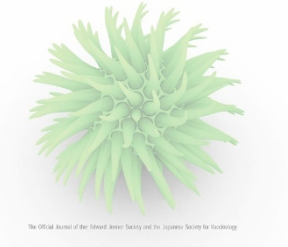
2016 — Initial Collaboration

2016 — CoV FP stabilization

2017 — PoC for CoV Spike immunization

2019 — Preparedness Pilot Program And PoC for mRNA vaccine development

Vaccine



Ledgerwood, Graham, et al

Pallesen, McLellan, et al

Safety as a Priority #2: FI-RSV Vaccine-Enhanced Disease

Vaccine	n*	Infected (%)	Hospitalized (%)**	Deaths***
Vaccine	31	20 (65)	16 (80)	2
Placebo	40	21 (53)	1 (5)	0

* 1 injection (n=2); 2 injections (n=8); 3 injections (n=21)

** In unpublished 1962/3 trial - 21/54 infected; 10/21 hospitalized

*** 14 and 16 mo. of age; 3 injections starting at 2 and 5 mo. of age. Both had bacterial pneumonia complicating RSV

Kim et al. Am J Epidemiol 1969; 89: 422

"At Risk" USG Vaccine Development in Context of the Pandemic Response

✓ **Financial Risk**

- Preparation of Phase 3 sites prior to finalizing Phase 1 and Phase 2 data
- Large-scale production of vaccine commercial lots prior to determination of efficacy

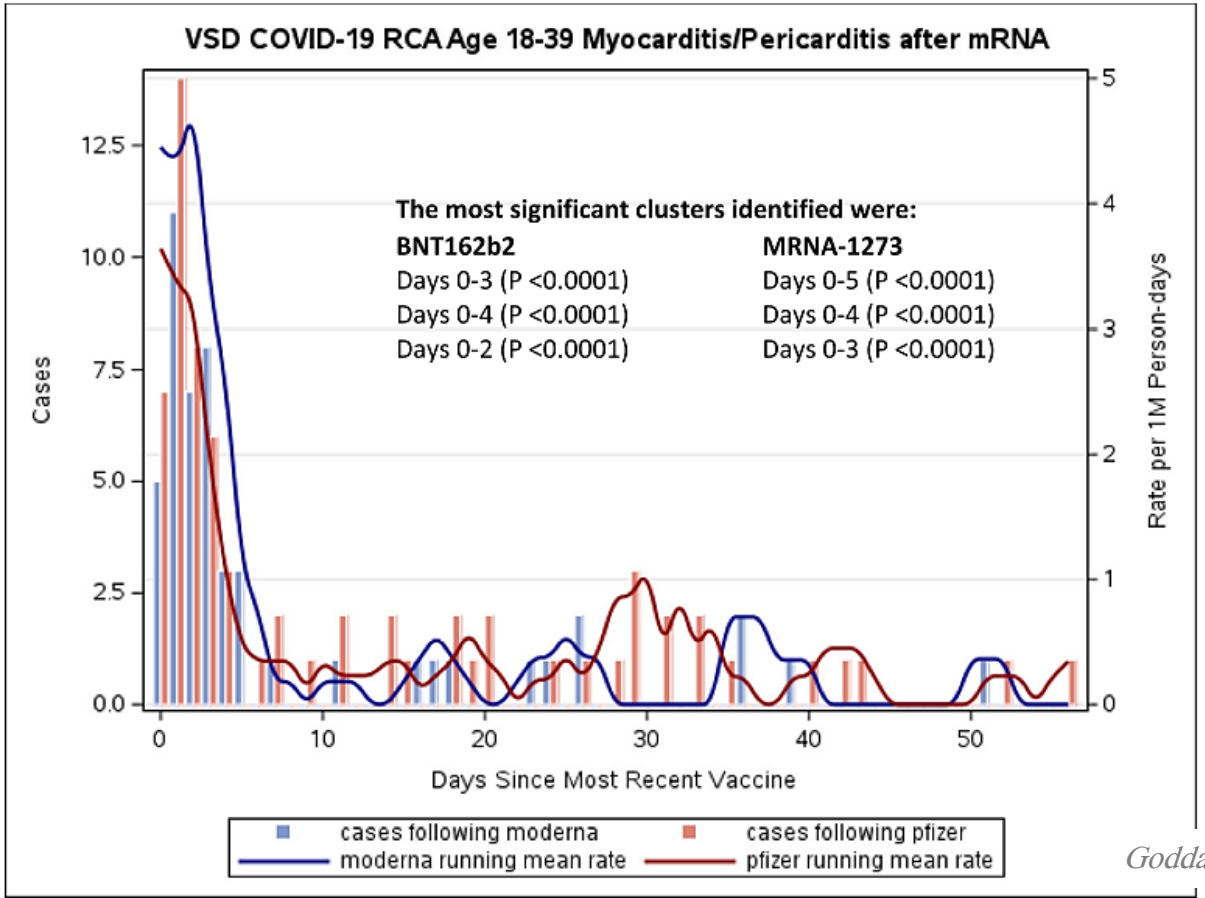
X **Safety Risk**

- No compromise on safety (other than shorter follow up by EUA determination)
- Standard Phase 1 and Phase 2 protocols
- Intensify safety considerations in Phase 3

X **Scientific Risk**

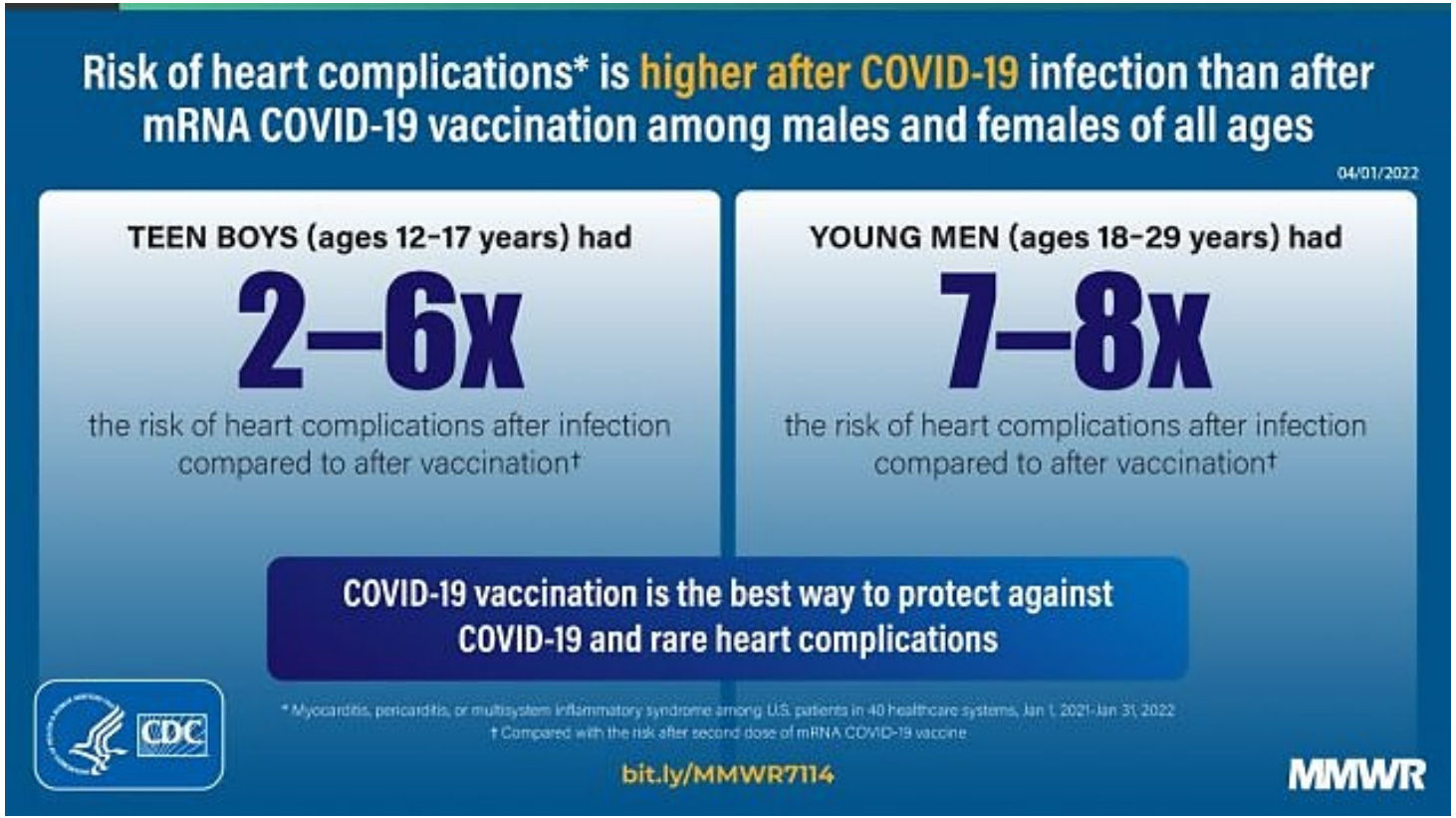
- No compromise of scientific integrity of the studies, vaccine design

Vaccine Benefit/Risk Analysis: Myocarditis and Pericarditis



Goddard et al. Vaccine 2022

Safety-Other Risks to Keep in Mind



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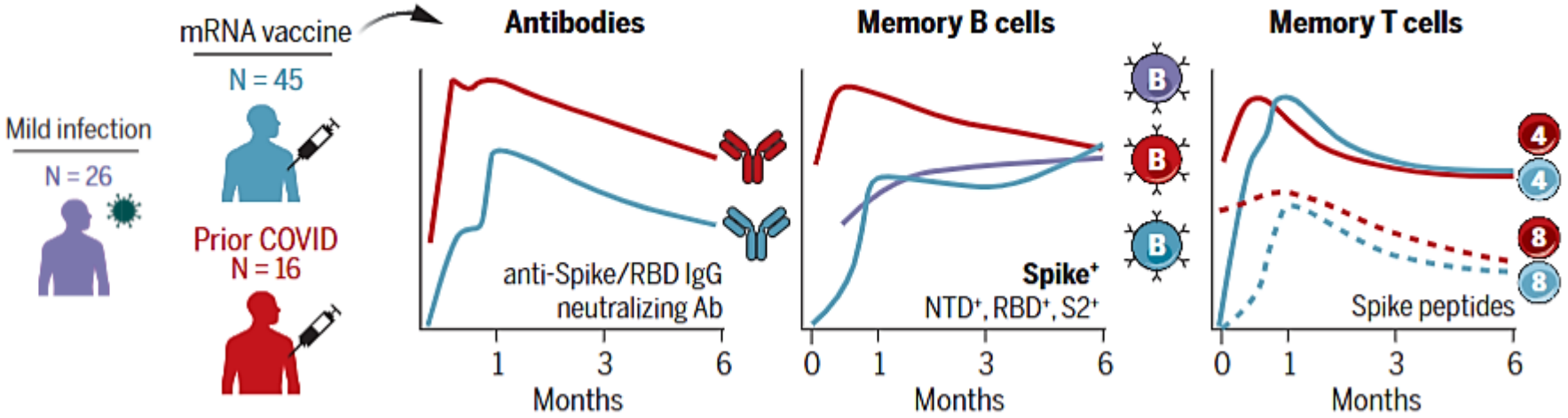
mRNA Vaccines Durability and Formula Updates

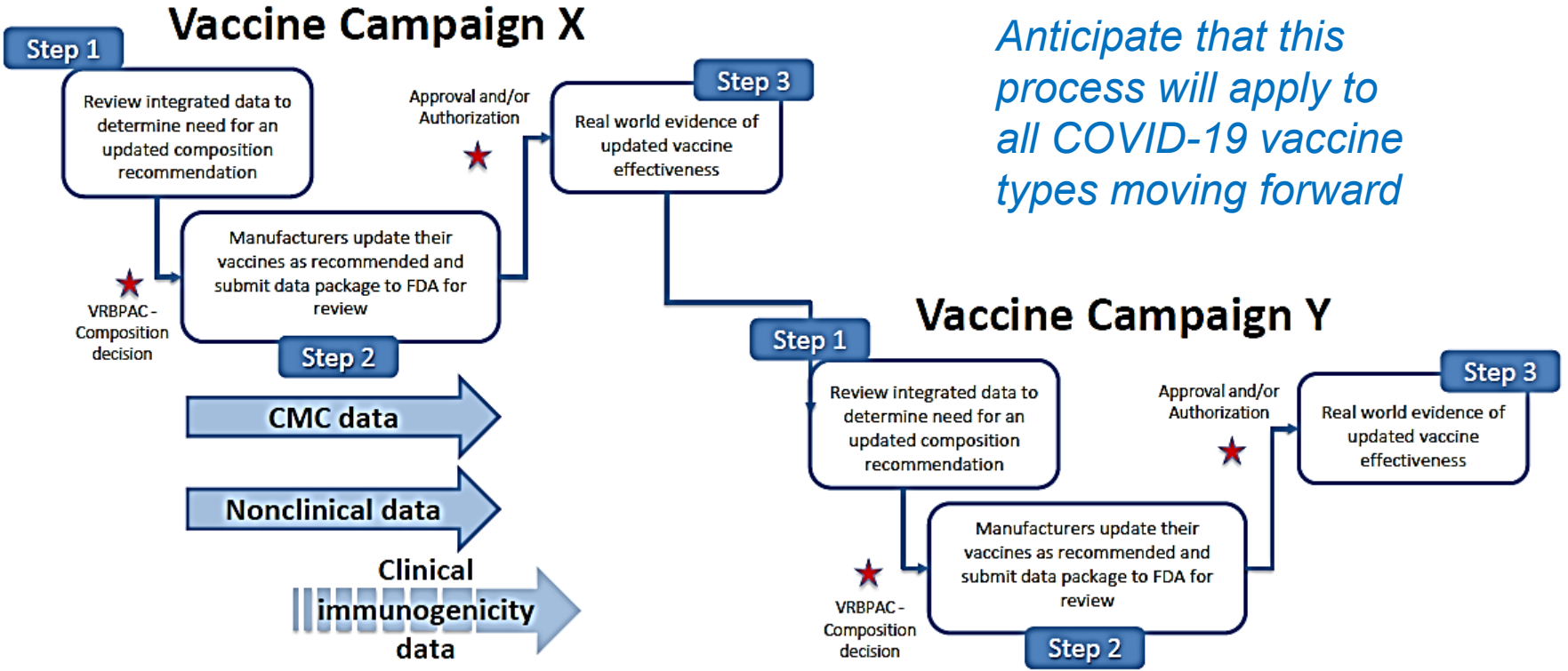
mRNA Vaccine Durability

- Is the immunity to mRNA-expressed antigens durable?
  - Virus evolution vs durable immune response
  - COVID-19 natural infection vs mRNA Vaccine immunity durability
  - How does seroprevalence affect durability?



Goel et al. Science 2021

Approach to Updating Vaccine Composition- High Level Overview

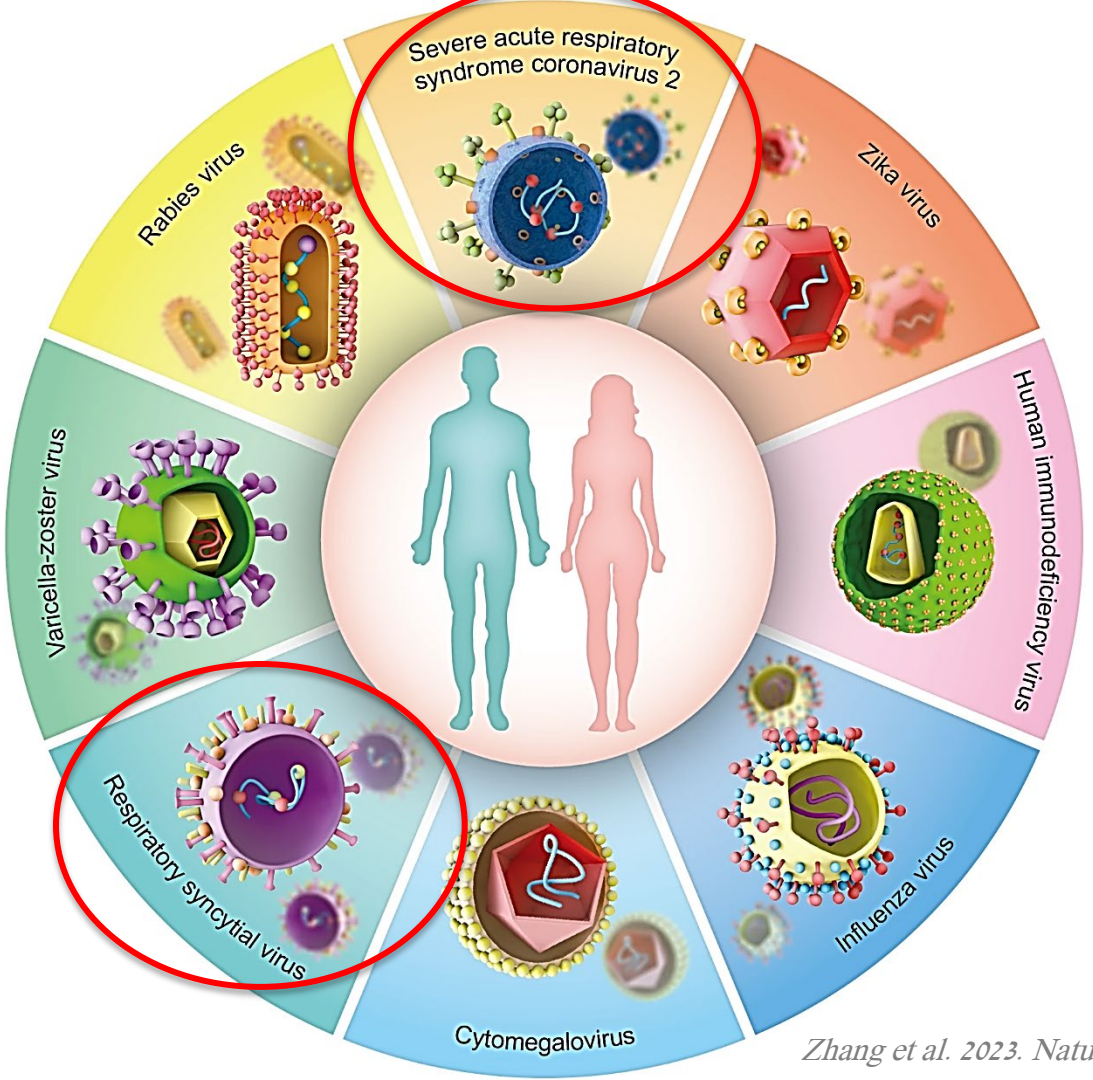


Anticipate that this process will apply to all COVID-19 vaccine types moving forward

FDA's Role for COVID Vaccines, including mRNA COVID Vaccines

- Strain selection and reference standard production
- Lot release
- Evaluation of safety and efficacy
- Post-market surveillance
- Advancing vaccine technology
- Helping to ensure public confidence
  - **Vaccination saves lives**

Approved mRNA Vaccines and mRNA Vaccines in Different Stages of Development



Zhang et al. 2023. Nature

Summary and Conclusions

- mRNA technology was being developed for decades before the emergence of SARS-CoV-2
- mRNA is an effective method to deliver an antigen; Careful vaccine design and antigen consideration is still needed
- mRNA vaccines have been demonstrated to be safe and effective against COVID-19, many other mRNA vaccines are in the pipeline, including a recently approved RSV mRNA vaccine
- The ability of the mRNA platform to induce durable immunity is incompletely understood and still being studied
- mRNA "platform" advantages and cell-free manufacturing make it the ideal system for rapid response and updates

Challenge Question #1

mRNA vaccines are the newest and most effective vaccines on the market.

TRUE

FALSE

Challenge Question #2

mRNA vaccines have the advantage of eliciting CD8+ immune responses through intracellular delivery of the target antigen

TRUE

FALSE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