



**U.S. FOOD & DRUG  
ADMINISTRATION**

# mRNA Vaccines

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**FDA Clinical Investigator Training Course**

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# FDA Disclaimer



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

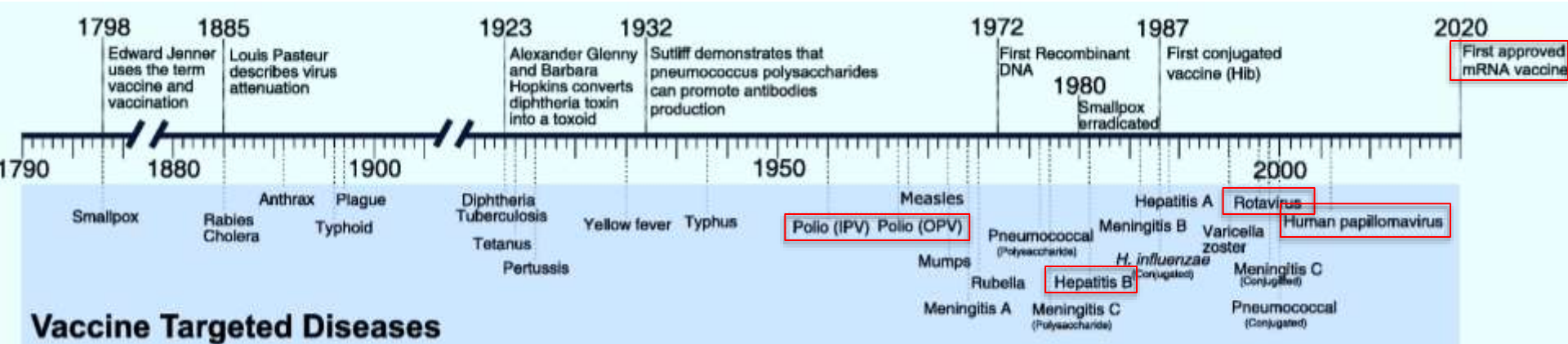
[N.B. No disclosures or conflicts of interest]

# At a Glance

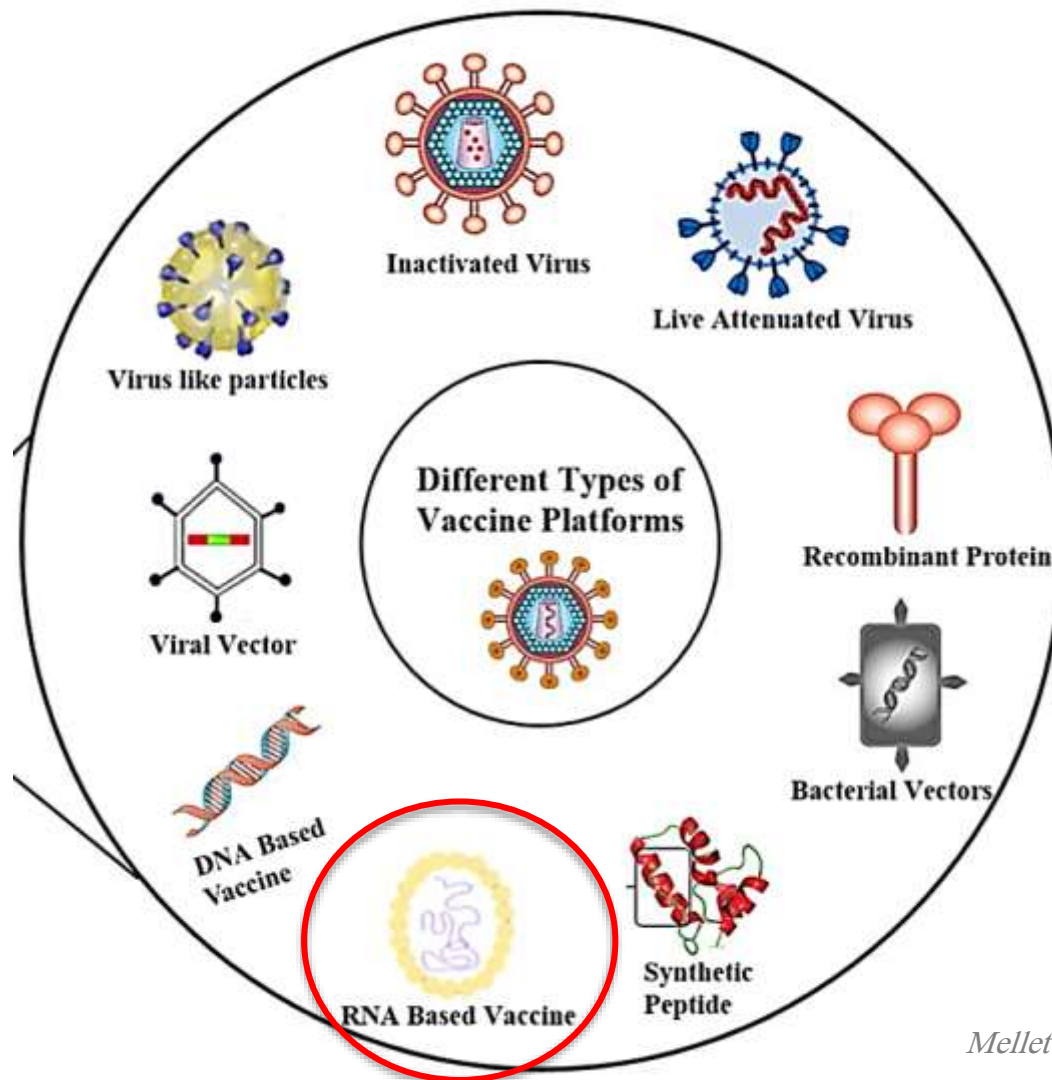


- Introduction
- mRNA Vaccines Technology
- mRNA Vaccines Efficacy
- mRNA Vaccines Biodistribution and Safety
- mRNA Vaccines Durability and Formula Updates
- Approved mRNA Vaccines and mRNA Vaccines in Different Stages of Development
- Summary and Conclusions
- Challenge Questions

# Vaccination Milestones

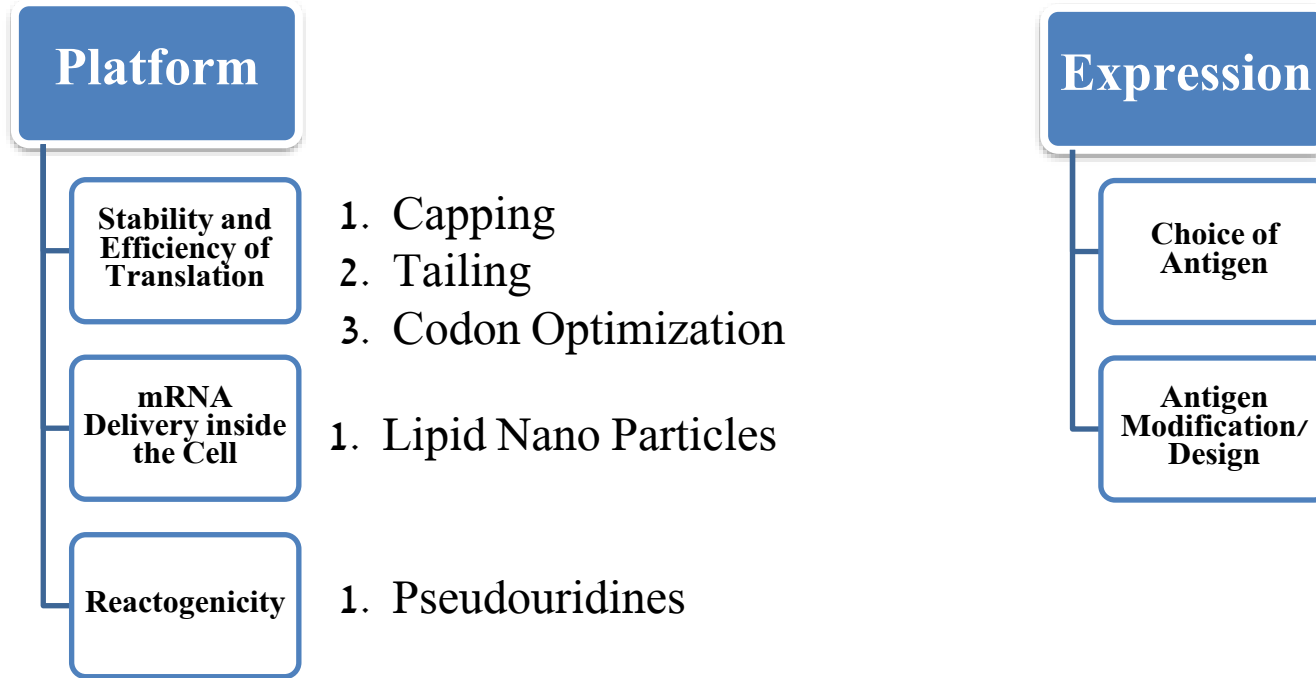


# Vaccine Types and Platforms



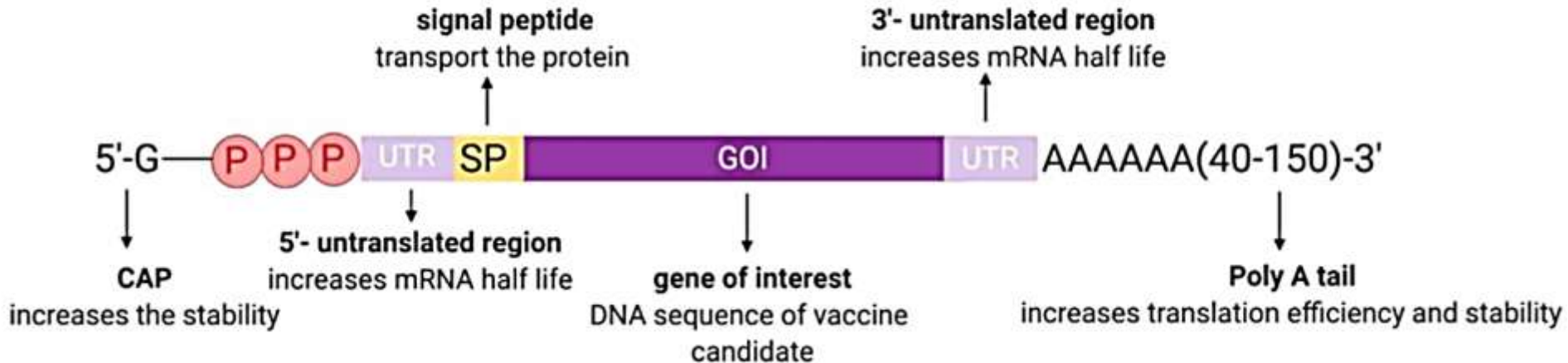
# mRNA Vaccines Technology

# mRNA Vaccine Technology Breakthroughs



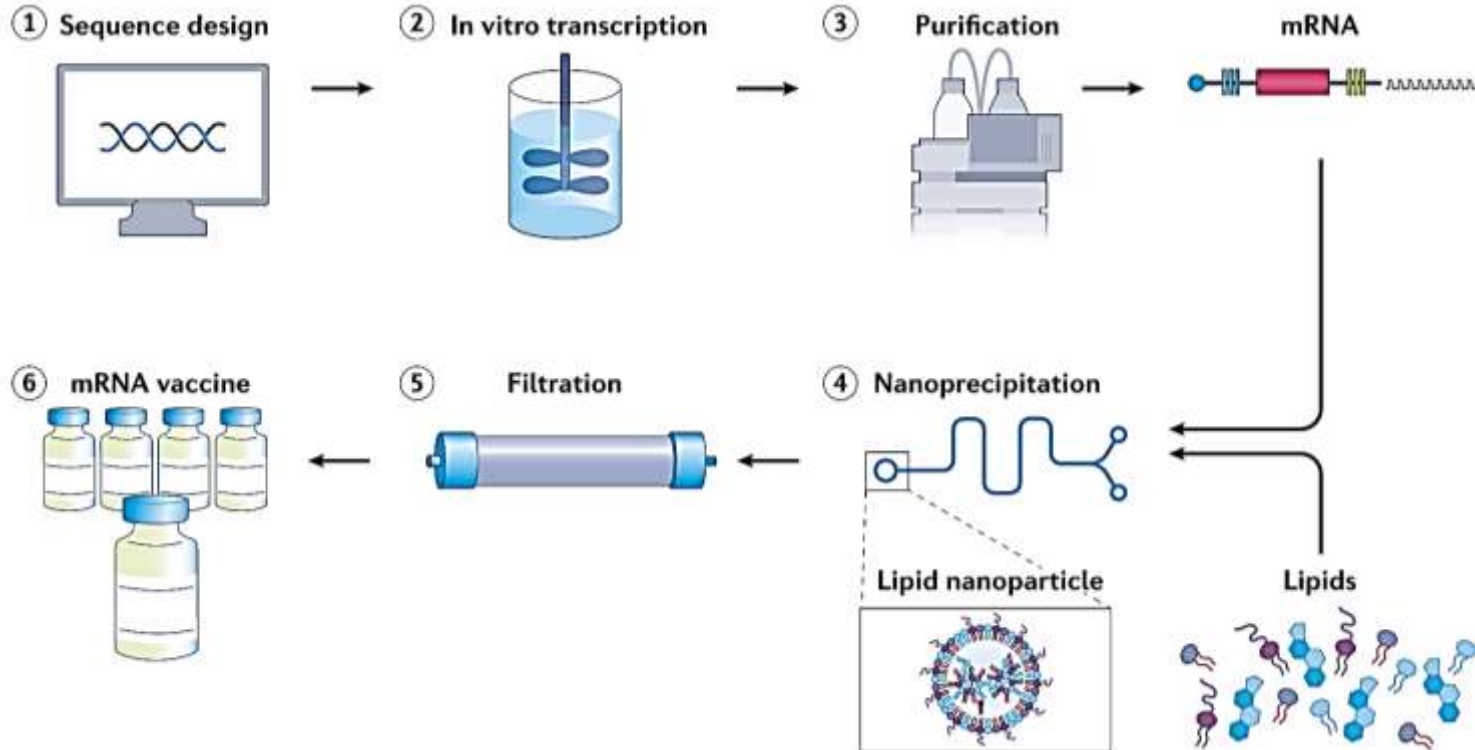
# mRNA Construct Overview

## mRNA Construct

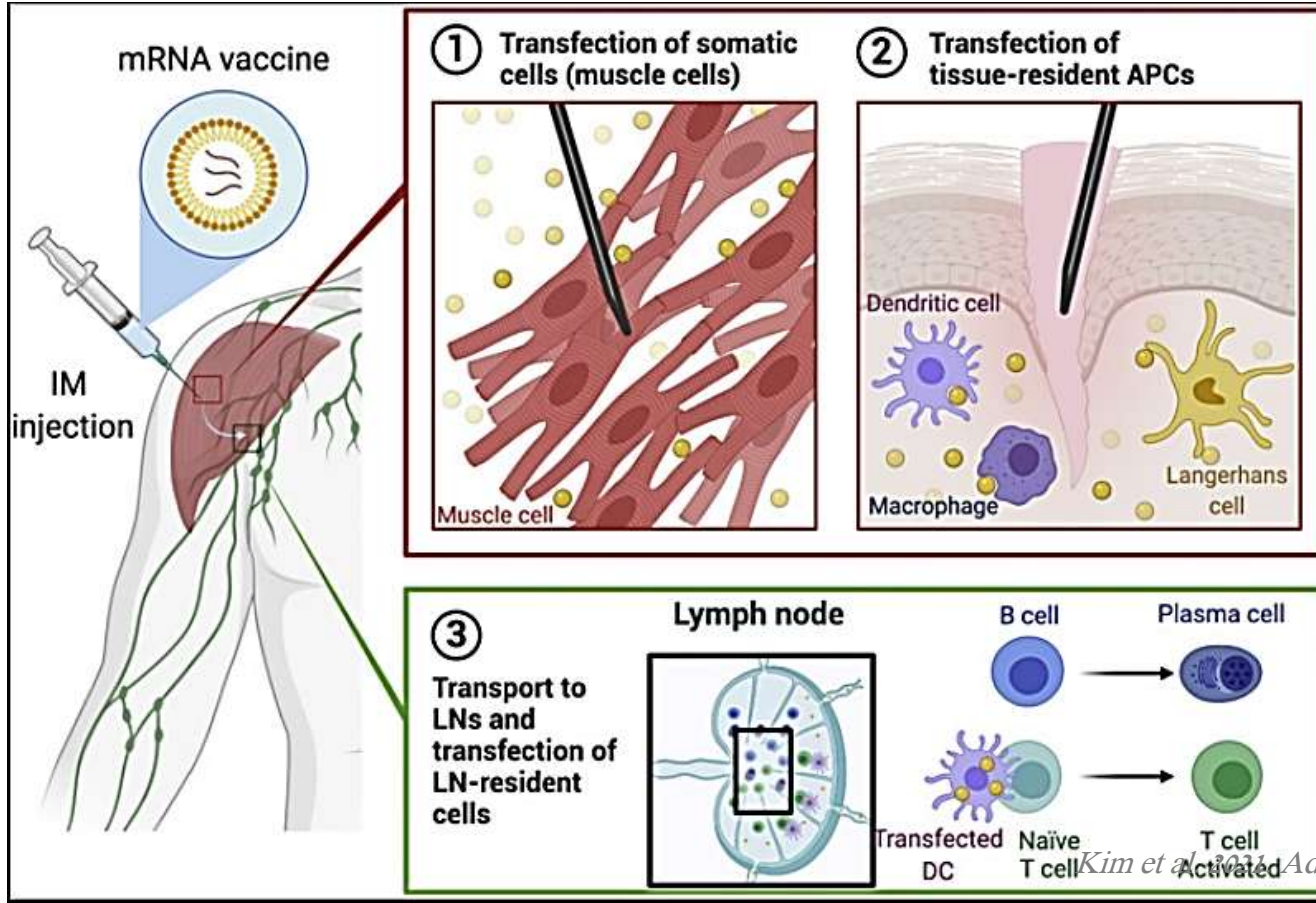




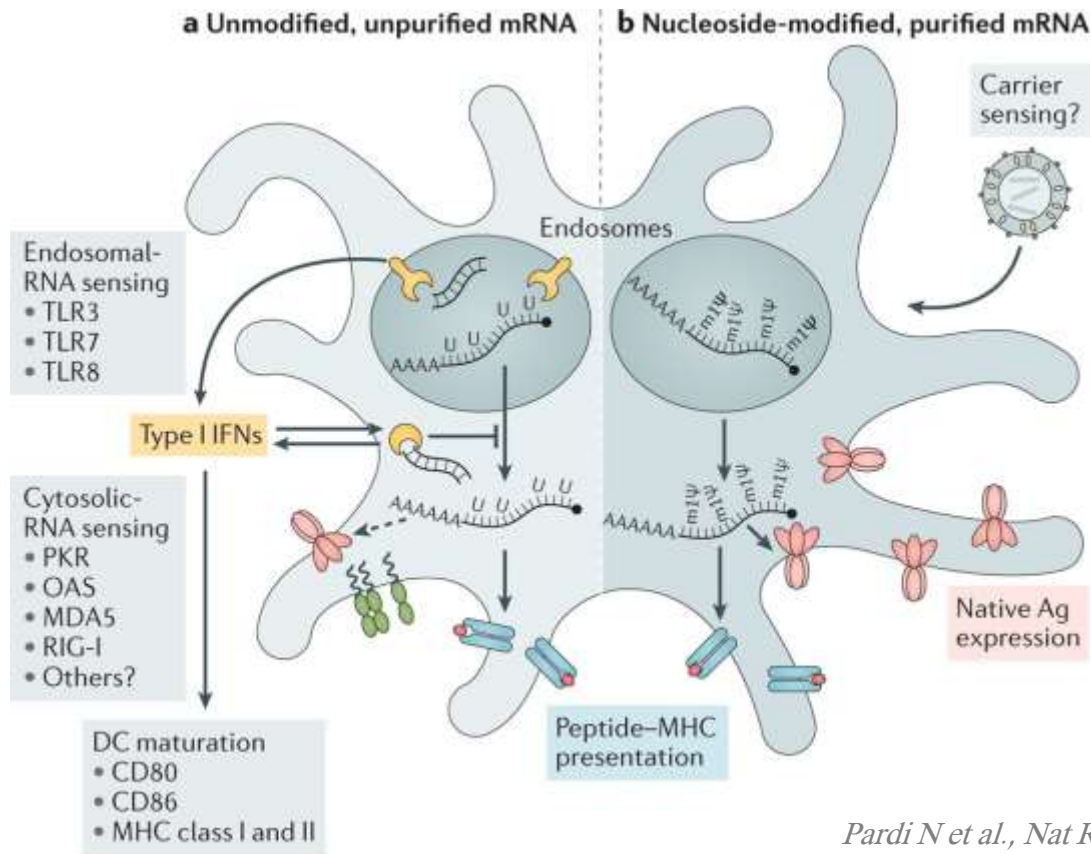
# Manufacturing of mRNA Vaccines



# Mechanism of mRNA Vaccines Immunity

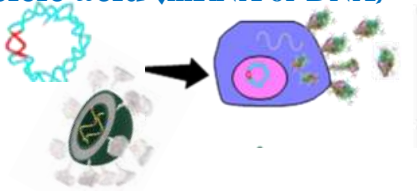
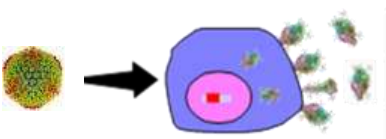
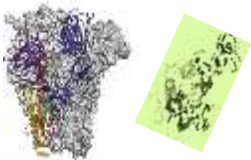


# Innate Immune Sensing of mRNA Vaccines

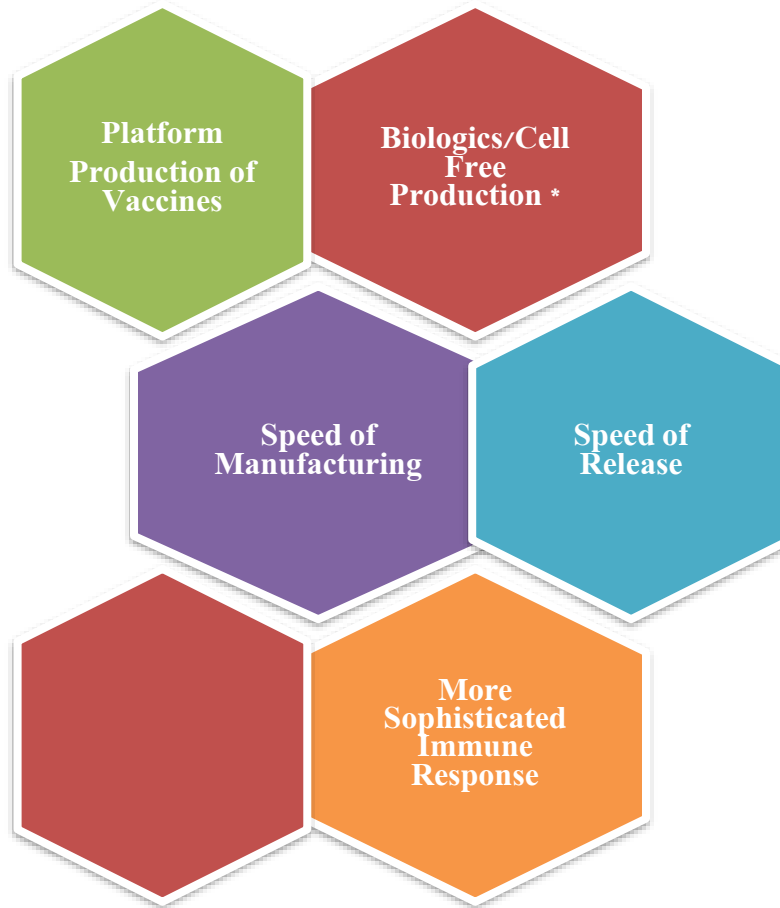


# Tailoring Immune Response by Vaccine Type



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

# Overall Advantages of mRNA Technology for Vaccines



# mRNA Vaccines Efficacy




# COVID-19 Vaccines in US Government Portfolio






**Nucleic acid**

	mRNA		→	VRC S2P Ag
	mRNA		+LNP	→

**Viral vector**

	Adenovirus vector		→	WT
	Adenovirus vector		→	VRC S2P Ag

**Protein subunit**

	Recombinant protein + adjuvant		→	VRC S2P Ag
	Recombinant protein + adjuvant		→	VRC S2P Ag

# First Vaccine Efficacy Results - Starting Nov 2020



## Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine

FP Polack et al. for the C4591001 Clinical Trial Group



## Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

LR Baden et al. for the COVE Study Group



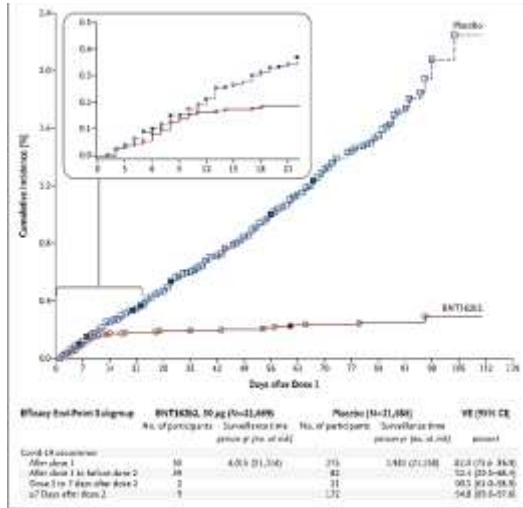
## Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

J Sadoff et al. for the ENSEMBLE Study Group

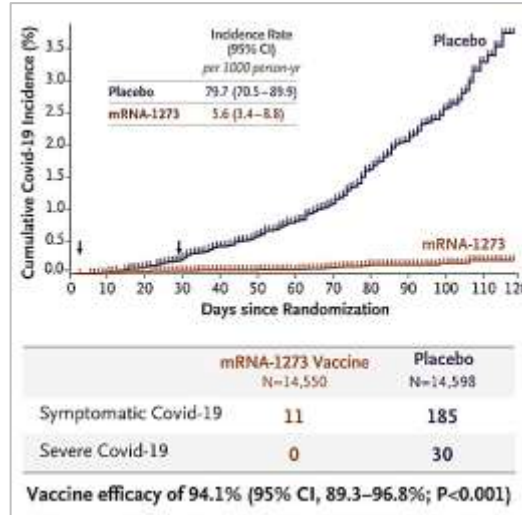
- 2-dose regimen of BNT162b2
- 43,548 participants randomized
- **95% Ve** (95% CI 90.3; 97.6)
- EUA issued December 11, 2020
- FDA approval August 23, 2021
- 2-dose regimen of mRNA-1273
- 30,420 participants randomized
- **94% Ve** (95% CI 89.3; 96.8)
- EUA issued Dec 18, 2020
- 1-dose regimen of Ad26.COV2.S
- 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



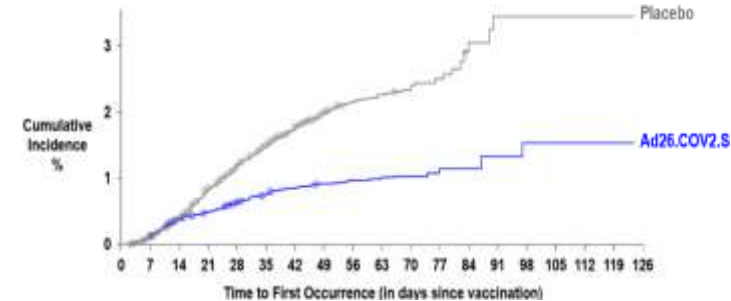
FP Polack et al. N Engl J Med 2020;383:2603-2615.



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



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)

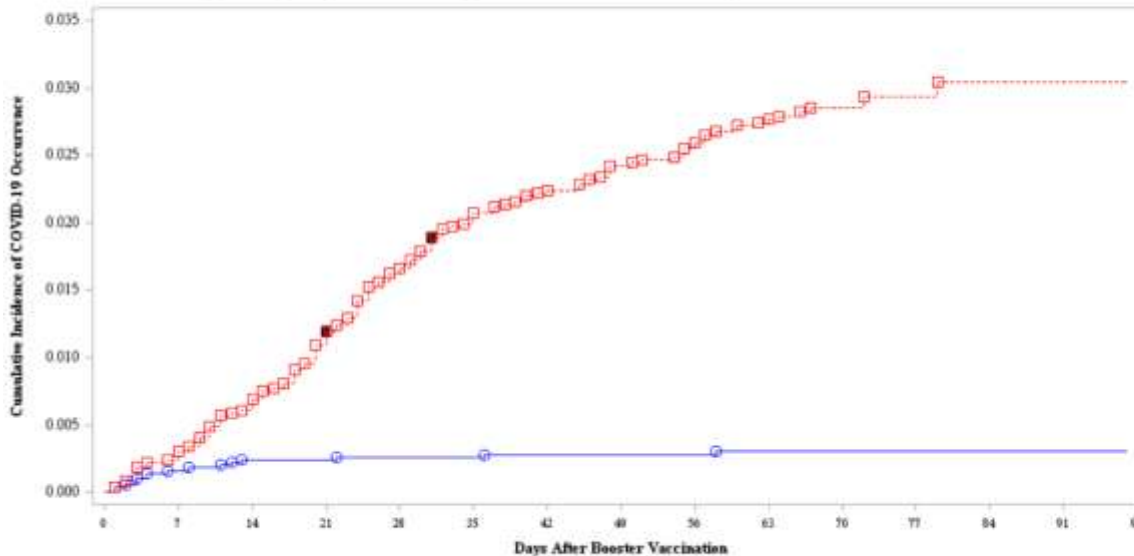


Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19  
J Sadoff et al. for the ENSEMBLE Study Group

# 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

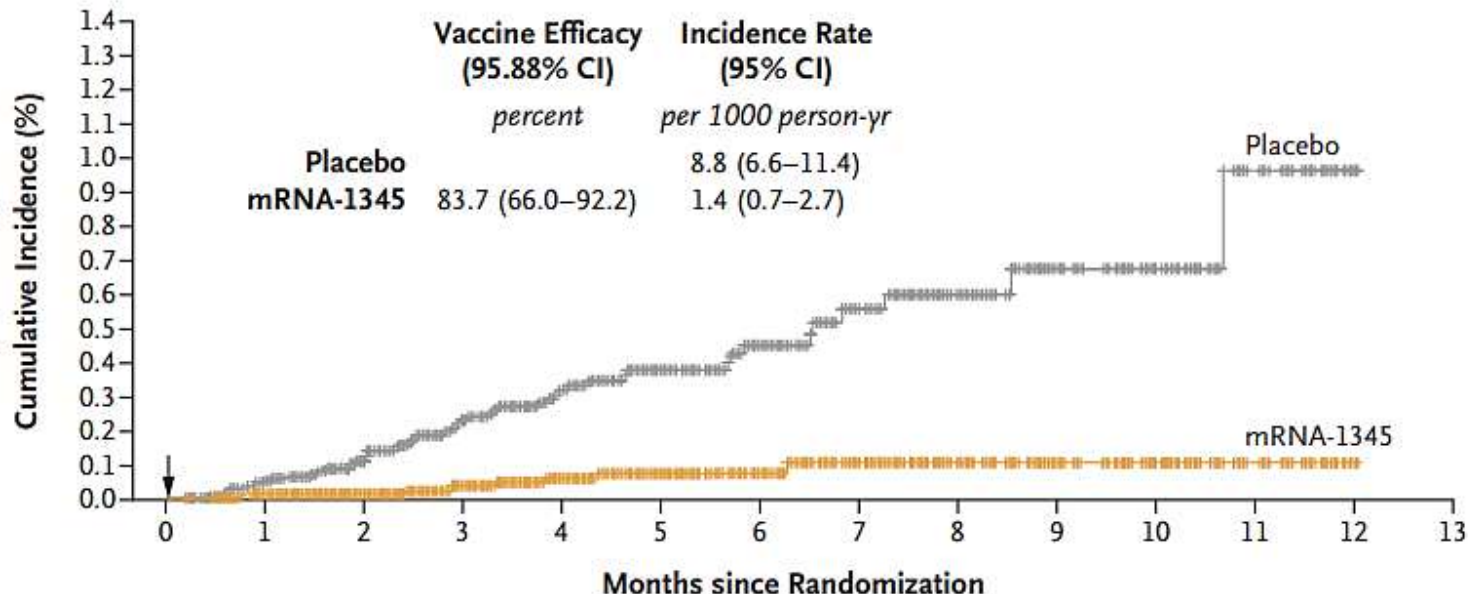


Note the 2 severe cases met the FDA definition only, based only on SpO2 <93%. They were not hospitalized

**123 vs 6 cases, no hospitalizations**

# Other mRNA Vaccines Efficacy-RSV

## A RSV-Associated Lower Respiratory Tract Disease with $\geq 2$ Signs or Symptoms



### No. at Risk

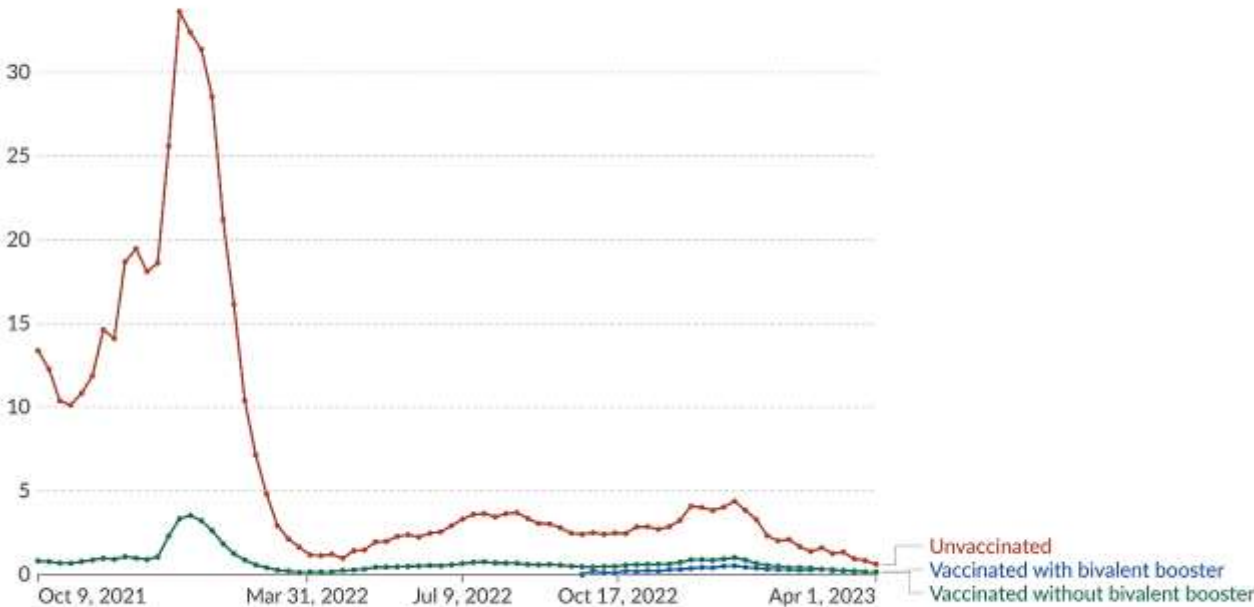
Placebo	17,516	17,433	14,735	11,275	7866	5314	3657	2384	1682	1058	629	267	43	0
mRNA-1345	17,572	17,514	14,783	11,293	7892	5333	3648	2389	1694	1062	645	273	47	0

# COVID-19 Vaccine Effectiveness in the US

## United States: COVID-19 weekly death rate by vaccination status, All ages



Death rates are calculated as the number of deaths in each group, divided by the total number of people in this group. This is given per 100,000 people.



Data source: Centers for Disease Control and Prevention (2023)

OurWorldinData.org/coronavirus | CC BY

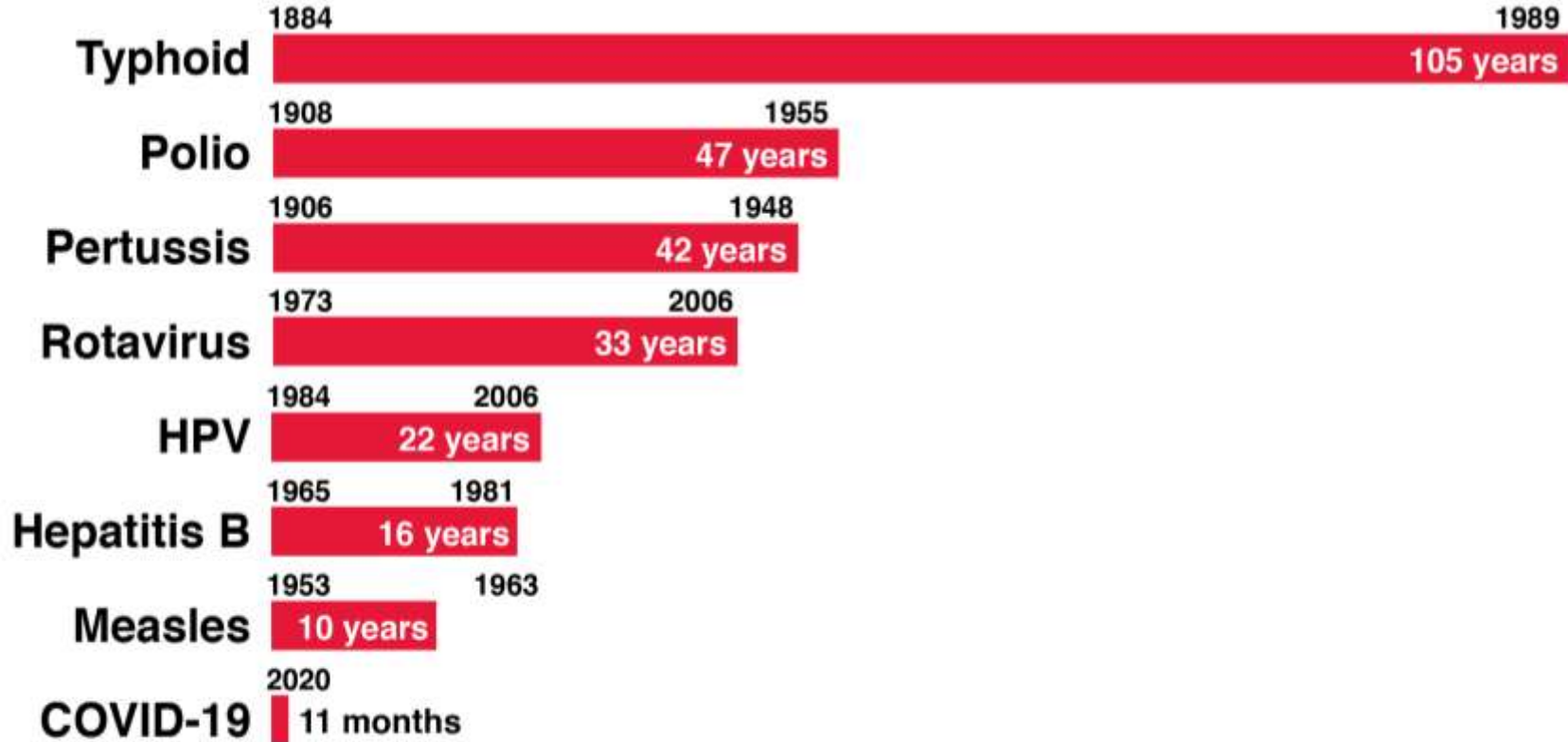
Note: The mortality rate for the 'All ages' group is age-standardized to account for the different vaccination rates of older and younger people.

# **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

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



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

FDA

PREPAREDNESS

RESPONSE

moderna



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



UNC  
UNIVERSITY OF NORTH CAROLINA  
SCHOOL OF MEDICINE



CEPI

Virus  
Sequence  
Released

Preclinical  
and GMP  
Production

Phase I

Phase 2

Phase 3

EUA  
Submission

Jan-5: 5 days

March 16: 65 days

May 29: 139 days

July 27: 198 days

November 30: 11 months

~ 10 years



# Studies Leading to mRNA-1273 Antigen Design and Selection



Response to  
CoV  
Outbreaks

*McLellan, Graham, et al*



Initial  
Collaboration

*Kirchdoerfer, Ward, et al*



PoC for CoV  
Spike  
immunization



2008

2013

2016

2016

2017

2019

Vaccine



RSV FP  
stabilization



CoV FP  
stabilization



Preparedness  
Pilot Program  
And PoC for  
mRNA  
vaccine  
development

## 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

# “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

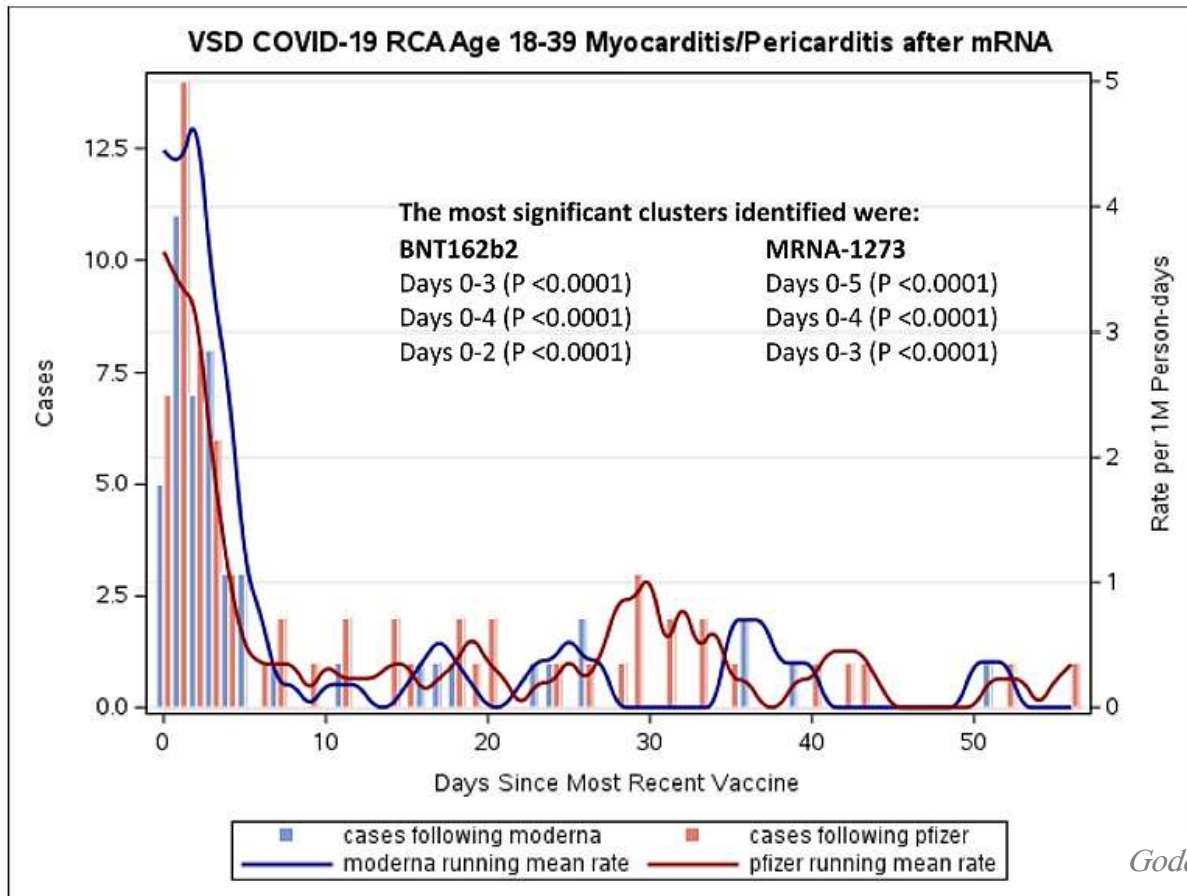
## X Safety Risk

- 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



# Safety-Other Risks to Keep in Mind

Risk of heart complications\* is **higher after COVID-19** infection than after mRNA COVID-19 vaccination among males and females of all ages

04/01/2022

TEEN BOYS (ages 12–17 years) had

**2–6x**

the risk of heart complications after infection  
compared to after vaccination†

YOUNG MEN (ages 18–29 years) had

**7–8x**

the risk of heart complications after infection  
compared to after vaccination†

**COVID-19 vaccination is the best way to protect against  
COVID-19 and rare heart complications**



\* Myocarditis, pericarditis, or multisystem inflammatory syndrome among U.S. patients in 40 healthcare systems, Jan 1, 2021–Jan 31, 2022

† Compared with the risk after second dose of mRNA COVID-19 vaccine

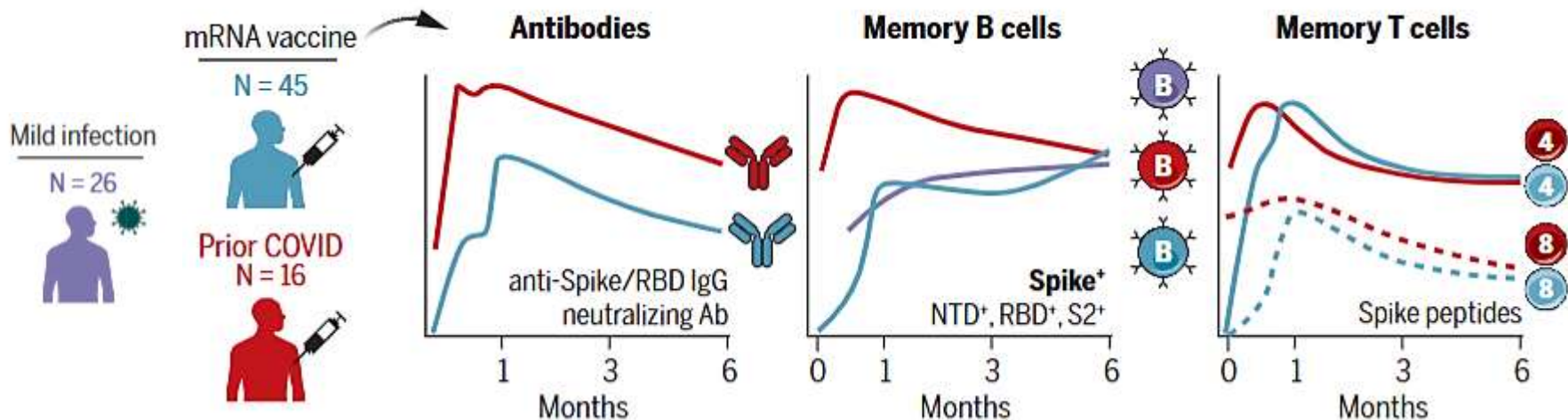
[bit.ly/MMWR7114](https://bit.ly/MMWR7114)

**MMWR**

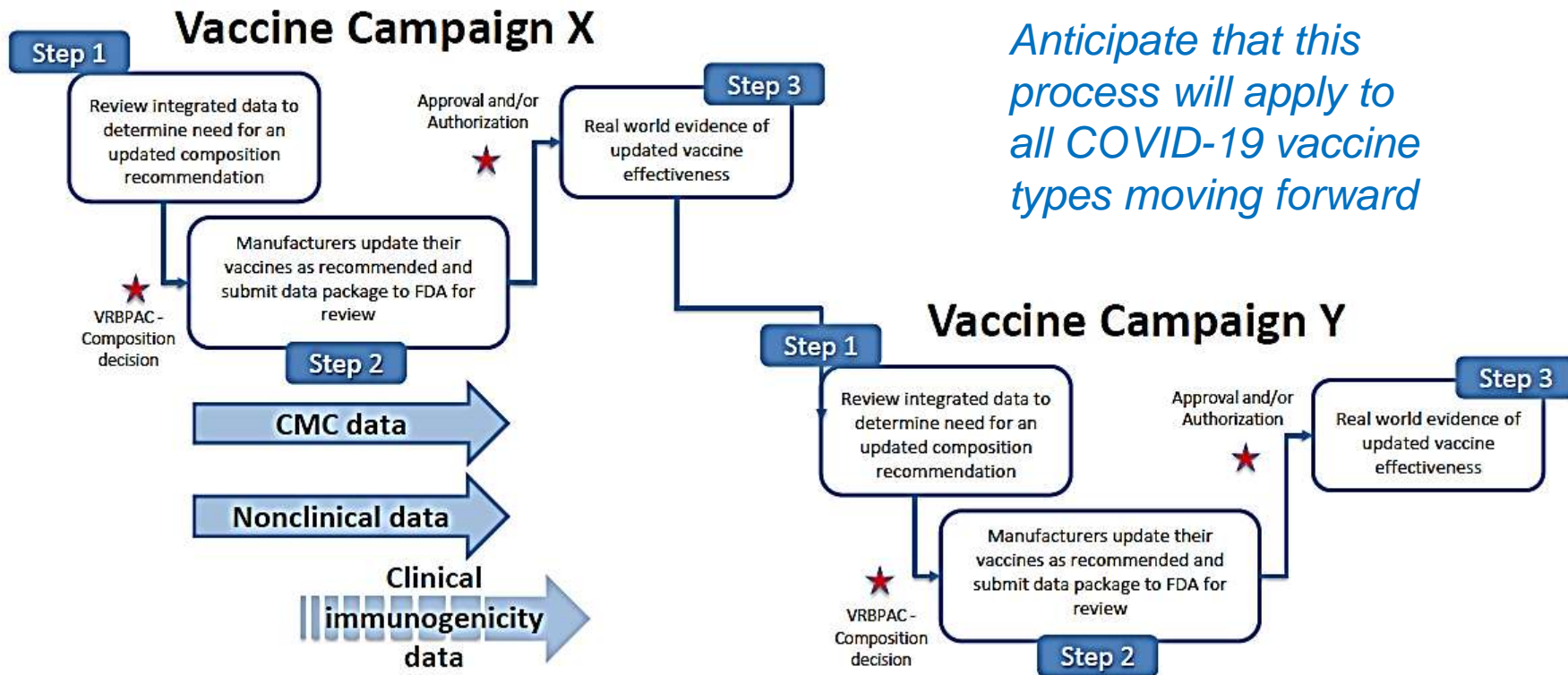
# **mRNA Vaccines Durability and Formula Updates**

# 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?



# Approach to Updating Vaccine Composition- High Level Overview





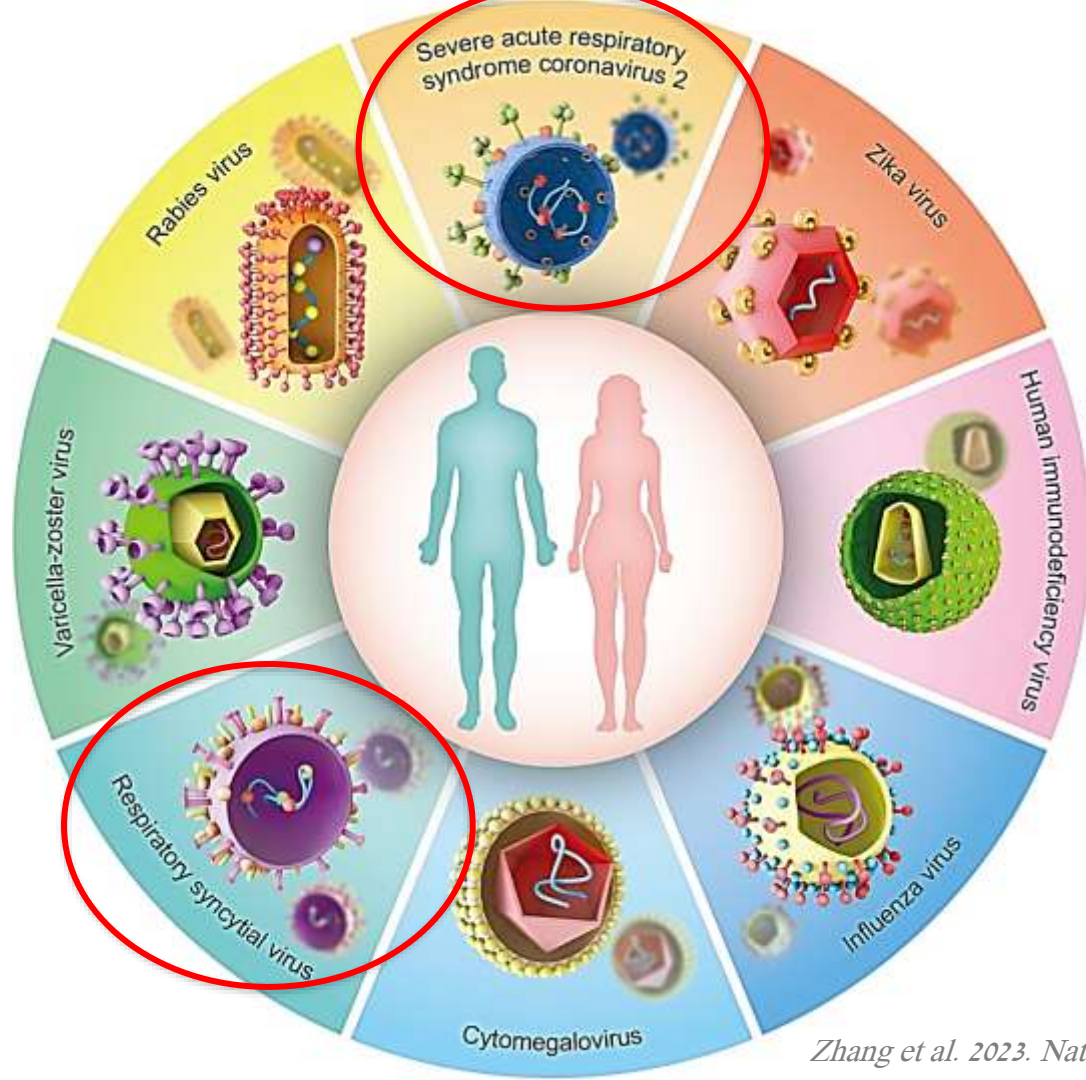
# FDA's Role for COVID Vaccines, including mRNA

## 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



# 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**

