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A Scientific Review of Covid 19 Vaccines

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Topics for Discussion

- What is COVID-19?
- What is Lipid Nanoparticles (LNP)
- How does LNP works
- Types of vaccines mRNA vs. DNA
- Current vaccines with efficacy and safety data
  - Pfizer – BioNTech Covid 19 Vaccine
  - Moderna Covid –19 Vaccine
  - Janssen Covid –19 Vaccine

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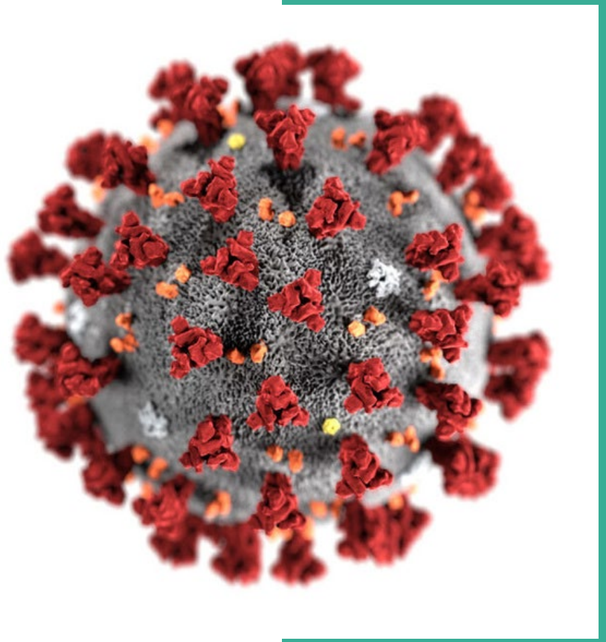
COVID-19

- On February 11, 2020, the WHO provide an official name for the novel coronavirus outbreak
- First emerged in Wuhan China in December 2019. Abbreviated name is COVID-19.
- In COVID-19,
  - 'CO' stands for 'corona,'
  - 'VI' for 'virus,'
  - 'D' for disease.
  - Formerly, this disease was referred to as "2019 novel coronavirus" or "2019-nCoV".
- COVID-19 is a new disease, caused by a novel (or new) coronavirus that has not previously been seen in humans.
  - SARS
  - MERS
    - CDC.GOV



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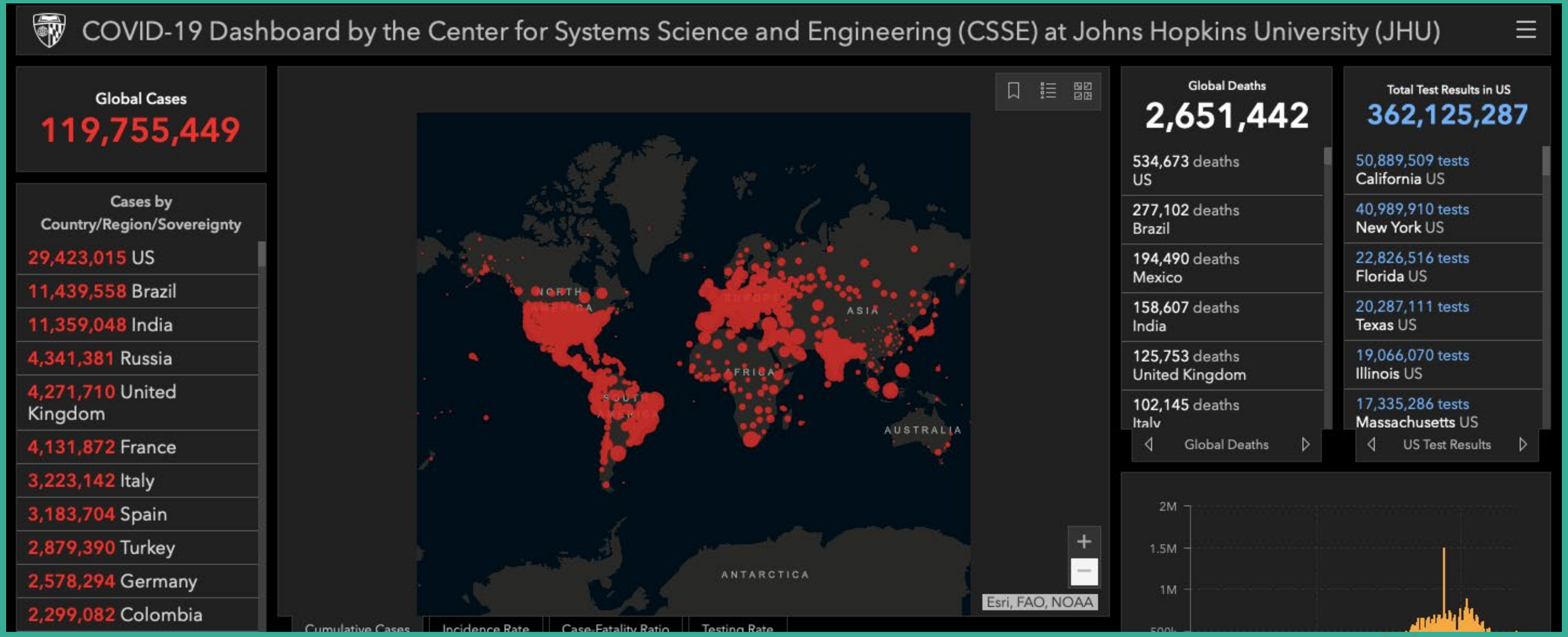
John Hopkins Covid Spread Map

March 14, 2021



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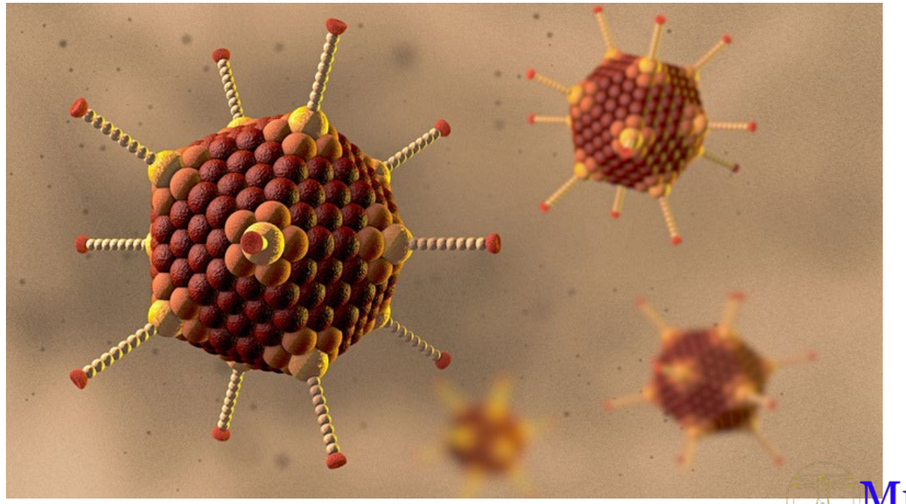
Adenovirus

What is it?

- A group of common viruses that infect the lining of your eyes, airways, lungs, intestines, urinary tract, and nervous system
- Responsible for a lot of common causes of fever, coughs, sore throats, etc.
- Double-stranded DNA
- No known drugs made specifically to treat adenoviruses



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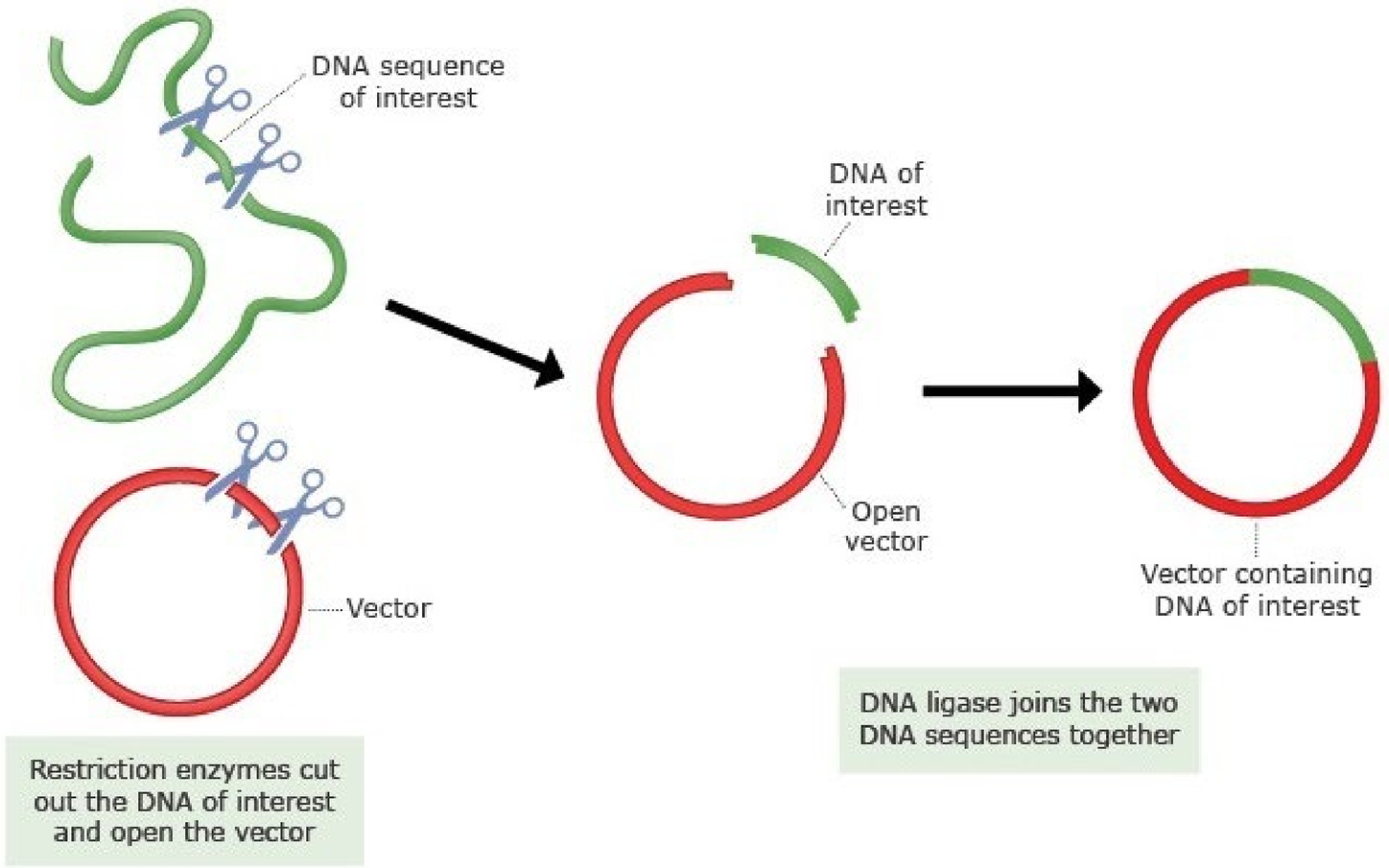
Adenovirus

Why are they important?

- Serve as vaccine vectors
  - A modified version that delivers your vaccine
- Stable to chemical and physical agents and adverse pH conditions
- Adenoviral genome is well characterized and comparatively easy to manipulate
- Additionally used as a delivery system for gene therapy or chemo drugs

How does it work?



Manipulating the Adenoviral Genome

- E1 and E3 genes are deleted - replication incompetent

Integration into the Viral Genome

- The gene of interest responsible for inducing an immune response is integrated into the adenovirus genome
- Example: Covid -19 spike protein

Administration

- Inject the adenovirus mediated vaccine into the host

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How does it work?

Once it is in the body...

- Adenovirus attaches to cell via the CAR receptor and is engulfed into the cell
- Modified viral genome encoding the spike protein is released inside the cell
- DNA → mRNA via host cellular machinery (transcription)
- mRNA → spike protein via host cellular machinery (translation)
- Fragments of spike protein are presented on cell (via MHCI receptor) and alerts our immune system
- Some spike proteins are released into blood and picked up by our immune cells

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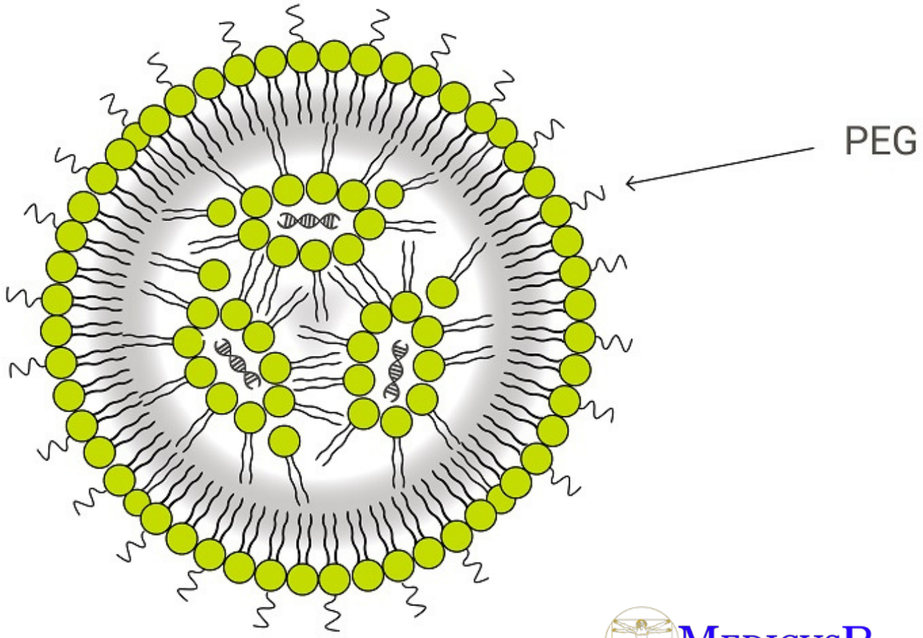
Lipid Nanoparticles (LNP)

What is it?

- Self-assembled nanostructures with the ability to encapsulate, protect, and deliver nucleic acids
- "fat bubbles"
- Up and coming drug delivery system or vaccines, nucleic acid, or chemotherapy drugs
  - Onpattro, 2018



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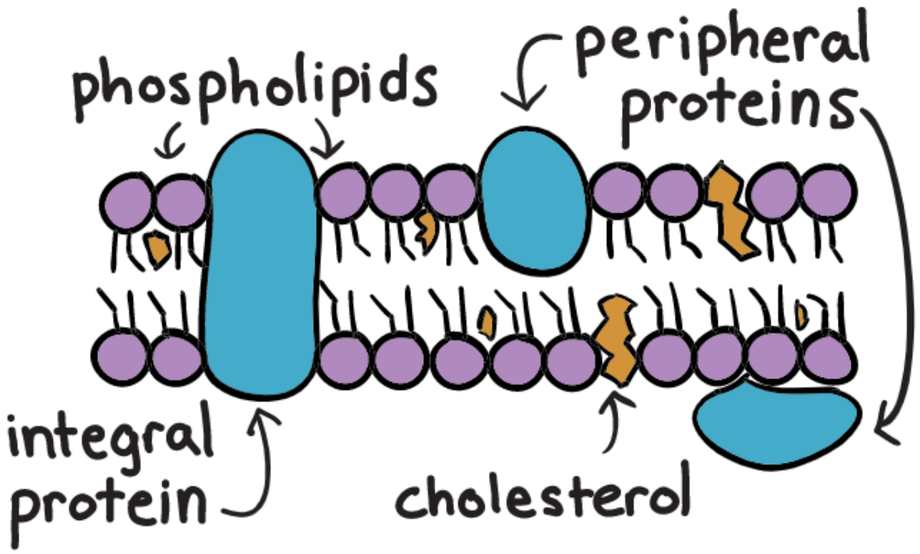
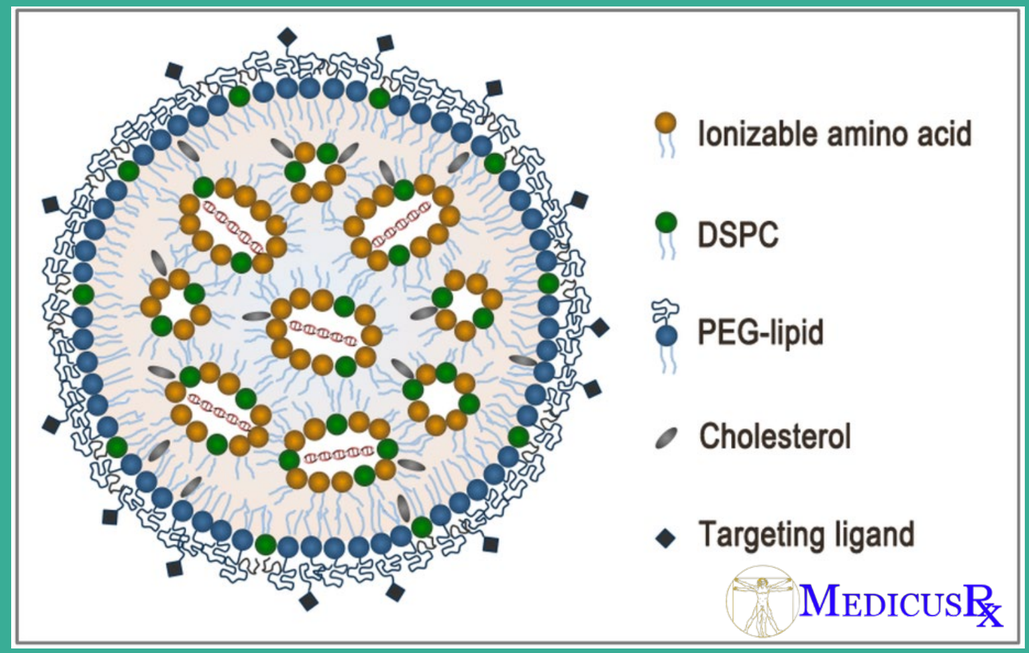
Why are LNPs referred to as "fat bubbles"?

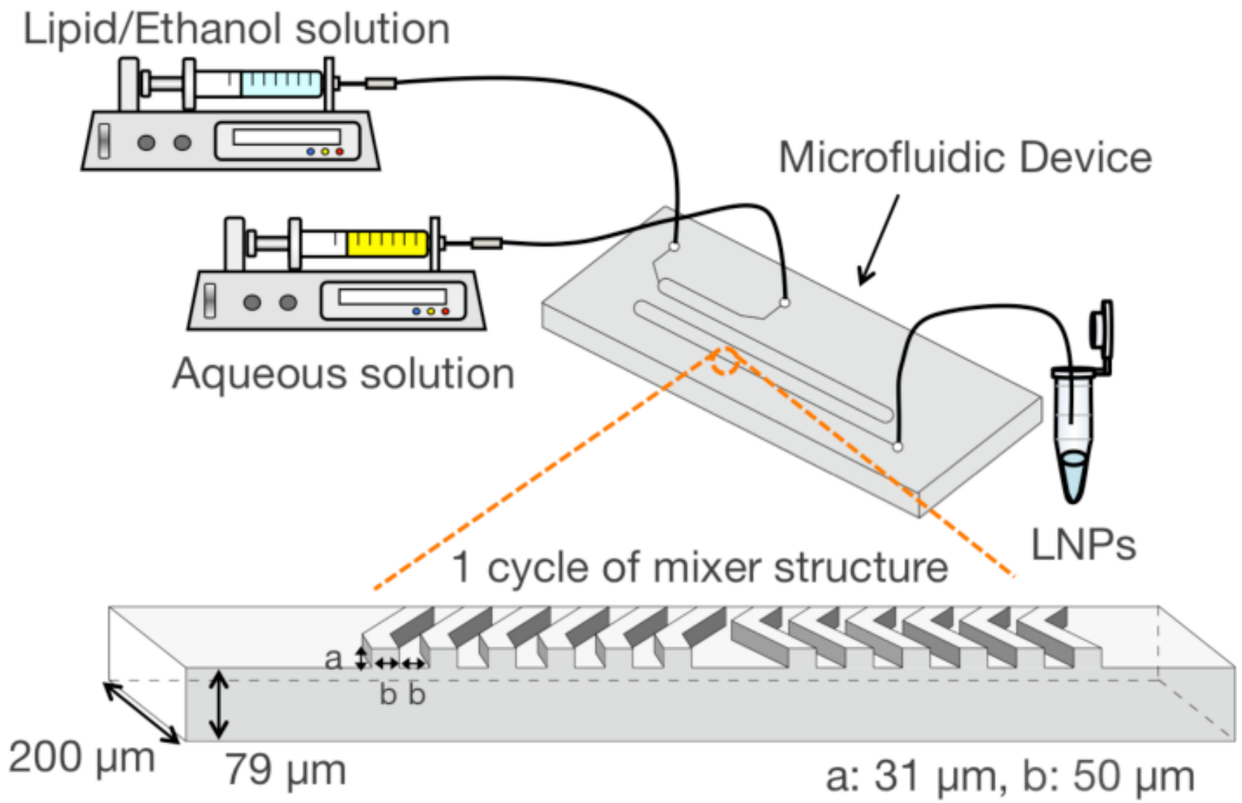
LNP Composition

- Ionizable lipid - DLin-MC3-DMA
- Cholesterol - Beta-Sitosterol
- Polyethylene glycol (PEG)
- DSPC
- Additional salts or lipids for customization





Making an LNP



- Lipids mixed within ethanol
- Nucleic acids mixed within sodium acetate (aqueous solution)
- Mix both solutions using microfluidic technology

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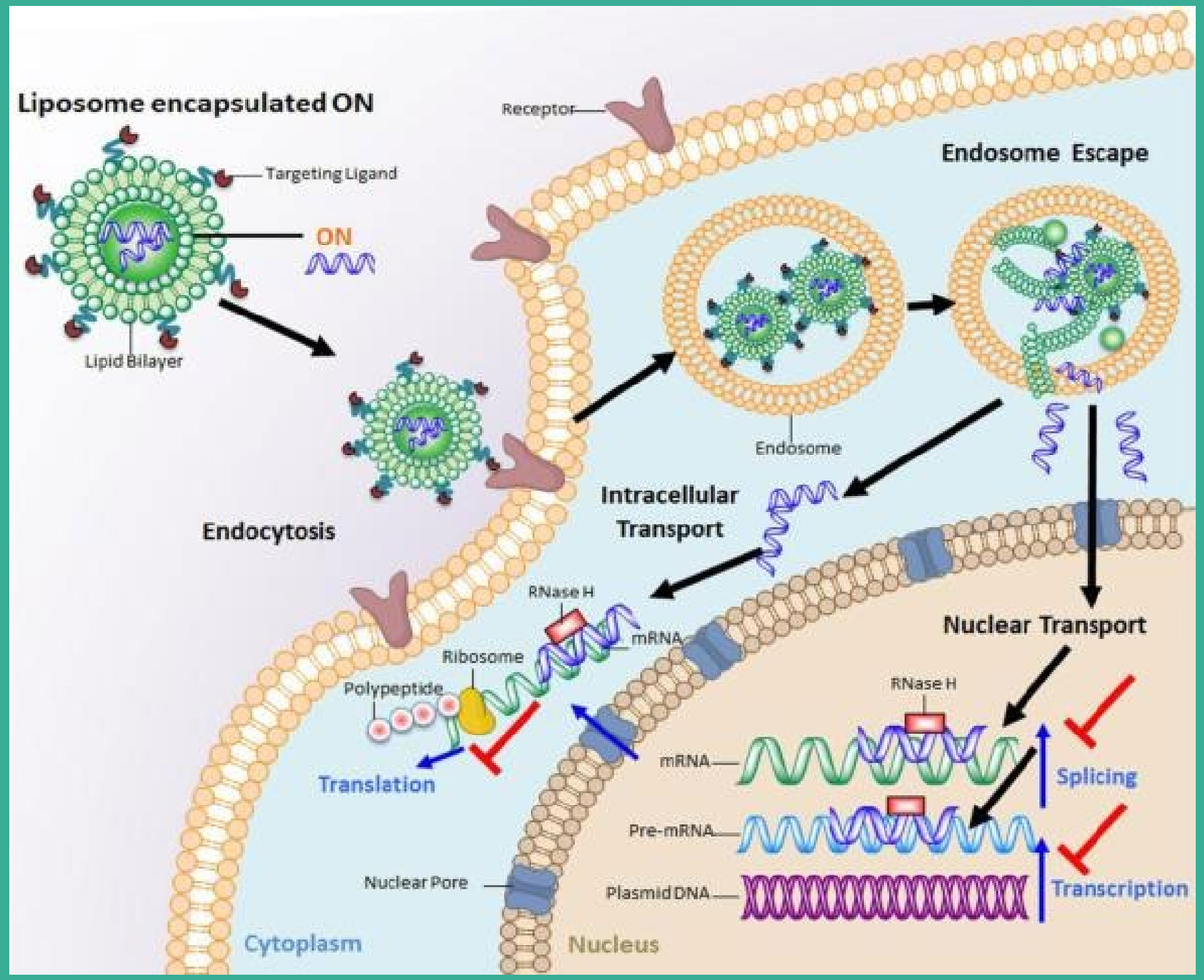
How does it work?



Once it is in the body...

- LNP is engulfed into the cell
- LNP releases cargo into the cell
- mRNA --> spike protein via host cellular machinery (translation)
- Fragments of spike protein are presented on cell (via MHCI receptor) and alerts our immune system
- Some spike proteins are released into blood and picked up by our immune cells

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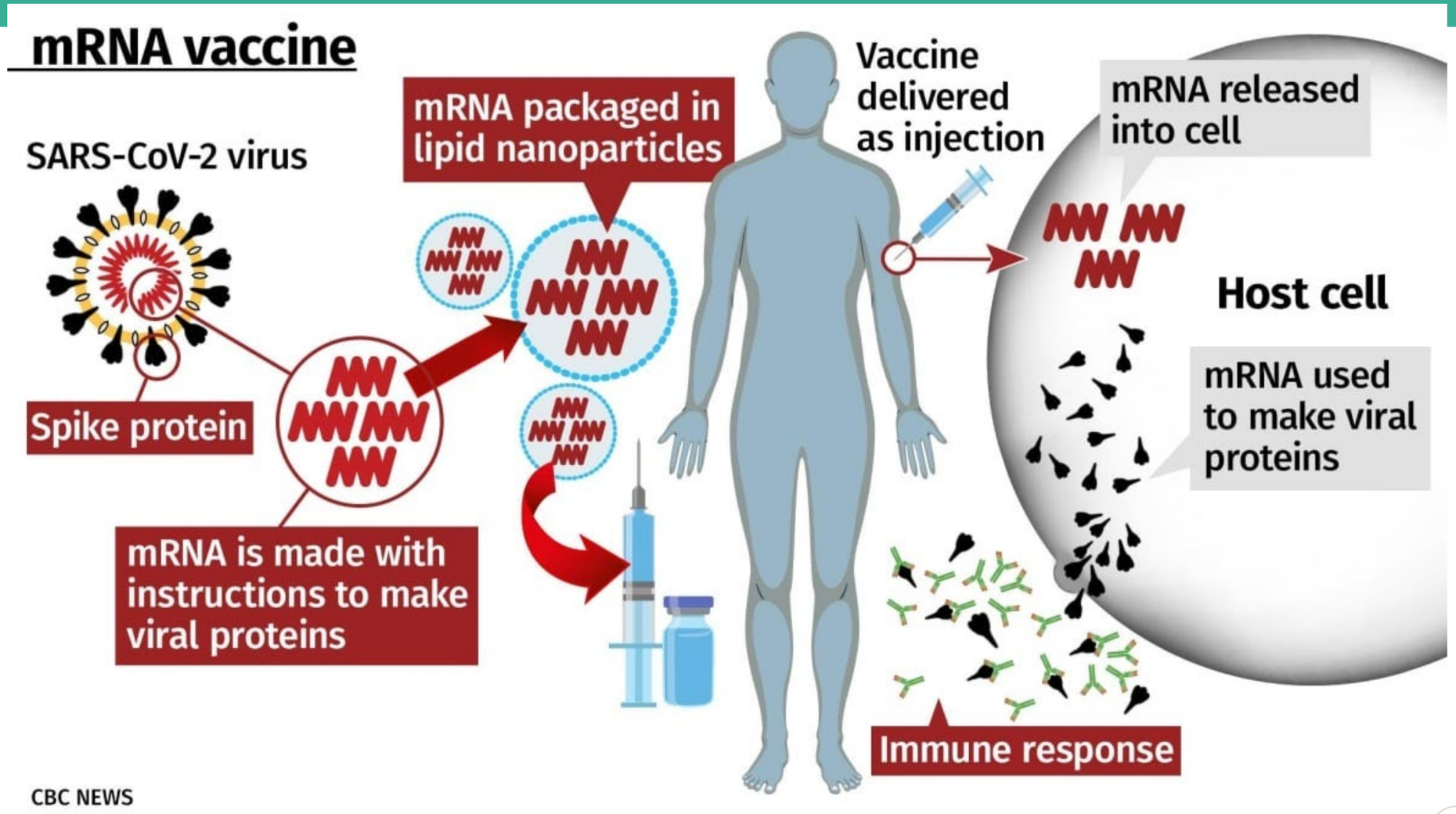
mRNA Vaccines



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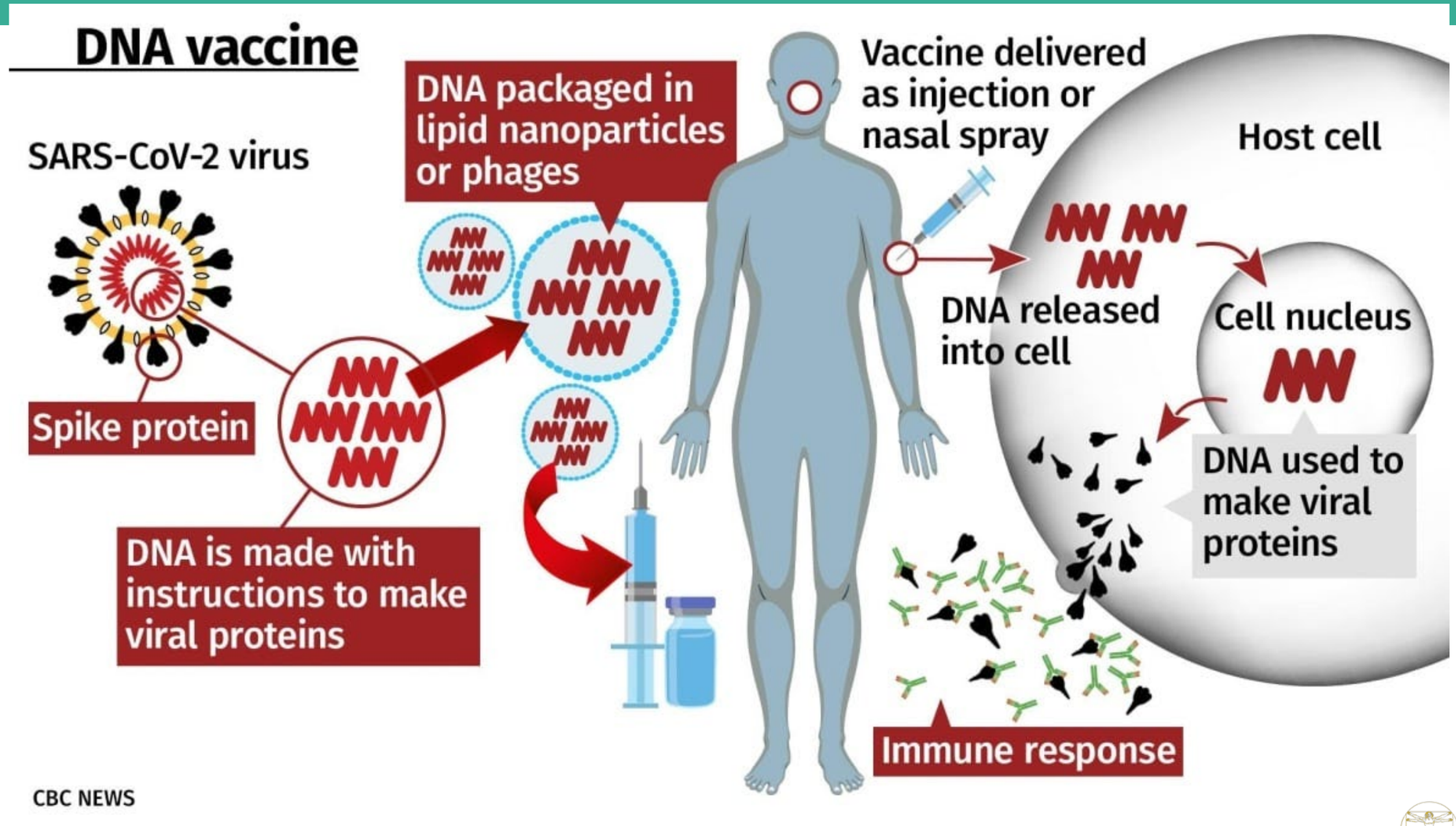
DNA Vaccines



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FDA issued EUA

- December 11, 2020, the FDA issued an Emergency Use Authorization (EUA) for the use of the Pfizer-BioNTech COVID-19 Vaccine.
- December 18, 2020, the FDA issued an EUA for the use of the Moderna COVID-19 Vaccine.
- February 27, 2021 the FDA issued an EUA for the use of the Janssen COVID-19 Vaccine. The issuance of an EUA is different than an FDA approval (licensure) of a vaccine.

mRNA Vaccines

- Not a live or killed virus vaccine
  - Cannot give someone COVID-19
- Does not enter the nucleus like DNA vaccines
- New type of vaccine
  - mRNA vaccines have been studied before for flu, Zika, rabies, and cytomegalovirus (CMV).
  - There are currently no licensed mRNA vaccines in the United States
    - (Clin Pharmacol Ther. 2008;83:788-93)

Vaccines in progress

NEJM 384;7 02/18/2021

Adenovirus vector (nonreplicating)	ChAdOx1-Sn Cov-19 Nonreplicating chimpanzee AdV5 expressing spike protein	AstraZeneca and University of Oxford (AZD1222)	One (day 0) or two (day 0, day 28) doses Intramuscular	Phase 3	10 mM histidine, 7.5% (w/v) sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% (w/v) **polysorbate 80**, 0.1 mM edetate disodium, 0.5% (w/v) ethanol, at pH 6.6
Adenovirus vector (nonreplicating)	Ad26.COV2.S Adenovirus 26 vectored vaccine using AdVac and PER.C6 technology	Janssen	One (day 0) or two (day 0, day 56) doses Intramuscular	Phase 3	Sodium chloride, citric acid monohydrate, **polysorbate 80**, 2 hydroxypropyl-B-cyclodextrin (HBCD), ethanol (absolute), sodium hydroxide
Protein subunit	Full-length recombinant SARS-CoV-2 glycoprotein nanoparticle with Matrix M adjuvant Spike prefusion protein	Novavax	Two doses (day 0, day 21) Intramuscular	Phase 3	Matrix M1 adjuvant Full-length spike protein formulated in **polysorbate 80** detergent and Matrix M1 adjuvant
Protein subunit	SARS-CoV-2 vaccine formulation with adjuvant (S-protein) (Baculovirus production) Spike protein	Sanofi Pasteur and GSK	Two doses (day 0, day 21) Intramuscular	Phase 1–2	Sodium phosphate monobasic monohydrate, sodium phosphate dibasic, sodium chloride **polysorbate 20**, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride

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Vaccines in progress

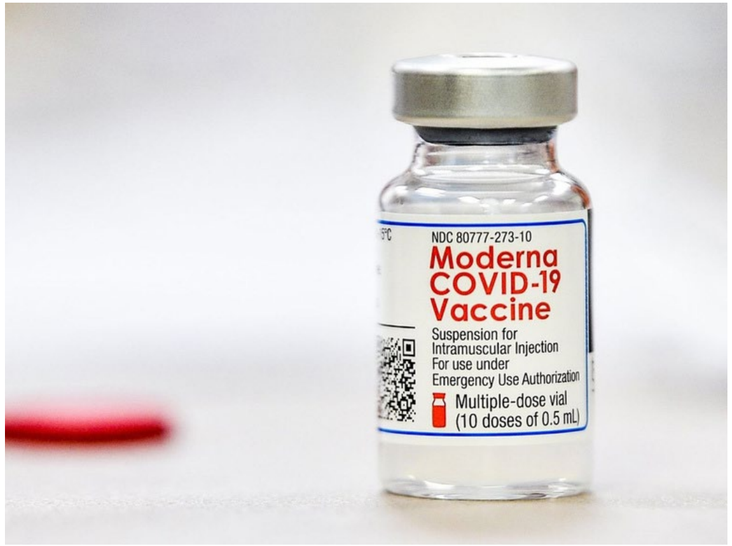
Pfizer – mRNA vaccine

- BNT162b2
- German company
- On July 22, 2020
  - HHS announced up to $1.95 billion in funds for Pfizer for the large -scale manufacturing and nationwide distribution of 100 million doses of their vaccine candidate.
  - The federal government will own the 100 million doses of vaccine initially produced as a result of this agreement, and Pfizer will deliver the doses in the United States if the product successfully receives FDA EUA or licensure, as outlined in FDA guidance, after completing demonstration of safety and efficacy in a large Phase 3 clinical trial, which began July 27th.

Vaccines in progress

Moderna - mRNA-1273

- Massachusetts based company
- Currently being tested in phase 2a dose -ranging trial with 600 adult participants
- $483 million grant from Biomedical Advanced Research and Development Authority (BARDA).
  - JAMA August 4,2020 v 324, n. 5, 437-438;



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Vaccines in progress

Johnson & Johnson/Janssen

- US Company- New Jersey
- Ad26.COV2-S
- $456 million grants from BARDA
- Uses replication-defective human adenovirus 26 vector
- Phase 2-2a clinical trials
- Single dose vaccine
  - JAMA August 4,2020 v 324, n. 5, 437-438;

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Vaccines in progress

Astra-Zeneca-Jenner Institute Univ. Oxford

- ChAdOx1nCoV-19
- $1.2 billion in funding from BARDA
- Replication defective simian adenovirus vector
- Single dose vaccine
- Phase 1-2 clinical trials
  - JAMA August 4,2020 v 324, n. 5, 437-438;

Discontinued Vaccines
Merck

- Two single dose vaccine candidates; V590 and V591
- US Company based in New Jersey
- Partnered with International AIDS Vaccine Initiative
- $38 million grant from BARDA
- Discontinued following Phase 1 clinical studies
  - Generally well tolerated, but had inferior immune responses to those seen following natural infection and those reported for other COVID -19 vaccines
- Continuing to manufacture two therapeutic medications; MK -7110 and MK-4482
  - MK-4482 (Molnupiravir) is being developed in collaboration with Ridgeback Bio
- Recombinant Vesicular Stomatitis Virus Vectored Vaccine
  - Similar to the Ebola vaccine (Ervebo)
  - Uses replication-competent virus as a vector
    - JAMA August 4,2020 v 324, n. 5, 437-438;

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Additional Trials

- July 7, 2020:
  - HHS announced $450 million in funds to support the large-scale manufacturing of Regeneron's COVID-19 investigational anti-viral antibody treatment, REGN-COV2.
    - First of a number of OWS awards to support potential therapeutics all the way through to manufacturing.
    - Doses of the medicine will be packaged and ready to ship immediately if clinical trials are successful and FDA grants EUA or licensure.
  - HHS announced $1.6 billion in funds to support the large-scale manufacturing of Novavax's vaccine candidate.
    - By funding Novavax's manufacturing effort, the federal government will own the 100 million doses expected to result from the demonstration project.
- https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html

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Additional Trials

- July 31, 2020:
  - HHS announced approximately $2 billion in funds to support the advanced development, including clinical trials and large-scale manufacturing, of Sanofi and GlaxoSmithKline's (GSK) investigational adjuvanted vaccine.
    - The federal government will own the approximately 100 million doses expected to result from the demonstration project.
    - The adjuvanted vaccine doses could be used in clinical trials or, if the FDA authorizes use, the doses would be distributed as part of a COVID-19 vaccination campaign.
  - https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html

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Pfizer – BNT162b2 mRNA COVID-19 Vaccine

- Ongoing clinical trial
- Multi-national, placebo-controlled, observer-blinded RCT
- > 16 years healthy or stable chronic diseases
- 1:1 ratio
- 2 doses of vaccine, 21 days apart
- BNT162b2 mRNA COVID-19 Vaccine-30microgram per dose or saline
- Primary outcomes – Efficacy of the vaccine (confirmed by lab testing)
  - Safety
    - NEJM 12/31/2020

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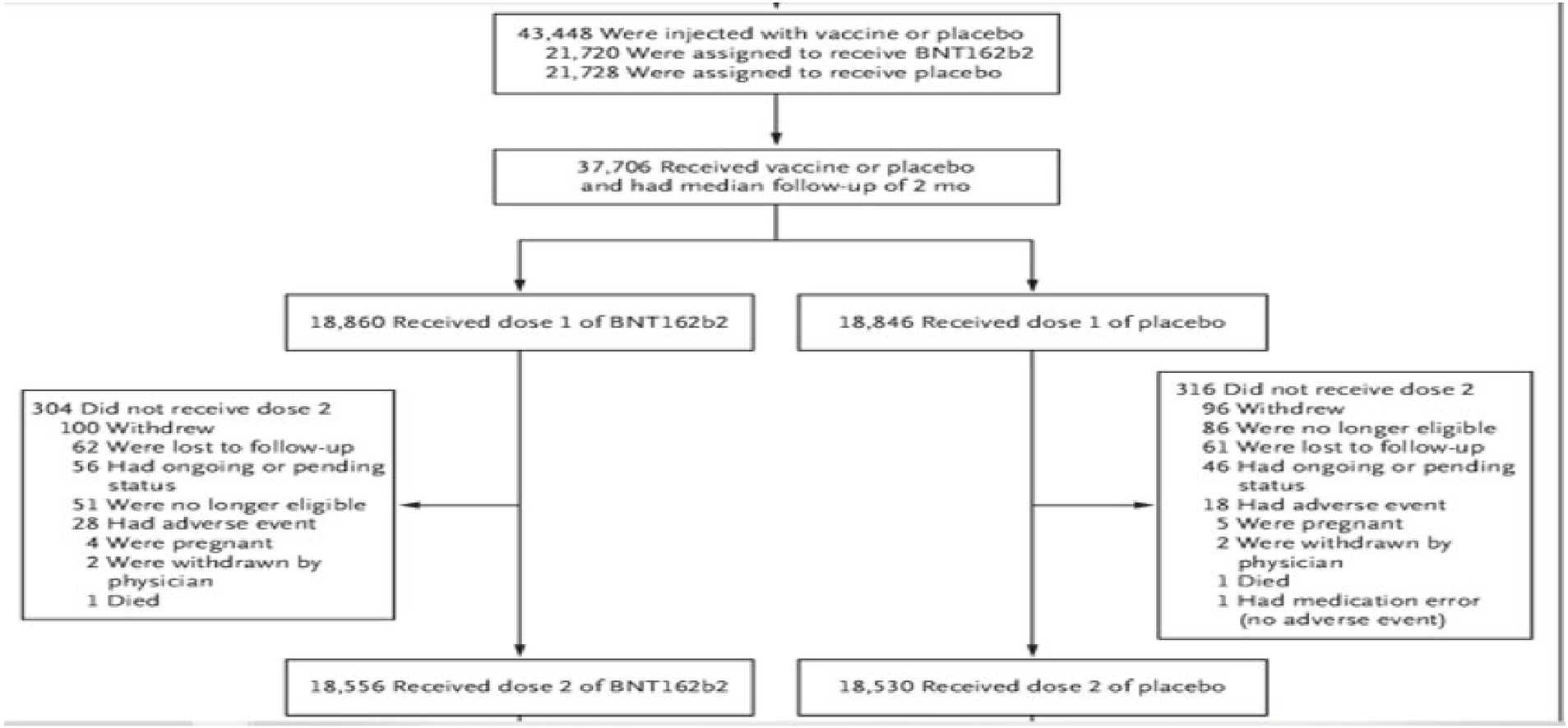
Pfizer – BNT162b2 mRNA COVID-19 Vaccine



N Engl J Med 2020; 383:2603-2615

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Pfizer – BNT162b2 mRNA COVID-19 Vaccine

N Engl J Med 2020; 383:2603-2615

Table 1. Demographic Characteristics of the Participants in the Main Safety Population.*

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Hispanic or Latinx	5,266 (27.9)	5,277 (28.0)	10,543 (28.0)
Country — no. (%)			
Argentina	2,883 (15.3)	2,881 (15.3)	5,764 (15.3)
Brazil	1,145 (6.1)	1,139 (6.0)	2,284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
United States	14,460 (76.7)	14,454 (76.7)	28,914 (76.7)
Age group — no. (%)			
16–55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Age at vaccination — yr			
Median	52.0	52.0	52.0
Range	16–89	16–91	16–91
Body-mass index‡			
≥30.0: obese	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)

* Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Pfizer – BNT162b2 mRNA COVID-19 Vaccine

N Engl J Med 2020; 383:2603-2615

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		**(N=18,325)**		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		**(N=20,172)**		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

Pfizer – BNT162b2 mRNA COVID-19 Vaccine

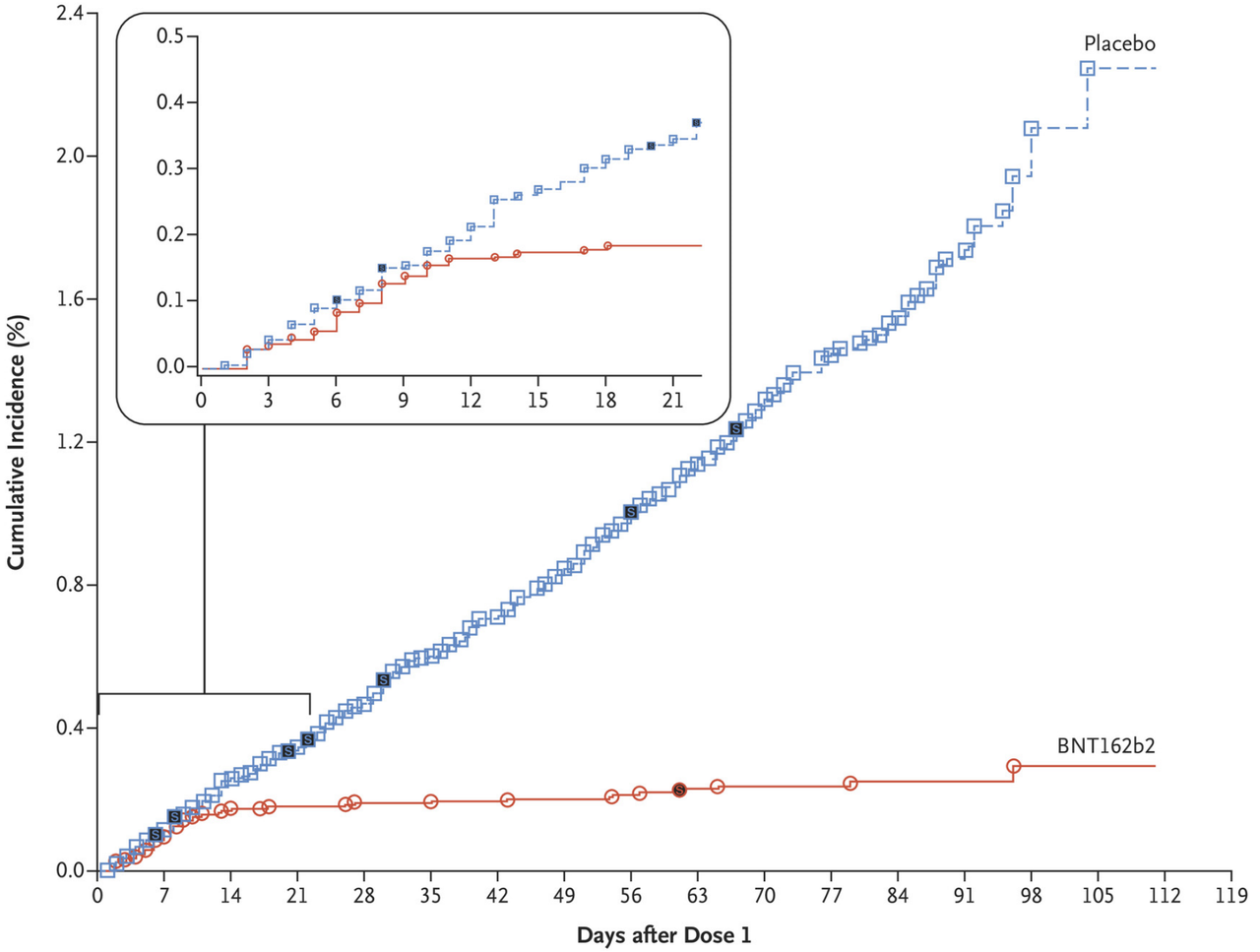
Table 3. Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.

Efficacy End-Point Subgroup	BNT162b2 (N=18,198)		Placebo (N=18,325)		Vaccine Efficacy, % (95% CI)†
	No. of Cases	Surveillance Time (No. at Risk)*	No. of Cases	Surveillance Time (No. at Risk)*	
Overall	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.0–97.9)
Age group					
16 to 55 yr	5	1.234 (9,897)	114	1.239 (9,955)	95.6 (89.4–98.6)
>55 yr	3	0.980 (7,500)	48	0.983 (7,543)	93.7 (80.6–98.8)
≥65 yr	1	0.508 (3,848)	19	0.511 (3,880)	94.7 (66.7–99.9)
≥75 yr	0	0.102 (774)	5	0.106 (785)	100.0 (–13.1–100.0)
Sex					
Male	3	1.124 (8,875)	81	1.108 (8,762)	96.4 (88.9–99.3)
Female	5	1.090 (8,536)	81	1.114 (8,749)	93.7 (84.7–98.0)
Race or ethnic group‡					
White	7	1.889 (14,504)	146	1.903 (14,670)	95.2 (89.8–98.1)
Black or African American	0	0.165 (1,502)	7	0.164 (1,486)	100.0 (31.2–100.0)
All others	1	0.160 (1,405)	9	0.155 (1,355)	89.3 (22.6–99.8)
Hispanic or Latinx	3	0.605 (4,764)	53	0.600 (4,746)	94.4 (82.7–98.9)
Non-Hispanic, non-Latinx	5	1.596 (12,548)	109	1.608 (12,661)	95.4 (88.9–98.5)
Country					
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2 (83.3–99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7 (8.1–99.7)
United States	6	1.732 (13,359)	119	1.747 (13,506)	94.9 (88.6–98.2)

* Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
† The confidence interval (CI) for vaccine efficacy is derived according to the Clopper–Pearson method, adjusted for surveillance time.
‡ Race or ethnic group was reported by the participants. "All others" included the following categories: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported.

N Engl J Med 2020; 383:2603-2615

Pfizer – BNT162b2 mRNA COVID-19 Vaccine



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*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 (89.8–97.6)

N Engl J Med 2020; 383:2603-2615

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Pfizer – BNT162b2 mRNA COVID-19 Vaccine

- Local reactions
  - Mild to moderate pain at the site of injection within 7 days after injection
  - <1% have severe pain across all age groups
  - Resolve in 1-2 days
- Systemic reactions
  - Most common: fatigue & headache (59%, 52%) younger patients; 23%,24% in placebo
  - Older patients- 51%, 39%; placebo 17%,14%
  - Severe systemic events <2% after either doses
  - Fatigue 3.8%; headache 2% after the 2nd dose

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Pfizer – BNT162b2 mRNA COVID-19 Vaccine

- Fever
  - Same for both vaccinated and controls (2 patients) > 104° F
  - Occurred 1-2 days after vaccination & resolve shortly after
- Adverse events

	Vaccinated	Placebo
Lymphadenopathy	64	6
Shoulder injury	1	0
V Arrhythmia	1	0
Leg paresthesia	1	0
Deaths	2	4

Pfizer – BNT162b2 mRNA COVID-19 Vaccine

- Observations
  - 152 sites (U.S. – 130; Argentina – 1; Brazil – 2; South Africa – 4; Germany – 6; Turkey – 9)
  - 196 patients with HIV data not included
  - Subjects > 16 years
  - No pregnant subjects
  - No long-term data > 3.5 months
  - Follow up continues for 2 years
  - Shipping and longer storage requires ultra-low freezing temperatures, about -100° Fahrenheit.
  - Refrigeration units that are commonly available in hospitals. The vaccine can be stored for five days at refrigerated 2-8°C conditions.

Pfizer – BNT162b2 mRNA COVID-19 Vaccine

- Ongoing: collection of data in phase 2/3 trial for durability of the immune response
  - NEJM 12/2020

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Moderna - mRNA-1273 SARS-CoV-2 Vaccine

- US Trial- observer -blinded, placebo - controlled trial
- 99 centers ; 1:1 ratio; 2 IM injections (100mcg) or placebo 28 days apart
  - >65 years
  - 18 to <65 years
  - Risks: Emphysema, chronic bronchitis, pulmonary fibrosis, severe asthma, CAD, cardiomyopathies, pulmonary hypertension, BMI>40, diabetes, liver disease, and HIV
- End point: Prevention of Covid 19 with onset > 14 days after vaccination
- Prevention of severe Covid-19
- NEJM 2/4/21; 384;5

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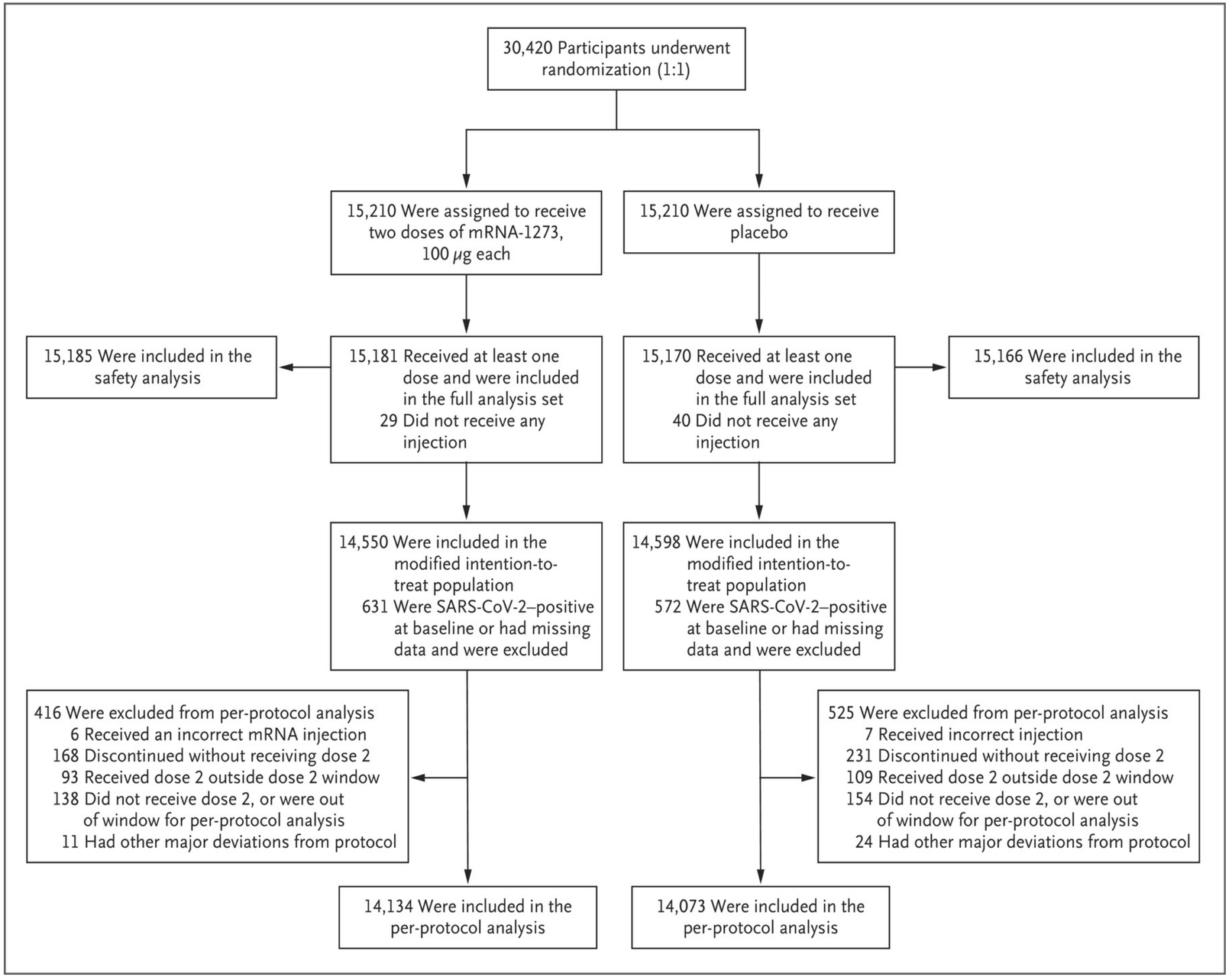
Moderna- mRNA-1273 SARS-CoV-2 Vaccine



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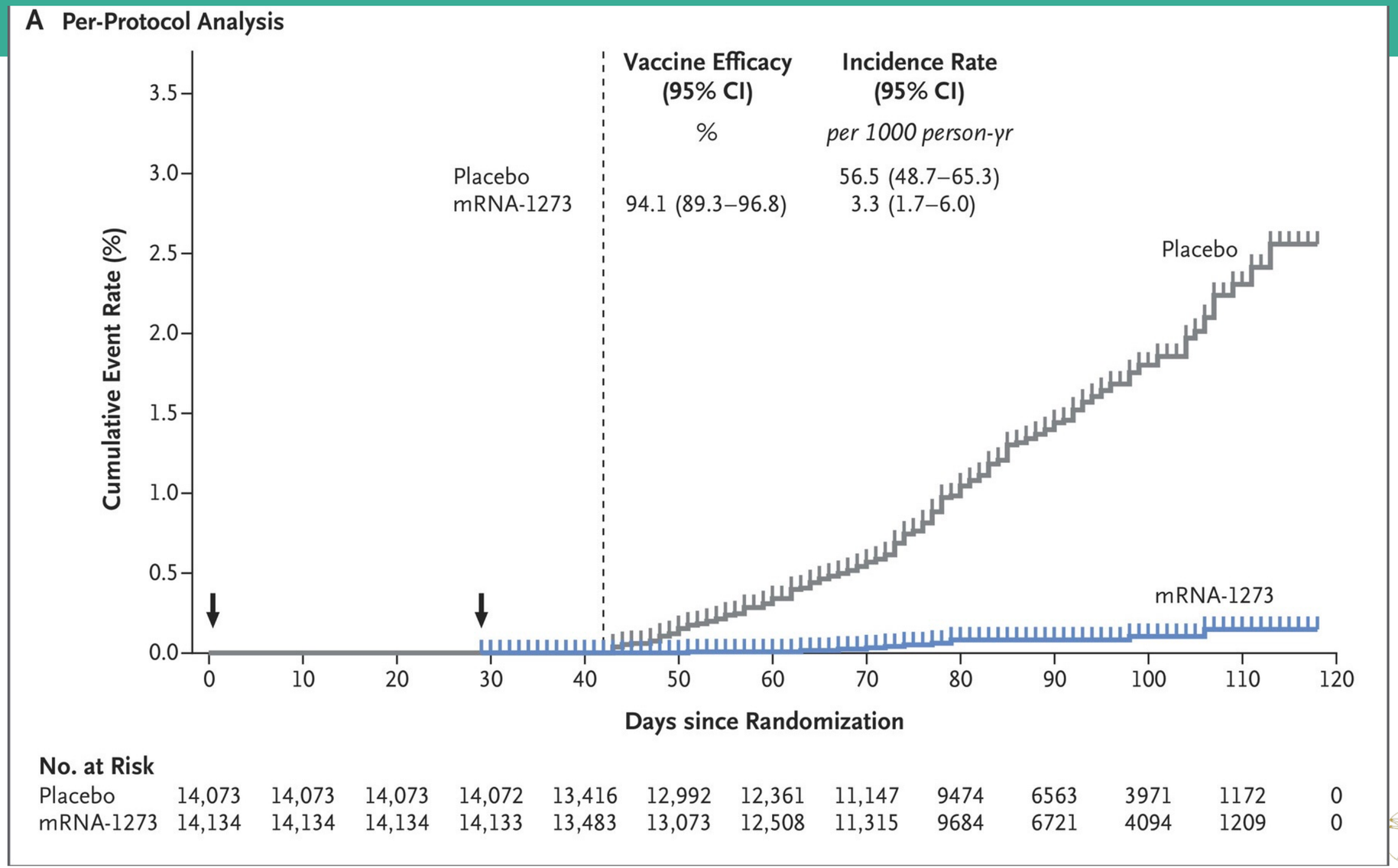

N Engl J Med 2021; 384:403-416

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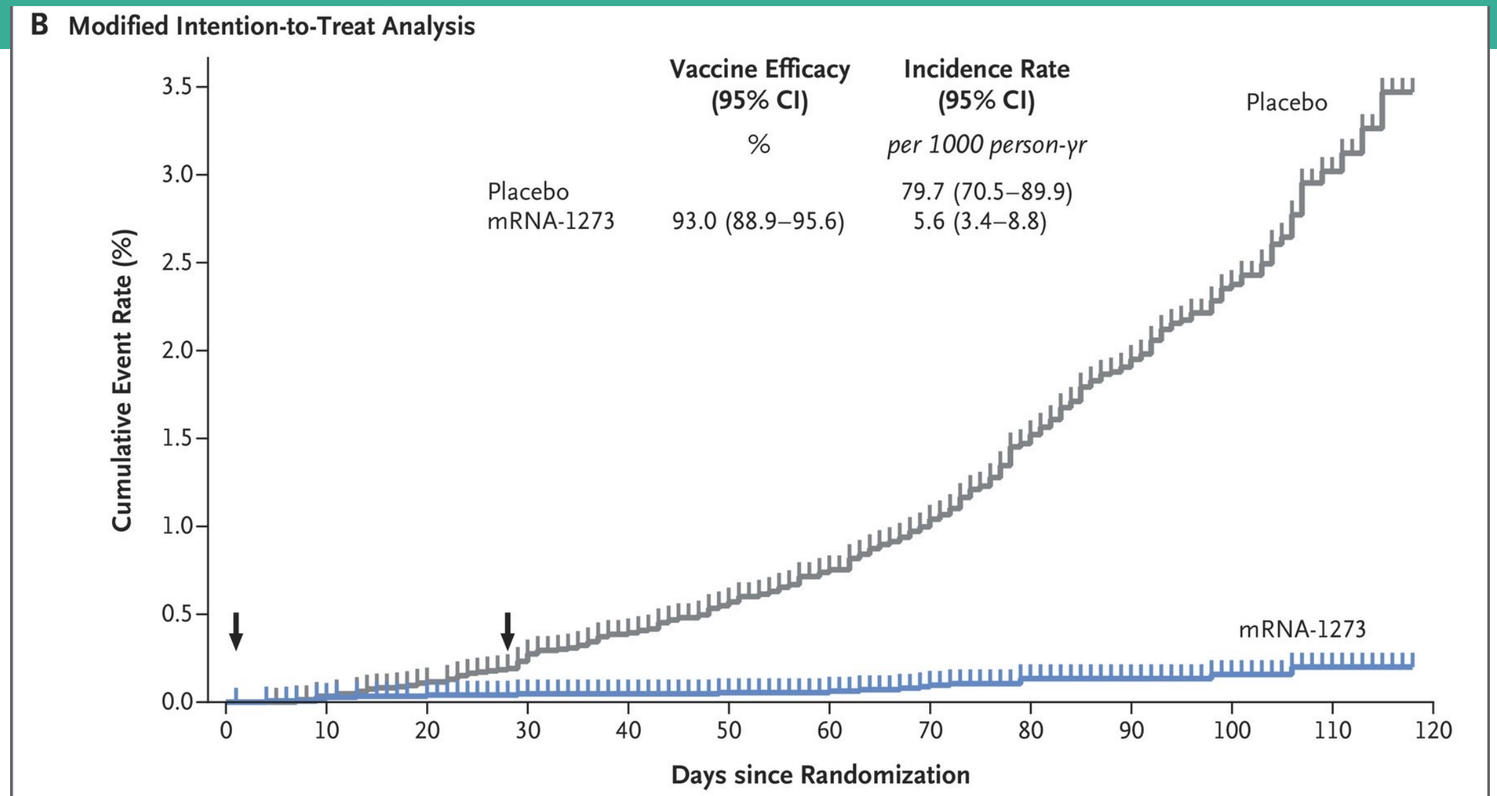
Moderna- mRNA-1273 SARS-CoV-2 Vaccine



No. at Risk

Placebo	14,598	14,590	14,567	14,515	13,806	13,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

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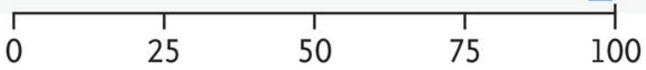
Moderna- mRNA-1273 SARS-CoV-2 Vaccine

Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)



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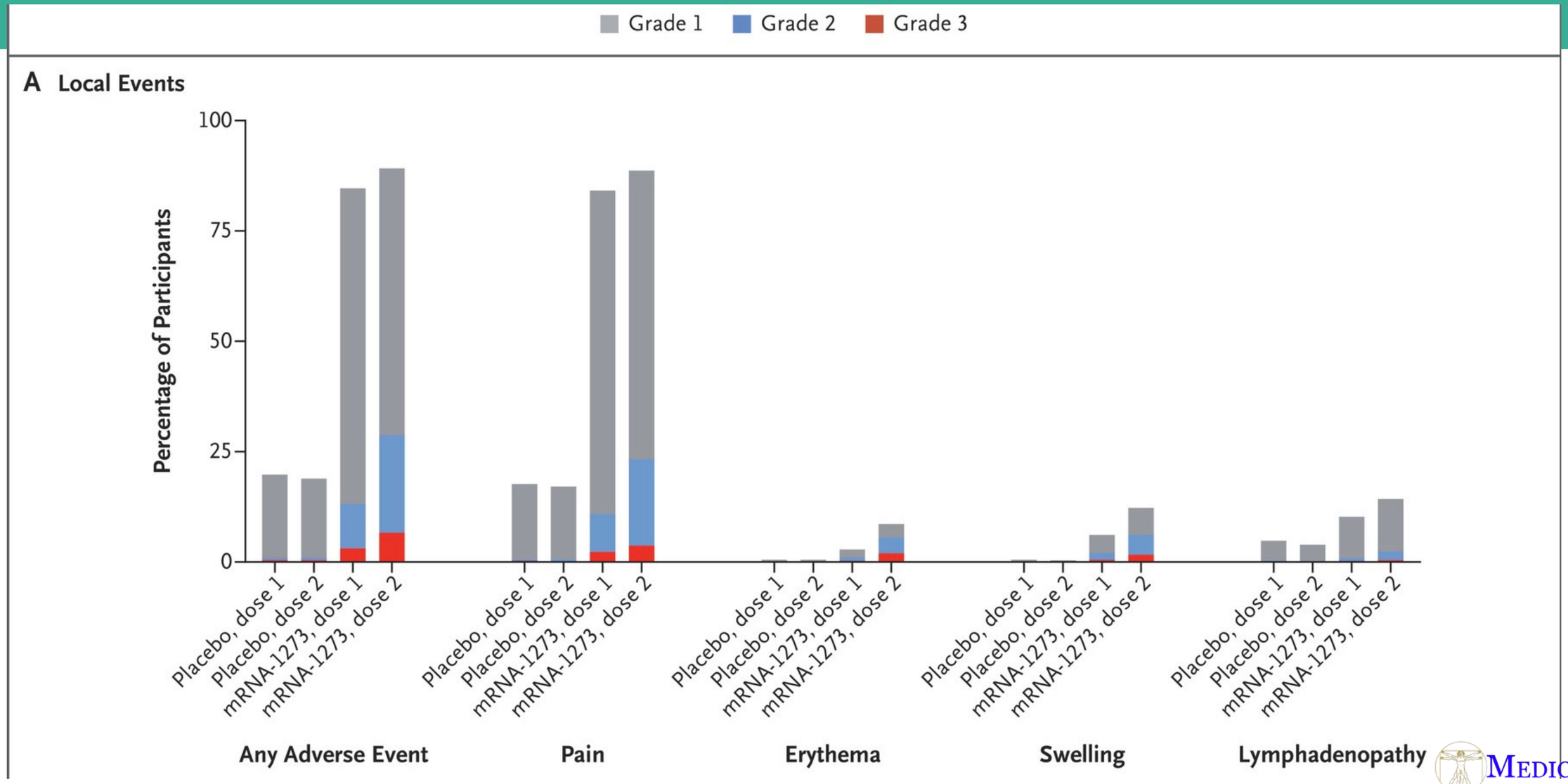
Moderna- mRNA-1273 SARS-CoV-2 Vaccine



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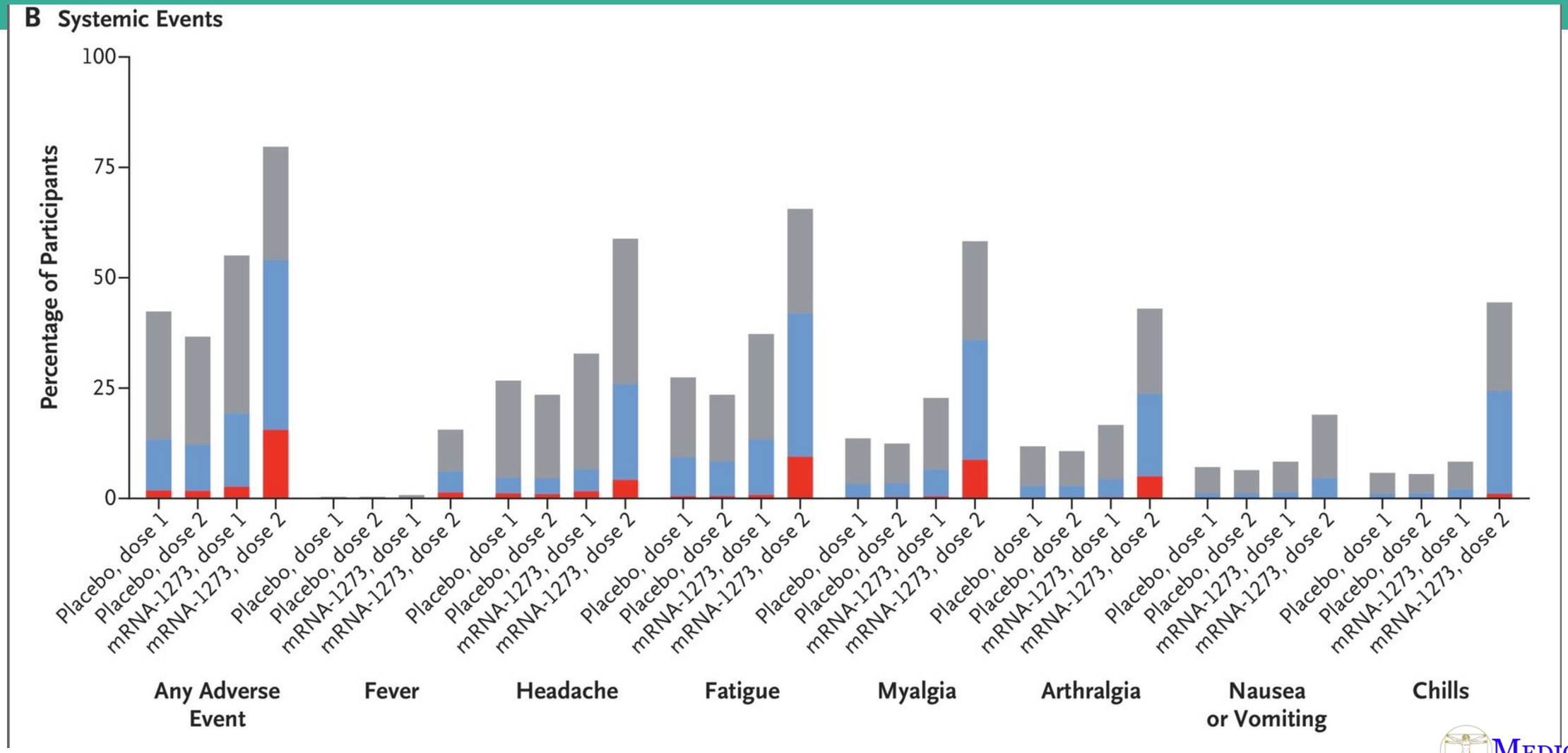
Moderna- mRNA-1273 SARS-CoV-2 Vaccine



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Janssen Covid-19 Vaccine

- Ensemble RCT, double blind, placebo controlled
- Uses incompetent Adenovirus 26 vector
- Multi-countries
  - Argentina, Brazil, Chile, Columbia, Mexico, Peru, S. Africa and US
  - 21,895 participants with and without co-morbidities;
  - UK- phase III in multiple countries- 2 dose regimen
- Ages 18-60, > 60 years
- Suspended enrollment and dosing in 10/2020
- Single dose, does not require ultra-cold storage

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Janssen Covid-19 Vaccine

- FDA issued EUA on 02/27/2021
- Preliminary data
  - After the 1st dose, 90% of the subjects developed antibodies
  - Antibodies increased after the 2nd dose
  - 66% effective in preventing Covid 19 with 1st dose
  - 100% effective in preventing hospitalization and death
  - Side effects similar to other vaccines
  - No severe allergic reactions
- Jama 03/01/2001

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Janssen Covid-19 Vaccine

How long does it last?

- IgG to the spike protein is stable 6+ months
- Spike specific memory B cells more abundant at 6 months than at 1 month post symptom onset.
- SARS Cov-2 specific CD4+ T cells and CD8+ T cells halflife 3-5 months
  - Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection
- Science. Feb.5, 2021; Vol. 371, Issue 6529

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Thank you for your time!

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