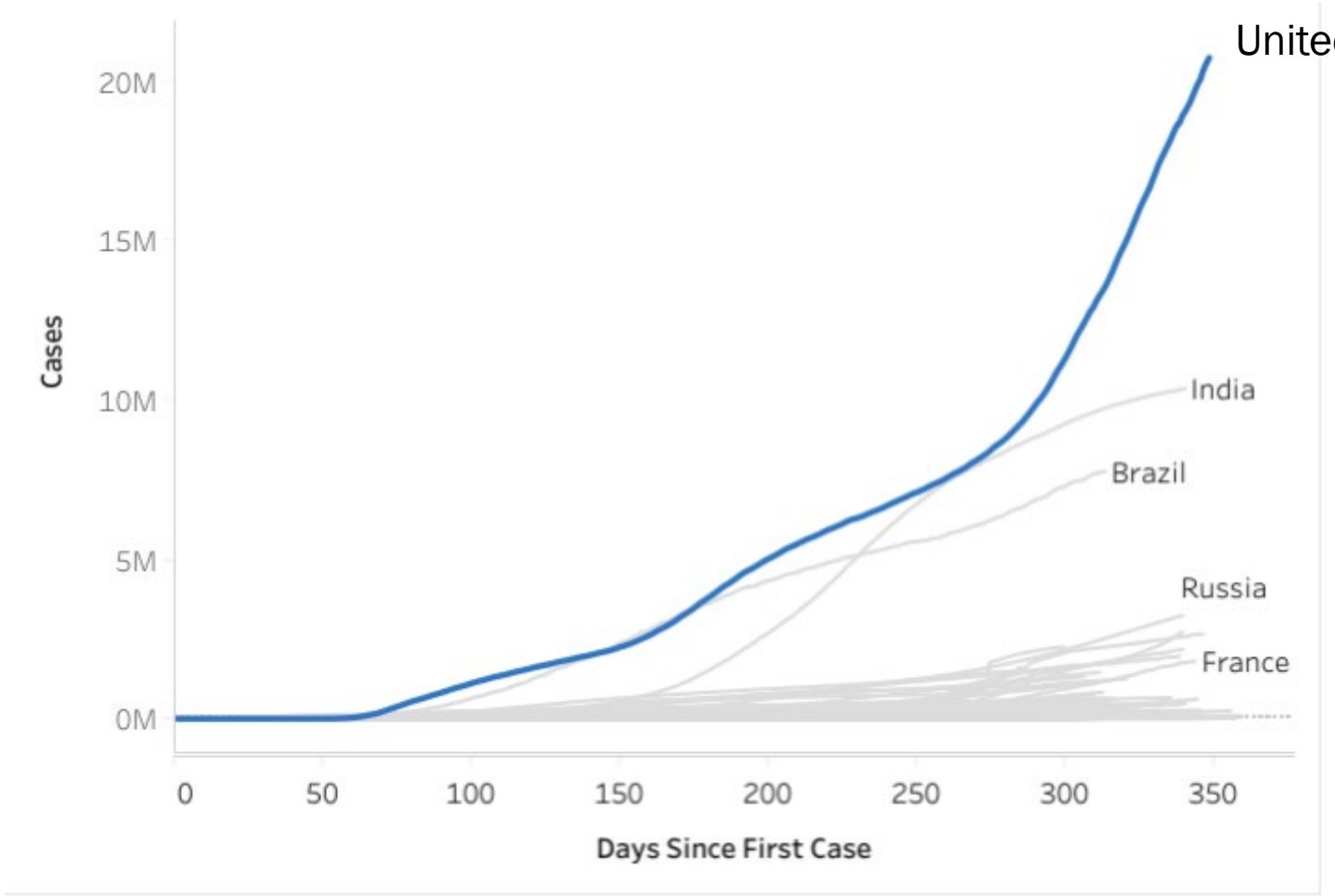
COVID-19 VACCINES

THOMAS V. NUNN, D. O.

SCOPE OF THE PROBLEM: COVID-19

U. S. COVID-19 CASES (AS OF 1/1/21): 22,409,132.
U. S. COVID-19 DEATHS (AS OF 1/1/21): 374,329.

JOHNS HOPKINS



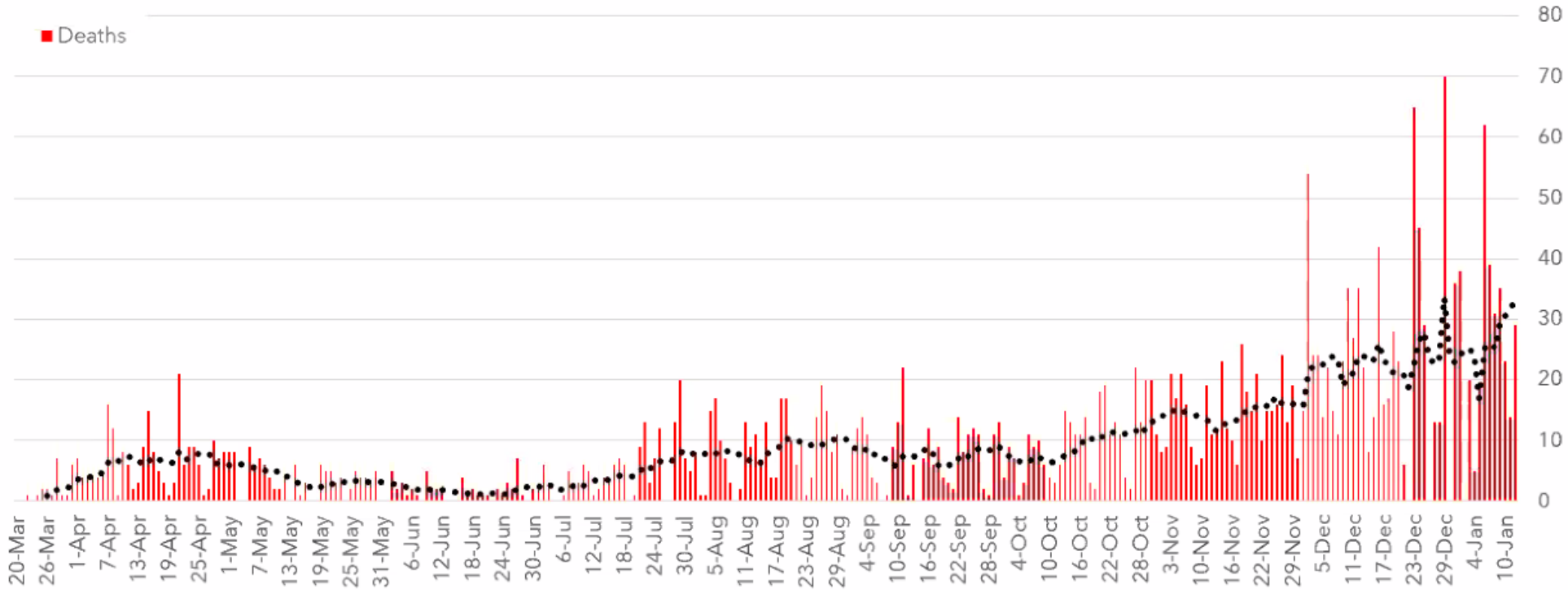
Kaiser Family Foundation

OKLAHOMA STATE DEPARTMENT OF HEALTH

- Oklahoma cases on 1/10/21:
  - 6,487 new cases
  - 23 new deaths
  - 1,961 persons hospitalized with confirmed COVID-19 diagnosis
- Oklahoma totals as of 1/10/21
  - 331,362 total cases
  - 2,761 total deaths (roughly the population of Stroud, OK)

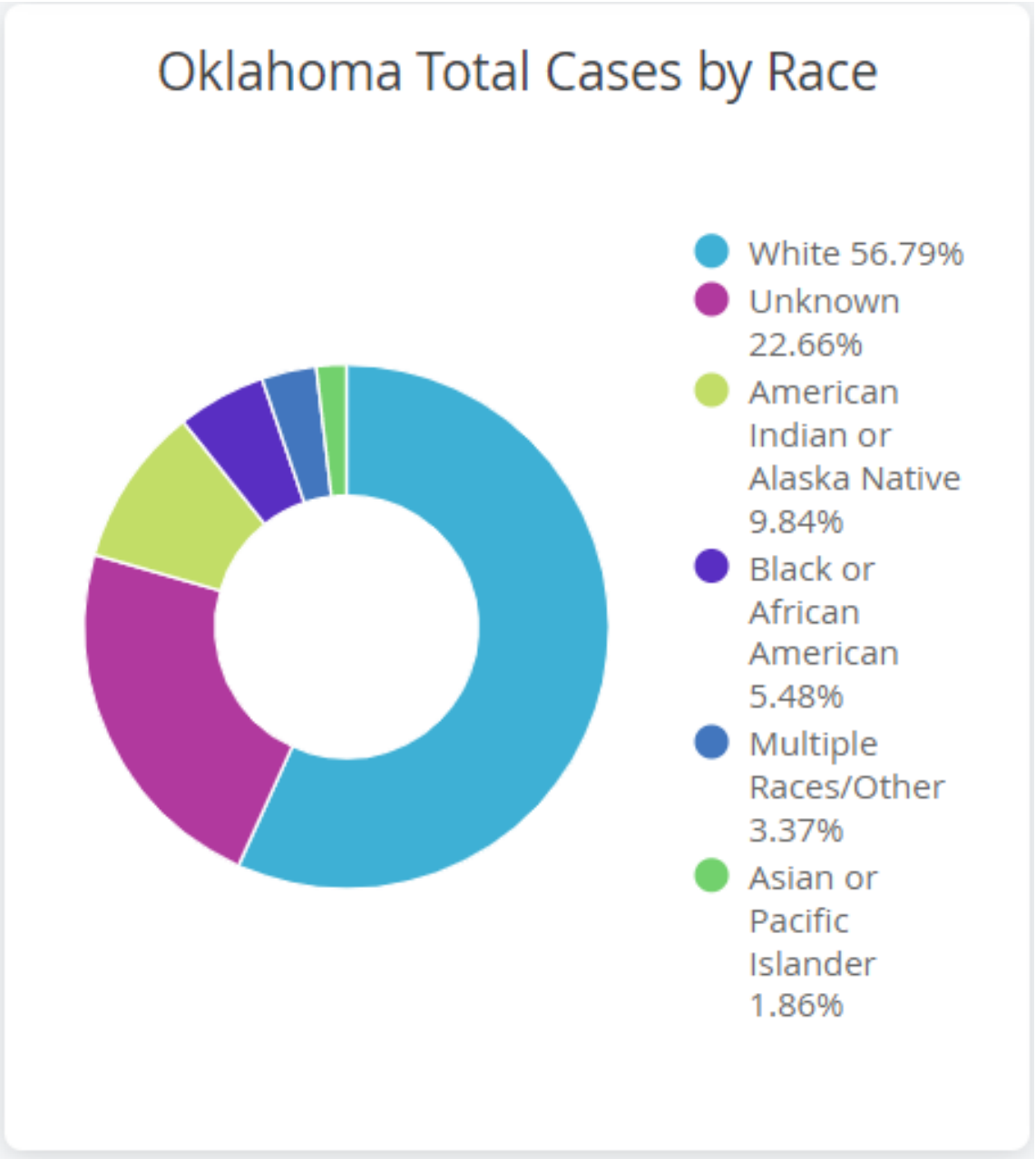
Oklahoma's Pandemic:

New COVID+ Deaths



CENTER FOR HEALTH SCIENCES

ECHO


Oklahoma Total Cases by Race
White 56.79%
Unknown 22.66%
American Indian or Alaska Native 9.84%
Black or African American 5.48%
Multiple Races/Other 3.37%
Asian or Pacific Islander 1.86%

OSDH

BLACK, ASIAN OR MINORITY ETHNIC BACKGROUND AMERICAN INDIAN OR ALASKAN NATIVES

- Increased illness from COVID-19
- Increased death from COVID-19

MMWR Weekly, Dec. 7, 2020

BLACK, ASIAN OR MINORITY ETHNIC BACKGROUND AMERICAN INDIANS OR ALASKAN NATIVES

- Barriers contributing to health disparities contributing to higher risk and death from COVID-19:
  - Access to health care
  - Employment
  - Education
  - Socioeconomic factors
  - Insurance coverage

MMWR Weekly, Dec. 7, 2020

VACCINE EFFICACY VS. VACCINE EFFECTIVENESS

- Vaccine efficacy refers to vaccine protection measured in RCTs usually under optimal conditions where vaccine storage and delivery are monitored, and participants are usually healthy.
- Vaccine effectiveness refers to vaccine protection measured in observational studies that include people with underlying medical conditions who have been administered vaccines by different health care providers under real-world conditions

EMERGENCY USE AUTHORIZATION

- According to the FDA website, an EUA “is a mechanism to facilitate the availability and use of medical countermeasures, including vaccines, during public health emergencies.”
- A product can receive EUA if it meets an effectiveness standard and an assessment of its benefit compared with its risk is favorable.

VACCINE DEVELOPMENT

HEALTH DEPARTMENT

What steps are taken to ensure that vaccines are safe?

The US Food and Drug Administration (FDA) oversees a careful process to ensure that vaccines are tested thoroughly before being offered to the public, including a three-phase review process for all new vaccines.

Phase 1

A small group of healthy volunteers receive the vaccine to test for safety and potential side effects.

Phase 2

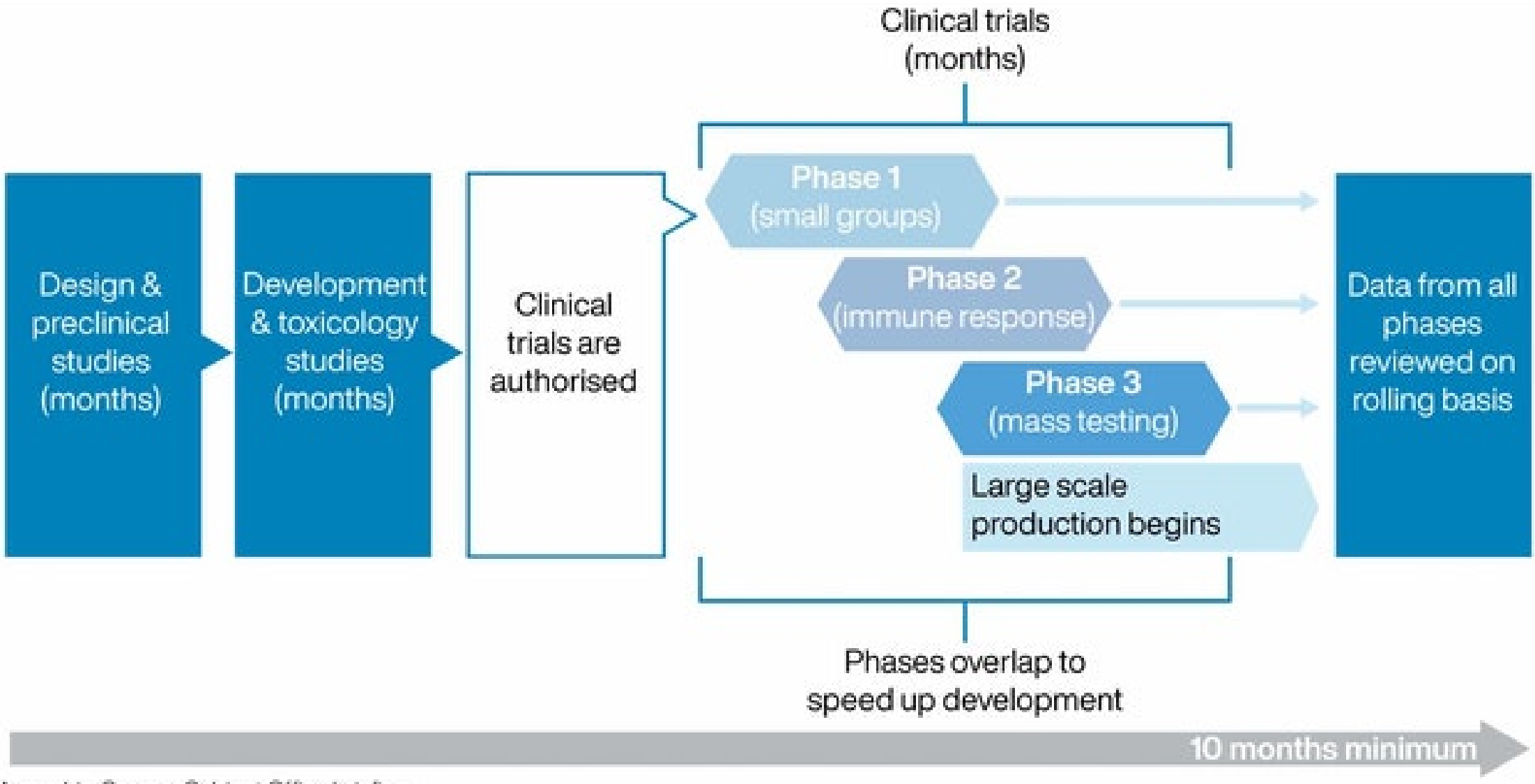
Several hundred people representative of the US population receive the vaccine to test how diverse immune systems respond.

Phase 3

Thousands of people receive the vaccine to test widespread effectiveness, side effects, and safety.

This graphic was adapted from information published in 2018 by the Centers for Disease Control and Prevention.

Covid-19: accelerated vaccine development timeline



PA graphic. Source: Cabinet Office briefing

1. - Number of vaccines in clinical development

60

2. - Number of vaccines in pre-clinical development

172

3. - Candidates in clinical phase

Filter	All	Select phase of development (default is all)

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	18	30%
VVnr	Viral Vector (non-replicating)	9	15%
DNA	DNA	8	13%
IV	Inactivated Virus	8	13%
RNA	RNA	7	12%
VVr	Viral Vector (replicating)	4	7%
VLP	Virus Like Particle	2	3%
VVr + APC	VVr + Antigen Presenting Cell	2	3%
LAV	Live Attenuated Virus	1	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	2%
		60	

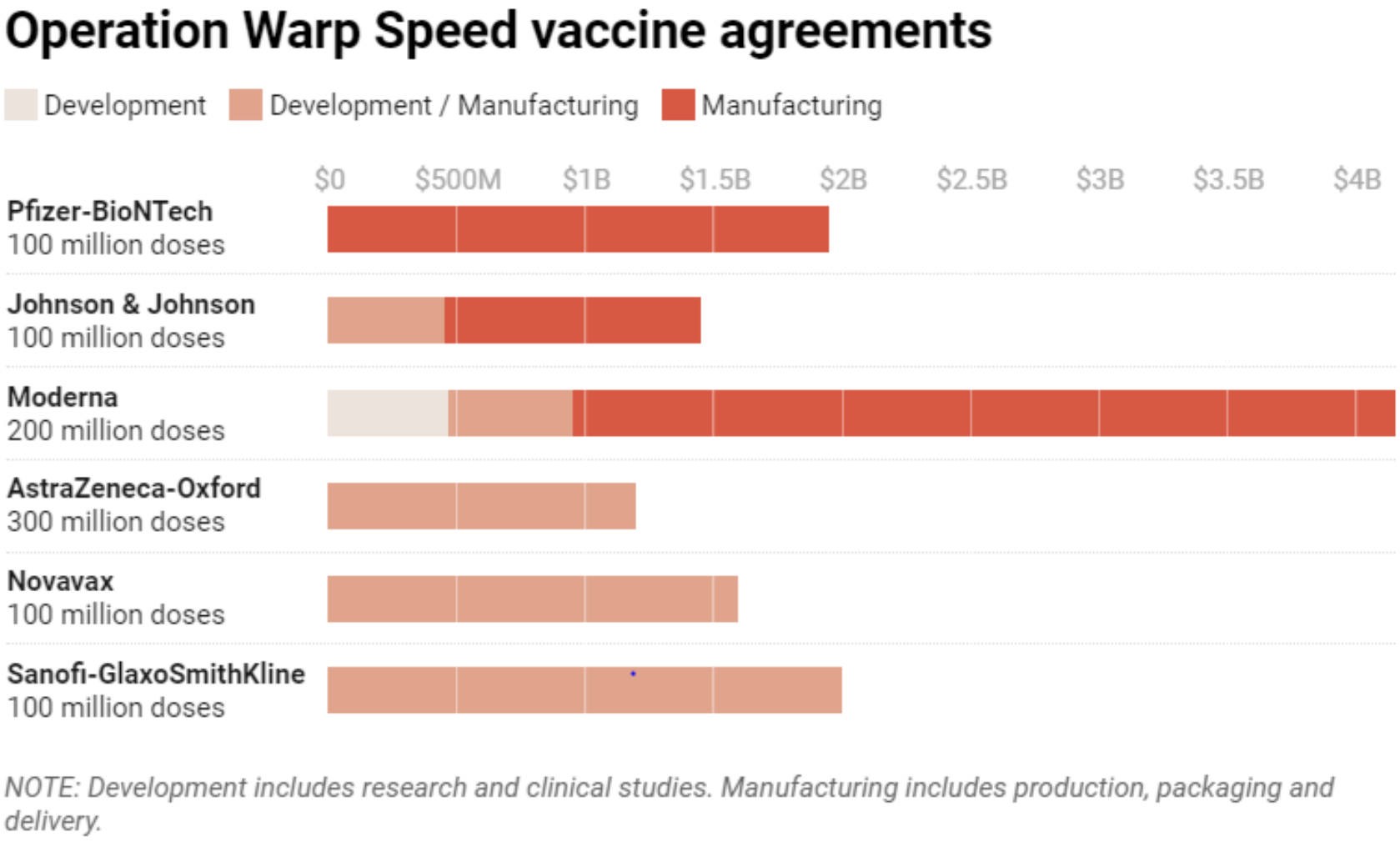
OPERATION WARP-SPEED

OPERATION WARP SPEED

Operation Warp Speed's goal is to produce and deliver 300 million doses of safe and effective vaccines with the initial doses available by January 2021, as part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics (collectively known as countermeasures).

- Sanofi-Glaxo (protein subunit)
- Moderna (mRNA)
- Pfizer-BioNTech (mRNA)
- Johnson and Johnson (vector-based)
- Oxford-AstraZeneca (vector-based)
- Novavax (protein subunit)

OPERATION WARP-SPEED



Time

TYPES OF COVID-19 VACCINES

mRNA VACCINE

Used by: Pfizer, Moderna

Doses: 2

mRNA vaccines are the newest approach. They use genetic material called messenger RNA, a kind of genetic software that instructs cells to make a piece of the coronavirus spike protein. That will get the attention of the immune system. The mRNA is coated in soft fatty lipids to protect it.

VECTOR VACCINES

Used by: AstraZeneca, Janssen, Sputnik

Doses: 1-2

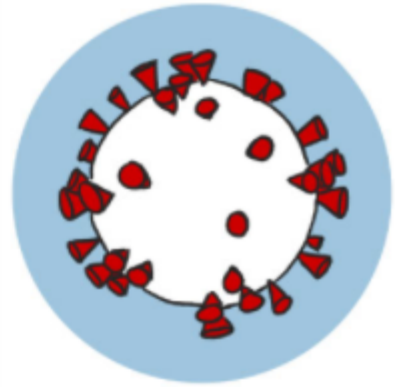
Vector vaccines use another virus to carry in the genetic instructions to make the spike protein. For coronavirus they all use adenoviruses, a type of common cold virus. They attach to cells and inject DNA that tells the cells to make coronavirus spike protein.

PROTEIN SUBUNIT VACCINE

Used by: Novavax, Sanofi

Doses: 1-2

Protein subunit vaccines just get little pieces of the target virus circulating in the system for the immune system to find and recognize. Instead of using the human body as the vaccine factory, genetically engineered insect viruses are used to infect moths, whose cells then produce the pieces of coronavirus spike protein. These are harvested and made into a vaccine.



WHOLE, KILLED VACCINES

Used by: Sinovac

Doses: 1

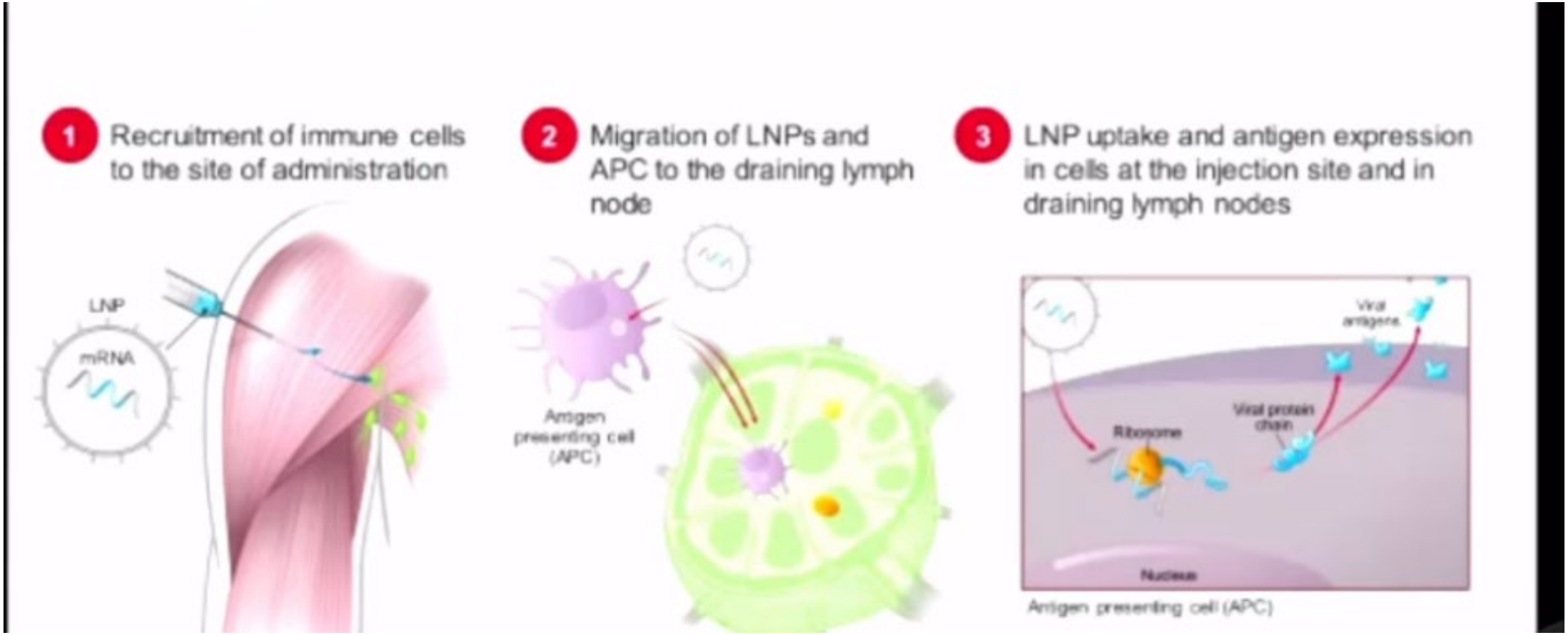
Whole inactivated virus vaccines take longer to make because batches of the coronavirus must first be grown and then killed using a chemical or heat, and then made into a vaccine that can be injected to elicit an immune reponse.

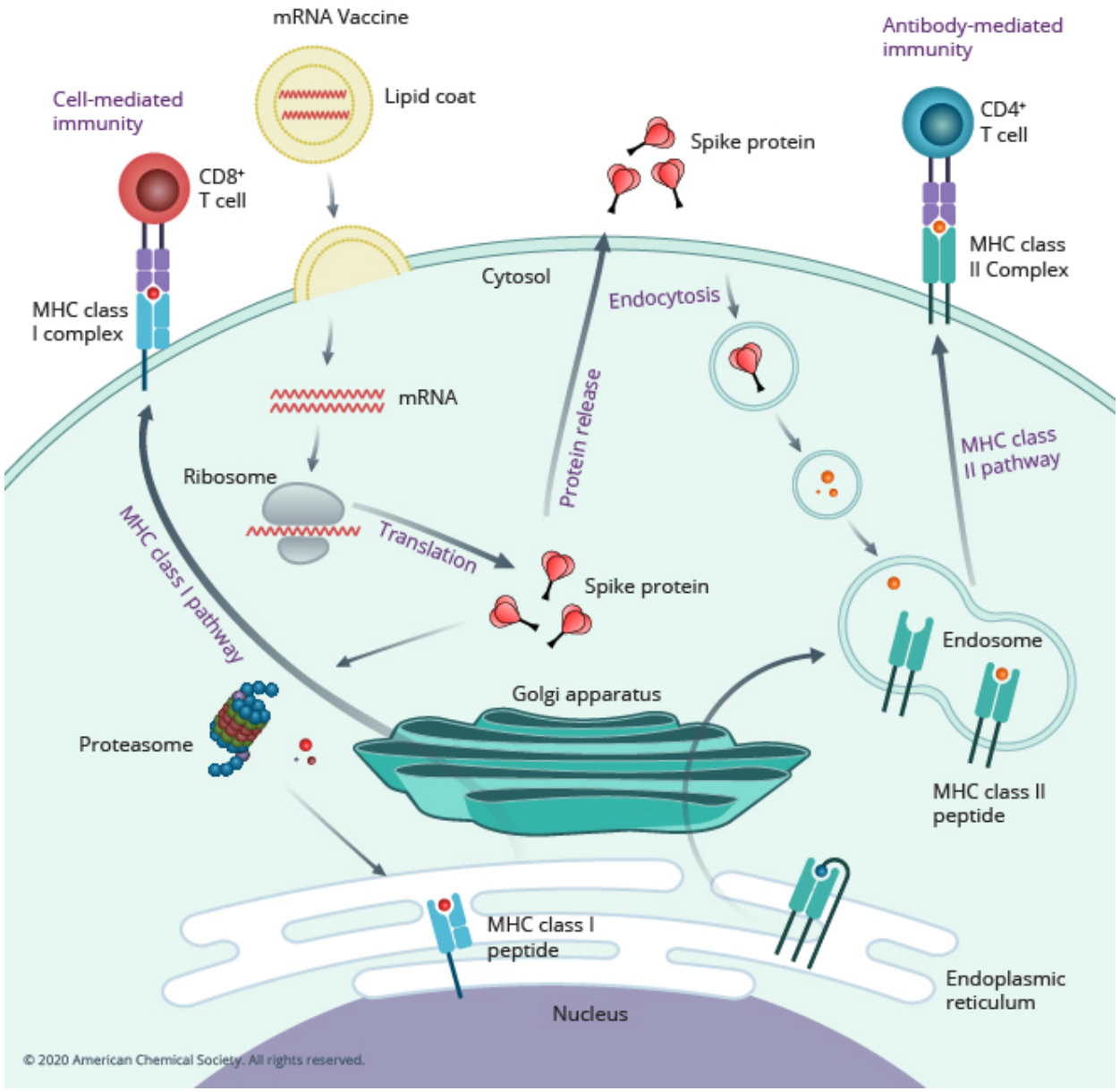
Source: CNN Reporting
Graphic: Will Mullery, CNN

M-RNA VACCINES
PFIZER-BIONTEC
MODERNA

MRNA VACCINES

STIMULATES BOTH CELL MEDIATED AND ANTIBODY MEDIATED IMMUNITY





CAS American Chemical Society

M-RNA DEVELOPMENT TIMELINE

- December 30, 2019: the International Society for Infectious Diseases posted online that people in Wuhan, a city of more than 11 million people in central China, had been diagnoses with an “unexplained pneumonia”
- January 10, 2020: Chinese scientists posted online the virus’s genetic sequence
- February 24, 2020: Moderna had its experimental vaccine ready to begin testing
- July 27, 2020: Pfizer/BioNtech and Moderna starts their phase III clinical trials
- December 11, 2020: Pfizer’s vaccine receives EUA approval
- December 18, 2020: Moderna’s vaccine receives EUA approval
- ----------
- mRNA vaccines do not contain live virus, so cannot cause infection or interact with our own DNA
- mRNA doesn’t enter the nucleus and doesn’t hang around (breaks down in hours)

PFIZER-BIONTECH VACCINE

- Must be kept at –70 degrees Celsius (- 94 degrees Fahrenheit)
- Can last in specialty freezer for 6 months
- Specialty freezer should not be opened more than twice a day and needs to be closed within one minute of opening. Once it's thawed, the vaccine can be refrigerated for five days.
- Specialty shippers can hold up to five "pizza box" trays of vials and be refreshed with dry ice every five days for up to 15 days to keep the vaccine at the right frozen temperature. (One tray=975 doses) (195 multidose vials).
- Some vials may contain more than 5 doses
- Boost dose given at 21 days

PFIZER-BIONTECH VACCINE
ANAPHYLAXIS AND ALLERGIC REACTIONS

- Out of the first 1.9 million doses administered in the U. S.,
  - there were 21 reported cases of severe allergic reactions. 71% of these occurred within 15 minutes of vaccination. (rate of 11.1 cases per 1 million vaccine doses; by contrast, rate of anaphylaxis with flu vaccine is 1.3 cases per 1 million doses).
- During the same period, non anaphylaxis allergic reaction with symptom onset within the 0–1-day risk window,
  - 72 (87%) of which were classified as nonserious.[§]
  - Commonly reported symptoms included pruritus, rash, itchy and scratchy sensations in the throat, and mild respiratory symptoms.
  - The median patient age was 43 years (range = 18–65 years),
  - 75 (90%) reported reactions occurred in women.
  - The median interval from vaccine receipt to symptom onset was 12 minutes (range = <1 minute–20 hours); in 61 (85%) cases, onset occurred within 30 minutes.

Morbidity and Mortality Weekly Report (*MMWR*) 1/6/21

MODERNA VACCINE

- Vaccine is stable at regular freezer temperature (- 20 degrees Celsius) (- 4 degrees Fahrenheit)— for up to six months.
- After thawing, it can last in the refrigerator for 30 days.
- Minimum size of orders currently 100 doses
- Boost dose given at 28 days.

PFIZER-BIONTECH COVID-19 VACCINE--EFFICACY

- Over 40,000 participants in placebo-controlled trial
  - 8 cases of symptomatic COVID-19 in the vaccine group
  - 162 cases of symptomatic COVID-19 in the placebo group
- 95% efficacy in preventing symptomatic COVID-19 infections
- Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions.
- Severe cases
  - 1 in the vaccine group
  - 9 placebo group

NEJMoa2034577. Epub 2020 Dec 10.

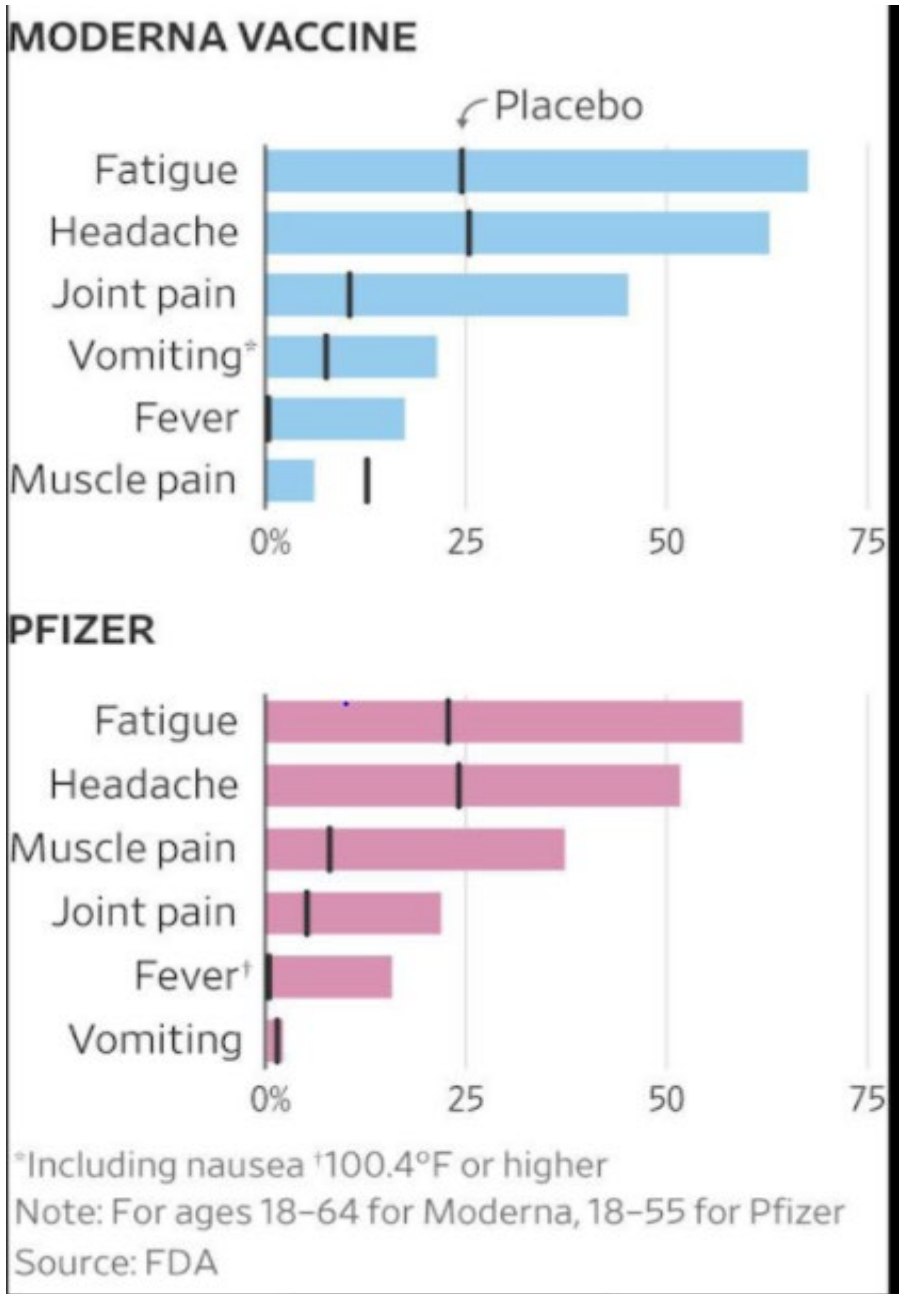
MODERNA COVID-19 VACCINE--EFFICACY

- Over 30,000 participants in placebo-controlled trial
  - 11 cases of symptomatic COVID-19 infections in the vaccine group
  - 185 cases of symptomatic COVID-19 in the placebo group
- 94.1% efficacy in preventing symptomatic COVID-19 infection
  - 95.6% efficacious in under 65 age group
  - 86.4% efficacious in the over 65 age group
- Severe cases
  - 0 in the vaccine group
  - 30 in the placebo group

The New England Journal of Medicine.
DOI: 10.1056/NEJMoa2035389.

M-RNA (MODERNA AND PFIZER) VACCINES

Common side effects



FACIAL NERVE (BELL'S) PALSY

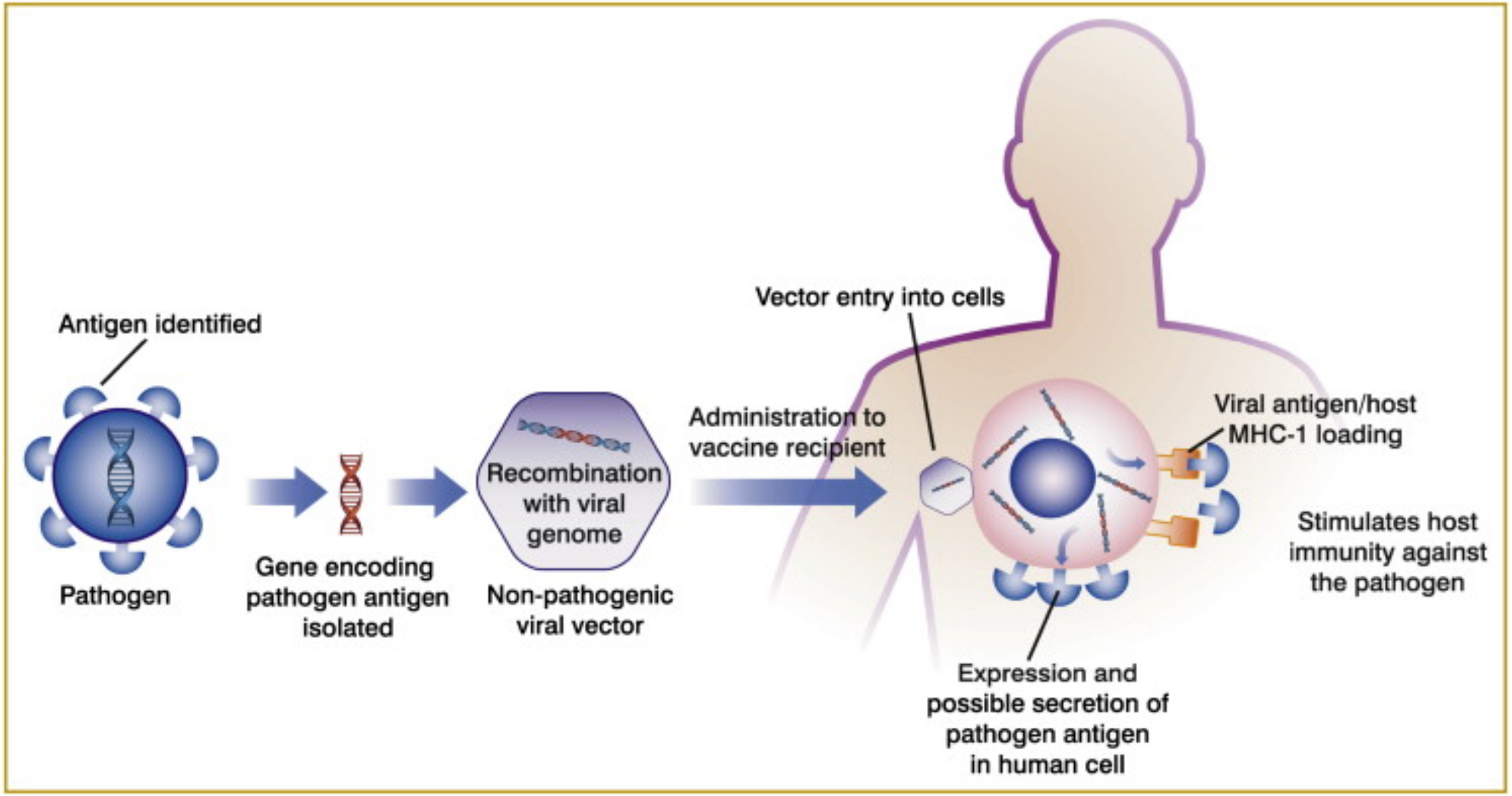
- 4 cases occurred in Moderna study participants
  - 3 in the vaccine group
- 4 cases occurred in the Pfizer study participants
  - All 4 occurred in the vaccine group
- All cases occurred within 3 months of vaccination and reportedly resolved in 3-6 months
- This equates to about 7 cases in 35K vaccine recipients, or about 20/100K
- The incidence of Bell's palsy in the general population is 20-30 cases/100K people *annually*.
- Overall, it is felt this risk is low.

NON-REPLICATING VIRAL VECTOR-BASED VACCINES

OXFORD-ASTRAZENECA

JOHNSON AND JOHNSON/JANSSEN

VIRAL VECTOR VACCINE



VECTOR-BASED VACCINES

- Easy and relatively cheap to make (cost-advantage)
- Does not require ultra-cold temperatures
- Once a pharmaceutical company has made a viral vector, it can be used for other vaccines
- In this approach a modified (so it carries the DNA of an antigenic protein from the target virus), inactivated virus (not pathogenic) is used to infect some of the body's cells, getting into the cell's nucleus but NOT integrating into the patient's own DNA, to utilize the normal cell protein manufacturing apparatus to create a desired spike protein to stimulate the immune system.
- ----------
- Downside: if patient has an antibody to the specific strain of human adenovirus, antibodies can target the vector rendering the vaccine ineffective

VECTOR BASED VACCINES

- J&J Janssen uses a relatively rare adenovirus subtype AD26 in its vaccine.
- Oxford AstraZeneca uses a chimpanzee adenovirus. Approximately 1% of the population have antibodies to the chimpanzee adenovirus.
  - Has been approved in the U.K.
  - Additional phase III trial ongoing in the U.S.
- Gorilla adenovirus and a replicating measles virus are also being investigated for use as vectors

OXFORD ASTRAZENECA COVID-19 VACCINE--EFFICACY

- Confusing data
  - 82% of participants were between the ages of 18 and 55
  - Only 12% were older adults
  - 83% of participants were white
- Control group received either saline or meningococcal vaccine
- Efficacy 14 days after 2ed dose: 70.4%
  - 62% efficacy in patients given a full dose of prime and boost (23K participants)
  - 90% efficacy in patients (mistakenly) given a ½ dose prime and full dose boost (2,800 participants)
    - However, none of these participants were over 55 years old.

JOHNSON AND JOHNSON/JANSSEN COVID-19 VACCINE

- Over 45K participants in placebo-controlled trial
- Results expected late January 2021
- Reportedly induced neutralizing antibodies in 98% of study's participants

VECTOR BASED VACCINES

- The European Medicines Agency: granted authorization in May 2020 for a new Ebola vaccine utilizing the Ad26 vector.

- Cheaper and easier to handle and store.
  - The Oxford-AstraZeneca shot requires only standard refrigeration and will remain viable for up to six months
  - J&J Janssen will likely only require one shot
    - expected to remain stable for at least three months at refrigerator-like temperatures

PROTEIN SUBUNIT VACCINES

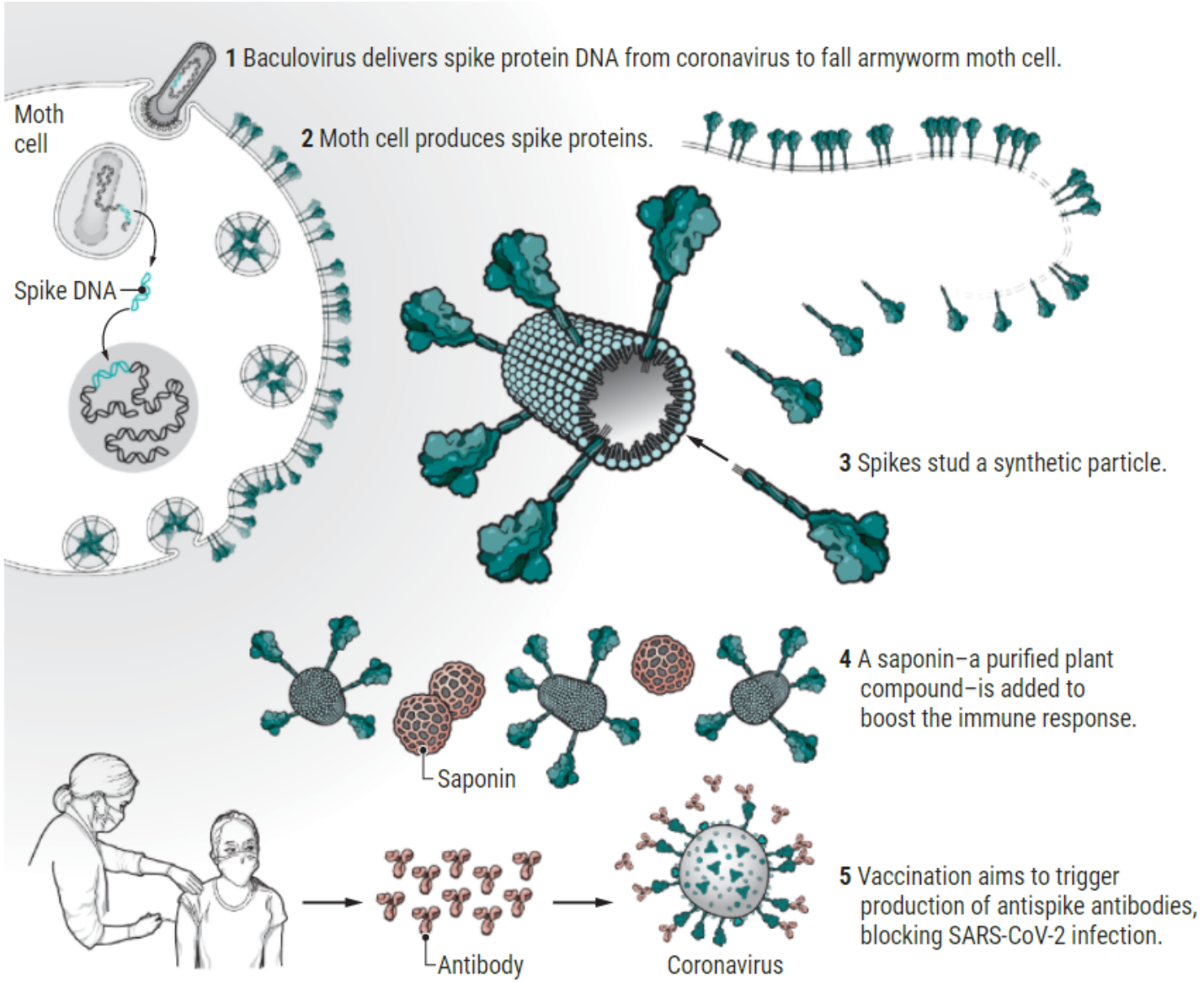
NOVAVAX

SANOFI-GSK

NOVAVAX

- Currently in Phase III trials
- Uses a lab-made version of SARS-CoV-2 spike protein
- Adds an adjuvant to boost immune response

- Modern influenza, HPV, and hepatitis B vaccines use a similar approach



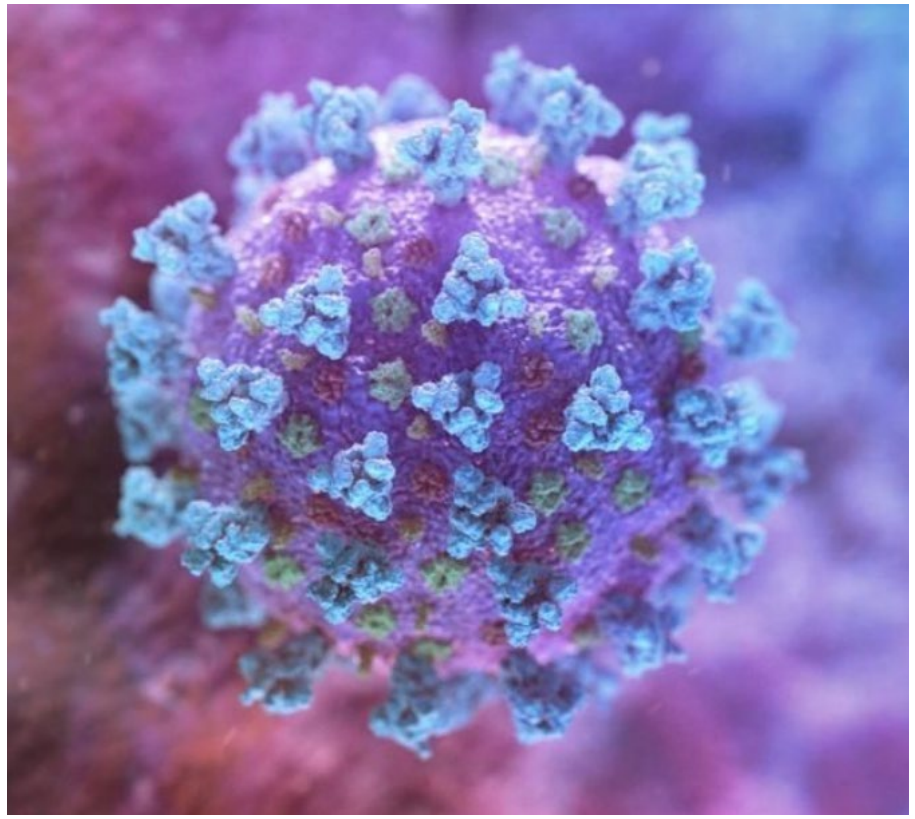
A. KITTERMAN AND V. ALTOUNIAN/*SCIENCE*

COVID-19 PROTEIN SUBUNIT VACCINES

- Contain only the antigenic parts of the pathogen.
- Once vaccinated, our immune system recognizes the proteins that doesn't belong in the body and begins making T-lymphocytes and antibodies
- This precision comes at a cost, as antigenic properties of the various potential subunits of a pathogen must be examined in detail to determine which combinations will produce an effective immune response within the correct pathway.
- Subunit vaccines do not contain live components and are considered as very safe
- Have an excellent stability profile
- Suitable for people with compromised immune systems
- Adjuvant (something you add to enhance, in the case of immunity, the immune response) or booster shots may be necessary

World Health Organization

VACCINE INFORMATION



WHO SHOULD NOT GET THE VACCINE?

- If the patient has a severe allergic reaction after the first injection, they should not be given the second injection. Patients who experience a severe allergic reaction should be referred for evaluation to possibly identify the etiology of the reaction.
  - Etiology may be polyethylene glycol. PEG is an inactive ingredient in some drugs, is used as a bowel prep for colonoscopies, and as a laxative.
  - Immediate allergic reaction (of any severity) to polysorbate
    - Polysorbate and polyethylene glycol are related structurally
- Those under the age of 16.

PEOPLE WHO MAY GET THE VACCINE AFTER CONSIDERING RISKS/BENEFITS AND/OR CONSULTING WITH HEALTHCARE PROVIDER

- Individuals with a history of severe or immediate allergic reaction to any vaccine or injectable medication
  - Data related to risk in individuals with a history of allergic reactions to other previous vaccinations and/or idiopathic anaphylaxis is very limited and evolving. Physician or other provider administering the vaccine using their professional judgement and in consultation with the patient, balancing the benefits and risks.
- Pregnant or lactating women may receive the vaccine if they choose, however, safety data is not known about this population at this time. A woman who is pregnant or lactating should consult with her physician about what is best for her and her baby.

SPECIAL CIRCUMSTANCES

- The COVID vaccine should not be given in combination with other vaccines
- The Centers for Disease Control and Prevention (CDC) recommends at least a two-week window between getting the COVID-19 vaccine and any other vaccine.
- People who received monoclonal antibodies or convalescent serum should wait at least 90 days before getting the vaccine.
- Persons with known COVID-19 illness should wait to get the vaccine till symptoms have cleared and have come out of isolation.

VACCINE INFORMATION

Individuals with common allergies to medications, foods, inhalants, venoms, and latex are no more likely than the general public to have an allergic reaction to the mRNA COVID-19 vaccines.

The mRNA COVID-19 vaccines should be administered in a healthcare setting where anaphylaxis can be recognized and treated. Vaccination providers should have appropriate medications and equipment—such as epinephrine and equipment for managing an airway. All anaphylactic reactions should be managed immediately with IM epinephrine as the first line treatment.

All people who receive a mRNA COVID-19 vaccine should be monitored on-site after receiving their dose. People with a history of severe allergic reactions should be monitored for 30 minutes after getting the vaccine. All others should be monitored for 15 minutes after getting the vaccine.

CDC

Appendix B: Triage of persons presenting for mRNA COVID-19 vaccination

	MAY PROCEED WITH VACCINATION	PRECAUTION TO VACCINATION	CONTRAINDICATION TO VACCINATION
CONDITIONS	**CONDITIONS** • Immunocompromising conditions • Pregnancy • Lactation **ACTIONS** • Additional information provided* • 15 minute observation period	**CONDITIONS** • Moderate/severe acute illness **ACTIONS** • Risk assessment • Potential deferral of vaccination • 15 minute observation period if vaccinated	**CONDITIONS** • None **ACTIONS** • N/A
ALLERGIES	**ALLERGIES** • History of food, pet, insect, venom, environmental, latex, or other allergies not related to vaccines or injectable therapies • History of allergy to oral medications (including the oral equivalent of an injectable medication) • Non-serious allergy to vaccines or other injectables (e.g., no anaphylaxis) • Family history of anaphylaxis • Any other history of anaphylaxis that is not related to a vaccine or injectable therapy **ACTIONS** • 30 minute observation period: Persons with a history of severe allergic reaction (e.g., anaphylaxis) due to any cause • 15 minute observation period: Persons with allergic reaction, but not anaphylaxis	**ALLERGIES** • History of severe allergic reaction (e.g., anaphylaxis) to another vaccine (not including mRNA COVID-19 vaccines†) • History of severe allergic reaction (e.g., anaphylaxis) to an injectable therapy **ACTIONS:** • Risk assessment • Potential deferral of vaccination • 30 minute observation period if vaccinated	**ALLERGIES** • History of severe allergic reaction (e.g., anaphylaxis) to any component of an mRNA COVID-19 vaccine† **ACTIONS** • Do not vaccinate

* See Special Populations section for information on patient counseling in these groups

† Refers only to mRNA COVID-19 vaccines currently authorized in the United States (i.e., Pfizer-BioNTech, Moderna COVID-19

VACCINE INFORMATION

- The current COVID-19 vaccines are not live vaccines and thus can be administered to immunocompromised patients. Providers should inform these immunocompromised patients of the possibility of a diminished immune response to the vaccine.
- Side effects usually mean a vaccine is generating an immune response.
- Most vaccines are administered IM (or intradermally) illicit primarily a systemic immune response, with less robust protection in the upper respiratory mucosa than after natural infection.

COVID-19 VARIANTS

- United Kingdom (UK) variant (B.1.1.7);
  - a new variant, found in Sept. 2020 in the UK with an unusually large number of mutations. (including N501Y)
  - This variant seems to spread more easily and quickly than other variants. (R-naught approximately 1 ½ times that of the wild type).
  - Currently, there is no evidence that it causes more severe illness or increased risk of death.
- South Africa variant (B.1.351):
  - a new variant that has emerged independently of the variant detected in the UK. First detected early Oct. 2020
  - Shares some mutations with the variant detected in the UK. This variant seems to spread more easily and quickly than other variants.
  - Currently, there is no evidence that it causes more severe illness or increased risk of death.
- Another variant recently emerged in Nigeria. CDC also is monitoring this strain but, at this time, there is no evidence to indicate this variant is causing more severe illness or increased spread of COVID-19
- Another variant just found in the U. K. in 4 travelers from Brazil's Amazonas state with 12 mutations.

CDC

DO EXISTING VACCINES WORK AGAINST NEW VARIANTS?

- Because existing vaccines elicit a broad immune response…that targets several areas of the spike protein, it is believed that these vaccines will be effective against the new variants.
- Monoclonal antibodies: some concerns about effectiveness as additional variants emerge.

COVID-19 VACCINE ACCEPTANCE/HESITANCY

COVID-19 VACCINE—PUBLIC ENTHUSIASM (KAISER FAMILY FOUNDATION) DECEMBER 2020

- Would you get the vaccine?:
- ASAP—34%
- Wait and see (how the vaccine is working for other people first)—39%
- Only if required (for working, school, or other activities)—9%
- Definitely not—15%
  - Low trust in public health messengers
  - Low rate of flu vaccinations
  - High rates of believing misinformation about other health measures like mask-wearing

COVID-19 VACCINE ACCEPTANCE (KAISER FAMILY FOUNDATION) DECEMBER 2020

- Vaccine acceptance 71% (up from 63% in September 2020)
- 27% of the public remain vaccine hesitant
  - Highest ages 30-49 (36%)
  - Rural residents (35%)
  - Black adults (35%)
  - Essential workers—self identified (33%)
    - 3/10 (25%) work in healthcare delivery settings

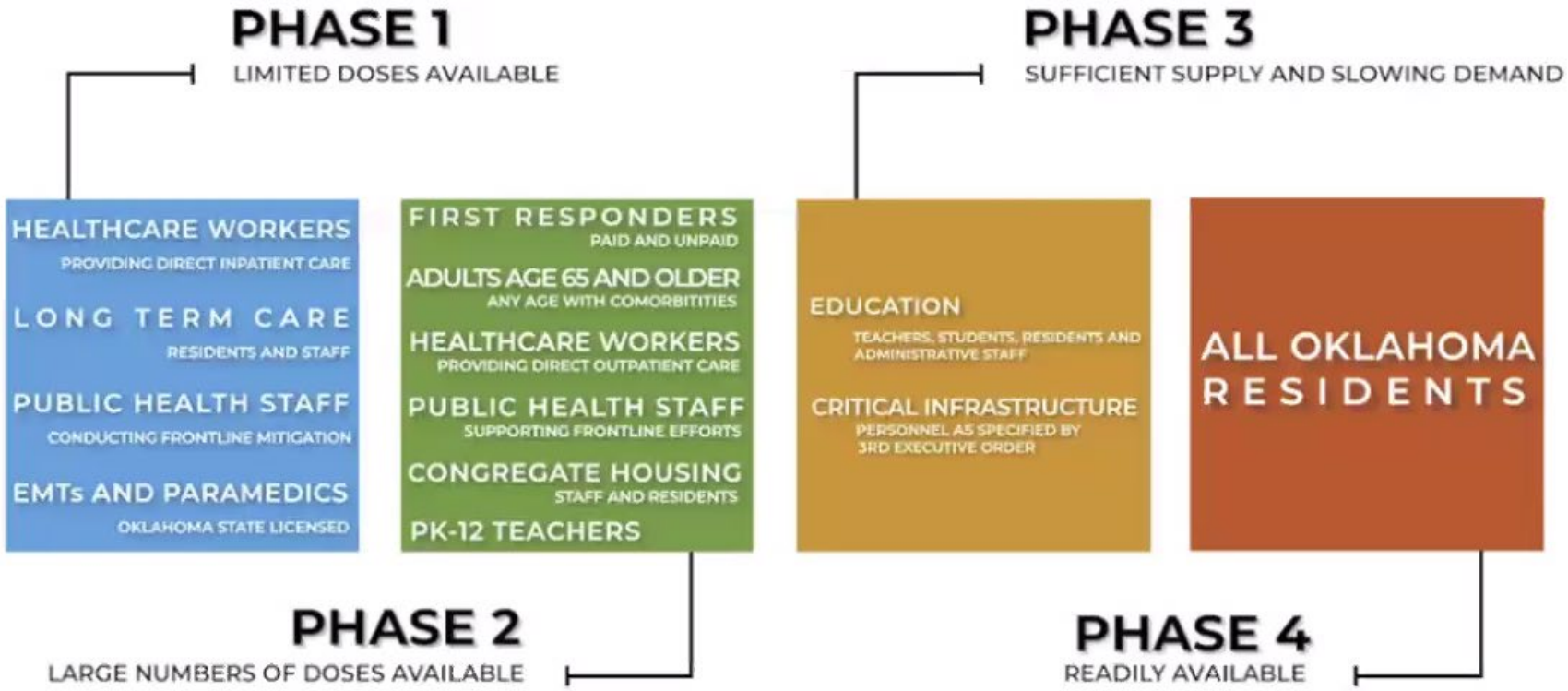
COVID-19 VACCINE HESITANCY (KAISER FAMILY FOUNDATION) DECEMBER 2020

- Stated reasons for hesitancy
  - Possible side effects (59%)
  - Lack of trust in government to ensure vaccines' safety and effectiveness (55%)
  - Vaccine too new (53%)
  - Concerns over the role of politics in the development process (51%)
  - About one-half of the black adults who say they probably or definitely won't get vaccinated cite
    - Don't trust vaccines in general (47%)
    - May get COVID from the vaccine (50%)

OKLAHOMA COVID-19 VACCINE ROLL-OUT

Oklahoma COVID-19 Vaccine Plan

Vaccine Information (oklahoma.gov)



CENTER FOR HEALTH SCIENCES

Project ECHO

PHASE II

- State entered phase II week of January 4, 2021
- Large group, initially including:
  - First responders
  - Elderly, age 65 and older
  - Healthcare workers including expanded healthcare worker groups such as allied health fields and general outpatient health service
  - Teachers
- OSDH working with each county health department to set up ‘pods’
  - Need appointments—initially utilizing SignUpGenius
- Social media has been the best place for information regarding vaccine sites
- OSDH portal went live on 1/7/21 to better coordinate vaccine sign-ups.
- Vaccinate.Oklahoma.gov

OKLAHOMA COVID-19 VACCINATION PROGRAM

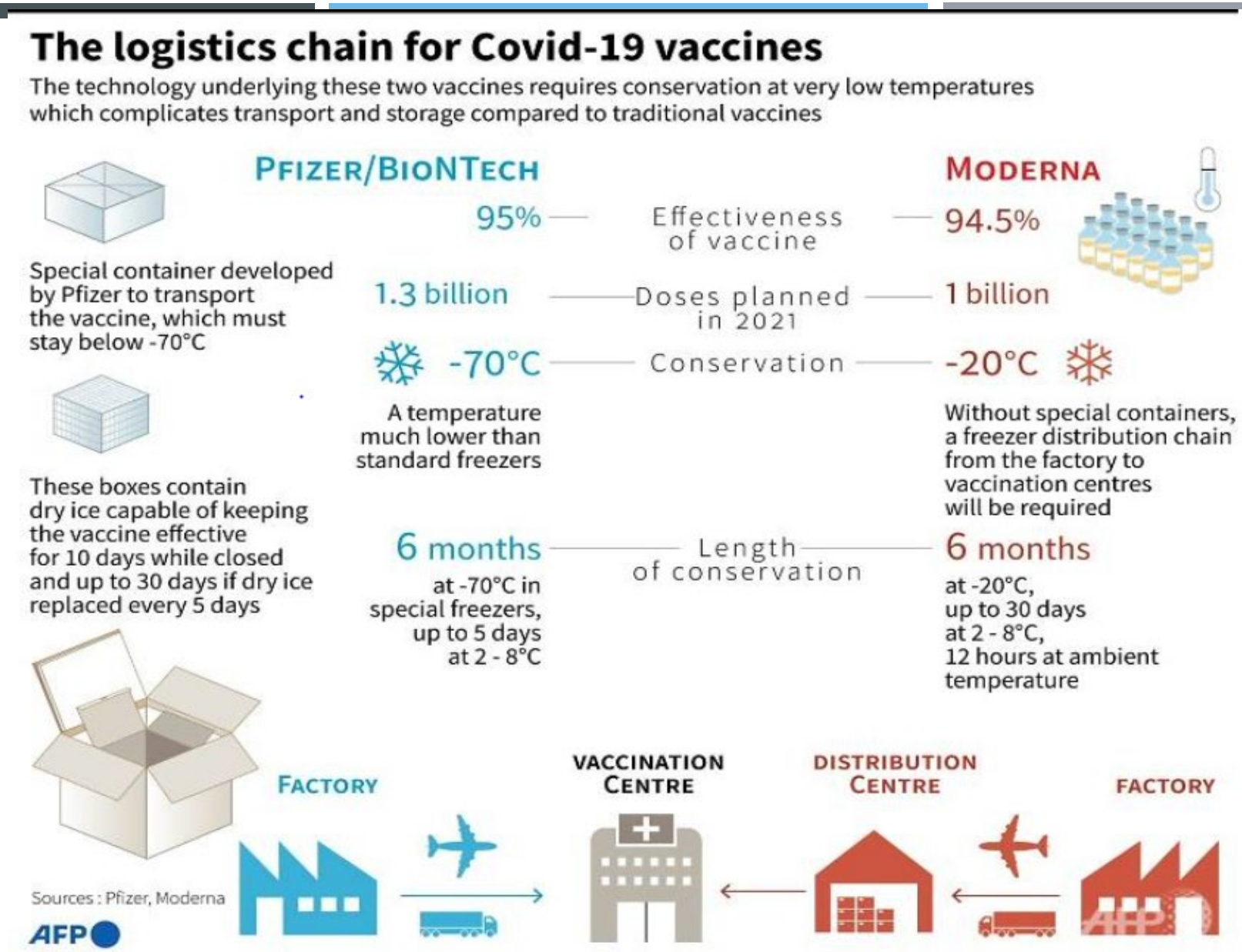
- Oklahoma receives 30-40K prime doses per week. The state is notified on the preceding Tuesday how many doses will be shipped.
- Supplies are also received from the federal government
- Varying distribution sites or PODS (point of distribution sites) will be announced as they are determined. Likely will not be the county health departments.

ANNOUNCED CHANGES TO VACCINE DISTRIBUTION

- Trump administration moved to accelerate vaccinations by releasing the doses being kept in reserve. (1/12/21)
- Biden administration announced it supports distributing most, but not all, the currently reserved doses.
  - Allows more people to get their initial ‘prime’ doses
  - Would invoke the Defense Production Act, if needed, to ensure manufacturers could make and distribute the second ‘boost’ dose on-time
  - Not suggesting going to only a single dose. Committing to giving the second dose on-time
- Biden announced, last night, that he has a goal of administering 100 million shots by the end of his first 100 days
  - Further information to be released today

OTHER PROPOSALS

- Delaying the second (boost) dose up to 12 weeks in order to giving as many people as possible their prime dose
  - Not recommended by the FDA
  - U. K is following this model
- Administering half strength of the Moderna vaccine
  - A clinical trial showed two ½ strength doses had a similar response as compared with two full strength doses. (participants in the trial ages 18 to 55).



The low-temperature logistics chain for two Covid-19 vaccines AFP/Paz PIZARRO

OTHER CONSIDERATIONS

- Will immunity be durable?
  - How often will the population need to be vaccinated
- Will vaccines perform well with emerging lineages or variants?
- Will acceptance be high?
- Will masks and physical distancing continue to be necessary?

SUMMARY

- mRNA vaccine administration is a tremendously complicated task.
  - Cold storage requirements
  - Matching supplies with vaccines
  - 2 dose requirements for optimum protection
  - Mitigation measures necessary while process is progressing
- Additional vaccine approvals without cold storage requirements and ability to provide larger number of vaccine doses will help tremendously.
  - J&J may be able to apply for EUA as early as end of January 2021.
  - AstraZeneca is on track to apply for EUA as early as March 2021.
- Correlates of protection assays—testing has begun
  - looking for mechanism for new vaccines that will be unable to do placebo-controlled trials to be able to get approved

INDIAN HEALTH SERVICE

- Indian Health conducting vaccinations outside of the OSDH
- They receive a separate allotment of vaccines to distribute to 38 tribal nations
  - Moderna vaccines distributed to sites directly from the manufacturer.
  - Pfizer vaccine, due to extreme cold requirements, are shipped to the larger tribal programs which are then distributed to smaller sites. .