The Prudent Prescriber

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Some observations on the Pfizer and Moderna COVID-19 vaccines

Quick Comparison:

	Type of vaccine	Dosage Regimen	Storage Temp	Efficacy	Typical A/E	Availability	Cost
Pfizer	mRNA	2 doses, 0 and 21 days	-70°C. May be kept in refrigerator for **5 days** after thawing	95% overall	Injection pain, fatigue, headache, fever	Available now under a EUA (emergency use authorization)	$0 Pharmacies will be paid an administration fee, usually around $22
Moderna	mRNA	2 doses, 0 and 28 days	-4°C, can be kept in refrigerator for **30 days** after thawing	94.5% overall (interim analysis)	Similar to Pfizer's, seem to be more common after the 2nd dose vs. Pfizer's	Undergoing FDA review, expect EUA approval and launch very soon	$0 Pharmacies will be paid an administration fee, usually around $22

Phil's observations of the Pfizer vaccine data

The COVID-19 Vaccine (BNT162b2) Phase 3 Trial
(NEJM December 10, 2020)

Methods:

- Multinational (US {77%}, Argentina Brazil, South Africa, Turkey and Germany) placebo-controlled, double blinded, randomized in a 1:1 ratio to receive two 30-ug doses, 21 days apart, of either saline placebo or BNT162b2 mRNA vaccine.
- Those studied were ages 16–91 years. There were few 15 and 16 year olds.

- The study included those who were healthy or had stable chronic medical conditions including, but not limited to HIV, Hepatitis B and Hepatitis C viral infections.
- Exclusion criteria included a medical history of COVID-19, treatment with immunosuppressive drugs or diagnosis with an immunocompromising condition.
- Race or ethnic group was reported by the participants: White (82.9%), African American (9.2%) and Latino (27.9%). And you're right, the total does not add up to 100%.
- The total study population without baseline infection was 36,523; the total population including those with and those without prior evidence of infection was 40,137.
- Vaccine can be stored for up to five days at standard refrigerator temperatures once ready for use, but very cold temperatures are required for shipping and storage.
- The participants were observed for 30 minutes after vaccination for acute reactions.
- The primary end points were efficacy of the vaccine against laboratory-confirmed COVID-19 and safety.

Efficacy Results:

- Cases of COVID-19 with onset at least seven days after the second dose among participants who
  - received vaccine: 8
  - received placebo: 162
- Thus this vaccine was 95% effective overall and 90-100% effective among subgroups defined by age, sex, race, ethnicity, body mass index including obesity), and in the presence of coexisting conditions like hypertension.
- The vaccine appears to be equally effective with those patients who had evidence of previously laboratory confirmed COVID-19 infection.
- Among 10 cases of severe COVID-19 (respiratory failure, evidence of shock, significant acute renal, hepatic or neurologic dysfunction, admission to an intensive care unit or death) with onset after the first dose, nine occurred in placebo recipients and one occurred in a vaccine recipient.
- Between the first dose and the second dose, 39 cases in the vaccine group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

Safety Results:

Pain at Injection Site

Dose of Vaccine	<55 years	>55 years
1st	83%	71%
2nd	78%	66%

- <1% complained of severe pain.
- A few in either age group complained of redness or swelling.
- Most local reactions were mild to moderate in severity and resolved within 1 to 2 days.

Systemic Symptoms after 2nd Dose

	<55 years	>55 years
fatigue	59%	51%
headache	52%	39%
fever	16%	11%

- Fatigue and headache were also reported by many placebo recipients (23% and 24%, respectively after the second dose among younger vaccine recipients and 17% and 14% among older recipients.
- Two participants each in the vaccine and placebo groups reported temperatures above 40°C (104° F)
- Severe fatigue was observed in approximately 4% of the vaccine recipients. This is higher than that observed in recipients of some vaccines recommended for older adults.

- Four related serious adverse events were reported among vaccine recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia and right leg paresthesias).
- Two vaccine recipients died (one from arteriosclerosis, one from "cardiac arrest") as did four placebo recipients. No deaths were considered by investigators to be related to the vaccine or placebo. During the trial, no Covid-19 associated deaths were observed.

Limitations of this study:

- This study was not powered to definitively assess efficacy by subgroup. The point estimates of efficacy for the subgroup are high however.
- The study was not designed to evaluate the efficacy of a single-dose regimen.
- The study has more than an 83% probability of detecting at least one adverse event if the true incidence is >0.01%, but it is not large enough to detect less common adverse events reliably.
- This study reports two months of follow-up after the second dose of vaccine for half the trial participants and up to 14 weeks maximum follow-up for a smaller subset. Therefore the occurrence of adverse events more than two to 3 ½ months after the second dose remains to be determined.

Phil's Take:

- My heart rejoices at this trial, but my brain recalls the biases inherent in pharmaceutical company sponsored studies. Oh that "N" was larger and the follow up was longer.
  Nonetheless:
    - The Really Good News #1 is that this vaccine appears to be highly effective in black people, fat people, brown people, healthy people, white people, old people, chronically ill people, hypertensive people, young people, and among residents of North and South America, South Africa and Europe. Unfortunately, Native Americans, Asians, Native Hawaiians and other Pacific Islanders are underrepresented in this trial.
    - The Really Good News #2 about this vaccine is that a single dose of the vaccine offers significant protection within 12 days of administration.
    - The Really Good News #3. This trial provides preliminary evidence of vaccine mediated protection against severe disease. This may help alleviate some theoretical concerns over vaccine mediated disease enhancement.
- The short term adverse events appear to be what one would expect and overall are acceptable.
- With the exception of severe fatigue in 4% of the vaccine recipients, both the local and systemic side effects resolved in a few days.
- Fortunately the dropout rates because of adverse events after the first dose were low in both the vaccine and placebo groups. (The vaccine group had 28 adverse events prompting no second dose and the placebo group had 18 adverse events prompting no second dose.)
- The short term follow-up in this study looking at both efficacy and side effects is troublesome, but you can't have it both ways.
    - I'll be in line when my turn comes.

Steve's observations on the Moderna vaccine:

This one is undergoing ACIP/FDA EUA review at the time of this writing

The mRNA -1273-P301 study (not published, data available from the EUA application to the FDA's ACIP)

- Ongoing, multi-center, randomized, blinded, placebo controlled, safety and efficacy study.
- 2 doses, 28 days apart, in 99 sites in the U.S.
- 30,351 participants: 15,181 received the vaccine, 15,170 received placebo.

- Patients were stratified by age and health risk into 3 groups:
    - Age 18-64 not at risk for progression to severe COVID-19 disease
    - Age 18-64 and at risk for progression to severe COVID-19
    - Age 65 and over.
- The "at risk" group was defined as those with underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV.

Primary endpoint: development of COVID-19 disease occurring at least 14 days after the second dose.

Some demographics: 25.3% over age 65 (avg. age 51), 36.5% representing communities of color, and 22% were considered high risk for progression to severe disease.

Efficacy of interim results:

- There were 5 confirmed cases in the vaccine group and 90 cases in the placebo group, for an overall efficacy of 94.5% for preventing COVID-19 at least 14 days after the second injection.
- In those aged 18-64, the efficacy was 93.4%, and in those 65 and up the efficacy was 100%.
- It was 100% effective in those of non-white race (all 5 cases were white ethnicity).
- It was also 100% effective at preventing severe disease (all 11 severe cases were in the placebo group).
- In those with underlying conditions efficacy was 95.9% and 94% for those without.

Efficacy after 1 dose

- 80.2% overall, showing 50.8% efficacy up to 14 days post dose, and 92.1% efficacy up to 28 days post first dose.
- This was a small, non-random sample which limits interpretation, and provides no evidence of efficacy after 28 days from one injection.

The final analysis of the completed study will likely show efficacy lower than this, as the data from the final scheduled efficacy analysis (9 weeks after second dose) looks like an overall efficacy of 94.1%, and 86.5% in those over 65 (considerably lower than the interim analysis).

Adverse effects:

Pain at Injection Site

Dose of Vaccine	<65 years	≥65 years
1st	87%	74%
2nd	90%	83%

Systemic Symptoms

	<65 years	≥65 years
Any systemic AE, 1st dose	57%	48%
Any systemic AE, 2nd dose	81%	72%
Fatigue, 1st dose	39%	33%
Fatigue, 2nd dose	68%	58%
Headache, 1st dose	35%	24%
Headache, 2nd dose	63%	46%
Fever, 1st dose	0.9%	0.3%
Fever, 2nd dose	17%	10%

The most common systemic adverse effect was fatigue, reported by 69% of vaccine recipients vs. 36% for placebo.

Limitations of the study data: The available Moderna vaccine data is less mature than Pfizer's, with 95% having completed the second dose, and only about 52% having completed 7 weeks of follow-up observation after the 2nd dose.

Steve's Take:

- As with the Pfizer vaccine, it appears we have a safe and effective vaccine from Moderna and this one's easier to store. ACIP approval is expected on December 17.
- Follow up time is short and based on the reduction in efficacy from the interim to final results, and some likely non-adherence to the second dose, we can expect somewhat lower efficacy in the real world than that presented to the FDA.
- Safety looks good with more reported A/E's after the second dose which may impact adherence to the two-dose regimen.
- With media coverage already beginning with those experiencing anaphylaxis and other severe adverse effects, it will be important to educate patients to put these effects into perspective!

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