COVID Vaccine Primer

January 5, 2021

Gérard Coste

Slowly he would cruise the neighborhood, waiting for that occasional careless child who confused him with another vendor.
Outline

- Vaccine development
- How do the Pfizer, and Moderna vaccines work?
- What do we know about efficacy and safety at this point?
- What are the side effects of the Pfizer and Moderna vaccines
How do vaccines help with our immunity?

Vaccination is the process of boosting protective adaptive immune responses against microbes by exposure to dead microbes or parts of dead microbes or parts that look like dead microbes.
### How seasonal flu and Covid-19 compare

<table>
<thead>
<tr>
<th>Metric</th>
<th>FLU</th>
<th>COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RO number</strong></td>
<td>1.3</td>
<td>2-2.5</td>
</tr>
<tr>
<td>Estimate of how many people</td>
<td></td>
<td>Top of the range</td>
</tr>
<tr>
<td>will be infected by an average individual with the disease</td>
<td></td>
<td>Bottom of the range</td>
</tr>
<tr>
<td><strong>Incubation time</strong></td>
<td>1-4</td>
<td>1-14</td>
</tr>
<tr>
<td>The time from exposure to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalization rate</strong></td>
<td>2%</td>
<td>19%</td>
</tr>
<tr>
<td>Average percentage for total cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Case fatality rate</strong></td>
<td>.1% or less</td>
<td>1-3.4%</td>
</tr>
<tr>
<td>Percentage of reported deaths among total cases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources: CDC, WHO, NCBI
What happens if we do not have or use a vaccine?

- Eventually most of the population will get infected
- 10-20% will be without symptoms
- 10-20% will be hospitalized
- 1-3% may die - (3-9 million)
- An unknown # of people will develop long term sequelae (heart, lungs, neurological complications) that could result in disability
YES! HERD IMMUNITY ACHIEVED!
Vaccine development usually takes 10-15 years

FIGURE 1 | Flowchart showing traditional process of vaccine development from exploratory, pre-clinical studies to Phase 1 studies in a comparatively few control volunteers as depicted by the figure to larger Phase 2 and Phase 3 studies. The symbol is a representation of the number of human subjects in trials.
Vaccine development usually takes 10-15 years
MIRACLE
How was the COVID vaccine developed so fast?

The world was able to develop COVID-19 vaccines so quickly because of years of previous research on related viruses and faster ways to manufacture vaccines, enormous funding that allowed firms to run multiple trials in parallel, and regulators moving more quickly than normal.

*SARS-CoV-2, is a virus that mutates relatively slowly* and that happens to belong to a well-studied family. Within weeks of identifying the virus scientists had mapped out its complete gene sequence. That information was shared immediately all over the world to vaccine researchers and developers.

With large sums given to vaccine firms by public funders and private philanthropists, they could do preclinical and phase I, II and III trials, as well as manufacturing, in parallel instead of sequentially.

In the final stages of trials, it helped that COVID-19 was everywhere because firms need infections to show that vaccines work. It’s hard to run efficacy trials when the diseases themselves aren’t prevalent.
30 years of painstaking research allowed several groups of scientists — including a group at Pfizer working with a German company called BioNTech, and a young company in Massachusetts called Moderna — to bring mRNA vaccine technology to the threshold of actually working. The companies had built platforms that, theoretically, could be used to create a vaccine for any infectious disease simply by inserting the right mRNA sequence for that disease.

Within weeks of identifying the responsible virus, scientists in China had determined the structure of all of its genes, including the genes that make the spike protein, and published this information on the Internet.

Within minutes, scientists 10,000 miles away began working on the design of an mRNA vaccine. Within weeks, they had made enough vaccine to test it in animals, and then in people. Just 11 months after the discovery of the SARS-CoV-2 virus, regulators in the United Kingdom and the US confirmed that an mRNA vaccine for COVID-19 is effective and safely tolerated, paving the path to widespread immunization. Previously, no new vaccine had been developed in less than four years.
Vaccines generally target the “spike protein”

- Spike Protein - is a protein on the surface of the virus.
- A latch/target for the immune system
- The whole virus “gene” can make a whole new virus
- The Spike protein gene can only make the spike protein NOT the VIRUS
Spike protein is like
A flag in front of a house.
It’s a way for the immune system to identify viruses
Three types of coronavirus vaccines in development

1. Protein-based
   - Spike protein is purified and injected

2. Viral vector
   - Adenoviral vector is injected
   - Body produces spike protein
   - Immune system produces antibody

3. mRNA
   - mRNA that codes for spike protein is purified and injected
   - Body produces spike protein

Source: National Institutes of Health presentation at Senate hearing on September 9, 2020
Pfizer and Moderna vaccines use mRNA

- How do they work?
  - A snippet of mRNA is coated in a synthetic lipid shell.
  - It enters cells near injection site and cell machinery creates the spike protein and sticks it on the outside of cells, generating an immune response.
mRNA vaccines are new but have great potential

● Are they safe?
  ○ Despite being a new technology, safety is actually a big advantage of mRNA vaccines
  ○ Content of vaccine is simple - it does not contain any live virus.
  ○ It does not go to the nucleus or interact with host genome
  ○ A number of mRNA vaccines have been shown to be safe in human trials since 2008 (mainly cancer vaccines, none effective enough to be approved)

● Advantages
  ○ Easy to rapidly develop new vaccines
  ○ Safety
  ○ Generates strong immune response (no need for adjuvants)

● Disadvantages
  ○ Highly unstable; needs to be kept cold, so a challenge for distribution
  ○ Expensive
Pfizer/BioNTech

- 2-dose mRNA vaccine
- Phase 2/3 trial with 43,000 participants, first trial to include children 12+
- Preliminary analysis:
  - Out of 170 cases of COVID-19, 162 were in the placebo group
  - Out of 10 severe cases, 9 were in the placebo group
  - Efficacy rate estimated at 95% (94% in adults 65+)
  - No serious side effects detected
- UK, Canada and US approved emergency use

Figure 13  Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

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No. with events/No. at risk

A: 0/1534  21/1230  37/11954  39/23484  41/19814  42/19377  43/17762  43/17168  44/15464  47/14038  47/12169  48/9951  48/7403  48/5374  50/1481  50/998  50/0

B: 0/1250  25/21170  55/20970  73/20356  97/20209  123/19018  145/17758  166/17025  192/15290  212/13876  235/11994  249/9471  257/6294  257/3201  274/0440  275/090  275/0

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A: BNT162b2 (30 µg)  B: Placebo
Moderna

- 2-dose mRNA vaccine
- Phase 3 testing with 30,000 participants
- Preliminary data:
  - Out of 196 cases of COVID-19, 185 were in the placebo group
  - All of the 30 cases of severe disease were in the placebo group
  - Efficacy rate estimated at 94.1%
- Approved by FDA for Emergency Use

Reactogenicity Side Effects within 7 days of vaccine Solicited Via E-Diary

**Most common reactogenicity symptoms**

<table>
<thead>
<tr>
<th>symptoms</th>
<th>Pfizer</th>
<th>Moderna</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
<td>84.1%</td>
<td>91.6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62.9%</td>
<td>68.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>55.1%</td>
<td>63.0%</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>38.3%</td>
<td>59.6%</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>23.6%</td>
<td>44.8%</td>
</tr>
<tr>
<td>Chills</td>
<td>31.9%</td>
<td>43.4%</td>
</tr>
<tr>
<td>Fever</td>
<td>14.2%</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

**Systemic reactogenicity symptoms**

- More common after second dose than first
- More common in younger age groups d/t more robust immune systems
- Generally occur on day 1 or day 2 and resolved within 2-3 days
- Most often mild or moderate in intensity
- More common in Moderna Phase 3 Trial than Pfizer Phase 3 Trial
- Should prompt staggering vaccines for hospital staff on same unit

**Nausea and Vomiting:**
- Moderna (*nausea and vomiting*): highest rate was in age < 64, after second dose: 21%
- Pfizer (vomiting): < 1%

**Lymphadenopathy:**
- Moderna: 10.2% after first dose, 14% after second dose
- Pfizer: < 5%
Reactogenicity Symptoms Are More Common in Younger Age Group

### Pfizer Vaccine

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Age 16-55</th>
<th>Age &gt; 55</th>
</tr>
</thead>
</table>
| Pain at Injection Site | 83% after first shot  
                       | 78% after second shot            | 71% after first shot  
                       | 66% after second shot            |
| Fatigue             | 59% after second dose             | 51% after second dose             |
| Headache            | 52% after second dose             | 39% after second dose             |
| Fever               | 16% after second dose             | 11% after second dose             |
| Muscle Aches        | 37% after second dose             | 29% after second dose             |
| Chills              | 35% after second dose             | 23% after second dose             |
| Joint Pain          | 22% after second dose             | 19% after second dose             |
## Vaccine Side Effects Compared

(<55 yr, after Dose 2 – highest side effect group found)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Shingrix</th>
<th>Moderna mRNA-1273</th>
<th>Pfizer COVID-19 BNT162b2</th>
<th>Flu FLUCELVAX QUADRIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Pain</td>
<td>88.4%</td>
<td>90.1%</td>
<td>77.8%</td>
<td>45.4%</td>
</tr>
<tr>
<td>Redness</td>
<td>38.7%</td>
<td>9.0%</td>
<td>5.9%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Swelling</td>
<td>30.5%</td>
<td>12.6%</td>
<td>6.3%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>56.9%</td>
<td>61.3%</td>
<td>37.3%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57%</td>
<td>67.6%</td>
<td>59.4%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Headache</td>
<td>50.6%</td>
<td>62.8%</td>
<td>51.7%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Chills</td>
<td>35.8%</td>
<td>48.3%</td>
<td>35.1%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Fever</td>
<td>27.8%</td>
<td>17.4%</td>
<td>15.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Overall Grade 3%</td>
<td>5.2%</td>
<td>4.1%</td>
<td>1.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Overall SE %</td>
<td>48%</td>
<td>46%</td>
<td>36%</td>
<td>15%</td>
</tr>
</tbody>
</table>

@JesseOSheaMD
What do we know about severe allergic reactions?

Emerging Story

Pfizer Clinical Trial
- No cases of anaphylaxis related following administration of the vaccine in the clinical trial
  BUT people with a history of anaphylaxis to vaccines were excluded from Pfizer clinical trial

Week 1 of Pfizer roll out:
- 2 cases of anaphylaxis in UK, 5 cases of anaphylaxis or severe allergic reaction in US (2 were in Alaska)
  - 2 individuals in UK both had history of anaphylaxis to food, needed epinephrine to treat vaccine induced anaphylaxis and recovered
- What is causing the anaphylaxis: not known, could be PEG (polyethylene glycol) which is an ingredient in both vaccines “but in different formulations”
- PEG is ubiquitous (ultrasound gel, miralax, injectable steroids) and allergy is rare

Moderna Clinical Trial
- People with a history of anaphylaxis were included
- No cases of anaphylaxis following administration of the vaccine
Pregnant Women

- Clinical trials did not include pregnant women (d/t fear of injuring fetus or threatening pregnancy)
- Not enough data to gauge whether they are safe for pregnant or lactating people
- DART animal studies
  - Moderna has completed animal studies the FDA demanded of manufacturers; these studies look for evidence that the vaccine might harm the pregnancy or the developing fetus. The company said it saw no such signals.
  - Pfizer has only interim data from its animal studies, but said it saw no concerning signs either.
- CDC has said pregnant women should be offered the chance to get the Pfizer vaccine
- (Great Britain advised against giving Pfizer vaccine to pregnant women)
- Pregnant women should discuss risks and benefits of vaccine with obstetrician taking into account
  - Pregnancy seems to increase risk of severe COVID course
  - Level of community transmission
  - Personal risk of exposure
- Post-vaccine fever should be treated with acetaminophen
Vaccine triggered anaphylaxis Non Covid vaccine 1.31/million doses

Pfizer/Moderna 2.6/million doses.
Summary

Early Data show that both Pfizer and Moderna vaccines are very effective and safe.

The Pfizer and Moderna vaccines often cause both local and systemic reactions. Most are minor and resolve within 24 hours.

Do the benefits of vaccination outweigh the risks?
References


Adenovirus as vaccine vectors: https://doi.org/10.1016/j.ymthe.2004.07.013

CDC overview of mRNA vaccines: https://www.cdc.gov/vaccines/covid-19/hcp/mrna-vaccine-basics.html

More detailed review of mRNA vaccines: https://www.tandfonline.com/doi/full/10.4161/rna.22269


https://www.nejm.org/doi/full/10.1056/NEJMra2035343?fbclid=IwAR2ul_J0s-mSLjFUtU00nf4UBIUMSbxbyePBu5Bpu-GuxSMkwMR19anfOUc