COVID Vaccines: Where are we now and where are we going?

Susan Buchbinder, MD
April 7, 2021
Excess deaths from COVID-19 in the US

• From March 1, 2020 to January 2, 2021, there were 22.9% more deaths than expected (previous years no more than 2.5% increase)

• Largest decline in life expectancy since World War II

• Total of 522,368 excess deaths from all causes
  • 208.4/100,000 among Black/African Americans
  • 157.0/100,000 among Whites
  • 139.8/100,000 among Latinx

• COVID was the 3rd leading cause of death in the US, after heart disease and cancer
The global impact of COVID-19

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins...
## Impact of Vaccines in the 20th & 21st Centuries

### Comparison of 20th Century Annual Morbidity & Current Morbidity: Vaccine-Preventable Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>20th Century Annual Morbidity</th>
<th>2017 Reported Cases</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>18,975</td>
<td>91%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>33</td>
<td>94%</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Measles</td>
<td>530,217</td>
<td>120</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>6,109</td>
<td>96%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>7</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>CRS</td>
<td>152</td>
<td>5</td>
<td>97%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>20,000 (est.)</td>
<td>33§</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

* JAMA. 2007;298(18):2155-2163  
§ *Haemophilus influenzae* type b (Hib) <5 years of age. An additional 10 cases of Hib are estimated to have occurred among the 203 notifications of H (5 years of age) with unknown serotype.
What could a COVID-19 vaccine do?

**Benefit the individual**
- Reduce the severity of illness
- Prevent infection

**Benefit the community**
- Reduce transmission
- Healthier communities
SARS-CoV-2 and its spike protein (the vaccine target)


This Photo by Unknown Author is licensed under CC BY-SA.
The coronavirus spike protein is on the surface of the virus. It directs how the virus attaches to cells to start the infection process. An ideal vaccine targets the coronavirus spikes in order to block infection.
The pieces involved - 2

- The coronavirus spike protein attaches to the ACE2 receptor to start an infection.
The goal: antibodies!

- Vaccine-induced antibodies can block the spike protein from attaching to human cells.
Timeline of first SARS-CoV-2 vaccine

- **1st report of respiratory virus outbreak in Wuhan, China**: Dec 31, 2019
- **VRC & Moderna decide on mRNA-1273 sequence**: Jan 13, 2020
- **Moderna validates in vitro expression of mRNA-1273**: Feb 2, 2020
- **VRC vaccinates mice**: Feb 4, 2020
- **Immunogenicity confirmed in mice**: Feb 19, 2020
- **Moderna ships clinical drug product**: Feb 24, 2020
- **Phase 1 clinical trial starts**: Mar 16, 2020
- **2019-nCoV sequences published**: Jan 10, 2020
- **Moderna initiates cGMP production**: Jan 14, 2020
- **Moderna ships pre-clinical drug product**: Feb 20, 2020
- **Spike structure published in Science**: Mar 2, 2020
- **IND submitted**: May 29, 2020
- **FDA safe-to-proceed**: May 29, 2020
- **Phase 2 clinical trial starts**: May 29, 2020
Stages of clinical trials

**PHASE 1**
Trials to test safety and whether the body can tolerate the product. Often involves comparing against a placebo with no active ingredients. Usually less than 100 people.

**PHASE 2**
Identifying the maximum tolerated dose, the best dosing schedule, and if the immune system is having the desired responses. Usually a few hundred to a few thousand people.

**PHASE 3**
“Does this product prevent infections, or help to reduce the severity of disease?” Involves thousands of people, including some at risk of infection.

With SARS-CoV-2, we are working as quickly as possible. No phases are skipped. Instead, we overlap the phases, starting the next phase as quickly as we have the necessary safety data collected and analyzed from the earlier phase. The new phase can start while the long-term follow-up of people in the earlier phase continues. Other steps can be done in parallel, instead of one after the other.
Traditional vs. Pandemic Vaccine Development

Traditional Vaccine Development — Multiple Years

- Preclinical Development
  - Phase 1
- Clinical Development
  - Phase 2
  - Phase 3
- Licensure
  - Large-scale production

Pandemic Vaccine Development Model — Overlapping Phases

- Shortens development time
- Define target product profile, preclinical development, assay development

Clinical Development
- Phase 1
- Phases 2 and 3

Licensure
- Regulatory pathway

Deming, NEJM 2020
What is an EUA?

“During a public health emergency, the FDA can use its Emergency Use Authorization (EUA) authority to allow the use of unapproved medical products...to diagnose, treat, or prevent serious or life-threatening diseases when certain criteria are met, including that there are no adequate, approved, and available alternatives.”

--FDA Website

For a COVID-19 vaccine, FDA stated issuance of an EUA would require:
• Minimum vaccine efficacy of 50%
• A median of 2 months of follow-up after full vaccination series
• Minimum 5 cases “severe” COVID disease in placebo recipients
Number of vaccines in development

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee  Updated April 3, 2021

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Authorized</th>
<th>Approved</th>
<th>Abandoned</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>33</td>
<td>23</td>
<td>6</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

- Vaccines testing safety and dosage
- Vaccines in expanded safety trials
- Vaccines in large-scale efficacy tests
- Vaccines in early or limited use
- Vaccines approved for full use
- Vaccines abandoned after trials

83 vaccines in clinical testing (humans)
77 vaccines in pre-clinical evaluation (animals)
Vaccines tested for efficacy in the US
COVID-19 Vaccines in Operation Warp Speed Development

- **mRNA**: rapid manufacturing facilitating efficient move to clinic, highly immunogenic
- **Adenovirus**: rapid manufacturing facilitating efficient move to clinic, vaccine using this platform is approved in Europe
- **Adjuvanted recombinant protein**: not as fast to manufacture but scalable, several approved vaccines use this approach
mRNA Vaccine

1. Scientists generated an mRNA sequence that codes for the virus spike protein

2. The RNA sequence, a blueprint for making the spike, is swathed in a lipid coating for delivery

3. Once it arrives, cells read the information in the mRNA sequence to produce millions of copies of the spike protein

4. The protein fragments spur the immune system to produce antibodies that can protect when a real virus enters the body

Sources: Pfizer, Bloomberg research
mRNA vaccines

**Pfizer vaccine**
- Pre-fusion spike protein
- 2 doses, 21 days apart
- Efficacy: 95%
- 162 cases of symptomatic disease in placebo, 8 in vaccine group
- 9 cases of severe disease in placebo, 1 in vaccine group
- No difference in efficacy by age
- Increased symptoms with 2\textsuperscript{nd} dose

**Moderna vaccine**
- Pre-fusion spike protein
- 2 doses, 28 days apart
- Efficacy: 94.1%
- 185 cases of symptomatic disease in placebo, 11 in vaccine group
- 30 cases severe disease in placebo, none in vaccine group
- No difference in efficacy by age
- Increased symptoms with 2\textsuperscript{nd} dose
## Pfizer Vaccine Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Younger (16-55 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47%</td>
</tr>
<tr>
<td>Headache</td>
<td>42%</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>21%</td>
</tr>
<tr>
<td>Chills</td>
<td>14%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>11%</td>
</tr>
<tr>
<td>Fever</td>
<td>4%</td>
</tr>
</tbody>
</table>
# Pfizer Vaccine Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Younger (16-55 years)</th>
<th>Older (&gt; 55 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47%</td>
<td>59%</td>
</tr>
<tr>
<td>Headache</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>21%</td>
<td>37%</td>
</tr>
<tr>
<td>Chills</td>
<td>14%</td>
<td>35%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>11%</td>
<td>22%</td>
</tr>
<tr>
<td>Fever</td>
<td>4%</td>
<td>16%</td>
</tr>
</tbody>
</table>
mRNA Vaccine Side Effects as Reported by V-safe
1.9 million respondents with 2 doses

<table>
<thead>
<tr>
<th></th>
<th>Dose 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pfizer</td>
</tr>
<tr>
<td>Local pain</td>
<td>64%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29%</td>
</tr>
<tr>
<td>Headache</td>
<td>25%</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>17%</td>
</tr>
<tr>
<td>Chills</td>
<td>7%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>7%</td>
</tr>
<tr>
<td>Fever</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
</tr>
</tbody>
</table>

Chapin-Bardales, JAMA 2021
## mRNA Vaccine Side Effects as Reported by V-safe

1.9 million respondents with 2 doses

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Dose 1</th>
<th>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pfizer</td>
<td>Moderna</td>
</tr>
<tr>
<td>Local pain</td>
<td>64%</td>
<td>71%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>Headache</td>
<td>25%</td>
<td>27%</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>Chills</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Fever</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Chapin-Bardales, JAMA 2021
Duration of side effects: v-safe

A. Persons ages less than 65 years

Dose 1

Dose 2

Chapin-Bardales, JAMA 2021
Duration of side effects: v-safe

B. Persons ages 65 years and older

Chapin-Bardales, JAMA 2021
Anaphylaxis

Context:
1 in 59 people diagnosed with COVID-19 in US will die of it
1-2 of every 400,000 people will have anaphylaxis – none have died
mRNA vs. Chimp Adenovirus

1. Scientists generated an mRNA sequence that codes for the virus spike protein.
2. The RNA sequence, a blueprint for making the spike, is swathed in a lipid coating for delivery.
3. Once it arrives, cells read the information in the mRNA sequence to produce millions of copies of the spike protein.
4. The protein fragments spur the immune system to produce antibodies that can protect when a real virus enters the body.

Sources: Pfizer, Bloomberg research

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1. The spike protein gene of the coronavirus is inserted in a harmless chimpanzee virus.
2. The chimpanzee virus is genetically changed so that it cannot grow in humans.
3. Once it arrives, cells read the information in the gene sequence to produce millions of copies of the spike protein.
4. The protein fragments spur the immune system to produce antibodies that can protect when a real virus enters the body.

Sources: University of Oxford, AstraZeneca, Bloomberg research
# Adenoviral vector vaccines

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Johnson &amp; Johnson</th>
<th>AstraZeneca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector</td>
<td>Human adenovirus 26</td>
<td>Chimpanzee adenovirus</td>
</tr>
<tr>
<td>Insert</td>
<td>Pre-fusion spike</td>
<td>Spike</td>
</tr>
<tr>
<td>Number of doses</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Efficacy: symptomatic dz</td>
<td>67% overall (74% in US)</td>
<td>76%</td>
</tr>
<tr>
<td>Efficacy: severe disease</td>
<td>85% (100% against death)</td>
<td>100%</td>
</tr>
<tr>
<td>Number vaccine: placebo</td>
<td>5 vaccine: 34 placebo</td>
<td>0 vaccine: 5 placebo</td>
</tr>
<tr>
<td>Efficacy by age</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Symptoms after 2\textsuperscript{nd} dose</td>
<td>NA</td>
<td>Better</td>
</tr>
</tbody>
</table>
Novavax vaccine

• Pre-fusion spike sub-unit protein vaccine

• **89.7% efficacy against symptomatic disease in UK study**
  • 10 cases in vaccine recipients vs. 96 cases in placebo recipients

• **100% efficacy against severe disease in UK study**
  • 5 cases overall, all in the placebo group

• Awaiting data from US trial
Vaccines tested outside of the US (a subset)
# Vaccines outside of the US

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sputnik V</th>
<th>Sinovac</th>
<th>Sinopharm</th>
<th>CanSinoBio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of vaccine</td>
<td>Ad26 and Ad5</td>
<td>Inactivated</td>
<td>Inactivated</td>
<td>Ad5</td>
</tr>
<tr>
<td>Insert</td>
<td>Spike</td>
<td>NA</td>
<td>NA</td>
<td>Spike</td>
</tr>
<tr>
<td># doses</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Days apart</td>
<td>21 days</td>
<td>14 days</td>
<td>21 days</td>
<td>NA</td>
</tr>
<tr>
<td>Efficacy: sx’ic</td>
<td>91.1%</td>
<td>50% Brazil*</td>
<td>79%*</td>
<td>66%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84% Turkey*</td>
<td>86%*</td>
<td></td>
</tr>
<tr>
<td>Efficacy: severe</td>
<td>100%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Storage</td>
<td>Freezer</td>
<td>Refrigerator</td>
<td>Refrigerator</td>
<td>Refrigeratator</td>
</tr>
</tbody>
</table>

*Data not published*
7 Challenges
Challenge 1: Vaccine shipping & storage

• Pfizer mRNA vaccine
  • Shipped and stored at -20°C for up to 6 months (regular freezer)
  • Stable at 2-8°C for up to 5 days (refrigerator)

• Moderna mRNA vaccine
  • Shipped and stored at -20°C for up to 6 months (regular freezer)
  • Stable at 2-8°C for up to 30 days (refrigerator)

• AZ chimp adenovirus vaccine, Janssen Ad26 vaccine
  • Stable at 2-8°C for up to 6 months (refrigerator)
Challenge 2: Vaccine distribution

New reported doses administered by day

4 million doses

3.07 million average doses per day

Source: Centers for Disease Control and Prevention | Note: Line shows a seven-day average. Data not updated on some weekends and holidays. Includes the Johnson & Johnson vaccine as of March 5.
When will all adults be vaccinated in the US?

At the current pace of vaccination, everyone could get a shot this year. But no vaccine has been authorized for children under 16.

Based on the seven-day average of people receiving a first or single dose each day.

100% of the total U.S. population

75%

70% June 14

78% June 29

90% July 22

At current pace

This is equal to all adults, 18 and older. Children under 16 are not yet eligible.

Source: Centers for Disease Control and Prevention | Note: Total population includes states, territories and three countries with special agreements with the United States: Palau, Micronesia and the Marshall Islands.
Vaccine distribution by state

CA: 32.7% at least one dose
17.3% fully vaccinated

Source: Centers for Disease Control and Prevention

New York Times, April 3, 2021
Challenge 3: Vaccine hesitancy
Proportion of US population who already got the vaccine or want it ASAP

Does The Public Want To Get A COVID-19 Vaccine? When?

Click on the buttons below to see the share of each demographic group by vaccination intentions:

- Already got/ASAP
- Wait and see
- Only if required
- Definitely not

61%

Total

NOTE: See topline for full question wording.
SOURCE: KFF COVID-19 Vaccine Monitor • Download PNG
Proportion of US population who definitely do **NOT** want to get the vaccine

Does The Public Want To Get A COVID-19 Vaccine? When?

*Click on the buttons below to see the share of each demographic group by vaccination intentions:*

- Already got/ASAP
- Wait and see
- Only if required
- Definitely not

NOTE: See topline for full question wording

SOURCE: KFF COVID-19 Vaccine Monitor - Download PNG
Vaccine enthusiasm growing in Black and Latinx adults

NOTE: See topline for full question wording.
SOURCE: KFF COVID-19 Vaccine Monitor (March 15-22, 2021) • Download PNG
Challenge 4: When do children get vaccinated?

- Currently, Pfizer vaccine is the only one licensed for 16+ years
- Pfizer recently released data on trial in 2260 12-15 year olds
  - 100% efficacy against symptomatic disease (18 cases, all in the placebo arm)
  - Robust antibody response, at least as high as 16-25 year olds
  - As well tolerated as in 16-25 year olds
  - Applying for an EUA “as soon as possible”
- Several companies also testing vaccines in children down to 6 months of age
  - Unlikely to have results until later in the year
Challenge 5: Viral variants

- Each SARS-CoV2 viral particle has nearly 30,000 “letters” of RNA that tell the infected cell how to make more copies of the virus.

- Occasionally, when the virus is replicating, errors are made. These are called mutations.

- A group of viruses that share the same mutation(s) is called a variant.
SARS-CoV-2 has a relatively low mutational rate compared with other viruses

From Galit Alter, CROI 2021
Variants

• Variants from UK (B.1.1.7), South Africa (B.1.351), Brazil (P.1)

• Appears that mRNA vaccines should be protective against UK variant, but may have reduced efficacy against South African variant
  • 6-8 fold reduction in neutralizing antibody titers, but mRNA levels are still supposed to be high enough for protection. No clinical data yet.

• Other vaccines have reduced efficacy against South African variant
  • J&J and Novavax vaccines lower efficacy in South Africa
  • AstraZeneca did not show efficacy in small South African trial; South Africa is not distributing this vaccine

• Manufacturers working on developing new versions that could be given as a “booster” dose, if needed
Challenge 6: Global distribution
From vaccine nationalism to vaccine equity

- Estimated that 80% of the population in low-resource settings will not have access to a COVID vaccine this year.
- Uncoordinated patchwork of immunity could exacerbate the rise of escape variants that could alter vaccine effectiveness.
- COVAX: Covid-19 Vaccines Global Access program: plans to vaccinate at least 20% of the population of participating countries by the end of 2021.
- Consider temporarily waiving pharmaceutical patent protection.

Katz et al, NEJM 2021
Challenge 7: Can we achieve herd immunity?

"It seems you promised them herd immunity, sir."

New Yorker caption contest, Nov 30, 2020
What is ‘herd immunity’?

If only a few people are vaccinated...

...then one person is infected...
the disease spreads very fast

But if lots of people are vaccinated...

...then the disease can’t spread very far, so the whole community stays safe. This is ‘herd immunity’

#CelebrateVaccines
The optimistic view to herd immunity

An estimate for the path to herd immunity

100% of population immune

New York Times, based on model from PHICOR
5 challenges to achieving herd immunity

It is estimated that need 70-90% of the population vaccinated or immune to achieve herd immunity, but:

1. It is unclear if the current vaccines prevent transmission

2. Vaccine roll-out is uneven
   a. Youth: Until youth are immunized, need to achieve 100% vaccination rate in adults before reaching herd immunity in the US
   b. Globally, nowhere near achieving herd immunity level
   c. Geographic pockets could allow for outbreaks within communities

3. Unknown impact of variants

4. Durability of immunity

5. Vaccines change behaviors
   a. While on the way to achieving herd immunity, loosening up masking/social distancing will increase spread

Aschwanden, Nature, 18 March 2021
Global distribution will thwart achieving herd immunity

Disparities in Distribution

The worldwide roll-out of COVID-19 vaccinations is uneven, as shown by this selection of countries. Even as some nations approach a theoretical threshold for herd immunity, quashing the spread of the virus will prove difficult.

- Fully vaccinated
- Received at least one dose

Data as of 17 March 2021.

Source: Our World In Data

Aschwanden, Nature 18 March 2021
Encouraging news
“Real world” effectiveness

- University of Texas,\textsuperscript{1} >90% effectiveness against staff isolation or quarantine

- Israel,\textsuperscript{2} estimated efficacy at population level after 2\textsuperscript{nd} dose:
  - 94% against symptomatic disease
  - 92% against severe disease
  - Included efficacy against B.1.1.7 variant

- Health care workers:\textsuperscript{3} 80% effective after 1\textsuperscript{st} dose, 90% effective after 2\textsuperscript{nd} dose

\textsuperscript{1} Daniel et al, NEJM 2021
\textsuperscript{2} Dagan et al, NEJM 2021
\textsuperscript{3} MMWR 2021
Durability (and a little about variants)

Pfizer just released data from their Phase 3 clinical trial that the vaccine was:

• 91.3% effective against symptomatic disease
• 95.3% effective against severe disease

at 6 months post-vaccination

Also, small numbers, but vaccine was effective against the (South African) B.1.351 variant

• 6 cases, all in the placebo group
• Just launched a full trial of the Moderna vaccine in South Africa
Summary

• Currently have 3 EUA vaccines in the US, may be more soon
  • Could have enough vaccine for all adults in US by summer
  • Teenagers will have access soon; younger children later in year
  • Need to address vaccine hesitancy
• “Real world” efficacy is very high, may be durable
  • Will have data on vaccine effects on transmission later this year
• Need to track variants, assess impact on vaccine efficacy
  • Booster doses possible in future
• Must work toward global access of vaccines
Questions?